AN INVESTIGATION OF DIRECT C-ALKYLATION OF 2,4-OXAZOLIDINEDIONE AND 5-PHENYL-2,4-OXAZOLIDINEDIONE UTILIZING DIALKALI SALT INTERMEDIATES

by

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Thesis submitted to the Graduate Faculty of the
Virginia Polytechnic Institute and State University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

in

Chemistry

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September, 1973

Blacksburg, Virginia

TO MY PARENTS

AND RUSTY

ACKNOWLEDGEMENTS

I would like to extend my appreciation to Dr. James F. Wolfe for the encouragement and understanding he provided in both the research and academic aspects of this investigation.

Particular thanks is due Dr. James V. Hay for his assistance during the course of this investigation and especially at those times when Dr. Wolfe was not available because of professional commitments.

Tom E. Glass performed all the spectral and elemental analyses reported in this work, and his help was greatly appreciated.

Finally, I wish to acknowledge the financial assistance received from the Chemistry Department in the form of teaching assistantships and the National Institute of Health for supporting this research during the summer months in the form of research assistantships.

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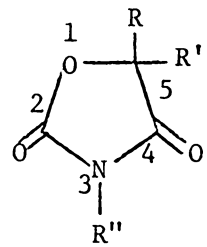
I. INTRODUCTION

The physiological activity demonstrated for a variety of 5,5-dialkyl- and 3,5,5-trialkyl-2,4-oxazolidinediones has created extensive interest in the development of new synthetic routes to 2,4-oxazolidinedione derivatives of this type. The purpose of this investigation was to determine the feasibility of preparing these physiologically active compounds by direct C-alkylation of 2,4-oxazolidinedione and selected 5-substituted-2,4-oxazolidinediones utilizing dialkali salt intermediates.

II. HISTORICAL

2,4-Oxazolidinediones are compounds having structural formula (1). Although approximately 200 derivatives are known in which R, R', and R" represent hydrogen, alkyl, aryl, aralkyl, or heterocyclic substituents, the 5,5-dialkyl- and 3,5,5,-trialkyl-2,4-oxazolidinediones are of particular interest because of the fact that central nervous system activity has been demonstrated for derivatives of this type. The 3-methyl derivatives of 5,5-dialkyl-2,4-oxazolidinedione (where the alkyl groups are small) are



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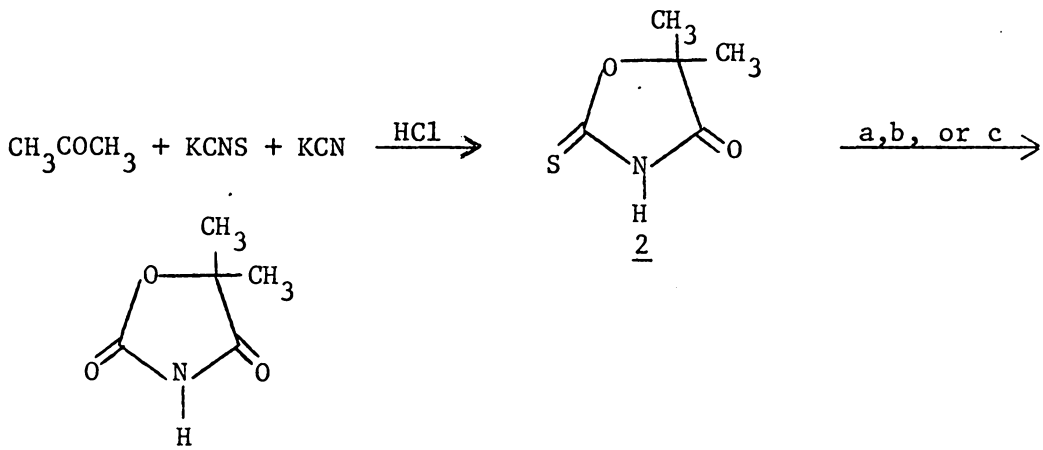
active anticonvulsant agents; 3,5,5-trimethyl-2,4-oxazolidinedione (trimethadione) is the compound most widely used in the symptomatic treatments of petit mal epilepsy. Mild hypnotic, sedative, and narcotic properties have been shown for 2,4-oxazolidinedione not bearing 3-alkyl substituents. For example, 5,5-di-n-propyl-2,4-oxazolidinedione has been studied clinically as an hypnotic and antiepileptic agent.[1]

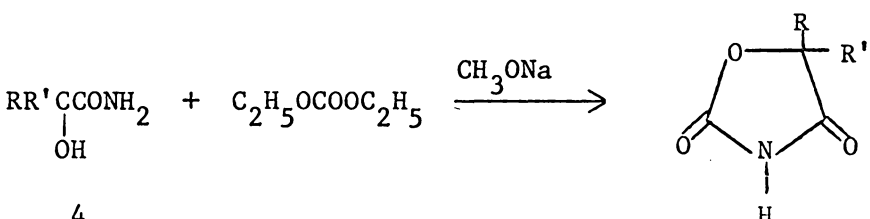
The synthetic procedures currently employed for the preparation of the various derivatives of 2,4-oxazolidinedione are quite numerous. One method involves the oxidation of 2-thio-4-oxazolidones. For example,

acetone, potassium cyanide, and potassium thiocyanate in the presence of concentrated hydrochloric acid give 5,5-dimethyl-2-thio-4-oxazolidone[2] (2) (eq 1). The subsequent conversion of 2 into 5,5-dimethyl-2,4-oxazolidinedione (3) can be effected (a) with bromine water,[3] (b) by heating 2 with aqueous lead acetate,[4] or (c) by oxidation with hydrogen peroxide at 70-100°:[5]



(1)

A second method involves the condensation of amides of α-hydroxy acids (4) with either dialkyl carbonates in the presence of a sodium, potassium, or magnesium alkoxide (eq 2) or alkyl chloroformates in the presence of potassium carbonate[6] (eq 3).



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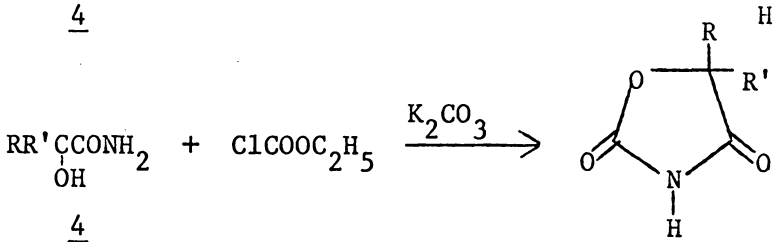

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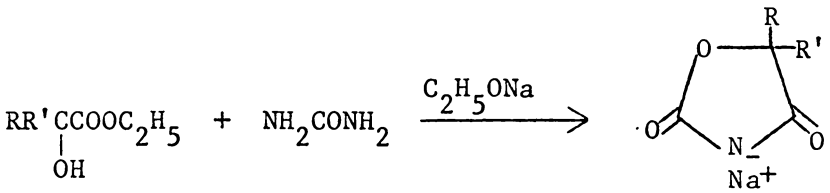
Perhaps the most convenient method available for the synthesis of 5-monosubstituted and 5,5-disubstituted-2,4-oxazolidinediones involves the condensation of the ester of an appropriate α-hydroxy acid (5) with urea in the presence of sodium ethoxide to yield the sodium salt of the desired 2,4-oxazolidinedione derivative[7] (6) (eq 4). This method permits

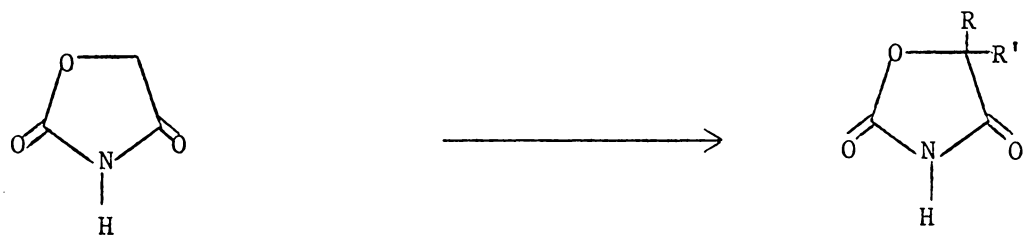


(4)

5 6

the preparation of a wide range of 5-monosubstituted and 5,5-disubstituted 2,4-oxazolidinediones because of the ready accessibility of the esters.

The major problem with all of the techniques currently used for the synthesis of 2,4-oxazolidinedione derivatives is that each derivative must be prepared from a different set of starting materials through a long synthetic route. Therefore, the purpose of this investigation was to start with the readily available unsubstituted 2,4-oxazolidinedione (7) and determine a means by which 7 could be directly alkylated at the 5-position. This approach would allow preparation of numerous derivatives from a single starting material.



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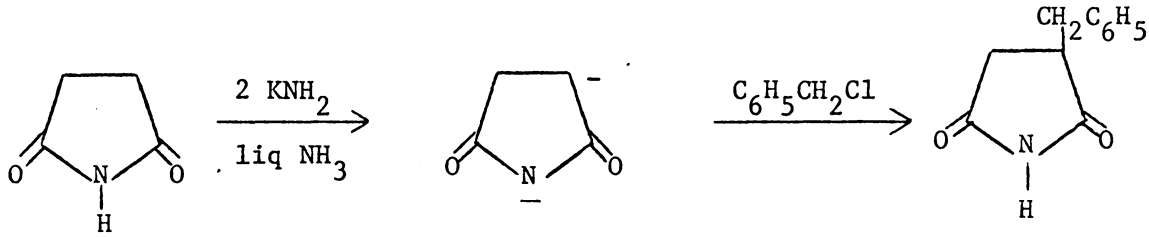
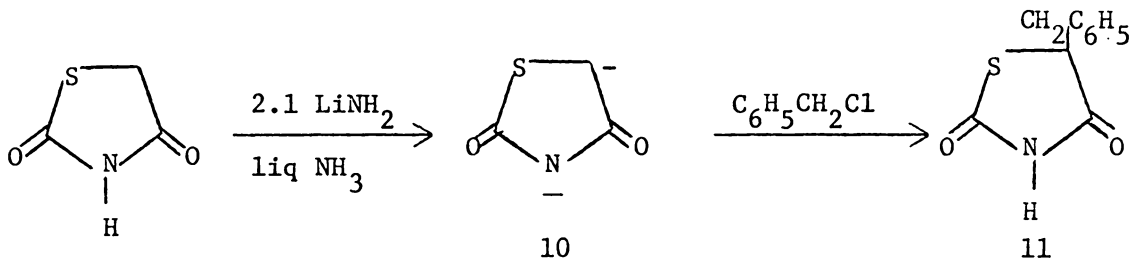
Bryant and Hauser[8] reported the formation of dianion 8 from the treatment of succinimide with two molecular equivalents of potassium amide in liquid ammonia. Subsequent alkylation of dianion 8 with benzyl chloride gave monobenzyl derivative 9 along with appreciable amounts of higher C-alkylated products; however, no N-benzyl derivative of succinimide was detected.



8 9

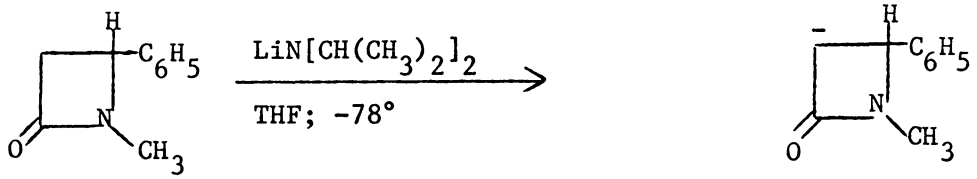
The selective reactivity at the carbanion site of dianions formed from 5-membered heterocyclic systems of this type was also demonstrated by Taylor and Wolfe.[9] Treatment of 2,4-thiazolidinedione with 2.1 molecular equivalents of lithium amide in liquid ammonia gave dianion 10, which upon alkylation with benzyl chloride afforded the 5-benzyl derivative 11 as the major product.



10 11

Durst and LeBelle[10] found that simple monocyclic N-methyl-β-lactams readily formed monoanion 12 upon addition to an equimolar amount of lithium diisopropylamide in tetrahydrofuran (THF) at -78°. Anion 12 readily

reacted with a variety of electrophiles to yield the 3-substituted derivatives 13, where R corresponds to the electrophilic reagent employed.



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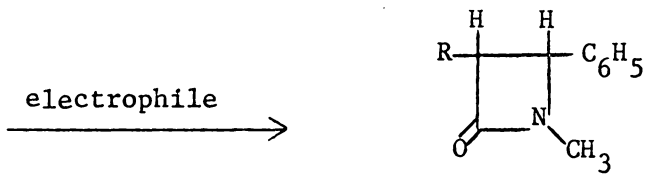
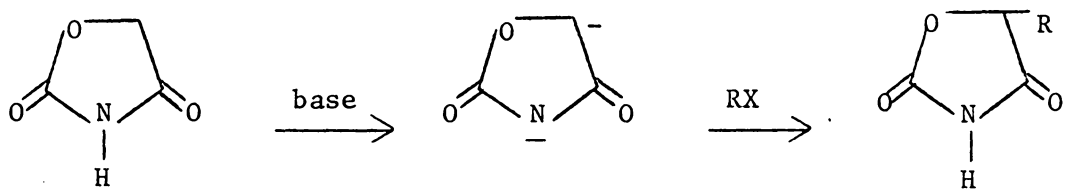
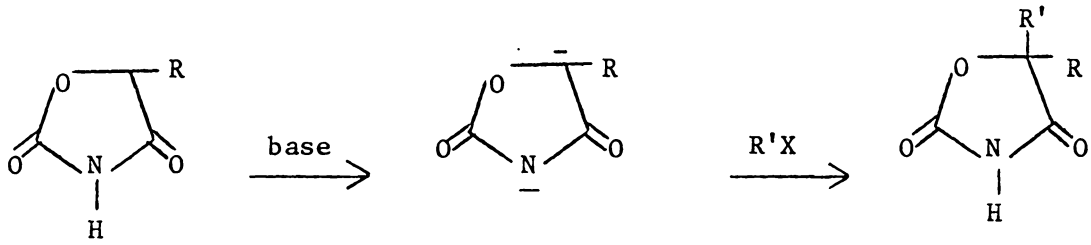


13

The successful formation and selective alkylation of dianions 8 and 10 and monoanion 12 led to the consideration of 2,4-oxazolidinedione (7) as a precursor to a new multiple anion, 14. If dianion 14 could be formed, selective alkylation at the 5-position might be expected to occur to give 5-substituted derivatives of type 15. If subsequent ionization of 15 were to give dianion 16, then alkylation of 16 should result in the formation of 5,5-disubstituted products 17.



7 14 15



15 16 17

Although previous alkylations of 2,4-oxazolidinedione (7) have been employed for the synthesis of N-alkyl derivatives, no direct method for C-alkylation of 7 has been reported.[1]

The primary factor under consideration for the use of 2,4-oxazolidinedione as a precursor to dianion 14 was whether or not the inductive effect of the oxygen hetero atom would stabilize dianion 14 to the same extent as the sulfur hetero atom stabilized dianion 10 of 2,4-thiazolidinedione.[9] A comparison of 3-d-orbital effects exhibited by sulfur with inductive effects exhibited by oxygen on carbanion stability was reported by Oae and coworkers.[11] In this investigation the rates at which compounds 18 and 19 underwent potassium alkoxide-catalyzed tritium-hydrogen exchange with alcohols was made. The two sulfur groups acidified the carbon acid

$C_6H_5\underset{\underset{T}{|}}{C}(SC_2H_5)_2$ $C_6H_5\underset{\underset{T}{|}}{C}(OC_2H_5)_2$

18 19

more than the two oxygens did by enough to make exchange of 18 occur six powers of ten faster than 19. It was felt that had the greater inductive

effect of the two oxygens not been operative, the difference in exchange rates could have been much greater.

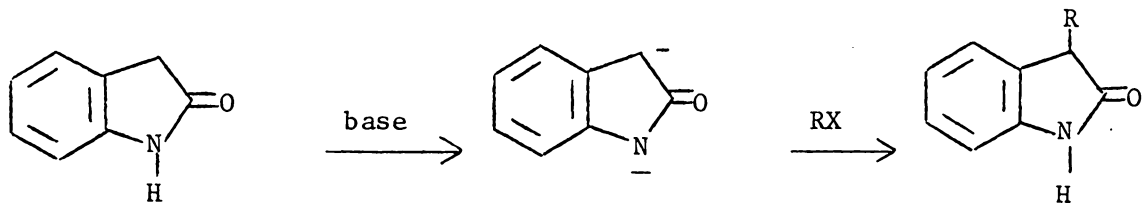
Similarly, Tarbell and Lovett[12] observed that allyl hexyl sulfide was isomerized to hexyl propenyl sulfide (eq 5) under conditions (78°, 3.7 M sodium ethoxide in ethanol) that left allyl hexyl ether unchanged (eq 6).

$$CH_2 = CHCH_2SCH_2(CH_2)_4CH_3 \longrightarrow CH_3CH = CHSCH_2(CH_2)_4CH_3 \quad (5)$$

$$CH_2 = CHCH_2OCH_2(CH_2)_4CH_3 \not\longrightarrow CH_3CH = CHOCH_2(CH_2)_4CH_3 \quad (6)$$

Therefore, the ease with which 2,4-oxazolidinedione could be ionized to give dianion 14 might be expected to be less than the ease with which 2,4-thiazolidinedione was ionized to afford dianion 10.

The structural similarity of oxindole (20) to 2,4-oxazolidinedione and succinimide led to the consideration of preparing derivatives of type 22 through the formation and subsequent alkylation of dianion 21.



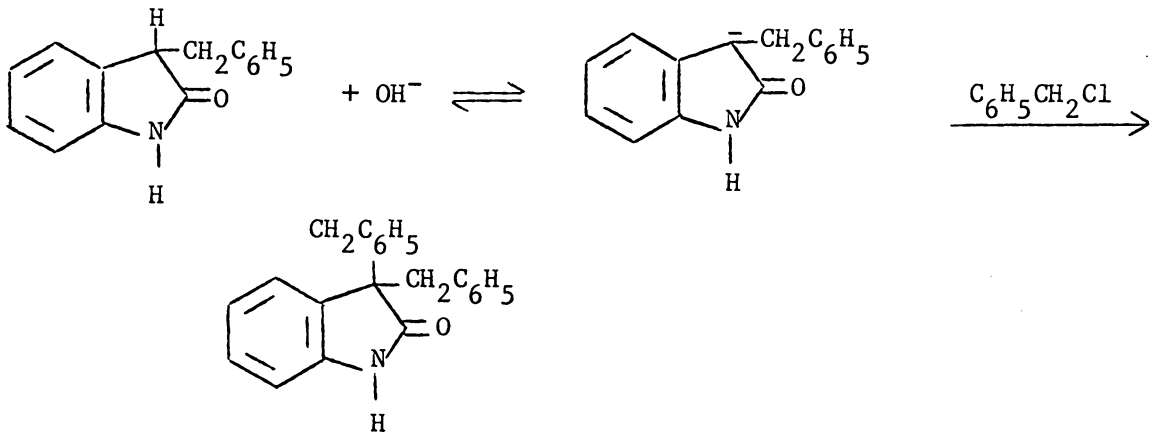
20 21 22

Previous attempts to alkylate 20 have resulted in dialkylation at the 3-position. Daisley and Walker[13] reported that attempts to alkylate N-methyloxindole using ethanolic sodium ethoxide as the base gave the 3,3-dialkyl derivative exclusively. With sodium hydride as the base,

the desired 3-alkyl derivatives were obtained in approximately 30% yields; however, appreciable amounts of the 3,3-dialkyl derivatives were still obtained.

Gruda[14] reported that treatment of oxindole with equimolar quantities of sodium hydroxide and benzyl chloride yielded 1,3,3-tribenzyloxindole (8.1%), 1,3-dibenzyloxindole (3.6%), 1-benzyloxindole (6.5%), 3,3-dibenzyloxindole (20.2%), and 3-benzyloxindole (13%). Scheme I depicts Gruda's explanation as to what may be occurring during the course of the reaction to cause formation of 3,3-dibenzyloxindole.

Scheme I



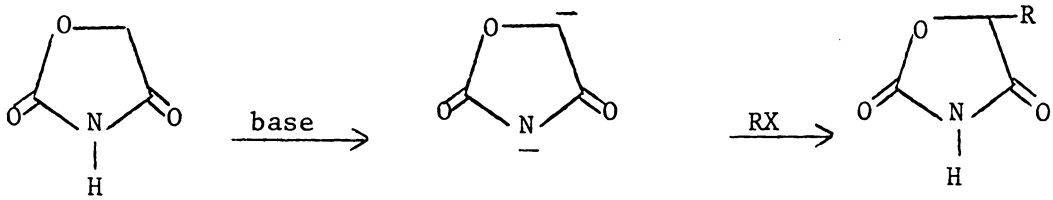
Therefore, the present investigation was extended to determine if dianion 21, formed by treating oxindole with slightly more than two equivalents of an alkali metal base, would display the same selective reactivity at the carbanion site which succinimide and 2,4-thiazolidinedione displayed for alkylations. If dianion 21 were to show this selectivity, then a synthetic route to 3-alkyloxindoles without the interference of polyalkylation would be available.

III. RESULTS AND DISCUSSION

A. 2,4-Oxazolidinediones

The major disadvantage of the currently employed synthetic method for 5,5-dialkyl- and 3,5,5-trialkyl-2,4-oxazolidinediones lies in the fact that for each derivative desired, different starting materials must be prepared and then converted to the desired 2,4-oxazolidinedione by one of the methods outlined in the Historical section.

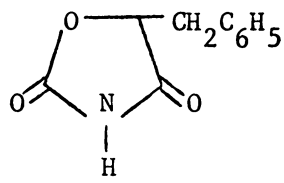
Although the carbanion-stabilizing ability of the oxygen hetero atom of 2,4-oxazolidinedione (7) was in question, it appeared that 7 possessed enough structural similarities to succinimide and 2,4-thiazolidinedione to permit conversion to dianion 14. If dianion 14 could be prepared and selectively alkylated at the carbanion position, then 5-alkyl-2,4-oxazolidinediones would be available in a one-step synthesis from a single starting material.



7 14

When 2,4-oxazolidinedione (7) was treated with two molecular equivalents of potassium amide in liquid ammonia and benzyl chloride was added to the reaction mixture, no product was obtained which corresponded to either recovered 7 or the desired benzyl derivative. Use of slightly more than two molecular equivalents of lithium amide in liquid ammonia

afforded 5-benzyl-2,4-oxazolidinedione (23) in only 15% yield (Table 1) as compared to a 57% yield of 5-benzyl-2,4-thiazolidinedione (24) obtained under identical conditions.[9]



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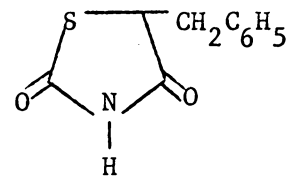
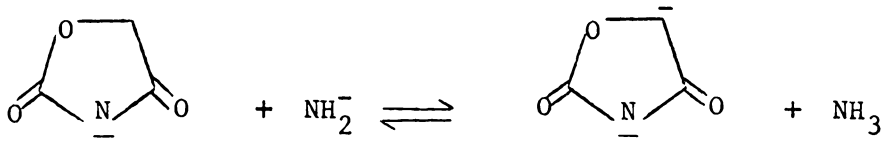


24

Several possible factors could have contributed to the low yields of 23. The first factor might have been lack of complete ionization of 7 to form dianion 14. The formation of 14 is probably a two-step equilibrium process with the last step (eq 7) being the most difficult, and monoanion 14' may not be completely converted to dianion 14 under these reaction conditions.



(7)

14' 14

Therefore, the concentration of 14 may be insufficient to afford a significant yield of the desired benzyl derivative. However, subsequent neutralization of the reaction mixture should convert monoanion 14' back to 2,4-oxazolidinedione (7), but no recovered 7 was isolated.

A second possibility might be that although dianion 14 was formed satisfactorily, it was not reactive enough toward the benzyl chloride to afford a significant yield of 23.

TABLE 1

Benzylations of 2,4-Oxazolidinedione

Base (Equiv)	Equiv of Benzyl Chloride	Temp °C	Yield %
KNH_2 (2.0)	1.0	-33[a]	--
$LiNH_2$ (2.1)	1.1	-33[a]	15
$LiN[CH(CH_3)_2]_2$ (2.10)	1.10	25[b]	10[d]
$LiN[CH(CH_3)_2]_2$ (2.14)	1.14	0[b]	10[d]
$LiN[CH(CH_3)_2]_2$ (2.62)	1.62	-78[b]	13[d]
$LiN[CH(CH_3)_2]_2$ (2.1)	1.1	0[c]	--

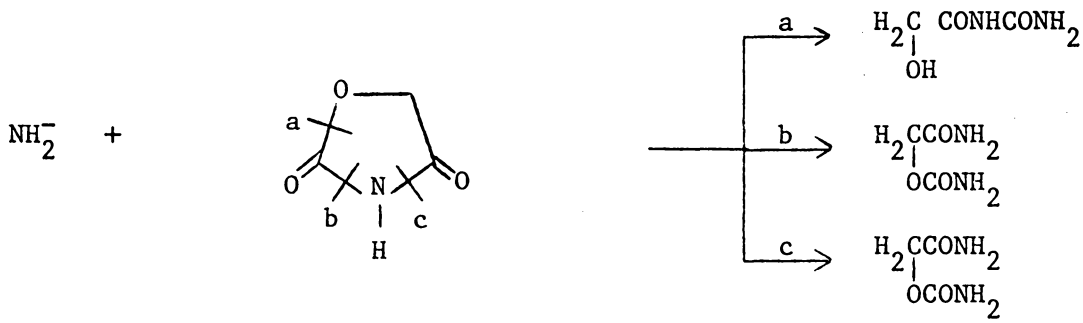
[a]Liquid ammonia as reaction solvent.

[b]THF-hexane as reaction solvent using 2,2'-bipyridyl as indicator.

[c]THF-hexane as reaction solvent; 1.1 equiv of hexamethylphosphoramide (HMPA) added prior to addition of substrate.

[d]Yields determined by pmr analysis.

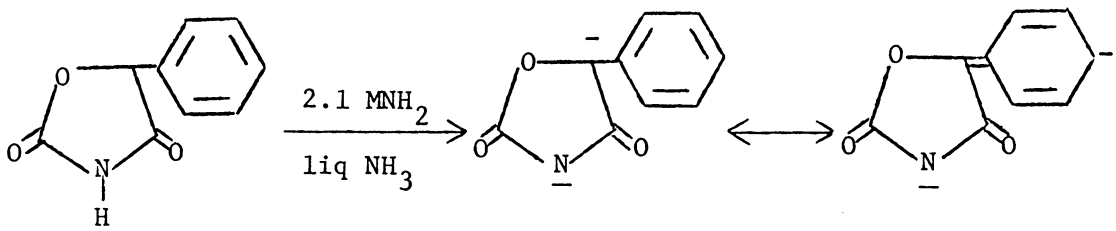
A third factor warranting consideration would be that under the reaction conditions employed for ionization, 2,4-oxazolidinedione was being cleaved by the base at any or all of the positions shown below.



If cleavage were occurring, then the expected water solubility of resulting products would have prevented their detection by the methods used.

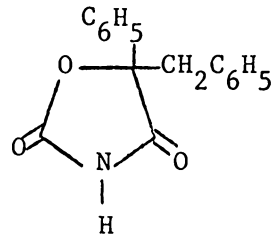
5-Phenyl-2,4-oxazolidinedione (25) was selected as the next system used to investigate the possibility of synthesizing selected 5-substituted-2,4-oxazolidinediones through a dianionic intermediate. Although 5,5-diaryl-2,4-oxazolidinediones do not possess the hypnotic and sedative properties which characterize the 5,5-dialkyl compounds, certain 5,5-diaryl derivatives are effective anticonvulsant agents; for example, 5,5-diphenyl-2,4-oxazolidinedione is ineffective in treating petit mal epilepsy but resembles 5,5-diphenylhydantoin in controlling grand mal seizures.[1]

The major advantage in using 5-phenyl-2,4-oxazolidinedione (25) as a precursor to dianion 26 was the anticipated stabilization the phenyl group would lend to 26 through resonance interaction.



25 26

A second advantage in using 25 was that successful benzylation would result in the formation of 5-benzyl-5-phenyl-2,4-oxazolidinedione (27) which should have limited solubility in water and therefore be relatively easy to isolate.



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A summary of yields obtained from the reactions of 5-phenyl-2,4-oxazolidinedione using 3.7 molar equivalents of potassium amide and various molar equivalents of lithium amide in liquid ammonia and alkylating with either benzyl chloride or ethyl bromide is given in Table 2. In this series the highest yield was 49% (isolated) of benzyl derivative 27 obtained from the use of 2.1 molar equivalents of lithium amide and alkylating with 1.1 molar equivalents of benzyl chloride.

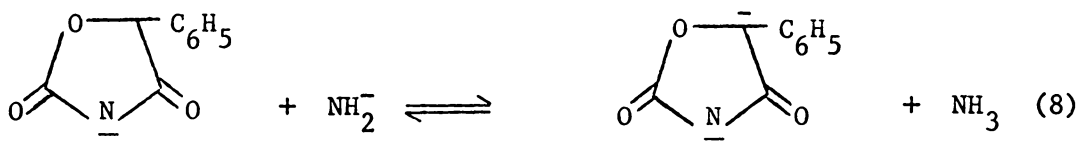
The ionization of 25 to form dianion 26 is probably a two-step equilibrium process also, with the final step (eq 8) being the most difficult. If the formulation of 26 is not sufficient to afford a high

TABLE 2

Alkylations of 5-Phenyl-2,4-Oxazolidinedione
Using Alkali Metal Amides in Liquid Ammonia

Amide (Equiv)	Halide (Equiv)	Yield[a] %
KNH_2 (3.7)	benzyl chloride (3.7)	8
$LiNH_2$ (3.7)	benzyl chloride (3.7)	34
$LiNH_2$ (2.1)	benzyl chloride (2.1)	41
$LiNH_2$ (2.1)	benxyl chloride (1.1)	49
$LiNH_2$ (2.1)	ethyl bromide (1.1)	29

[a]Yield of ethyl derivative was determined by pmr analysis; all others are isolated yields.



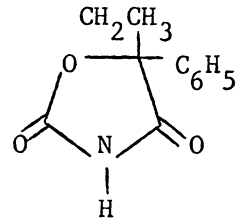
26' 26 (8)

yield of the desired product after alkylation and neutralization, then addition of more than 2.1 molar equivalents of lithium amide should increase the extent of ionization to form dianion 26 and subsequently increase the yield of alkylated product. Use of 3.7 molar equivalents of lithium amide and 3.7 molar equivalents of benzyl chloride decreased rather than increased the yield of 5-benzyl-5-phenyl-2,4-oxazolidinedione (27) from 49% to 34%. This result seemed to indicate that 2.1 equivalents of lithium amide was sufficient to effect the desired ionization to the maximum extent possible with this system, and that any excess base was not increasing the amount of dianion 26 formed, but was reacting with either 25, 26', or 26 by some additional pathway to decrease the yield of the 5-benzyl derivative.

Benzylation of 5-phenyl-2,4-oxazolidinedione using 3.7 molar equivalents of potassium amide rather than lithium amide and 3.7 molar equivalents of benzyl chloride also decreased the yield of benzyl derivative 27 (from 34% to 8%). This decrease in yield might be attributed to the increased base strength of potassium amide resulting in possible cleavage of the ring.

Use of excess benzyl chloride (2.1 molar equivalents) in conjunction with 2.1 molar equivalents of lithium amide did not increase the yield of

27; an increase in yield would be expected using excess halide if the reactivity of dianion 26 toward benzyl chloride was low. Using 1.1 equivalents of ethyl bromide as the alkylating agent afforded 29% of 5-ethyl-5-phenyl-2,4-oxazolidinedione (28) as determined by pmr analysis. Therefore, changing the halide from benzyl chloride to ethyl bromide decreased the yield of the 5-substituted derivative by approximately 20%; the isolated yield of benzyl derivative 27 was 49%.



28

The next aspect examined was the effect of using lithium diisopropylamide rather than lithium amide as the base and alkylating with ethyl bromide would have on the yield of 5-ethyl-5-phenyl-2,4-oxazolidinedione (28). Treatment of 25 with 2.1 molar equivalents of lithium diisopropylamide in THF-hexane at 0° and -78° followed by treatment with 1.1 molar equivalents of ethyl bromide afforded 5-ethyl-5-phenyl-2,4-oxazolidinedione (28) in yields of 16% and 19%, respectively, as determined by pmr analysis (Table 3); with lithium amide in liquid ammonia, 5-ethyl derivative 28 was produced in 29% yield.

Base strength and the number of equivalents of base used for ionization appeared to be of primary importance in determining the yield for a given ethylation. House[15] reported that the presence of lithium diisopropylamide in THF can be detected by means of the red to purple colored charge-transfer complex it forms with small amounts

TABLE 3

Alkylations of 5-Phenyl-2,4-Oxazolidinedione Using Lithium Diisopropylamide in THF-Hexane (A) and THF-Hexane-HMPA (B)

Equiv of Base (solvent)	Halide (Equiv)	Temp °C	Yield %
2.1 (A)	ethyl bromide (1.1)	-78	19 [a]
2.1 (A)	ethyl bromide (1.1)	0	16[a]
2.1 (B)	ethyl bromide (1.1)	0	78[a,b]
2.1 (B)	ethyl bromide (1.1)	0	70[a,c]
2.14 (A)	benzyl chloride (1.14)	25	
2.31 (A)	benzyl chloride (1.31)	0	
2.10 (A)	benzyl chloride (1.10)	-78	
2.1 (B)	benzyl chloride (1.1)	0	39[a,b]

[a] Yields were determined by pmr analysis.

[b] 1.1 Equiv of HMPA added prior to addition of substrate.

[c] 1.1 Equiv of HMPA added after addition of substrate.

of 2,2'-bipyridyl added to the reaction mixture as an indicator. The structure of this charge-transfer complex is not known,[16] but a similar complex between 2,2'-bipyridyl and the enolate ions investigated by House did not form under the reaction conditions employed. This technique appeared to be suitable for determining the number of equivalents required to effect formation of dianions 14 and 26 from 2,4-oxazolidinedione and 5-phenyl-2,4-oxazolidinedione, respectively.

Solutions of 2,4-oxazolidinedione (7) and 5-phenyl-2,4-oxazolidinedione (25) in THF containing a small amount of 2,2'-bipyridyl were titrated with a solution of lithium diisopropylamide of known molarity in THF-hexane, and the number of equivalents required to maintain the red-purple color of the complex (indicating excess lithium diisopropylamide) for a two to three minute period were noted. A two to three minute requirement was judged to be sufficient because of the reported instability of the charge-transfer complex under certain reaction conditions.[16] Similar reactions were performed without 2,2'-bipyridyl to insure that any color present in the reaction mixture characteristic of the dianion under investigation would not mask the red-purple color of the charge-transfer complex. A series of benzylations of both 7 and 25 were performed at -78°, 0°, and 25°, and summaries of the results for 7 and 25 are listed in Tables 1 and 3, respectively.

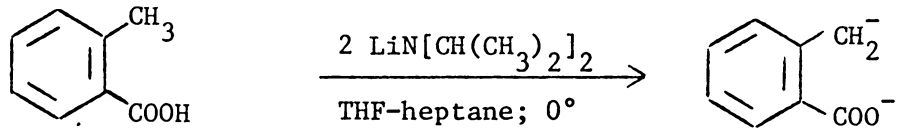
Examination of Table 1 shows that for 2,4-oxazolidinedione (7), decreasing the temperature increased the number of equivalents of lithium diisopropylamide required while only slightly increasing the yield of 5-benzyl-2,4-oxaxolidinedione (as determined by pmr analysis).

No such temperature dependence was observed for the number of equivalents of base required by 5-phenyl-2,4-oxazolidinedione (25) (Table 3). In all instances, however, at least 2.1 equivalents of lithium diisopropylamide were required, indicating that ionization of 7 and 25 to their respective dianions should be complete.

Table 3 lists no yields for the benzylations of 5-phenyl-2,4-oxazolidinedione (25) in which 2,2'-bipyridyl was used with lithium diisopropylamide. Although the pmr spectra for these benzylations indicated that the ratios of 25 to 5-benzyl-5-phenyl-2,4-oxazolidinedione (27) were 4:1, 3:1, and 3:1 for the 25°, 0°, and -78° reactions, respectively, a broad singlet was present in all the spectra, and at -78° integration of this singlet indicated it to be the most intense peak appearing in the spectrum. The chemical shift of the broad singlet relative to tetramethylsilane was 6.60 ppm, 6.32 ppm, and 4.82 ppm in the spectra of crude product mixtures derived from the reactions performed at 25°, 0°, and -78°, respectively.

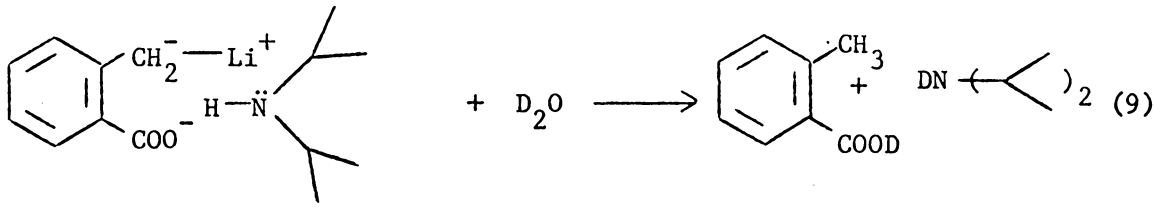
In order to determine whether or not this anomalous peak was characteristic of a compound other than 25 or benzyl derivative 27 which was present in the crude mixture, deuteration of dianion 26 from 5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide was attempted. The pmr spectrum of the crude reaction mixture indicated the presence of not only the anomalous broad singlet at 4.74 ppm but also a doublet at 1.20 ppm and a multiplet at 3.30 ppm which appeared from integration ratios to be an isopropyl group. However, the intensity of the singlet at 4.74 ppm did not lend itself to the possibility of residual diisopropylamine present in the isolated oil. Neglecting the presence of all the extraneous

peaks led to the conclusion that no deuterium incorporation had occurred. The fact that a compound will alkylate but not undergo deuterium incorporation is not unprecedented. Creger[17] reported such an occurrence with o-toluic acid. Treatment of o-toluic acid with two equivalents of lithium diisopropylamide was effective in the formation of dianion 29.



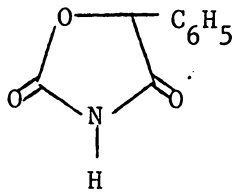
29

Treatment of 29 with 1-bromobutane gave o-pentylbenzoic acid; however, treatment of 29 with deuterium oxide revealed the absence of deuterium incorporation as determined by pmr spectral analysis. The spectrum obtained after removal of the THF-heptane from a solution of 29 prepared from lithium diisopropylamide displayed integrated signals for diisopropylamine in the ratio of one molecule of amine per molecule of 29. Creger's proposal for the absence of deuterium incorporation was that proton transfer on deuterium oxide addition was a complicated process in which the diisopropylamine proton is transferred exclusively to the carbanionic site by a noncompetitive process (eq 9).



(9)

Although alkylation without deuterium incorporation of dianion 26 was possible, the presence of the anomalous peaks in the pmr spectrum suggested the additional possibility that cleavage of 5-phenyl-2,4-oxazolidinedione might also be occurring in the presence of lithium diisopropylamide. 5-Phenyl-2,4-oxazolidinedione is reported to cleave in the presence of hydroxide ion according to eq 10.[18]



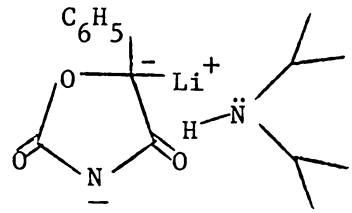
$$\xrightarrow{OH^-} \quad C_6H_5\underset{\underset{OH}{|}}{CH}CONHCOOH + C_6H_5\underset{\underset{OH}{|}}{CH}CONH_2 + C_6H_5\underset{\underset{OH}{|}}{CH}COOH + C_6H_5\underset{\underset{OCONH_2}{|}}{CH}COOH \qquad (10)$$

Hydrolysis of the reaction mixture following initial treatment of 25 with lithium diisopropylamide (2.1 equivalents) also gave an oil with a pmr spectrum containing the same extraneous peaks which were present in the spectrum obtained for the attempted deuterium incorporation; however, the phenyl peak was slightly split, and the broad singlet was found to be exchangeable with deuterium oxide. This splitting reinforced the possibility that cleavage might be occurring. Although tlc analysis of the oil obtained from the hydrolysis indicated the presence of four components, their R_f values were so similar that two different attempts at isolation by column chromatography were not successful.

Observation of cleavage products containing a diisopropyl group may have been maximized in the deuteration and hydrolysis reactions because deuterium oxide and water were the only proton sources which came into contact with the respective reaction mixtures; therefore, any

diisopropylamino group present on a cleavage product created by attack of the amide at either or both of the carbonyl groups of 5-phenyl-2,4-oxazolidinedione (25) would appear in the pmr spectrum. The absence of the peaks corresponding to a diisopropylamino group in the pmr spectra of the crude reaction products obtained from the benzylations of 25 using lithium diisopropylamide and 2,2'-bipyridyl may have been caused by the treatment of the final reaction mixture (after addition of benzyl chloride and quenching with water) with concentrated hydrochloric acid.

On the basis of the benzylations of 5-phenyl-2,4-oxazolidinedione (25) using lithium diisopropylamide as base and 2,2'-bipyridyl as indicator, 2.1 molar equivalents of base appeared to be sufficient to effect formation of dianion 26 (Table 3). Deuteration and hydrolysis of 25 indicated that cleavage and/or association of the type shown in structural formula (30) might be causing the low yields of 5-benzyl-5-phenyl-2,4-oxazolidinedione (27).



30

Since attempts to isolate the four components of the mixture obtained from hydrolysis of 25 were not successful, attention was focused on the possibility that a complex such as 30 or a contact ion pair, in which the carbanion-lithium interaction is highly covalent, was present in the

reaction mixture, thus preventing maximum reactivity with benzyl chloride and ethyl bromide. If dianion 26 did exist in THF-hexane as a complex with diisopropylamine or as a contact ion pair with lithium, then addition of a highly dipolar solvent might be expected to solvate the lithium ion, thus separating it from dianion 26 and increasing the reactivity of 26 toward the added halide. In an investigation of the formation and alkylation of α-metalated aliphatic acids using lithium diisopropylamide in solutions of THF, Pfeffer and coworkers[19] found that addition of hexamethylphosphoramide (HMPA) assisted the reactions by solubilizing dianions of straight chain acids and by accelerating their rate of alkylation in producing nearly quantitative yields of α-branched acids. Maximum yields were obtained when HMPA and the dianion were present in equimolar amounts.

Addition of 5-phenyl-2,4-oxazolidinedione (25) to a solution containing 2.1 molar equivalents of lithium diisopropylamide and 1.1 molar equivalents of HMPA in THF-hexane at 0° and subsequent alkylation with 1.1 equivalents of ethyl bromide afforded 5-ethyl-5-phenyl-2,4-oxazolidinedione (28) in 78% yield as determined by pmr analysis. The ethylation of 25 under identical reaction conditions without the addition of HMPA afforded a 16% yield of 28 (Table 3). Addition of HMPA had effected a 61% increase in yield.

Based on the assumption that if cleavage were occurring to any great extent, then addition of HMPA after lithium diisopropylamide had a sufficient amount of time (one-half hour) to react with 25 should give a yield of 28 comparable to that obtained for the ethylation of 25 in

the absence of HMPA. The yield obtained from addition of HMPA after ionization of 25 with 2.1 equivalents of lithium diisopropylamide in THF-hexane at 0° and subsequent alkylation (one-half hour after the addition of HMPA) with 1.1 equivalents of ethyl bromide was 70%. Approximately the same increase in yield was observed with the addition of HMPA after ionization of 25 (54%) as was seen with the addition of HMPA before ionization of 25 (61%).

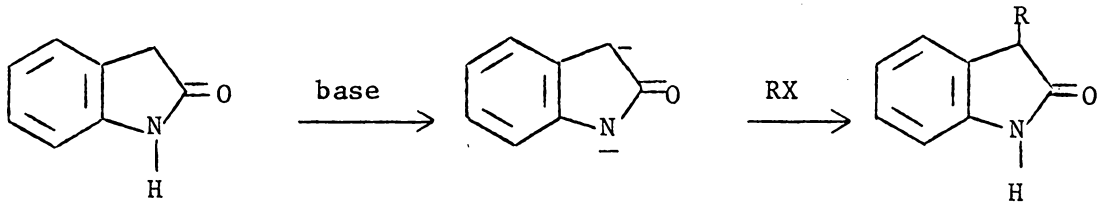
Benzylation of 25 using lithium diisopropylamide in THF-hexane-HMPA at 0° gave 0.90g of crude product. Analysis of the product by pmr indicated the ratio of 25 to 5-benzyl-5-phenyl-2,4-oxazolidinedione (27) was 1:1.3 with a 39% overall yield of 27 (Table 3). Benzylation of 25 under identical conditions (using 2,2'-bipyridyl as indicator) in the absence of HMPA had given 0.97g of product; the ratio of 25 to benzyl derivative 27 was 3:1 (no overall yield could be determined because of the presence of an anomalous broad singlet). Although the overall yield of benzyl derivative 27 was much lower than that obtained for ethyl derivative 28 where HMPA was added as a co-solvent, the effect of HMPA on the ratio of 25 to 5-benzyl-5-phenyl-2,4-oxazolidinedione was definitely significant.

The effect of HMPA on the extent of benzylation of 2,4-oxazolidinedione (7) was examined next. HMPA (1.1 equivalents) was added to a solution of 2.1 equivalents of lithium diisopropylamide in THF-hexane at 0° prior to the addition of 7, and the reaction mixture was alkylated with 1.1 equivalents of benzyl chloride. Stilbene was the only product isolated, and in a yield just sufficient to obtain a pmr spectrum. In

order to insure complete removal of HMPA from the ethereal extracts of the reaction mixture, the extracts were washed with approximately 300 ml of water. For the benzylations of 7 using 2,2'-bipyridyl as indicator yields of benzyl derivative 23 averaged 10% (Table 1); however, the ethereal extracts of these reactions did not require subsequent washing with water. Therefore, water solubility of 5-benzyl-2,4-oxazolidinedione seems to contribute to the low yields obtained with this system.

B. Oxindole

The second phase of this investigation was to determine if the structural similarity of oxindole (20) to succinimide was sufficient to enable successful formation of dianion 21. If the carbanion site of dianion 21 were to display the same selective reactivity toward alkyl halides as was reported for succinimide,[8] then a new route to 3-alkyloxindoles without the interference of dialkylation at the 3-position would be available.

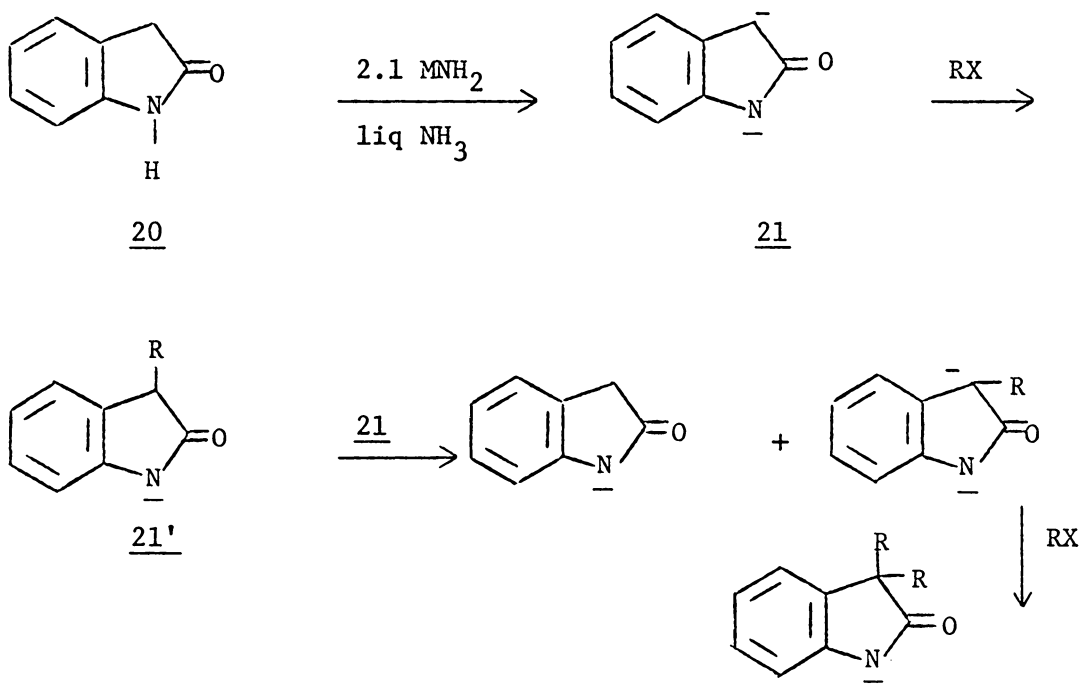


20 21

Previous attempts to alkylate either oxindole (20) or N-methyl-oxindole using one molar equivalent of base resulted in the formation of 3,3-dialkyloxindole as the major product because of proton-metal exchange. If this type of exchange were important in alkylations involving the

monoanion of 20, then there was no reason to suspect that attempted alkylation of 20 through dianion 21 would not be hampered by rapid proton-metal exchange between the initial monoalkylated derivative and unreacted dianion 21 (Scheme II).

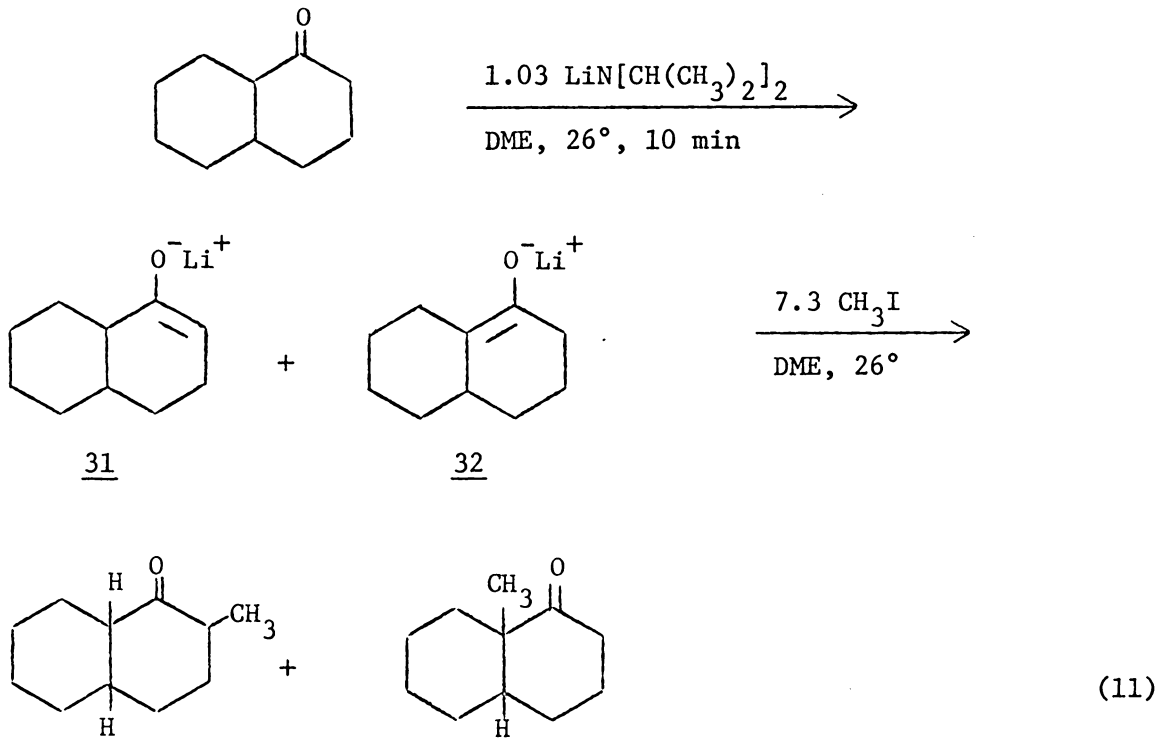
Scheme II



To minimize this possibility of proton-metal exchange between 20 and 21', lithium amide was selected to effect ionization of 20 because of the highly covalent nature of dilithio salts. Treatment of oxindole (20) with 2.1 molar equivalents of lithium amide in liquid ammonia followed by alkylation with 1.1 molar equivalents of benzyl chloride gave 3,3-dibenzyloxindole as the major product.

In order to determine if ionization of 20 to form dianion 21 had been successful and proton-metal exchange of the type shown in Scheme II was responsible for the formation of 3,3-dibenzyloxindole, an attempt was made to trap 21. An equimolar quantity of benzophenone was added to a solution of oxindole and 2.1 molar equivalents of lithium amide in liquid ammonia. After five minutes, the reaction mixture was poured into a large excess of ammonium chloride in liquid ammonia. The size of benzophenone, short reaction time, and addition of the reaction mixture to a large excess of ammonium chloride might be expected to maximize conditions for observing a monoalkylated product from dianion 21; however, benzophenone and oxindole were the only products obtained.

House and coworkers[15] reported that in their investigations of the alkylations of enolates from unsymmetrical ketones, the monoalkylated product contained at least 90% of material resulting from alkylation at the less highly substituted position under reaction conditions of kinetic control (eq 11). Kinetic control was achieved by adding the ketone to a slight excess of lithium diisopropylamide, adding a large excess of methyl iodide to the enolate mixture before equilibrium could be established between 31 and 32 and before proton-metal exchange could occur, and then quenching the reaction mixture rapidly so that the alkylated product could not equilibrate with the starting enolate. Therefore, it was decided to attempt monoalkylation of oxindole from dianion 21 under conditions similar to those reported by House. The only modifications employed were that THF-hexane at -78° would be used as the solvent system and 2,2'-bipyridyl would be used as indicator to determine the



(11)

(66% yield) (3% yield)

number of equivalents of lithium diisopropylamide required for ionization. The presence of excess base was indicated after the addition of 1.47 equivalents of lithium diisopropylamide, the total base concentration was quickly increased to 2.1 equivalents, a ten-fold excess of methyl iodide was added, and after five minutes the reaction mixture was poured into water. Analysis by pmr indicated that 3,3-dimethyloxindole was the major product. Although not attempted, an alternate route which might prevent formation of 3,3-dimethyloxindole would be to add the anion to an excess of methyl iodide rather than adding excess halide to the anion.

IV. EXPERIMENTAL

A. General

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected; boiling points are also not corrected. Temperature is reported in degrees centigrade, and pressure is reported in millimeters (mm) of mercury. Weight of samples and products are reported in grams (g) or milligrams (mg); volumes of samples in liters (l) or milliliters (ml); molar quantities of samples are reported in moles (mol) or millimoles (mmol). Molecular equivalents are reported as equivalents (equiv).

Thin layer chromatograms were performed with Eastman Chromagram sheets Type 13181 (silica gel) with fluorescent indicator using designated solvent systems. Spots were visualized with ultraviolet light or iodine vapors.

Elemental analyses were performed in this laboratory using a Perkin-Elmer Model 240 C, H, and N Elemental Analyzer; mass spectra were obtained using a Perkin-Elmer RMU-7.

Proton magnetic resonance (pmr) spectra were obtained on a JEOL JNM-PS-100 spectrometer. Chemical shifts were measured to the center of a singlet or multiplet and are given in δ units (ppm) relative to tetramethylsilane. The following designations were used in describing multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

The liquid ammonia used in the reactions was distilled from potassium metal-benzophenone. Tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), and diisopropylamine were distilled from lithium aluminum hydride, calcium hydride, and sodium metal, respectively. n-Butyllithium was obtained as a 1.9 M solution in hexane from Ventron Corporation, Beverly, Massachusetts.

Unless specified otherwise, chemicals were commercial reagent grade, and were used without further purification.

B. 2,4-Oxazolidinediones

1. Preparation of 2,4-oxazolidinediones

a. Ethyl glycolate*.--To a 2000 ml round-bottomed flask equipped with a Dean-Stark separator were added 160g (2.10 mol) of glycolic acid, 245 ml (4.20 mol) of 95% ethanol, 1050 ml of benzene, and 100g of Dowex 50W-X8 (20-50 mesh) ion exchange resin. The contents of the flask were refluxed for 24 hr during which time a total of 145 ml of water was removed. The reaction mixture was filtered (suction) to remove the resin, and the residue was washed with benzene. The filtrate plus 17.5g of calcium carbonate were shaken, filtered, and washed with benzene. The excess benzene and ethanol were removed on a roto-evaporator, and the residue was distilled yielding 137 ml (68%) of ethyl glycolate: bp 154-155° (lit.[20] 153-157.9°); pmr (neat) δ 1.28 (t,3,CH_3) and 4.28 (m,5, O-CH_2, O-CH_2, and OH).

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*Attempts to synthesize this ester by the Fischer method were not successful because of the high degree of water solubility exhibited by ethyl glycolate, thus preventing removal of the sulfuric acid catalyst from the reaction mixture.

b. 2,4-Oxazolidinedione (7).--The method of Stoughton[7] was employed for this synthesis. To a cool solution of 11.5g (0.5 mol) of sodium metal in 250 ml of absolute ethanol were added 30g (0.5 mol) of urea and 48 ml (0.5 mol) of ethyl glycolate. The reaction mixture was refluxed on a steam bath for 24 hr, and then as much ethanol as possible was removed on the roto-evaporator. The residue was dissolved in the minimum amount of water. The aqueous solution was adjusted to pH 5 with concentrated hydrochloric acid, saturated with sodium chloride, and continuously extracted with ether for 40 hr. The ethereal layer was dried ($MgSO_4$), filtered, and concentrated to give a colorless oil. The oil was crystallized from absolute ethanol to give 17.9g (35%) of 2,4-oxazolidinedione; mp 88-89° (lit.[18] 89-90°); pmr (DMSO-d_6) δ 4.75 (s, CH_2).

c. Ethyl mandelate.--To a 500 ml round-bottomed flask containing 233 ml (4 mol) of 95% ethanol were added 76.1g (0.5 mol) of mandelic acid and 5 ml of concentrated sulfuric acid. The contents of the flask were refluxed for 4 hr, concentrated to one-third the original volume using a roto-evaporator, and placed in a separatory funnel along with 50 ml of ether and 75 ml of water. The ethereal layer was washed with 25 ml of water, 50 ml of 10% sodium bicarbonate, and 25 ml of a saturated sodium chloride solution, dried ($MgSO_4$), filtered, and concentrated on the roto-evaporator. Vacuum distillation of the residue yielded 59.6g (66%) of ethyl mandelate: bp 107.5-108° (6 mm) [lit.[21] 112-118° (3 mm)]; pmr (neat) δ 1.03 (t, 3, CH_3), 3.95 (q, 2, CH_2), 5.14 (s, 1, CH or OH), 5.30 (s, 1, CH or OH), and 7.38 (m, 5, C_6H_5).

d. 5-Phenyl-2,4-oxazolidinedione (25).--The method of Sheehan and Laubach[21] was used for the synthesis of 25. To a cool solution of 2.3g (0.1 mol) of sodium metal in 300 ml of absolute ethanol were added 6.01g (0.1 mol) of urea and 18.0g (0.1 mol) of ethyl mandelate. The reaction mixture was refluxed on a steam bath for 4 hr during which time the color changed from pale yellow to burgundy. As much ethanol as possible was then removed on the roto-evaporator, and the resulting residue was dissolved in the minimum amount of water and acidified with concentrated bydrochloric acid. The resulting crystals were collected by suction filtration and recrystallized twice from water resulting in 9.31g (53%) of 25: mp 106.5-107.5° (lit.[21] 108.8-110°); pmr (acetone-d_6) δ 5.95 (s, 1, CH-O) and 7.41 (s, 5, C_6H_5).

2. Benzylations of 2,4-oxazolidinedione using potassium amide and lithium amide

a. With 1.1 equivalents of benzyl chloride using 2.1 equivalents of lithium amide.--This reaction is representative of the general procedure used for all alkali metal amide alkylations of both 2,4-oxazolidinedione and 5-phenyl-2,4-oxazolidinedione and is given in detail. To a stirred solution of 350 ml of anhydrous liquid ammonia containing a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ was added 0.36g (53 mmol) of lithium metal. After 20 min, 2.5g (25 mmol) of solid 2,4-oxazolidinedione (7) was added; the color changed from dark gray to black, and stirring was continued for 30 min. A solution of 3.48g (28 mmol) of benzyl chloride in anhydrous ether was added, and the color returned to dark gray. After an additional 1.5 hr the reaction mixture was neutralized with excess

ammonium chloride. The liquid ammonia was removed on a steam bath while ether was slowly added to maintain a constant volume. After the removal of the liquid ammonia was complete, 200 ml of water was added, and the mixture was filtered (suction) to remove the brown particles of catalyst present between the layers. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. Concentration of the ethereal extracts gave 2.27g of an oil. Analysis by tlc [benzene-acetone (3:1)] showed two components, one with an R_f value greater than that of 7 and the second with an R_f value equal to that of 7. Column chromatography (silica gel) was not effective in obtaining separation. Recrystallization first from benzene-hexane then from absolute ethanol gave 0.70g (15%) of 5-benzyl-2,4-oxazolidinedione. The analytical sample had mp 85.5-86.5° (lit.[22] 99-100°); pmr (acetone-d_6) δ 3.28 (m, 2, CH_2-Ph), 5.29 (m, 1, CH-O), and 7.37 (s, 5, C_6H_5); mass spectrum (70eV) m/e (rel intensity) 191 (100, molecular ion), 146 (31), 91 (27), 77 (10), metastable 145.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.61; H, 4.70; N, 7.15.

b. With 1.1 equivalents of benzyl chloride using 2.1 equivalents of potassium amide.--This reaction was performed in the same manner as above except potassium rather than lithium amide was used to effect ionization. Concentration of the ethereal extract (after a 24-hr continuous extraction) of the acidified aqueous layer yielded nothing which could be identified as benzyl derivative 23 based on tlc R_f values [heptane-ether (1:3) and toluene-ethyl acetate-heptane (4:3.5:2.5)].

3. Alkylations of 5-phenyl-2,4-oxazolidinedione using potassium amide and lithium amide

a. With 1.1 equivalents of benzyl chloride using 2.1 equivalents of lithium amide.--Dianion 26 of 5-phenyl-2,4-oxazolidinedione (25) was formed and alkylated according to the procedure given for 2,4-oxazolidinedione. The original ethereal layer plus additional ethereal extracts of the basic aqueous layer were dried ($MgSO_4$), filtered, and concentrated yielding 2.20g of oil which had the odor of benzyl chloride and which crystallized on standing overnight in hexane. The hexane was decanted, and the solid was recrystallized from ethyl acetate-hexane to give 0.80g of 5-benzyl-5-phenyl-2,4-oxazolidinedione (27).

The basic aqueous layer was poured onto an ice slurry of concentrated hydrochloric acid. The resulting crystals were collected by suction filtration giving 1.43g of crude product which after recrystallizing from ethyl acetate-hexane yielded 1.03g of 27, for a total yield of 1.83g (49%). The analytical sample had mp 115-116.5°; pmr (acetone-d_6) δ 3.45 (q, 2, CH_2-Ph) and 7.40 (m, 10, aromatics); mass spectrum (50eV) m/e (rel intensity) 267 (26, molecular ion), 105 (67), 92 (30), 91 (100), 77 (63).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.70; H, 4.60; N, 5.28.

b. With 2.1 equivalents of benzyl chloride using 2.1 equivalents of lithium amide.--Dianion 26 was prepared as above but was alkylated with 2.1 equiv of benzyl chloride. The basic aqueous layer was separated, and the ethereal layer was washed with two 25 ml portions of

10% sodium hydroxide. The combined aqueous extracts were filtered to remove traces of the catalyst, poured onto an ice slurry of concentrated hydrochloric acid, and then extracted with ether. Concentration of the ethereal extracts yielded 2.34g of an oily substance which crystallized on standing. Analysis by tlc [hexane-acetone (1:1)] indicated the presence of starting material and the 5-benzyl derivative. Recrystallization from benzene-hexane yielded 1.55g (41%) of crude 5-benzyl-5-phenyl-2,4-oxazolidinedione: mp 86-101°.

c. With 3.7 equivalents of benzyl chloride using 3.7 equivalents of lithium amide.--This reaction was performed using 0.36g (53 mmol) of lithium metal and 2.5g (14 mmol) of 5-phenyl-2,4-oxazolidinedione and alkylating with 6.04 ml (53 mmol) of benzyl chloride. Concentration of the original ethereal layer plus additional ethereal extracts of the basic aqueous layer yielded 7.40g of a brownish oil which had the odor or benzyl chloride and which crystallized on standing overnight in hexane. Recrystallization of the oil from benzene-heptane gave 1.28g (34%) of benzyl derivative 27: mp 113-116.5°.

Acidification followed by ether extraction of the basic aqueous layer yielded no additional 27.

d. With 3.7 equivalents of benzyl chloride using 3.7 equivalents of potassium amide.--Preparation of dianion 26 was effected using 2.05g (53 mmol) of potassium metal and 2.5g (14 mmol) of 5-phenyl-2,4-oxazolidinedione, and alkylation was accomplished using 6.04 ml (53 mmol) of benzyl chloride. Concentration of the original ethereal layer yielded

1.26g of an oil which crystallized on standing overnight in hexane. Recrystallization from benzene-heptane gave 0.28g (8%) of benzyl derivative 27: mp 113-115°.

No additional product was obtained from the ethereal extracts of the acidified aqueous layer.

e. With 1.1 equivalents of ethyl bromide using 2.1 equivalents of lithium amide.--This reaction was performed following the procedure of the benzyl chloride alkylations. The basic aqueous layer was separated and poured onto an ice slurry of concentrated hydrochloric acid. The resulting oil was extracted into ether, and concentration of the ether gave 1.80g of a solid material. Analysis by tlc [hexane-acetone (1:1)] of the solid indicated that the crude product was a mixture of starting material and a compound with an R_f value larger than that of the starting material. A pmr spectrum (DMSO-d_6) of the mixture gave the following peaks: δ 7.42 (s, C_6H_5), 6.02 (s, CH-O), 2.18 (m, CH_2), and 0.82 (t, CH_3). The singlet at 6.02 ppm corresponded to the methine proton of the starting material and integrated to twelve units. The triplet at 0.82 ppm corresponded to the methyl protons of ethyl derivative 28 and integrated to eighteen units for three protons or six units for one proton. A total of eighteen units represented the substitution pattern at the 5-position; therefore, twelve-eighteenths of the mixture was starting material, and six-eighteenths of the mixture was 5-ethyl-5-phenyl-2,4-oxazolidinedione. Based on the 1.80g of material which had been isolated, this represented 0.60g (29%) of the ethyl derivative. This same procedure was used to calculate all subsequent

ethylations of 5-phenyl-2,4-oxazolidinedione where a yield is reported based on pmr analysis.

f. Attempted benzylation of 2,4-oxazolidinedione using lithium diisopropylamide in the presence of HMPA.--To a solution containing 0.765 ml (10.5 mmol) of diisopropylamine and 1.00 ml (5.5 mmol) of HMPA in anhydrous THF maintained at 0° under a nitrogen atmosphere was added 5.55 ml (10.5 mmol) of n-butyllithium. After 15 min 0.50g (5.0 mmol) of 2,4-oxazolidinedione was added, and stirring was continued for 1 hr at which time 0.63 ml (5.5 mmol) of benzyl chloride was added. After an additional 2 hr, the reaction mixture was poured into 50 ml of water and acidified with concentrated hydrochloric acid. The THF layer was separated, and the aqueous layer was extracted with ether. The final THF-ether layer was washed with six 50 ml portions of water to insure complete removal of HMPA, dried ($MgSO_4$), filtered, and concentrated to afford only stilbene (based on pmr spectra comparisons with an authentic sample) in a yield just sufficient to obtain a pmr spectrum.

4. Alkylations of 5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide

a. With ethyl bromide at 0°.--To a solution of 1.48 ml (21 mmol) of diisopropylamine in 20.00 ml of anhydrous THF maintained at 0° under a nitrogen atmosphere was added 11.1 ml (21 mmol) of n-butyllithium. The solution was stirred for 15 min, and was then added dropwise, from a syringe, to a solution of 1.77g (10 mmol) of 5-phenyl-2,4-oxazolidinedione in THF at 0° under a nitrogen atmosphere. After the addition of 21 mmol of lithium diisopropylamide, the color of the reaction mixture

was pale yellow. Stirring was continued for 1 hr at which time 1.20g (11 mmol) of ethyl bromide was added. After an additional 2 hr, the reaction mixture was poured into 50 ml of water and acidified with concentrated hydrochloric acid. The THF layer was separated, and the aqueous layer was extracted with ether. The combined THF-ether extracts were dried ($MgSO_4$), filtered, and concentrated yielding 1.43g of an oil. The yield of 5-ethyl-5-phenyl-2,4-oxazolidinedione, based on pmr analysis, was 0.33g (16%).

b. With ethyl bromide at -78°.--To a solution of 0.765 ml (10.5 mmol) of diisopropylamine in 25.00 ml of anhydrous THF maintained at -78° under a nitrogen atmosphere was added 5.55 ml (10.5 mmol) of n-butyllithium. After 15 min 0.89g (5.0 mmol) of 5-phenyl-2,4-oxazolidinedione was added, and stirring was continued for 1 hr at which time 0.60g (5.5 mmol) of ethyl bromide was added. The reaction mixture was maintained at -78° for 1 hr and was allowed to warm to room temperature during the second hour. At the end of the two-hour period, the mixture was poured into 50 ml of water, acidified with concentrated hydrochloric acid, and extracted with ether. Concentration of the final THF-ether layer yielded 0.90g of a semi-solid material. The yield of ethyl derivative, based on pmr analysis, was 0.19g (19%).

c. With ethyl bromide at 0° in the presence of HMPA.--To a solution containing 0.765 ml (10.5 mmol) of diisopropylamine and 1.00 ml (5.5 mmol) of HMPA in THF at 0° under a nitrogen atmosphere was added 5.55 ml (10.5 mmol) of n-butyllithium. After 15 min 0.89g (5.0 mmol) of

5-phenyl-2,4-oxazolidinedione was added, and stirring was continued for 1 hr at which time 0.60g (5.5 mmol) of ethyl bromide was added. After an additional 2 hr, the reaction mixture was poured into 50 ml of water, acidified with concentrated hydrochloric acid, and extracted with ether. Concentration of the final THF-ether layer afforded 1.03g of a colorless oil. Analysis by pmr indicated that 0.80g (78%) of the crude mixture was 5-ethyl-5-phenyl-2,4-oxazolidinedione.

d. With ethyl bromide at 0° in the presence of HMPA.--The reaction conditions and quantities used were identical to the previous ethylation at 0° in the presence of HMPA except that HMPA was added to the reaction mixture 0.5 hr after the addition of 5-phenyl-2,4-oxazolidinedione. Stirring was continued for 0.5 hr at which time the reaction mixture was alkylated with ethyl bromide. Concentration of the final THF-ether yielded 0.94g of an oil. The yield of ethyl derivative 28, based on pmr analysis, was 0.72g (70%).

e. With benzyl chloride at 0° in the presence of HMPA.--The reaction conditions and quantities used were identical with those used in part (c) of this section except that the reaction mixture was alkylated with 0.63 ml (5.5 mmol) of benzyl chloride. Concentration of the final THF-ether layer gave 0.90g of a solid material. A pmr spectrum of the solid showed the following peaks: δ 7.50 (m, aromatics), 6.00 (s, CH-O), and 3.50 (q, CH_2-Ph). Using the intensities of the peaks at 3.50 ppm (methylene protons of the benzyl derivative) and 6.00 ppm (methine proton of the starting material), the ratio of starting material to benzyl

derivative 27 was calculated as 1:1.3. The overall yield of 27 was 0.52g (39%).

f. Attempted deuteration of 5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide.--To a solution containing 10.5 mmol of lithium diisopropylamide, prepared from 10.5 mmol of n-butyllithium and 10.5 mmol of diisopropylamine, in anhydrous THF at -78° under a nitrogen atmosphere was added 0.89g (5.0 mmol) of 5-phenyl-2,4-oxazolidinedione. After 15 min of stirring 0.5 ml (29 mmol) of deuterium oxide was added, and stirring was continued for 5 min. The reaction mixture was filtered to remove lithium deuteroxide, diluted with anhydrous ether, dried ($MgSO_4$), filtered, concentrated, and dried at 50° in a vacuum oven overnight to give 0.70g of an oil. A pmr spectrum (DMSO-d_6) of the oil showed the following peaks: δ 7.32 (s, C_6H_5), 5.24 (s, CH-O), 4.74 (s), 3.30 (m), and 1.20 (d). The peaks at 4.74 ppm, 3.30 ppm, and 1.20 ppm appeared to be diisopropylamine, but integration of these peaks gave the ratio 7:2:12 which does not agree with the expected 1:2:12 ratio for diisopropylamine. Integration of the peaks at 7.32 ppm and 5.24 ppm (neglecting the presence of the anomalous peaks) indicated no deuterium incorporation.

g. Hydrolysis of 5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide.--This reaction was performed in the same manner and using the same molar quantities of reagents as the deuteration except that the reaction mixture was quenched with 0.5 ml of water rather than deuterium oxide. Concentration of the THF-ether gave 0.82g of an oil. A pmr spectrum (DMSO-d_6) of the oil showed the same peaks as the spectrum

for the deuteration of 5-phenyl-2,4-oxazolidinedione except that the singlet at 7.32 ppm now appeared as a singlet imposed on a doublet, and the broad peak corresponding to the peak at 4.74 ppm for the deuteration had shifted to 5.95 ppm and was determined to be exchangeable with deuterium oxide. Analysis by tlc [hexane-acetone (1:1)] showed the presence of two components, one with an R_f value less than and the second with an R_f value equal to that of the starting material. Column chromatography (silica gel) was used to attempt separation, and although tlc [hexane-acetone (1:1)] indicated the presence of the extraneous component in one of the fractions, the presence of two additional components in this fraction was also indicated. These three components had very similar R_f values, and attempts to separate them by rechromatographing that fraction were not successful.

5. Benzylations of 2,4-oxazolidinedione using lithium diisopropylamide as titrant and 2,2'-bipyridyl as indicator

Two different methods were used to prepare the titrant, lithium diisopropylamide. The first method (a) involved pipetting a 25.00 ml aliquot of THF into a 50.00 ml volumetric flask. A serum cap containing two syringe needles for the inlet and outlet of nitrogen was placed on the flask, and the flask was placed into an ice-water bath. Diisopropylamine (2.96 ml, 42 mmol) and n-butyllithium (22.2 ml, 42 mmol) were then injected into the flask. The contents of the flask were mixed by shaking manually, and after the lithium diisopropylamide had equilibrated at 0° for 20 min, sufficient THF was injected into the flask to dilute the mixture to 50.00 ml; such solutions were assumed to be 0.84 M in

THF-hexane. Difficulties were encountered in preventing the amide solution from backing up into the nitrogen inlet tube while shaking the flask and in withdrawing the last 5-10 ml of the amide with a syringe. Therefore, a second technique was tried.

In the second technique (b) a 50 ml round-bottomed flask equipped with a mechanical stirrer and an inlet and outlet for nitrogen was used, and the volume used to calculate the molarity of the lithium diisopropylamide was the total of volumes of all liquids at 25°.

Technique (b) was used to prepare a solution of lithium diisopropylamide formed from the reaction of 5.35 ml (10.5 mmol) of 1.9 M n-butyllithium with 0.765 ml (10.5 mmol) of diisopropylamine in 20.00 ml of THF-hexane at 0°. In order to determine the number of moles of lithium diisopropylamide present in the solution, water was injected into the flask after the amide solution had been stirred for 20 min. The resulting lithium hydroxide was titrated with 0.500 N hydrochloric acid using phenolphthalein as indicator; the end point was reached after the addition of 15.90 mmol of hydrochloric acid. A second titration was performed on 0.765 ml (10.5 mmol) of diisopropylamine alone, and 5.05 mmol of hydrochloric acid was required to reach the phenolphthalein end point indicating that 10.85 mmol of lithium hydroxide was present in the original hydrolysis solution. Although a 0.35 mmol excess of lithium hydroxide was found, the calibrations on the syringes available for injecting the n-butyllithium limited the accuracy with which the determination could be made. The n-butyllithium had been recently opened so that the extent of hydrolysis to form lithium hydroxide was minimal.

All lithium diisopropylamide titrations using 2,2'-bipyridyl as indicator for any given compound at the various temperatures were performed with the same solution of titrant so that relative yields and equivalents of base required would be significant.

a. At -78°.--The procedure for this reaction was employed for all alkylations involving 2,2'-bipyridyl as indicator and is described in detail. The lithium diisopropylamide titrant (maintained at 0° under a nitrogen atmosphere) was prepared from the reaction of 22.2 ml (42 mmol) of n-butyllithium and 2.96 ml (42 mmol) of diisopropylamine in 15.00 ml of anhydrous THF and was assumed to be 1.05 M. A solution of 0.50g (5.0 mmol) of 2,4-oxazolidinedione and 20mg of 2,2'-bipyridyl in anhydrous THF was cooled to -78°, and the titrant was injected dropwise into the flask. After the addition of 12.5 ml (13.1 mmol, 2.62 equiv) of titrant, 3 min were required for the solution to return from the pink color indicative of excess lithium diisopropylamide to a turbid white. An additional drop of titrant was injected to return the color of the solution to pink, and 0.93 ml (8.1 mmol) of benzyl chloride was added. The reaction mixture turned to an orange-yellow color and was stirred for 1 hr at -78°. During the second hr interval, the flask was allowed to warm to room temperature, and the color changed from orange-yellow to rose pink. The reaction mixture was poured into 50 ml of water, acidified with concentrated hydrochloric acid, and extracted into ether. Analysis by tlc [benzene-acetone (3:1)] of the THF-ether solution showed the presence of starting material and a compound with an R_f value greater than that of the starting material. Concentration

of the THF-ether yielded 0.99g of a yellow oil which had the odor of benzyl chloride. The crude product was dissolved in methanol, adsorbed onto 1g of silica gel, evaporated to dryness, and placed onto a chromatography column containing 8g of silica gel. The column was washed first with 200 ml of hexane-ether (9:1) to remove the benzyl chloride and then with methanol. Concentration of the methanol yielded 0.44g of a yellow oil. A pmr spectrum (DMSO-d_6) of the mixture gave the following peaks: δ 7.32 (s, C_6H_5), 5.30 (m, CH-O), 4.75 (s, CH_2-O), and 3.20 (m, CH_2-Ph). Using the intensities of the peaks at 7.32 ppm (the phenyl protons of the benzyl derivative) and 4.75 ppm (the methylene protons of the starting material), the yield of 5-benzyl-2,4-oxazolidinedione was calculated to be 120mg (13%).

b. At 0°.--The same procedure and solution of lithium diisopropylamide (1.05 M) were used for this benzylation except both the titrant and 2,4-oxazolidinedione solutions were maintained at 0°. At this temperature 10.2 ml (10.7 mmol, 2.14 equiv) of lithium diisopropylamide was required to maintain the red-purple color, indicating the presence of excess titrant, for a period of 3 min. Benzyl chloride (0.63 ml, 55 mmol) was added to the reaction mixture. After treating the crude product in the same manner as in the reaction at -78°, concentration of the methanol fraction from the chromatography column yielded 0.42g of a yellow oil. Analysis by pmr showed that 97mg (10%) of the oil was 5-benzyl-2,4-oxazolidinedione.

c. At 25°.--The 1.05 M lithium diisopropylamide and 2,4-oxazolidinedione solutions were maintained at 0° and 25°, respectively, for

this benzylation. After the addition of 10.0 ml (10.5 mmol, 2.1 equiv) of titrant, the red-purple color indicative of excess lithium diisopropylamide persisted for 3 min. Benzyl chloride (0.63 ml, 55 mmol) was added. Concentration of the methanol after column chromatography gave 0.45g of a yellow oil. Analysis by pmr indicated that 90mg (10%) of the crude material was 5-benzyl-2,4-oxazolidinedione.

6. Benzylations of 5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide as titrant and 2,2'-bipyridyl as indicator

a. At -78°.--A fresh solution of 1.05 M lithium diisopropylamide was prepared for this series of reactions according to the procedure given above. The same reaction procedure as given for 2,4-oxazolidinedione was used. The titrant and 5-phenyl-2,4-oxazolidinedione solutions were maintained at 0° and -78°, respectively. At -78°, 10.0 ml (10.5 mmol, 2.10 equiv) of lithium diisopropylamide was required to maintain the red-purple color of the indicator. Benzyl chloride (0.63 ml, 55 mmol) was then added to the reaction mixture. Concentration of the methanol after column chromatography (silica gel) gave 0.52g of a semi-solid material. A pmr spectrum (DMSO-d_6) of the crude material showed the following peaks: δ 3.55 (m, CH_2), 4.82 (s), 6.04 (s, CH-O), and 7.49 (s, aromatics). Using the intensities of the peaks at 3.55 ppm (methylene protons of the benzyl derivative) and 6.04 ppm (methine proton of the starting material), the ratio of 5-benzyl-5-phenyl-2,4-oxazolidinedione to 5-phenyl-2,4-oxazolidinedione was calculated as 1:3. However, the broad singlet at 4.82 ppm integrated as the largest peak in the spectrum.

b. At 0°.--The titrant (1.05 M lithium diisopropylamide) and 5-phenyl-2,4-oxazolidinedione solutions were both maintained at 0° for this benzylation. After the addition of 11.0 ml (11.6 mmol, 2.31 equiv) of titrant, the red-purple color of 2,2'-bipyridyl persisted for 2 min. Benzyl chloride (0.75 ml, 66 mmol) was added to the reaction mixture. Concentration of the methanol fraction from column chromatography 0.95g of a semi-solid material. Analysis by pmr of the crude mixture indicated that the ratio of the 5-benzyl derivative to starting material was 1:3. The broad singlet which had appeared on the pmr spectrum for the benzylation at -78° at 4.82 ppm was now located at 6.32 ppm. However, relative to the other peaks, this singlet was of moderate intensity.

c. At 25°.--The 1.05 M lithium diisopropylamide and 5-phenyl-2,4-oxazolidinedione solutions were maintained at 0° and 25°, respectively, and 10.2 ml (10.7 mmol, 2.14 equiv) of titrant was required to maintain the color of the indicator for 2 min. Benzyl chloride (0.63 ml, 55 mmol) was added to the reaction mixture. Concentration of the methanol after column chromatography gave 0.61g of a semi-solid material. Analysis by pmr indicated that the ratio of 5-benzyl derivative to starting material was 1:4. The broad singlet, characteristic of these benzylations, appeared in this pmr at 6.60 ppm and was of moderate intensity.

C. Oxindole

1. Alkylation with benzyl chloride using lithium amide.

To a solution of 350 ml of anhydrous liquid ammonia containing a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ was added 0.36g (53 mmol) of lithium

metal. After 15 min, 3.33g (25 mmol) of solid oxindole was added; the color changed from light to dark gray (almost black), and stirring was continued for 20 min. A solution of 3.16 ml (27.5 mmol) of benzyl chloride in anhydrous ether was added, and the color changed from dark gray to brown. After an additional 1.5 hr, the reaction mixture was neutralized with excess ammonium chloride. The liquid ammonia was removed by heating the reaction flask on a steam bath while ether was slowly added to maintain a constant volume. After the removal of the liquid ammonia was complete, 200 ml of water was added, and the mixture was filtered (suction) to remove the brown particles of catalyst present between the layers. The original ethereal layer plus additional ethereal extracts of the basic aqueous layer were dried ($MgSO_4$), filtered, and concentrated yielding 5.15g of crude product. Attempts to recrystallize the product from 95% ethanol gave 1.05g of solid which after a second recrystallization from benzene-pet ether gave 0.64g of 3,3-dibenzyloxindole: mp 201-202.5° (lit.[23] 201-202°); pmr (DMSO-d_6) δ 9.90 (s, 1, NH), 6.90 (m, 14, aromatics), and 3.14 (s, 4, CH_2-Ph). Analysis by tlc (benzene) of the ethanol filtrate indicated that the remaining crude product was a mixture of starting material, 3,3-dibenzyloxindole, and two components with R_f values greater than those of either oxindole or the 3,3-dibenzyl derivative. The ethanol was concentrated yielding 3.75g of an oil which was dissolved in methanol, adsorbed onto 5g of silica gel, evaporated to dryness, and placed onto a chromatography column containing 100g of silica gel. Gradient elution from 100% benzene to 100% acetone was employed for separation. An additional 0.24g (after recrystallization

from benzene-pet ether) of 3,3-dibenzyloxindole, and 0.17g (after recrystallization from benzene-pet ether) of starting material were isolated. Analysis by tlc [benzene-acetone (7:3)] of the remaining 1.03g indicated the presence of three components. A pmr spectrum (DMSO-d_6) showed a singlet at 10.37 ppm (NH proton), a singlet at 7.16 ppm (phenyl protons) imposed on a multiplet (aromatic protons of the ring), and a singlet at 3.49 ppm (methylene protons of an unsubstituted 3-position) imposed on a multiplet (methine proton at the 3-position). Integration of the pmr spectrum indicated that the components were probably 1-benzyl-, 3-benzyl, and 1,3-dibenzyloxindole.

Acidification and ether extraction of the basic aqueous layer resulted in the isolation of 0.13g of 3,3-dibenzyloxindole, based on a comparison of R_f values [benzene-acetone (7:3)]. Relative to oxindole, the total yield of 3,3-dibenzyloxindole was 1.91g (24%), and the amount of starting material recovered was 0.17g (5%).

2. Attempted condensation with benzophenone using lithium amide

Dianion 21 was prepared according to the procedure given for the benzylation. After 30 min 5.0g (27.5 mmol) of benzophenone in anhydrous ether was added, and the color changed from brown-black to green-gray. After an additional 5 min of stirring, the reaction mixture was poured into an Erlenmeyer flask containing 5.35g (100 mmol) of ammonium chloride in liquid ammonia. The liquid ammonia was replaced with ether, 100 ml of water was added, and the reaction mixture was filtered (suction) to remove traces of catalyst present between the layers. Concentration of

the ethereal extracts of the basic aqueous layer gave 7.59g of a slushy material. The basic aqueous layer was poured onto an ice slurry of concentrated hydrochloric acid and extracted with ether. Concentration of the ether yielded 0.07g of a solid. Analysis by tlc [hexane-acetone (9:1)] of the crude products obtained from the ethereal extracts of the basic and acidified aqueous layer indicated, from comparison of R_f values, that only benzophenone and oxindole were present.

3. Alkylation with excess methyl iodide using lithium diisopropylamide as titrant and 2,2'-bipyridyl as indicator

This reaction was performed in the same manner as that described for the benzylations of 2,4-oxazolidinedione using lithium diisopropylamide as titrant. The titrant (1.05 M lithium diisopropylamide) and oxindole (0.67g, 5 mmol) solutions were maintained at 0° and -78°, respectively. After the addition of 7.0 ml (7.35 mmol, 1.47 equiv) of base, the red-purple color indicative of excess lithium diidopropylamide persisted for 3 min. An additional 3.0 ml (3.15 mmol, 0.63 equiv) of base were added to bring the total equivalents to 2.10, and 3.4 ml (55 mmol) of methyl iodide was added. The color turned to a clear, pale yellow. The mixture was stirred at -78° for 5 min then poured into 50 ml of water and acidified with concentrated hydrochloric acid. The reaction mixture was extracted with ether. The ether-THF layer was washed with sodium thiosulfate and water, dried ($MgSO_4$), filtered, and concentrated yielding 0.75g of a yellow-brown oil. Analysis by tlc [benzene-acetone (7:3)] of the crude oil showed four components, one with an R_f value greater than that of oxindole (21), two with R_f values

less than that of 21, and one with an R_f value equal to that of 21. A pmr spectrum (DMSO-d_6) of the crude mixture showed a singlet at 10.40 ppm (NH proton), a multiplet at 7.05 ppm (aromatic protons), a small singlet at 3.43 ppm (methylene protons of starting material) imposed on a small multiplet (methine proton of 3-methyloxindole), and a large singlet at 3.24 ppm (methyl protons of 3,3-dimethyloxindole) imposed on a small doublet (methyl protons of 3-methyloxindole). Integration of the spectrum indicated that the major component was 3,3-dimethyloxindole.

V. SUMMARY

Attempts to synthesize 5-benzyl-2,4-oxazolidinedione (23) by selective C-benzylation of dianion 14 formed from the reaction of 2,4-oxazolidinedione (7) with 2.1 equivalents of lithium diisopropylamide in THF-hexane, lithium diisopropylamide in THF-hexane-HMPA, lithium amide in liquid ammonia, and potassium amide in liquid ammonia afforded very low yields of 23 and in some instances no products which could be identified as 23 or recovered 7. The low yields of 23 might be attributed to several factors: incomplete formation of dianion 14, lack of reactivity of 14 toward benzyl chloride, water solubility of benzyl derivative 23, or possible cleavage of 2,4-oxazolidinedione under the reaction conditions employed for ionization. Indicator reactions using 2,2'-bipyridyl and lithium diisopropylamide in THF-hexane showed that 2.1 equivalents of base were being consumed by 7. In an attempt to increase the reactivity of dianion 14 toward benzyl chloride, an equimolar amount of HMPA was added to the solution of lithium diisopropylamide in THF-hexane; however, no 5-benzyl-2,4-oxazolidinedione was isolated from the crude reaction mixture. The results of the investigation on 2,4-oxazolidinedione as a possible precursor to dianion 14 seem to indicate that the formation and subsequent benzylation of dianion 14 are being hampered by all of the factors listed above, and that use of dianion 14 to form 5-alkyl-2,4-oxazolidinediones through selective C-alkylation is probably not feasible on a preparative scale.

In order to eliminate some of the factors which may have contributed to the low yields obtained from benzylation of 2,4-oxazolidinedione, 5-phenyl-2,4-oxazolidinedione (25) was chosen as the next system to investigate. The advantages of 25 seemed to be (1) the increased stability the phenyl group would lend to dianion 26 formed from ionization of 25, and (2) the low water solubility of 5-benzyl-5-phenyl-2,4-oxazolidinedione (27) resulting from alkylation of dianion 26 with benzyl chloride. The highest isolated yield (49%) of benzyl derivative 27 was obtained from the reaction of 25 with 2.1 equivalents of lithium amide in liquid ammonia followed by addition of 1.1 equivalents of benzyl chloride. Under identical reaction conditions, use of ethyl bromide as the alkylating agent afforded 5-ethyl-5-phenyl-2,4-oxazolidinedione in only 29% yield. Indicator reactions using lithium diisopropylamide and 2,2'-bipyridyl showed that formation of dianion 26 appeared to be complete. If ionization were complete, then addition of deuterium oxide to 26 should result in a significant percentage of deuterium incorporation at the 5-position of 25. However, deuteration showed no deuterium incorporation in recovered 25. On the assumption that deuterium incorporation was not occurring, attention was focused on the possibility that dianion 26 was forming some type of complex with diisopropylamine or a carbanion-lithium contact ion pair, thus hindering the reactivity of 26 toward both alkyl halides and deuterium oxide. In an attempt to solvate any such complex or contact ion pair, 25 was added to a solution of 2.1 equivalents of lithium diisopropylamide in THF-hexane containing 1.1 equivalents of HMPA; subsequent alkylation with ethyl bromide afforded ethyl derivative

28 in 78% yield. Addition of HMPA after addition of 25 to lithium diisopropylamide gave similar results. Although attempts to prepare benzyl derivative 27 with HMPA added prior to ionization of 25 resulted in an overall yield of 39%, pmr analysis showed that for similar amounts of crude reaction products, the ratios of 25 to 27 with and without HMPA present in the reaction mixture changed from 3:1 to 1:1.3, respectively. From the studies with HMPA it appeared that 25 was being converted to dianion 26, but that 26 was present in solution as a relatively unreactive complexed species. From the results obtained with the ethylation and benzylation of dianion 26 in the presence of HMPA, this technique might be used successfully in other alkylations.

Attempts were made to effect monoalkylation at C-3 of oxindole (20) through the intermediacy of dianion 21 in hopes that the carbanion site would react selectively and rapidly enough with alkyl halides to prevent polyalkylation, which is a serious problem in previous reports of C-alkylation of oxindole; however, treatment of oxindole with 2.1 equivalents of lithium amide in liquid ammonia and 1.1 equivalents of benzyl chloride afforded 3,3-dibenzyloxindole as the major product. Using lithium diisopropylamide (2.1 equivalents) followed by treatment with excess methyl iodide still gave 3,3-dimethyloxindole as the major product.

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AN INVESTIGATION OF DIRECT C-ALKYLATION OF 2,4-OXAZOLIDINEDIONE AND 5-PHENYL-2,4-OXAZOLIDINEDIONE UTILIZING DIALKALI SALT INTERMEDIATES

by

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(ABSTRACT)

The effects of solvent, base strength, nature of halide, number of equivalents of base, and number of equivalents of halide on the course of C-alkylation of 2,4-oxazolidinedione and 5-phenyl-2,4-oxazolidinedione were investigated.

The highest isolated yield (49%) of 5-benzyl-5-phenyl-2,4-oxazolidinedione was obtained using 2.1 equivalents of lithium amide in liquid ammonia followed by alkylation with 1.1 equivalents of benzyl chloride. Although the yield of 5-benzyl-5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide in THF-hexane-HMPA was only 39% (determined by pmr analysis), the addition of HMPA as a co-solvent had a beneficial effect on the ratio of 5-phenyl-2,4-oxazolidinedione to the benzyl derivative. The addition of HMPA as a co-solvent in the ethylation of 5-phenyl-2,4-oxazolidinedione using lithium diisopropylamide in THF-hexane increased the yield of the ethyl derivative by 60% over that obtained in the absence of HMPA.

Using potassium amide in liquid ammonia, lithium amide in liquid ammonia, lithium diisopropylamide in THF-hexane, or lithium diisopropylamide

in THF-hexane-HMPA failed to produce 5-benzyl-2,4-oxazolidinedione in a significant yield.

Several attempts were made to form the dianion of oxindole and selectively alkylate it at the 3-position without the interference of dialkylation at that position. No evidence was obtained which indicated that the dianion had been successfully formed, and the major products afforded from these attempts were the 3,3-dialkyl derivatives of oxindole.