Unsaturated Heterocyclic Systems. XXVI. New Aspects of the Phenoxide Ion to 1,3-Dihydro-2H-azepin-2-one Ring Expansion[1,2]

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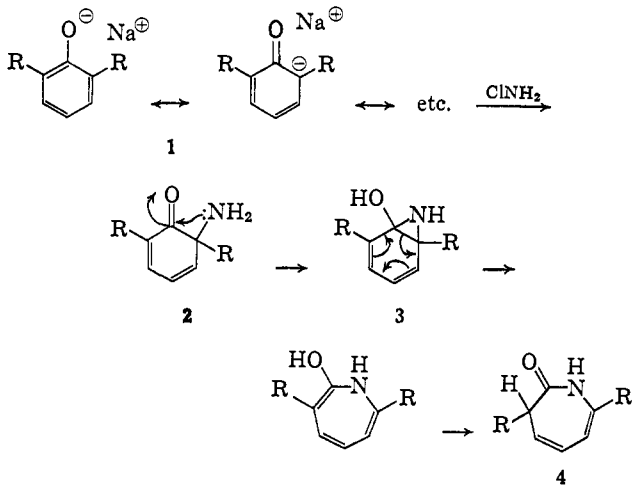
Abstract: The interaction of various unsymmetrically substituted sodio-2,6-dialkylphenoxides with chloramine has been studied quantitatively. The isomeric 1,3-dihydro-2H-azepin-2-ones which result from ring expansion of the aromatic systems have been fully characterized. In contrast, sodio-1-methyl-2-naphthoxide was found to give 1-amino-1-methyl-2(1H)-naphthalenone. These results have been interpreted in terms of steric and electronic effects operative in the nucleophilic attack of the ambident phenoxide and β-naphthoxide ions at the chloramine nitrogen atom.

Previously, the remarkable one-step ring expansion which results when hot (125–150°) solutions of sodio-2,6-dialkylphenoxides in excess 2,6-dialkylphenols are treated with cold (−70°) ethereal chloramine was examined qualitatively,[5,6] and it was concluded that the mechanistic profile of this process very likely involved initial C-amination of ambident phenoxide ions (**1**) followed by thermal rearrangement of the resulting 2-aminocyclohexadienones (**2**) to give the observed 1,3-dihydro-2H-azepin-2-ones (**4**) (Chart I).[5]

Chart I



The purpose of the studies described in the present and subsequent reports was to examine further the mechanistic subtleties of this unusual reaction and to investigate the nature of certain other transformations which accompany this ring enlargement under selected conditions. The present paper confines its attention to the details surrounding the genesis of the dihydroazepinones (**4**).

Steric Considerations. One intriguing aspect of the mechanistic pathway outlined in Chart I resides in the realization that the initial step which triggers the ultimate destruction of the aromatic species involves amination on carbon by an electrophilic nitrogen-containing species (chloramine). Examination of the literature has revealed that such types of reactions have been the subject of only limited experiment.[7] In contrast, there exists a large number of documented examples describing C-amination by molecular entities endowed with electrophilic carbon centers. Given this paucity of information relating to the formation of **2**, we were led to examine the effect of steric influences on dihydroazepinone production.

The significance of such a study rests upon two widely divergent considerations. The first of these centers about our limited knowledge of the intimate details concerning the properties of an SN2 transition state where nitrogen is the atomic center of the bond-forming and bond-breaking processes. Certainly, significant differences are to be expected between nitrogen and the well-studied carbon atom under such circumstances. Because of the greater electronegativity of the former, it is reasonable to conclude that the central nitrogen atom in an SN2 transition state will tolerate less positive charge than a carbon atom. The net result of this particular effect would be a minimization of electrostatic restriction in SN2 displacements at nitrogen relative to similar bimolecular nucleophilic reactions at carbon. It may logically be expected, therefore, that the extent of bond making and bond breaking will also differ substantially in the two transition states under comparison. Some measure of support for these inferences comes from comparison of the rates of SN2 displacement of chloramines and alkyl halides by hydroxide ion. Anbar and Yagil[8] and leNoble[9] have observed that chloramine, methylchloramine, and dimethylchloramine all hydrolyze in aqueous base (SN2 reaction) at similar rates and with similar activation energies. In contrast, related reaction rates for methyl and isopropyl halides differ by a factor of 10^{3-4}.[10]

(1) For paper XXV in this series, refer to L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.*, **88**, 2590 (1966).

(2) Support of this work by the National Science Foundation, Grant GP-2939, is gratefully acknowledged.

(3) Alfred P. Sloan Foundation Research Fellow.

(4) Sinclair Oil Fellow, 1965–1966; Esso Summer Fellow, 1964.

(5) L. A. Paquette, *J. Am. Chem. Soc.*, **84**, 4987 (1962); **85**, 3288 (1963).

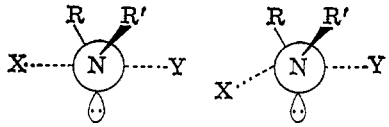
(6) W. Theilacker, K. Ebke, L. Seidl, and S. Schwerin, *Angew. Chem.*, **75**, 208 (1963).

(7) Most of the examples encountered dealt with the synthesis of primary amines by the action of chloramine or various hydroxylamine derivatives on organometallic reagents; for a partial review, consult W. Theilacker and E. Wegner, *ibid.*, **72**, 127 (1960).

(8) M. Anbar and G. Yagil, *J. Am. Chem. Soc.*, **84**, 1790 (1962).

(9) W. J. leNoble, *Tetrahedron Letters*, 727 (1966).

The remarkable insensitivity of methyl substitution on the rate of bimolecular displacement of chloramines, *i.e.*, the absence of a noticeable steric effect, is explainable at this time on the basis of the above rather vague lines of reasoning, although a number of reasonable alternative possibilities suggest themselves. For example, the tacit assumption has been made heretofore that the activated complex for an SN2 displacement on nitrogen resembles exactly that proposed originally by the Ingold group for tetravalent carbon[11] and now universally accepted;[12] that is, the two substituents and the electron pair bound to nitrogen are essentially coplanar, and the entering nucleophile and departing entity are exactly collinear with the central nitrogen atom, *e.g.*, **5**. However, it is entirely possible that the relatively small size of the nitrogen electron pair may in fact render more energetically favorable the attack of the nucleophile from a noncollinear direction as shown

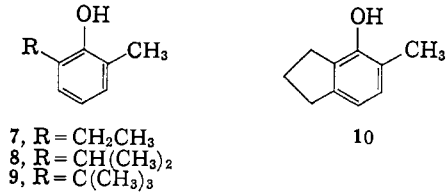


5 **6**

in **6**, and thereby allow substantial minimization of the steric influence of the R and R′ groups. Obviously, much additional study is needed before such points are clarified.

The second consideration which prompted this study resides in the fact that the course of homogeneous ambident anion alkylations is controlled in great part by the hydrogen-bonding capability of the solvent and its dielectric properties.[13] The reactions of ambident phenoxide ions with chloramine are conducted in the particular excess phenol as solvent and therefore are subject to a type of medium which is unusually effective at forming hydrogen bonds.[13a] The net results of this phenomenon is that the oxygen atom of the phenoxide ion is so intensely solvated that its nucleophilicity is dramatically reduced, and displacements employing the *o*-carbon atoms now compete successfully for the chloramine. By the mere expediency of altering the steric properties of the two requisite[5] *ortho* substituents of the phenolic component, a convenient probe of the steric demands of the phenoxide anion for SN2 displacement on chloramine was at hand.

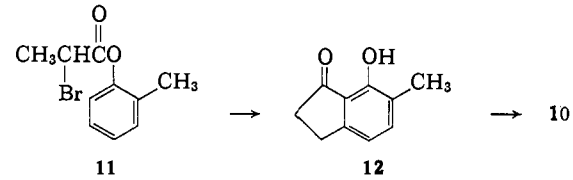
Our attention was directed therefore to a series of 2-methyl-6-substituted phenols. The 2-methyl group, which was to be employed as a requisite internal standard for the series, was selected because of its minimal steric size and ready accessibility. Of the desired phenols, the first three (**7–9**) were either readily synthesized or commercially available. Phenol **10** was discovered to have been prepared earlier by the Fries rearrangement of *o*-tolyl α-bromopropionate (**11**) to **12**



7, R = CH_2CH_3
8, R = $CH(CH_3)_2$
9, R = $C(CH_3)_3$

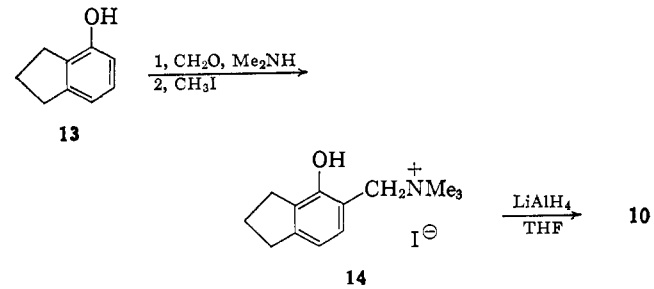
10

followed by the Clemmensen reduction of **12**.[14] However, in our hands this conversion proceeded in only 4% average over-all yield and thus was not of preparative utility. In addition, attempts to alkylate the



11 **12**

sodium salt of 4-indanol (**13**) with methyl iodide in water or 2,2,2-trifluoroethanol[13a,15] also proved unsatisfactory.[16] The desired phenol (**10**) was conveniently obtained by lithium aluminum hydride reduction of the Mannich base methiodide of 4-indanol (**14**). This synthetic sequence, which represents a facile means of introducing an alkyl substituent into a position *ortho* to a phenolic hydroxyl group is believed to proceed *via* the corresponding quinonemethiodide.[17]



13

14

When hot (130–150°) solutions of the sodium salts of phenols **7–10** were treated with cold ethereal chloramine in the usual fashion,[18] the resulting dihydroazepinones could be obtained in 30–40% yield (Table I); the analytical methods employed in the determination of the product compositions are discussed at length in the Experimental Section.

It is clear from these results that C-amination of ambident phenoxide ions by chloramine is subject to steric control. Thus, amination at the methyl-bearing *o*-carbon atom, the process which ultimately leads to dihydroazepinones of type **15**, is always preferred (see Chart II). Of added significance is the observation that the steric factor appears to be proportional to the space present at the nucleophilic sites.[19,20] The phen-

(10) For a summary of these data, see A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 12.

(11) I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 173 (1946).

(12) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 169 ff; F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York N. Y., 1956, pp 538 ff.

(13) (a) N. Kornblum, P. J. Berrigan, and W. J. leNoble, *J. Am. Chem. Soc.*, **85**, 1141 (1963); (b) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963), and references cited in these papers.

(14) R. E. Dean, A. Midgley, E. N. White, and D. McNeil, *J. Chem. Soc.*, 2773 (1961).

(15) N. Kornblum, P. J. Berrigan, and W. J. leNoble, *J. Am. Chem. Soc.*, 82, 1257 (1960).

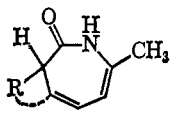
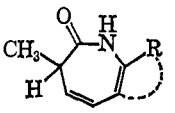
(16) It is conceivable that the *ortho* methylation of sodio-4-indanoxide would have been successful in excess 4-indanol (**13**) as solvent. However, because our supply of this material was limited this possibility was not examined.

(17) P. D. Gardner, H. Sarrafizadeh R., and L. Rand, *J. Am. Chem. Soc.*, **81**, 3364 (1959); P. D. Gardner, H. Sarrafizadeh R., and R. L. Brandon, *ibid.*, **81**, 5515 (1959).

(18) L. A. Paquette, *Org. Syn.*, **44**, 41 (1964).

(19) For the purposes of this discussion, the *p*-carbon atom has been omitted from consideration. This course of action is forced upon us by the fact that our capability to evaluate the role played at this nucleophilic

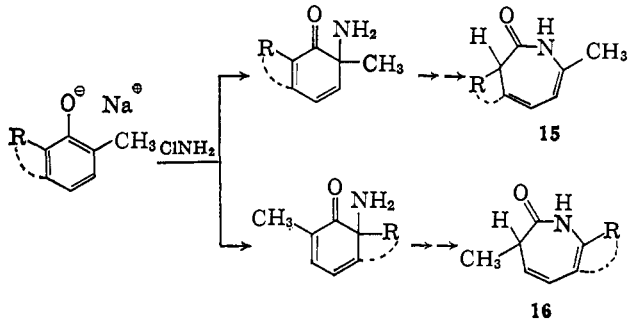
Table I. Reaction of Chloramine with Sodio 2-Methyl-6-Substituted Phenoxides

Phenol	Yield, %	% Composition		Method of analysis
		 **15**	 **16**	
7	32[a]	60 (**15a**)	40 (**16a**)	Vpc and nmr
8	30[a]	79 (**15b**)	21 (**16b**)	Vpc
9	33[a]	100 (**15c**)	*b*	Vpc and nmr
10	37[c]	62 (**15d**)	38 (**16d**)	Nmr

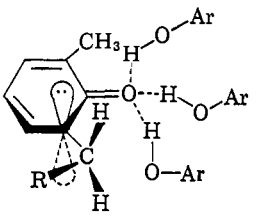
[a] Average values from three experiments. [b] Not detected; technique reliable to less than 1%. [c] Average value from two experiments.

oxide oxygen atom need not be considered here because, as discussed earlier, it is strongly hydrogen bonded to the solvent and is quite unavailable as a nucleophile. As a consequence, the two *o*-carbon atoms may be pictured as competing for the chloramine. In a symmetrical species such as sodio-2,6-dimethylphenoxide, both possible cyclohexadienone anions are equivalent and it may be reasonably concluded that C-amination proceeds to an equal extent at either site.[5] On the other hand, in the case of **7**, the statistical balance would be expected to be altered (if steric effects are influential) because of the added steric bulk introduced by the replacement of a hydrogen by methyl (see **17**, R = CH_3).[21] In fact, because one-third of the volume surrounding the original substituent (CH_3) at this position is now occupied, amination at this ring position should be disfavored by a factor of 3:2, and this ratio corresponds exactly to the observed percentage composition (see Table I). Similarly, phenol **10** gave rise to a 60:40 isomer ratio, thus suggesting that the preferred conformation of the side chain in **7** approximates closely the description given by **17** in which the R group is situated as distant as possible from the bulky hydrogen-bonded carbonyl oxygen.[22]

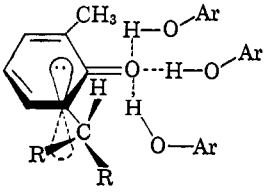
Chart II



15 **16**



17



18

On the basis of these considerations, the anion of **8** in which added methyl substitution has been introduced (*i.e.*, **18**, R = CH_3) would be expected to display an orienting effect of 3:1 in favor of the methyl-substituted carbon, a value which is in good agreement with our observations.[23] Not unexpectedly, therefore, C-amination of sodio-2-methyl-6-*t*-butylphenoxide (**9**) occurs exclusively at the 2 position.

Thus, whatever the precise nature of the transition state for SN2 displacement at trivalent nitrogen, the process is subject to steric control when very bulky nucleophiles such as cyclohexadienone anions **17** and **18** are employed.[24]

Electronic Considerations. An important aspect of the chloramine–phenoxide anion reaction concerns the nucleophilicity of the *o*-carbon atoms. In considering the β-naphthoxide ion, several groups of workers have demonstrated that this entity is an ambident anion capable of alkylation at oxygen or at the α-carbon.[13b,26] Several significant differences exist between the β-naphthoxide and phenoxide systems. Firstly, because of the higher acidity of β-naphthol relative to most alkyl-substituted phenols, the oxygen atom of the β-naphthoxide ion can be expected to be endowed with lower electron density. Secondly, in the β-naphthoxide ion, the nucleophilicity of the α-carbon atom is apparently increased so that competition between oxygen and carbon for the alkylating agent can be considered more equitable than in phenoxides. These conclusions have been borne out by alkylation studies of sodium β-naphthoxide with alkyl and aralkyl halides in a variety of solvents.[13b] Notably absent from this list of solvents, however, is β-naphthol itself. Therefore, an investigation of the reaction of sodio-1-methyl-2-

center is lost. That is to say, C-amination at the *para* position eventuates in the formation of a *p*-aminophenol [*o*-aminophenols have been isolated in low yields from the reaction of *ortho*-unsubstituted phenoxide ions with chloramine [W. Theilacker, *Angew. Chem.*, 72, 498 (1960)]. Because of the amphoteric nature of such substances, and because the pK_a values of the ionizable groups are unknown, it is extremely difficult to isolate such a product from the strongly alkaline reaction mixture. In addition, the *p*-aminophenols are very likely subject to extensive oxidation during the amination process (see subsequent papers).

(20) The low yields reported in Table I (30–37%) may be attributed to at least three causes: *para*-amination on carbon, O-amination, and flash evaporation of the chloramine from the surface of the hot phenol solution prior to reaction. The extent to which each phenomenon occurs is not measurable because of ultimate tar formation. As **16** becomes a less important product due to the steric effect of R, it can be expected that O-amination (if operative) will decrease and that C-amination (if operative) will increase. The constancy of the yield of dihydroazepinone in passing from **7** to **9** suggests that the effects, whatever they may be, are self-compensating.

(21) The negative charge in **17** and **18** has been localized for the sake of simplicity, and these structures are not meant to convey the concept that they exist independently of the resonance hybrid.

(22) It is, of course, imperative that the cyclohexadienone form of **10** reside in this particular conformation.

(23) The slight deviation from theory in this case may be a reflection of the difference in the inductive effects of the methyl and isopropyl groups operating on the cyclohexadienone anion.

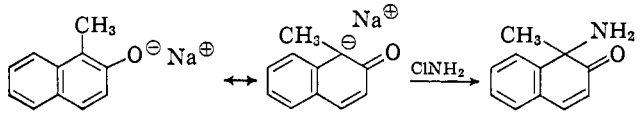
(24) At the outset of this work, it was our intention to examine methylchloramine in a similar study.[5] However, although the reactions have been performed, we have been unable to determine with any precision the product compositions by vpc or nmr. In addition, a comparison of the results in Table I with a parallel study involving benzyl chloride was attempted, but abandoned, when the well-known difficulties realized earlier[25] in analyzing the resulting products on a quantitative basis were also encountered by us.

(25) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Am. Chem. Soc.*, 80, 1391 (1958); D. Y. Curtin and D. H. Dybvig, *ibid.*, 84, 225 (1962), and other related papers by this research group.

(26) N. Kornblum and A. P. Lurie, *ibid.*, 81, 2705 (1959), and references cited therein.

naphthoxide (**19**) with chloramine in molten 1-methyl-2-naphthol at 120–150° seemed in order.[27]

In contrast to earlier findings, however, this reaction afforded in low yield a pale yellow liquid which has been identified as 1-amino-1-methyl-2(1H)-naphthalenone (**20**). The remainder of the reaction mixture proved



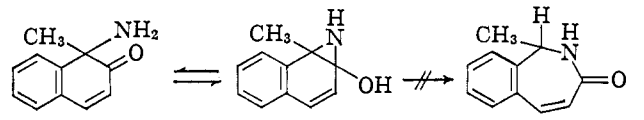
19 **20**

to be highly colored intractable tars. In agreement with structure **20**, this substance exhibited infrared peaks (in CCl_4) at 3400 and 1675 cm^{-1}. Its ultraviolet spectrum [λ_{max}^{EtOH} 236 mμ (ε 12,800) and 308 mμ (ε 10,000)] was in excellent agreement with the known 2(1H)-naphthalenone chromophore.[28] The nmr spectrum (in CCl_4) was fully compatible with the proposed structure; a low-field, one-proton multiplet at δ 7.77 was assigned to the vinyl proton at position 4 and a complex four-proton multiplet centered at 7.25 to the aromatic protons. In addition, the absorption peaks of the vinyl hydrogen at position 3 was located at 6.00 (doublet, J = 10 cps), the amino group protons at 1.85 (singlet),[29] and the methyl group at 1.28 (singlet).

The α-amino ketone **20** could be readily converted to its hydrochloride salt; the nmr spectrum of this derivative (in D_2O) was very similar to that of the free base. In addition, **20** was quite stable at room temperature, showing little propensity for dimerization[30] after standing for several months.[31] It was noted, however, that **20** is destroyed under the reaction conditions, especially if excess chloramine is added. Undoubtedly, this instability of **20** is the reason for the low yield in the amination reaction.

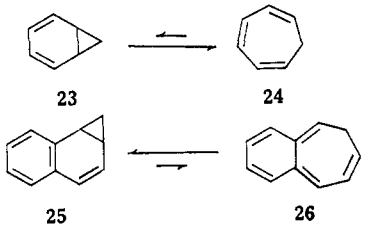
The isolation of **20** is suggestive of the fact that the solvation effect of the β-naphthol is comparable to that of phenols and likewise is important in controlling C-amination in this instance.

One intriguing aspect of this study is embodied in the fact that amino ketone **20** does not undergo ring expansion to dihydroazepinone **22**. Given the very probable interaction of the amino group with the carbonyl function as in **21** (at the elevated temperatures),



20 **21** **22**

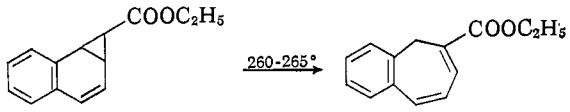
one desires a rationale for the lack of isomerization to **22**. One point of relevance is the relationship between the two pairs of valence-bond isomers **23**:**24** and **25**:**26**. Although the height of the energy barrier separating norcaradiene (**23**) from cycloheptatriene (**24**) is unknown, cycloheptatriene is heavily favored at equilibrium.[32] In contrast, **25** and **26** are separated by an



23 **24**

25 **26**

energy barrier of 19.4 kcal/mole but the benzonorcaradiene **25** is so heavily favored that the concentration of **26** remains below that detectable over a wide temperature range by nmr spectroscopy.[33] The elevated temperatures required to transform ester **27** into its valence isomer **28**[34] serve as a further frame of reference



27 **28**

for the interpretation of the inability of **21** to proceed to **22**. On the basis of such data, it may be concluded that the absence of dihydroazepinone **22** in the reaction of **19** with chloramine is due to the presence of the fused benzene ring,[35] and is a reflection of the normal resistance of benzonorcaradienes to rearrange to benzocycloheptatrienes.

Experimental Section[36]

5-Methyl-4-indanol (10). A stirred mixture of 10 g (0.075 mole) of 4-indanol and 15 g of 25% aqueous dimethylamine was cooled to 15°, and 10 g of 30% formalin was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 4 hr. Salt and ether were added, and the resulting ether layer was dried and evaporated. The residue was dissolved in ether, and 15 g of methyl iodide was added. The solution was refluxed briefly and cooled in ice; the deposited solid was filtered to give 16 g (64%) of a white solid. Because this material decomposed on attempted recrystallization, it was reduced without further purification.

To a slurry of 10 g (0.15 mole) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was slowly added in portions 10 g (0.03

(27) The 1-methyl substituent was present in order to prevent the formation of 1-amino-2-naphthol (if β-naphthol were the precursor) as discussed earlier for phenols in this paper and in ref 5.

(28) For example, R. C. Cambell and N. H. Cromwell [*J. Am. Chem. Soc.*, **79**, 3456 (1957)] list the following data for 1,1-dimethyl-2(1H)-naphthalenone: λ_{max}^{EtOH} 230 sh (15,400), 236 (15,800), 294 sh (10,200), and 300 mμ (ε 10,100).

(29) The size of this peak was greatly reduced upon the addition of D_2O to the nmr tube.

(30) For examples of dimerization of α-amino ketones, see G. H. Alt and W. S. Knowles, *J. Org. Chem.*, **25**, 2047 (1960); H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954), and other references cited therein.

(31) More prolonged standing of **20**, at ambient temperatures did result in polymerization.

(32) E. J. Corey, H. J. Burke, and W. A. Remers, *J. Am. Chem. Soc.*, 77, 4941 (1955).

(33) E. Vogel, D. Wendisch, and W. R. Roth, *Angew. Chem. Intern. Ed. Engl.*, **3**, 443 (1964).

(34) R. Huisgen and G. Juppe, *Chem. Ber.*, **94**, 2332 (1961).

(35) A similar reaction of chloramine with the sodium salt of 2-methyl-1-naphthol has afforded only highly colored oxidation products, none of which has been obtained crystalline. This result is in line with the known ease of oxidation of 2-methyl-1-naphthol [R. Lesser, *Ann.*, 402, 1 (1914); B. Alberti, *ibid.*, 450, 304 (1926); M. Tishler, L. F. Fieser, and W. L. Sampson, *J. Am. Chem. Soc.*, **62**, 1881 (1940); B. R. Baker and G. H. Carlson, *ibid.*, **64**, 2657 (1942); P. P. T. Sah, *Rec. Trav. Chim.*, **60**, 373 (1941)] and the oxidizing capabilities of chloramine [E. Colton and M. M. Jones, *J. Chem. Educ.*, **32**, 485 (1955); R. S. Drago, *ibid.*, **34**, 541 (1957); L. A. Paquette and W. C. Farley, subsequent paper].

(36) Melting points and boiling points are uncorrected. The microanalyses were determined by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were obtained with a Perkin-Elmer Model 237 Infracord spectrometer fitted with sodium chloride prisms. Ultraviolet measurements were made with a Cary Model 14 recording spectrometer. The nmr spectra were determined with a Varian A-60 spectrometer purchased with funds available from the National Science Foundation.

mole) of the methiodide of 5-dimethylaminomethyl-4-indanol, and the mixture was refluxed with stirring for 3 days. With cooling, 3 *N* sulfuric acid was added dropwise until the aluminum salts dissolved. The mixture was extracted with ether, and the combined ether layers were washed with water, dried, and evaporated. The residue was sublimed to give 2.4 g (55%) of a pale yellow solid, mp 87–90°.[37] Several recrystallizations of this material from benzene–hexane (1:4) afforded **10** as a white solid, mp 97–99° (lit.[14] mp 100°), identical in all respects with an authentic sample.

Reaction of Sodio-2-ethyl-6-methylphenoxide with Chloramine. To a solution of 13.6 g (0.1 mole) of 2-ethyl-6-methylphenol[38] in 100 ml of methanol was added a solution of 3.2 g (0.08 mole) of sodium hydroxide in 20 ml of water, and the solution was refluxed for 5 min. The solvents were removed under reduced pressure, and the resulting salt was dried overnight at 90° (1 mm). To a rapidly stirred solution of this salt in 35 g of 2-ethyl-6-methylphenol preheated to 140° in an oil bath was added cold ethereal chloramine[6,39] in a thin stream until the color of the reaction mixture changed from greenish black to reddish brown.[40] The major portion of the excess phenol was removed by distillation [bp 85° (2 mm)], and the residue was dissolved in ether and water. The ether layer was extracted four times with 1 *M* sodium hydroxide solution, washed with water, dried, and concentrated. The residue was chromatographed on Florisil; elution with hexane–ether (4:1) and ether gave a reddish solid which when sublimed afforded 3.9 g (32%) of the dihydroazepinone mixture as a white solid, mp 71–73°. Vpc of this mixture[41] at 140° indicated the presence of only two components in the ratio of 60:40 (planimeter measurements). Unfortunately, these two materials were eluted in sufficient proximity to each other under a variety of conditions and columns that preparative vpc proved unfeasible.

The major isomer was shown to be **15a** on the basis of the nmr spectrum of the mixture (Figure 1). Analysis of the spectrum was assisted substantially by the fact that the C_3-methyl group in **16a** appears as a distinct nonoverlapping doublet centered at δ 1.42 (J = 6 cps).[42] Accurate integration of this set of peaks (relative 3 H equivalency) and the doublet of doublets centered at δ 6.14 (J = 10 and 5 cps) characteristic of the C_5 proton in both **15a** and **16a**[43] (absolute 1 H equivalency) indicated that **16a** was present to the extent of 40%. The percentage of **15a** was calculated by difference as justified by the vpc data.

An analytical sample of the mixture was obtained by preparative vpc, followed by sublimation at 70° (0.2 mm) and recrystallization from ligroin, mp 78–83°; $\nu_{max}^{CCl_4}$ 3200 (N–H) and 1675 cm^{-1} (amide carbonyl); λ_{max}^{EtOH} 252 mμ (ϵ 5950).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.20. Found: C, 71.58; H, 8.70; N, 9.26.

Reaction of Sodio-2-isopropyl-6-methylphenoxide with Chloramine. To a solution of 15 g (0.1 mole) of 2-isopropyl-6-methylphenol in 100 ml of methanol was added a solution of 3.2 g (0.08 mole) of sodium hydroxide in 20 ml of water, and the solution was refluxed for 5 min. The solvents were removed under reduced pressure, and the resulting salt was dried overnight at 100° (1 mm). A rapidly stirred solution of this salt in 35 g of 2-isopropyl-6-methylphenol at 140° was treated with cold ethereal chloramine as described above. The same work-up yielded 4.1 g (30%) of a tan solid, mp 70–74°, after sublimation. Vpc analysis[41] of this mixture indicated the presence of only two components in the ratio of 79:21 (planimeter measurements).

The mixture of dihydroazepinones was separated by preparative vpc.[41] The major isomer **15b** displayed the following properties:

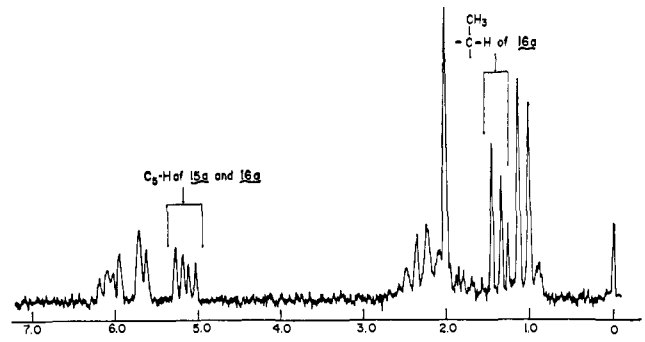


Figure 1. Nmr of a mixture of dihydroazepinones **15a** annd **16a.**

mp 90–91° (from ethanol); $\nu_{max}^{CCl_4}$ 3200 (N–H) and 1675 cm^{-1} (amide carbonyl); λ_{max}^{EtOH} 253 mμ (ϵ 6180); $\delta_{TMS}^{CDCl_3}$ 1.06 [two sets of doublets, J = 6 cps, 6 H (CH_3)$_2$CH], *ca.* 1.2 [overlapping multiplet, 1 H, (CH_3)$_2$C*H*], 2.00 (singlet, 3 H, C_7-CH_3), 2.25 (multiplet, 1 H, C_3-H), 5.32 (doublet of doublets, J = 10 and 6 cps, 1 H, C_4-H), 5.67 (doublet, J = 6 cps, 1 H, C_6-H), and 6.08 (doublet of doublets, J = 10 and 6 cps, 1 H, C_5-H).[44]

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.58; H, 9.12; N, 8.38.

The minor isomer **16b** was a white solid, mp 113.5–114° (from ligroin); $\nu_{max}^{CCl_4}$ 3200 (N–H) and 1675 cm^{-1} (amide carbonyl); λ_{max}^{EtOH} 253 mμ (ϵ 6200); $\delta_{TMS}^{CDCl_3}$ 1.09 [doublet, J = 6 cps, 6 H, (CH_3)$_2$CH], 1.33 (doublet, J = 7 cps, 3 H, C*H*$_3$CH<), *ca.* 2.0 [multiplet, 1 H, (CH_3)$_2$C*H*], *ca.* 2.4 (multiplet, 1 H, CH_3C*H*<), 5.12 (doublet of doublets, J = 10 and 5 cps, 1 H, C_4-H), 5.66 (doublet, J = 5 cps, 1 H, C_6-H), and 6.04 (doublet of doublets, J = 10 and 5 cps, 1 H, C_5-H).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.74; H, 9.14; N, 8.56.

Reaction of Sodio-2-*t*-butyl-6-methylphenoxide with Chloramine. A 150-g (0.92 mole) sample of 2-*t*-butyl-6-methylphenol was heated to 100°. With stirring, 4.6 g (0.2 g-atom) of sodium metal was slowly added at such a rate that the temperature did not exceed 120°. The reaction mixture was heated to 130° and while rapidly stirred under nitrogen was treated with a thin stream of cold ethereal solution containing approximately 0.22 mole of chloramine, the internal temperature being maintained at 120–130° throughout the addition.

The dark brown reaction mixture was distilled at 90° (1 mm) to remove most of the phenol. The contents of the distillation flask were cooled and treated with 250 ml of ether and 200 ml of water. The ether layer was dried and concentrated. The residue was slurried in cold hexane and filtered. The off-white solid thus obtained was recrystallized twice from ligroin to give 15 g (42%) of **15a** as a white solid, mp 131–131.5°;[45] $\nu_{max}^{CCl_4}$ 3200 (N–H) and 1675 cm^{-1} (amide carbonyl); λ_{max}^{EtOH} 253 mμ (ϵ 6250); $\delta_{TMS}^{CDCl_3}$ 1.15 [singlet, 9 H, (CH_3)$_3$C], 2.00 (singlet superimposed upon multiplet, 4 H, C_3-H and CH_3), 5.42 (doublet of doublets, J = 9 and 6 cps, 1 H, C_4-H), 5.54 (doublet, J = 6 cps, 1 H, C_6-H), and 6.10 (doublet of doublets, J = 9 and 6 cps, 1 H, C_5-H).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.62; H, 9.70; N, 7.81.

Reaction of Sodio-5-methyl-4-indanoxide with Chloramine. 5-Methyl-4-indanol (14.8 g, 0.1 mole) was treated with 3.2 g (0.08 mole) of sodium hydroxide as described above, and the resulting sodium salt was dissolved in 30 g of hot (140°) 5-methyl-4-indanol. After the addition of cold ethereal chloramine in the usual fashion, the dark reaction mixture was worked up as above. Chromatography of the crude residue on Florisil (elution with ether) afforded 6 g (41%) of an off-white solid, mp 80–85°.

The relative proportions of **15d** and **16d** could be calculated readily from the nmr spectrum of the mixture (Figure 2) at this stage of purification. Thus, because of the differing points of fusion of the three-carbon methylene unit to the dihydroazepinone nucleus

(37) The crude material was found to be quite acceptable for use in the chloramine ring expansion step.

(38) A. V. Kalabina, N. A. Tyukavkina, M. I. Bardamora, and A. S. Lavrova, *Zh. Obshch. Khim.*, **31**, 3222 (1961); *Chem. Abstr.*, **57**, 2115 (1962).

(39) G. H. Coleman and H. L. Johnson, *Inorg. Syn.*, **1**, 59 (1939).

(40) This very noticeable color change can be utilized as a quite accurate indication of the fact that sufficient chloramine has been added to consume the existing phenoxide anion.

(41) A 15 ft × 0.25 in. aluminum column packed with 1% Carbowax 20M on Chromosorb P was employed, in conjunction with a Varian A90-P3 (thermal conductivity) gas chromatograph.

(42) The identical methyl group in 1,3-dihydro-3,7-dimethyl-2H-azepin-2-one is found as a doublet at δ 1.42; this region in the spectrum of the 3,7-diethyl homolog is devoid of absorption.

(43) This point was unequivocally established by examination of the nmr spectra of 1,3-dihydro-3,7-dimethyl-2H-azepin-2-one and 3,7-diethyl-1,3-dihydro-2H-azepin-2-one in which the C_5 proton was located in both instances at δ 6.17 as a doublet of doublets (J = 10 and 5 cps).[5]

(44) For the sake of simplicity, the long-range coupling phenomena known to be prevalent in the dihydroazepinone ring system [L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4096 (1964); *J. Org. Chem.*, **28**, 3590 (1963)] are omitted from consideration in the spectral assignments of this paper.

(45) Vpc and nmr analysis of the crude product indicated the presence of **15b** and **9**, but no additional components.

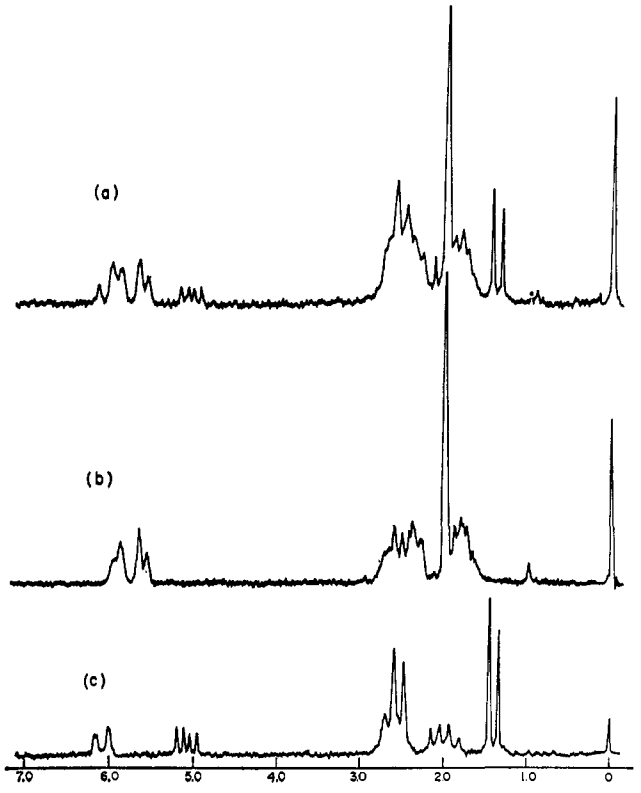


Figure 2. Nmr spectra of (a) a mixture of dihydroazepinones **15d** and **16d**; (b) pure dihydroazepinone **15d**; and (c) pure dihydroazepinone **16d**.

in these isomers, the doublet of the C_6 proton in **15d** (δ 5.62) and the quartet of the C_4 proton in **16d** (δ 5.07) (both protons are absent in the respective isomeric structures) are endowed with unique chemical shifts, and the areas of these multiplets can be quantitatively measured (planimeter). As a further check of the validity of this technique, the total area of these two absorptions was compared to the area of the two overlapping doublets in the δ 5.97–6.07 region attributable to the C_5 proton common to both molecules. The values invariably checked to within ±2%.

This mixture of dihydroazepinones was separated by careful chromatography on Woelm neutral alumina (elution with hexane–benzene, 9:1). Dihydroazepinone **15d** displayed the following properties: mp 114–115° (from ethanol); $\nu_{max}^{CCl_4}$ 3200 (N–H), 1675 (amide carbonyl), and 1650 cm^{-1} (C=C); λ_{max}^{EtOH} 253 mμ (ε 6200); nmr, see Figure 2.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.43; H, 8.06; N, 8.46.

The isomeric dihydroazepinone was obtained as a fluffy white solid from ethanol, mp 157–158°; $\nu_{max}^{CCl_4}$ 3200 (N–H), 1675 (amide carbonyl), and 1610 cm^{-1} (C=C); λ_{max}^{EtOH} 253 mμ (ε 6200); nmr, see Figure 2.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 7.93; N, 8.71.

Reaction of Sodio-1-methyl-2-naphthoxide with Chloramine. A 100-g (0.63 mole) sample of 1-methyl-2-naphthol[46] was heated under nitrogen to 120°, and 3.45 g (0.15 g-atom) of sodium was added in small pieces. After the sodium was completely consumed, the reaction mixture was heated to 150° and a cold (−70°) ethereal solution containing *ca.* 0.20 mole of chloramine was added in a thin stream at 120–150°. The excess naphthol was removed by distillation [bp 115–120° (1 mm)], and the cooled residue was treated with ether and water. The ether layer was washed with three 25-ml portions of 1 *M* sodium hydroxide and water, dried, and concentrated. The very dark resulting viscous oil (16.5 g) was twice chromatographed on Florisil (elution with hexane–ether, 9:1) to afford 2.0 g of a light brown oil. Molecular distillation afforded 1.1 g (4%) of 1-amino-1-methyl-2(1H)-naphthalenone (**20**) as a pale yellow oil.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.19; H, 6.56; N, 7.66.

The hydrochloride was prepared by the addition of a slight excess of ethereal hydrogen chloride to an ether solution of **20**. The resulting white crystals melted at 264° dec (from ethanol–ether); ν_{max}^{Nujol} 2900 (NH_3^+) and 1675 cm^{-1} (ketone carbonyl); λ_{max}^{EtOH} 237 (ε 23,000) and 311 mμ (ε 15,000).

Anal. Calcd for $C_{11}H_{12}ClNO \cdot H_2O$: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.20; H, 6.19; N, 6.10.

Acknowledgment. We wish to thank Dr. J. C. Wollensak, Ethyl Corp., Detroit, Mich., for generous gifts of **8** and **9** and Dr. S. W. Tinsley, Union Carbide Corp., South Charleston, W. Va., for a sample of **13**.

(46) D. Lavil, *J. Chem. Soc.*, 2776 (1955).

The Total Synthesis of *dl*-Crinine[1]

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Contribution from the Department of Chemistry, University of Wisconsin. Madison, Wisconsin 53706. *Received January 25, 1967*

Abstract: A stereospecific total synthesis of the alkaloid crinine is described.

Those amaryllidaceae alkaloids possessing the **5**-**10b** ethanophenanthridine skeleton have been the focus of a considerable amount of synthetic work recently.[2-4] Crinine (**1**), the subject of the present communication, has been recently synthesized by Muxfeldt and collaborators.[5] We wish now to report the total synthesis of *dl*-crinine by what we feel is both an economical and stereochemically rational route.

The key reaction in the proposed synthesis was the rearrangement of an N-vinylaziridine to a Δ^1-pyrroline. The desirability of working with rather large functionalized molecules led us to explore the heterolytic rearrangement of N-vinylaziridines possessing carbonyl groups on the 2 position of the vinyl residue as in eq

(1) Preliminary accounts of portions of this work have appeared: H. W. Whitlock and G. L. Smith, *Tetrahedron Letters*, 1389 (1965); G. L. Smith and H. W. Whitlock, *ibid.*, 2711 (1966).

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(4) H. Irie, S. Uyeo, and A. Yoshitake, *Chem. Commun.*, 635 (1966).

(5) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *J. Am. Chem. Soc.*, **88**, 3670 (1966).