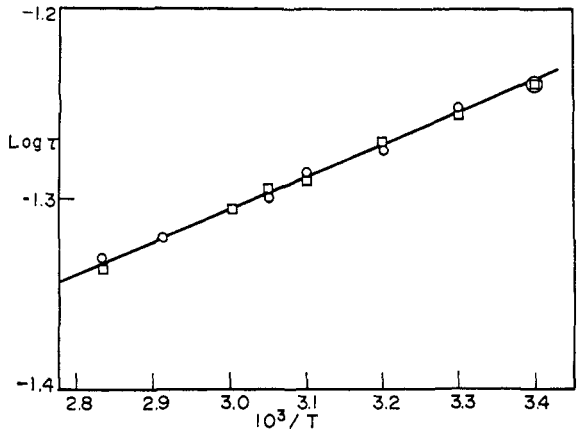

Figure 6. Arrhenius plot for exchange, **4a** ⇌ **4b**: □, acetyl resonance; ○, aryl resonance.

for **4a** and **b** as a function of temperature. The acetyl lines broaden and move together with increasing temperature, as do the lines for H_5 and H_8. Similar effects are seen in the methoxy absorption (Figure 5). The multiplet for ring C which spans 20 Hz at 0° narrows to ~1 Hz by 90°. Finally the resonances for H_1 broaden and move together but do not completely average out.

The acetyl and aromatic hydrogen line shapes in Figures 1 and 2 were employed to calculate the mean lifetime between successive exchanges of a hydrogen between different environments.[10] At each temperature the values of τ obtained from the acetyl and aromatic line shapes are very similar. The Arrhenius plot in Figure 6 yields an activation energy of 7.8 ± 0.4 kcal.

Evidently the changes for the aromatic and acetyl line shapes described above must result from the same process. It is tentatively concluded that inversion at C_1 brings about the temperature behavior reported here.

In summary, the compounds listed in Table II exist in two forms and interconversion rates between them have been measured with the nmr line-shape method.

Experimental Section

Compounds. The compounds used in this research were synthesized by Dr. K. Buck.[11]

Nmr Spectra. All nmr spectra were determined with a Varian A-60 nmr spectrometer equipped with a variable-temperature probe.

Acknowledgment. This research was supported by a Public Health Service Fellowship from the National Institute of General Medical Sciences (D. R. D.) and grants from the National Institute of Neurological Diseases and Blindness (NB 04529) and the National Institute of General Medical Sciences (GM-08686-03).

(10) (a) H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, 21, 279 (1953); H. S. Gutowsky and C. H. Holm, *ibid.*, 21, 1688 (1953). (b) We have employed a treatment for an unequal doublet 100/80. It is recognized that the isomer ratio may vary with temperature; however, altering it by 10% in either direction changes ΔE by less than 4%, within our experimental error. The line shapes for H_1 and the methoxy groups were not sufficiently reproducible to use for rate measurements.

(11) K. Buck, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1966. We thank Dr. Buck for making these compounds available to us.

Quinazolines and 1,4-Benzodiazepines. XXXIII. Three Tautomeric Forms of the Benzodiazepine Ring System[1]

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Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received September 16, 1966*

Abstract: The reaction of 6-chloro-2-chloromethyl-1,2-dihydro-4-phenylquinazoline 3-oxides (**1**) with base gives either the 1,3-dihydro-2H-azirino[1,2-*a*]quinazoline 4-oxides (**4**) which are valence isomeric with the unknown 2H-1,4-benzodiazepine 4-oxide ring system or a 3H-1,4-benzodiazepine 4-oxide (**7**). The effect of substituents in the 2 position as well as solvent on the course of the reaction is discussed. The 2H isomers **4** are readily isomerized to 5H-1,4-benzodiazepine 4-oxides (**5**).

The properties of the heterocyclic congeners of tropilidene are of interest, and considerable attention has been devoted to the synthesis of these compounds.[2] An entry into this area of chemistry which deserves more extensive exploitation is the ring expansion of dihydro derivatives of aromatic heterocycles bearing a chloromethyl group.[3] An easily accessible set of such dihydro derivatives is the 2-chloromethyl-1,2-dihydroquinazoline 3-oxides (**1**) which are obtained by condensation of 2-amino-5-chlorobenzophenone *anti*-oxime with α-chloro aldehydes or α-chloro ketones.[4]

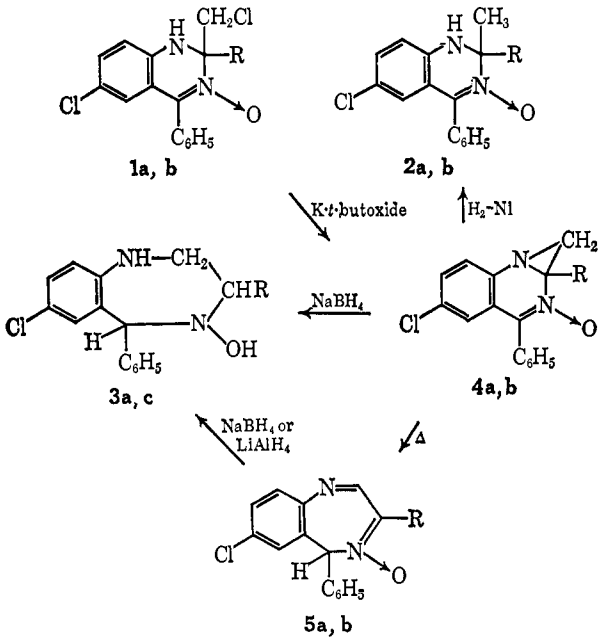
(1) A part of this work has been reported in preliminary form: paper XXXI, G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Letters*, 2609 (1966); paper XXXII, R. Ian Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc.*, in press.

(2) F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.*, **87**, 3529 (1965); R. J. Colter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964); L. A. Paquette, *J. Am. Chem. Soc.*, **85**, 3288 (1963); G. Maier, *Chem. Ber.*, **98**, 2438 (1965); E. Vogel, W. A. Böll, and H. Günther, *Tetrahedron Letters*, 609 (1965); J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959); W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966); F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.*, **2**, 26 (1965).

(3) The ring enlargement of 4-chloromethyl-1,4-dihydropyridines has been studied. See R. F. Childs and A. W. Johnson, *Chem. Commun.*, 95 (1965); M. Andersen and A. W. Johnson, *J. Chem. Soc.*, 2411 (1965), and earlier papers.

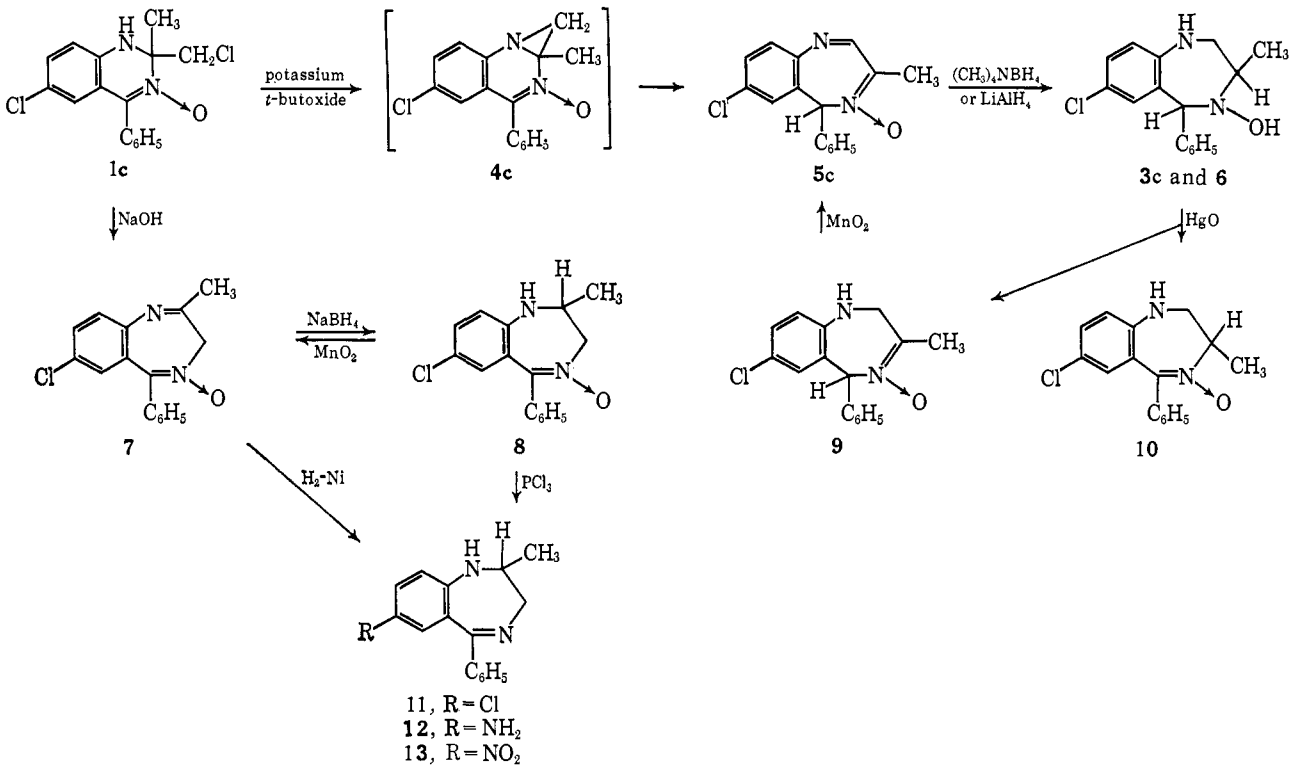
(4) *Cf.* G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).

Scheme I



of the aziridinomethylene group, J_{AB}, is fortuitously zero.[5] Two doublets at δ 2.05 (J = 3 cps) and 2.9 (J = 4 cps) are ascribed to the methylene protons, and a doublet of doublets centered at δ 4.63 is ascribed to the methine proton. Compound **4b** shows a similar spectrum; the aziridine ring protons appear as singlets at δ 2.94 and 3.18. The protons of the chloromethyl group which are rotationally nonequivalent give doublets at δ 3.5 and 5.01 (J = 12 cps). The presence of the aziridine ring was confirmed by the chemical behavior of these compounds. Hydrogenation of **4a** and **b** with Raney nickel catalyst gave the dihydroquinazolines **2a** and **b**, respectively, in 50% yield. Reduction with sodium borohydride in diglyme gave products containing a seven-membered ring. Compound **4a** gave the known tetrahydrobenzodiazepine derivative **3a**;[6] reduction of **4b** was accompanied by the loss of the side-chain chlorine and gave the 3-methyltetrahydrobenzodiazepine **3c**. The proof for the position of the methyl group will be discussed in connection with the products obtained from **1c**. On heating, the aziridinoquinazolines **4a** and **b** are isomerized, by a 1,5-hydrogen shift,[7] to the 5H-benzodiazepines **5a** and **b**. With the exception of a singlet in the spectrum of **5b** at δ 4.72 which is due to the chloromethyl group, their nmr spectra show only a complex

Scheme II



The reaction of three of these chloromethyl derivatives, **1a**, **b**, and **c**, with potassium *t*-butoxide has been studied. Compound **1a** and **b** gave the valence isomers **4a** and **b** of the 2H-benzodiazepine ring system (Scheme I). The structure of these compounds was deduced from their spectral properties and corroborated by their chemical reactions. Neither compound shows a band ascribable to an NH in the infrared, or an exchangeable proton in the nmr spectrum. The high-field portion of the nmr spectrum of **4a** may be rationalized as an ABX pattern in which the geminal coupling constant set of multiplets in the area usually assigned to aromatic protons. Reduction of **5a** with sodium borohydride gave the tetrahydrobenzodiazepine derivative **3a**, and reduction of **5b** with lithium aluminum hydride again resulted in the loss of the aliphatic chlorine and formation of **3c**.

(5) See H. M. Hutton and T. Schaefer, *Can. J. Chem.*, 41, 684 (1963), for discussion of geminal coupling constants of three-membered rings.

(6) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, 28, 2459 (1963).

(7) See, for example, A. P. Terborg and H. Kloosterziel, *Rec. Trav. Chim.*, 82, 1189 (1963).

The reaction of the methyl-substituted compound **1c** with potassium *t*-butoxide in ether was more complex. Thin layer chromatography of the crude reaction mixture indicates that two primary products were formed. One of these, as will be shown later, has structure **7**. The other is assumed to be the aziridino compound **4c**. This was substantiated by its transformation during the work-up into the 5H-benzodiazepine **5c** which was isolated.

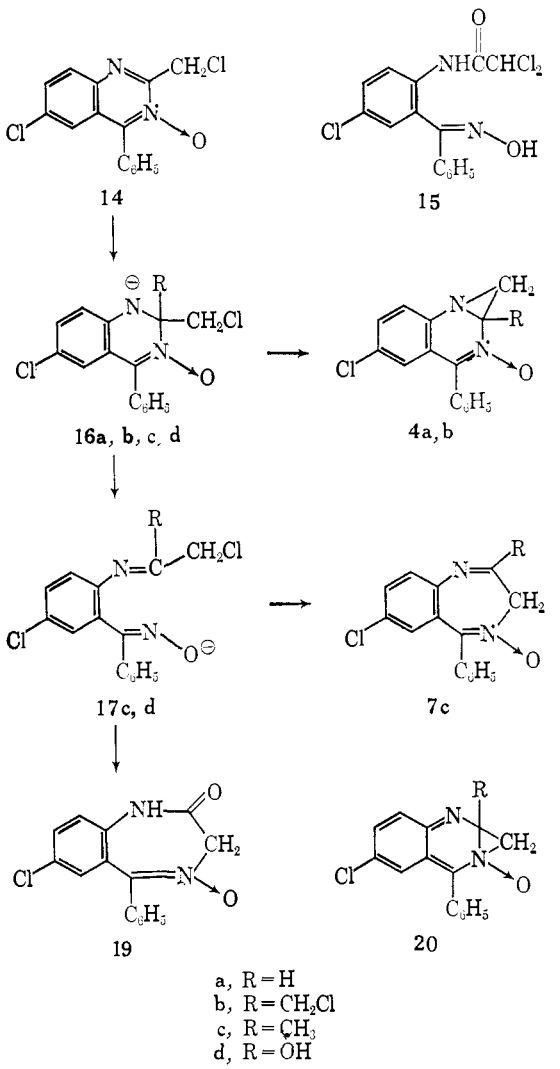
The structure of compound **5c** was indicated by the nmr spectrum (a singlet at δ 2.17 for the methyl group and no other high-field signals) and confirmed by the transformations shown in Scheme II. Hydride reduction yielded the hydroxylamine **3c** previously mentioned, as well as a stereoisomer **6**. Oxidation of either of these with mercuric oxide gave a mixture of the isomeric nitrones **9** and **10** whose structures were assigned on the basis of their nmr spectra. The methyl group in compound **9** appeared as a singlet at δ 2.08, whereas in compound **10** a doublet was observed at δ 1.3 (J = 6 cps). These structural assignments were also supported by the ultraviolet spectra. The spectrum of **10** is identical with that of the known desmethyl compound[6] whereas that of **9** shows significant differences. Chemical transformations which also support the structural assignments of **9** and **10** are the ready oxidation of **9** with manganese dioxide[8] to regenerate **5c** and the conversion of **10** into the known 7-chloro-2,3-dihydro-3-methyl-1H-1,4-benzodiazepine[9] by removal of the oxygen of the N-oxide with phosphorus trichloride. This sequence of reactions unequivocally establishes the structure of the 3-methyl-5H-benzodiazepine **5c** and, thereby, also that of the 3-chloromethyl-5H-benzodiazepine **5b**.

The second primary product, which was formed in minor amounts on treatment of **1c** with potassium *t*-butoxide in ether, was the major product on reaction of **1c** with sodium hydroxide in ethanol. This compound has structure **7**. The nmr spectrum shows a singlet at δ 2.5 (methyl group) and another singlet at δ 4.4 (methylene group). Hydrolysis with acid gave 2-amino-5-chlorobenzophenone. The 1,2-double bond could be selectively reduced with sodium borohydride to give **8**, which had the appropriate ultraviolet spectrum.[6] The nmr spectrum of this compound shows, as expected, the methyl group as a doublet at δ 1.33 (J = 6 cps). Oxidation of **8** with manganese dioxide reintroduced the 1,2 double bond,[8] whereas reduction with phosphorus trichloride resulted in the formation of **11**. Compound **11** was also obtained from the minor product **13** of the reaction of propylenediamine with 2-chloro-5-nitrobenzophenone[9] by reduction to the 7-amino derivative **12** and a Sandmeyer reaction. This alternative synthesis then provides final confirmation for the position of the methyl group.

Discussion

The ring expansions of the 1,2-dihydroquinazolines **1** described in this paper can be accommodated within the mechanistic scheme which has been proposed for the transformation of the chloromethylquinazoline **14** to the benzodiazepinone **19**.[10] This transformation is believed to proceed by addition of hydroxide ion to the 2 position of the quinazoline ring to give an intermediate anion **16d** which immediately rearranges to the ring–chain tautomer **17d**.[11] The existence of the open-chain anion is supported by the isolation of the amide **15** on treatment of the dichloromethylquinazoline corresponding to **14** with alkali. In this latter case the subsequent cyclization to the 3-chlorobenzodiazepinone corresponding to **19** is sufficiently retarded to allow isolation of the intermediate.

Scheme III



In the quinazoline series the anion **16d** is formed by an addition reaction whereas in the 1,2-dihydroquinazoline series (Scheme III) the related anions **16a, b,** and **c** are produced by abstraction of a proton from the 1-nitrogen. If the analogy between the two series were perfect, all of the 1,2-dihydroquinazolines should yield products of structure **7**. It was however possible to isolate only a product of this type when R = CH_3; in the other two cases the aziridines **4a** and **b**, which are obviously derived from the first anion **16**, were obtained. The formation of the aziridines **4** or the 3H-benzodiazepine **7c** can be readily rationalized when

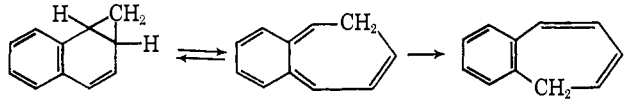
(8) R. M. Evans, *Quart. Rev.* (London), 13, 61 (1959).
(9) L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, 28 3013 (1963).
(10) A. Stempel, E. Reeder, and L. H. Sternbach, *ibid.*, **30**, 4267 (1965).
(11) This intermediate is depicted with the amide group in its tautomeric form to emphasize the analogy to the reaction of the 1,2-dihydroquinazoline (1c).

the effect of the substituent R on the relative stability of the two anions **16** and **17** is considered. Thus, when R is an electron-releasing group such as hydroxyl or methyl, the anion **16** is destabilized and converts to anion **17** in which the negative charge is removed from the vicinity of substituent. The reaction products are then derived from **17**. If, however, R is hydrogen or chloromethyl, **16** is relatively more stable and exists long enough to allow the formation of the aziridines **4**.

The solvent effect which was observed when studying the transformations of compound **1c** can be rationalized in a similar manner. In a nonpolar solvent, anion **16**, with its more extensive charge delocalization, should be relatively more stable than **17** in which the negative charge is largely localized on the oxygen. Thus in a nonpolar solvent (ether), the 5H-benzodiazepine **5c** derived from anion **16c** *via* the aziridine **4c** is obtained, but in a polar solvent (aqueous ethanol), the major product is the 3H-benzodiazepine **7c** derived from anion **17**.

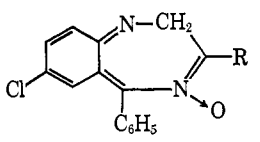
An alternative reaction scheme in which **16** is postulated to react as an ambident anion[12] is not cogent. In this scheme, since both nitrogen atoms of **16** are centers of electron density, ring closure may take place at either to give **4** or **20** as primary products. The aziridine **20** would be expected to isomerize immediately to **7**. However, based on this scheme, it is not possible to give satisfactory reasons for the pronounced effects of the substituents R and the solvent on the course of the reaction. Furthermore, although substantial quantities of the amide **15** can be isolated, its formation would have to be regarded as an irrelevant side reaction.

The thermal instability of the aziridines **4** is also of interest. In the benzonorcaradiene **21**,[13] a temperature of 260° for 1 hr is required to form **23**, presumably



21 22 23

by a 1,5-hydrogen shift. At lower temperatures an equilibrium between the two forms **21** and **22** has been postulated.[14] In contrast the aziridines **4a** and **b**, dissolved in tetrachloroethane, have half-lives of approximately 2 hr and 15 min, respectively, at 75°. It is not clear what factors cause this large increase in the rate of isomerization; it may, however, be that the 1,5-hydrogen shift occurs only after isomerization to a 2H-benzodiazepine **24** analogous to **22**. In this form the 2-hydrogen is activated by the nitrone double bond which is now between positions **3** and **4**. This rationalization gains some credence since a substituent



24

in position 3, which would be expected to favor **24**, further increases the rate of isomerization.

Finally, it is interesting to note that none of the three tautomeric forms of the benzodiazepine ring system which have been isolated show any tendency to isomerize further to a 1H isomer in which the heterocyclic ring would contain eight π electrons.

Experimental Section[15]

6-Chloro-2-chloromethyl-1,2-dihydro-4-phenylquinazoline 3-Oxide (1a). A mixture of 46 ml (0.3 mole) of chloroacetaldehyde diethyl acetal and 46 ml of 1.5 *N* hydrochloric acid was heated under reflux for 15 min. This solution was cooled to 10° and added to a solution prepared by dissolving 49.3 g (0.2 mole) of 2-amino-5-chlorobenzophenone *anti*-oxime in 100 ml of hot ethanol and cooling to 10°. An exothermic reaction occurred, and the mixture was stirred for 15 min without further cooling. The precipitate was collected and washed with hexane to give 34.7 g (56%) of **1a**, mp 162–166°. Recrystallization from 2-propanol gave yellow plates, mp 165–167°.

Anal. Calcd for $C_{16}H_{12}Cl_2N_2O$: C, 58.65; H, 3.94. Found: C, 58.94; H, 4.19.

6-Chloro-2,2-bis(chloromethyl)-1,2-dihydro-4-phenylquinazoline 3-Oxide (1b). a. A solution of 10 g (40.6 mmoles) of 2-amino-5-chlorobenzophenone *anti*-oxime in 100 ml of methanol containing 5 ml of 1 *N* methanolic hydrogen chloride was cooled to 10°. After a solution of 7.74 g (60.9 mmoles) of 1,3-dichloropropanone in 25 ml of methanol had been added to the reaction mixture, it was allowed to warm to *ca.* 25° and stand for 0.5 hr at this temperature. The mixture was then cooled in an ice bath, and the product (7.6 g, 45%), mp 167–173°, was collected and washed with hexane. Recrystallization from ethyl acetate gave yellow needles, mp 171–172°.

Anal. Calcd for $C_{16}H_{13}Cl_3N_2O$: C, 54.03; H, 3.68. Found: C, 54.27; H, 4.00.

b. From 6-Chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-Oxide.[4] A mixture of 200 g (0.7 mole) of 6-chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-oxide, 200 g (1.57 moles) of 1,3-dichloropropanone, 2 l. of ethanol, 400 ml of benzene, and 2 ml of concentrated hydrochloric acid was heated while part of the solvent was distilled. During 1 hr, 1.2 l. of distillate was collected. The reaction mixture was then cooled in an ice bath and neutralized with 40 ml of 2 *N* ammonium hydroxide. Filtration and washing of the solid with 200 ml of 1:1 ethanol–ether gave 191.5 g (77%) of **1b**, mp 169–171°.

6-Chloro-2-chloromethyl-1,2-dihydro-2-methyl-4-phenylquinazoline 3-Oxide (1c). a. Reaction of 6-chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-oxide with chloro-2-propanone as in procedure b above gave 158 g (71%) of **1c**, 150–158° dec. Recrystallization from methylene chloride–petroleum ether gave yellow prisms, mp 163–166° dec.

Anal. Calcd for $C_{16}H_{14}Cl_2N_2O$: C, 59.82; H, 4.39. Found: C, 59.86; H, 4.63.

b. From 4b. A solution of 1.5 g (4.89 mmoles) of **4b** in 225 ml of ethanol was hydrogenated over 5.0 g of Raney nickel at room temperature and atmospheric pressure. The reaction was stopped when approximately 10 mmoles of hydrogen had been consumed. The catalyst was filtered and the filtrate concentrated *in vacuo*. The residue was finally crystallized from acetone–water to yield 0.8 g (*ca.* 50%) of yellow rods, mp 162–167° dec. Recrystallization from methylene chloride–hexane gave material of mp 163–165° dec, identified by spectra as **1c**.

7-Chloro-1,3-dihydro-5-phenyl-2H-azirino[1,2-*a*]quinazoline 4-Oxide (4a). A solution of 42.2 g (0.137 mole) of 6-chloro-2-chloromethyl-1,2-dihydro-4-phenylquinazoline 3-oxide (**1a**) in 700 ml of dry tetrahydrofuran was cooled in a Dry Ice–acetone bath, and 15.4 g (0.139 mole) of potassium *t*-butoxide was added. The cooling bath was removed, and the mixture was stirred for 4.5 hr as it came to room temperature. The inorganic solids were removed by

(12) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, 77, 6296 (1955).

(13) E. Muller, H. Fricke, and H. Kessler, *Tetrahedron Letters*, 1525 (1964).

(14) E. Vogel, D. Wendisch, and W. R. Rothe, *Angew. Chem.*, 76, 432 (1964).

(15) All melting points were determined in capillaries and are corrected. The ultraviolet spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer. The nmr spectra were determined with a Varian A-60 instrument. The infrared spectra were determined on a Beckman IR-9 spectrophotometer. Thin layer chromatography was done on silica gel G plates using 5% methanol in chloroform as developer. Alumina refers to Woelm neutral alumina, activity I, and petroleum ether to a fraction of bp 40–60°.

filtration through Celite, and the filtrate was concentrated *in vacuo*. The residue was crystallized from benzene–hexane to give 22.0 g (57%) of crude **4a**, mp 122–127°. Recrystallization from benzene–hexane gave off-white needles, mp 135–136.5°; ultraviolet maxima: 224 mμ (ε 16,000), 254 (19,000), 308 (8000), 319 (7500), and 342 (inflection) (5000); nmr spectrum (in δ) ($CDCl_3$): doublet at 2.05 (1 H), doublet at 2.9 (1 H), doublet of doublets at 4.63 (1 H), and multiplets at 7.3 (*ca.* 8 H).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10. Found: C, 66.79; H, 4.26.

7-Chloro-3-chloromethyl-1,3-dihydro-5-phenyl-2H-azirino[1,2-*a*]quinazoline 4-Oxide (4b). Reaction of 6-chloro-2,2-bis(chloromethyl)-1,2-dihydroquinazoline 3-oxide (**1b**) with potassium *t*-butoxide as above gave crude **4b**, mp 130–131°, in 82% yield. Recrystallization from benzene–hexane gave colorless prisms, mp 136–138.5°; ultraviolet maxima: 225 mμ (ε 16,000), 254 (19,000), 308 (8000), 319 (7600), and 345 (inflection) (5000); nmr spectrum (in δ) (DMSO): singlets at 2.94 (1 H) and 3.18 (1 H), doublets at 3.5 (1 H) and 5.10 (1 H), multiplets 7.5 (*ca.* 8 *H*).

Anal. Calcd for $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79; Cl, 22.22. Found: C, 60.47; H, 3.80; Cl, 22.26.

6-Chloro-1,2-dihydro-2-methyl-4-phenylquinazoline 3-Oxide (2a). A solution of 1.35 g (5 mmoles) of 7-chloro-1,3-dihydro-5-phenyl-2H-azirino[1,2-*a*]quinazoline 4-oxide (**4a**) in 225 ml of ethanol was hydrogenated at room temperature and atmospheric pressure with 2 g of Raney nickel until 1 equiv of hydrogen had been taken up. The solution was filtered through Celite to remove the catalyst and concentrated to dryness *in vacuo*. The residue was crystallized from a mixture of methylene chloride and petroleum ether to give 0.7 g (50%) of yellow needles, mp 159–169°. Two recrystallizations from methylene chloride and petroleum ether raised the melting point to 166–169°, undepressed on admixture of authentic **2a**.[4] The infrared spectra were also identical.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-1H-1,4-benzodiazepin-4-ol (3a). a. From 4a. A solution of 2.7 g (0.010 mole) of **4a** in 100 ml of diglyme was cooled and treated at 5–10° with 2.7 g of sodium borohydride for 1 hr. The excess sodium borohydride was destroyed with glacial acetic acid, and the mixture was poured into 500 ml of water and extracted with methylene chloride. The methylene chloride extracts were washed with water and brine and dried over sodium sulfate. The solution was concentrated to dryness, and the residue was crysallized from benzene–hexane to give 1.8 g (65%) of off-white needles, mp 164–166°, undepressed on admixture of an authentic sample.[6]

b. From 5a. A solution of 2.0 g (7.4 mmoles) of the 5H-benzodiazepine **5a** in 80 ml of methanol was cooled in an ice bath and treated with 2.0 g of sodium borohydride. After 1 hr, the reaction mixture was neutralized with acetic acid and diluted with a large volume of water. The solid (2.0 g, 95%), mp 165–167°, which separated was collected and washed with water and petroleum ether. It was identified as the hydroxylamine derivative **3a** by its infrared spectrum.

7-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-1,4-benzodiazepin-4-ol (3c). a. From 4b. A cold solution of 13.0 g (41 mmoles) of **4c** in 600 ml of diglyme was treated with 13.0 g of sodium borhydride and kept in the refrigerator for 14 hr. The mixture was neutralized with glacial acetic acid, diluted with water, and extracted with ether. The ethereal extracts were washed with water, dried over sodium sulfate, and concentrated to small volume *in vacuo*. The residue was crystallized from petroleum ether to give 9.4 g of pale yellow solid, mp 174–200°, which was shown to be a mixture of the isomers **3c** and **6** by thin layer chromatography. A pure sample of **3c** was obtained by recrystallization from acetone–hexane and repeated crystallization from ethanol; white needles, mp 204–210° dec; ultraviolet maxima: 248 mμ (ε 11,200) and 290 mμ (ε 2000).

Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93. Found: C, 66.48; H. 5.88.

b. From 5b. A mixture of 1.0 g (3.14 mmoles) of the 5H-benzodiazepine **5b**, 0.7 g of lithium aluminum hydride, and 100 ml of tetrahydrofuran was refluxed for 1 hr. The excess lithium aluminum hydride was decomposed with 25 ml of ethyl acetate, 50 ml of 10% sodium bicarbonate solution was added, and the tetrahydrofuran removed *in vacuo*. To the residue was added 100 ml of methylene chloride and 50 ml of water, the mixture was filtered, and the methylene chloride layer was separated and dried over sodium sulfate. The residue left on concentration of the methylene chloride was crystallized from ether to give 0.3 g of a mixture, mp 150–170° dec. Two recrystallizations from ethyl acetate gave white prisms, mp 202–206° dec, identified by infrared spectrum as **3c**.

c. From 5c. A solution of 10 g of **5c** in 500 ml of dry tetrahydrofuran was heated under reflux for 0.5 hr with 2 g of lithium aluminum hydride. The mixture was cooled and excess lithium aluminum hydride was decomposed with ethyl acetate and aqueous sodium bicarbonate. The residue after removal of the inorganic material by filtration through alumina and concentration of the filtrate *in vacuo* gave 7 g of a solid mixture of isomers on trituration with ether. Recrystallization from ethanol gave 1.6 g of the isomer **3c**, mp 202–208° dec, identified by infrared spectrum.

7-Chloro-5-phenyl-5H-1,4-benzodiazepine 4-Oxide (5a). A solution of 4 g (14.8 mmoles) of **4a** in 200 ml of toluene was heated under reflux for 40 min. The toluene was removed *in vacuo*, and the residue was crystallized from ether–petroleum ether to give 3.0 g (75%) of **5a**, mp 151–158°. An analytical sample was obtained as yellow prisms, mp 157–158.5°, by recrystallization from ethanol; ultraviolet maxima: 239 mμ (ε 16,600), 285 (inflection) (4400), 322 (7400), and 350 (inflection) (4800); nmr spectrum (DMSO): four multiplets centered at δ 7.2.

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10. Found: C, 66.41; H, 4.23.

7-Chloro-3-chloromethyl-5-phenyl-5H-1,4-benzodiazepine 4-Oxide (5b). A solution of 10 g (31.4 mmoles) of **4b** in 50 ml of dimethyl sulfoxide was heated on the steam bath for 15 min, at which time the solution began to darken appreciably. After the mixture had been cooled, it was diluted with 500 ml of water and 500 ml of ether. The phases were separated, and the aqueous phase was extracted with 250 ml of ether. The combined etheral extracts were washed with 250 ml of water and dried over sodium sulfate. The soluton was concentrated *in vacuo* to leave 9.5 g of residue which crystallized from ether to give 7.5 g (75%) of **5b**, mp 120–130° dec. The analytical sample was obtained as yellow prisms by two recrystallizations from ethyl acetate, mp 125–128° dec; ultraviolet spectrum: 245 mμ (ε 17,000) and 320 mμ (ε 6500); nmr spectrum (DMSO): singlet at δ 4.72 (2 H), multiplet at δ 7.5 (*ca.* 10 H).

Anal. Calcd for $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79. Found: C, 60.32; H, 3.64.

7-Chloro-3-methyl-5-phenyl-5H-1,4-benzodiazepine 4-Oxide (5c). a. From 1c. To a suspension of 96.3 g (0.3 mole) of 6-chloro-2-chloromethyl-1,2-dihydro-2-methyl-5-phenylquinazoline 3-oxide (**1c**) in 3 l. of ether was added, in portions, 33.6 g (0.3 mole) of potassium *t*-butoxide. The mixture was stirred at room temperature for 5 hr and then filtered through Celite. Thin layer chromatography of the reaction mixture at this point indicated the presence of the 3H-benzodiazepine **9**. a small amount of **5c**, and a major amount of a third product which is considered to have been **4c**. Vacuum distillation of the filtrate (hot bath) gave a residue which was crystallized from ether to give 60 g of solid. Recrystallization from ethyl acetate gave 36 g (42%) of **5c**, mp 165–175° dec. Further recrystallization from methylene chloride–hexane gave pale yellow prisms, mp 169–170° dec; ultraviolet maxima at 236 mμ (ε 17,800), 280 mμ (ε 4400), and 324 mμ (ε 6800); nmr spectrum (DMSO): singlet at δ 2.17 (3 H), four multiplets at δ 7.4 (*ca.* 10 H).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.48; H, 4.60; Cl, 12.45. Found: C, 67.58; H, 4.52; Cl, 12.55.

b. From 9. A solution of 1 g (3.5 mmoles) of **7** in 200 ml of chloroform was stirred with 10 g of active manganese dioxide for 1.5 hr. The manganese dioxide was removed by filtration, and the filtrate was concentrated *in vacuo* to leave 1.3 g of tar which was crystallized from ether to give 0.6 g of tan solid, mp 163° dec. Recrystallization from ethyl acetate gave 0.4 g (40%) of **5c**, mp 167–170° dec, identified by mixture melting point and infrared spectrum.

7-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-1,4-benzodiazepin-4-ol (6). To a suspension of 4.8 g (16.8 mmoles) of 7-chloro-3-methyl-5-phenyl-5H-1,4-benzodiazepine 4-oxide (**5c**) in 250 ml of methanol was added 2 g (22.4 mmoles) of tetramethylammonium borohydride, and the mixture was stirred at room temperature for 3 hr. Dilution with 100 ml of water gave 3.7 g of solid, mp 175–195° dec, which thin layer chromatography indicated was a mixture of **3c** and **6**. Recrystallization from ethyl acetate gave 1.6 g (25%) of **6**, mp 180–195° dec. A further recrystallization from ethyl acetate gave colorless prisms, mp 185–200° dec.

Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.53; H, 5.93. Found: C, 66.36; H, 6.01.

Oxidation of 7-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-1,4-benzodiazepin-4-ol (6) with Mercuric Oxide. A solution of 10.5 g (36.4 mmoles) of **6** in 500 ml of acetone containing 10% water was stirred for 5 hr at room temperature with 11.3 g (52 mmoles) of yellow mercuric oxide. The mixture was filtered and, after removal of solvent *in vacuo* from the filtrate, the residue

was crystallized from methanol to give 7 g of crude **9**. Recrystallization from methanol gave colorless prisms, mp 170–176° dec; ultraviolet maxima at 243 mμ (ε 15,800), 267 mμ (sh) (ε 7000), and 322 mμ (ε 3200); nmr spectrum (DMSO): singlet at δ 2.08 (3 H), multiplet at δ 3.4 (2 H), multiplet at δ 7.1 (*ca.* 10 H).

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27. Found: C, 66.87; H, 5.05.

From the first mother liquor there was obtained, on concentration *in vacuo*, 1.1 g (10%) of crude **10**, mp 170–204° dec. Recrystallization from ethyl acetate gave yellow prisms, mp 200–203°; ultraviolet maxima at 240 mμ (ε 25,400), 264 (16,800), 302 (9300), and 380 (5200); nmr spectrum (DMSO): doublet at δ 1.3 (3 H), multiplets at δ 3.7 (2 H), 4.4 (1 H), and 7 (9 H).

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27. Found: C, 67.35; H, 5.46.

Oxidation of the other stereoisomer **3c** in a similar manner gave a mixture of the same two products in which the isomer **10** predominated as indicated by thin layer chromatography.

Reduction of 7-Chloro-2,3-dihydro-3-methyl-5-phenyl-1H-1,4-benzodiazepine 4-Oxide (10) to 7-Chloro-2,3-dihydro-3-methyl-5-phenyl-1H-1,4-benzodiazepine. A mixture 2.4 g (8.36 mmoles) of **10**, 25 ml of chloroform, and 5 ml of phosphorus trichloride was heated under reflux for 1 hr. The reaction mixture was cooled and poured into 100 ml of 3 *N* sodium hydroxide solution containing 100 ml of ice. The mixture was further diluted with 100 ml of methylene chloride, and the phases were separated. The aqueous phase was extracted twice with 50 ml of methylene chloride and the combined organic phases were washed with 100 ml of 10% sodium bicarbonate solution and dried over sodium carbonate. The residue left on removal of solvent was dissolved in ether and filtered through 50 g of alumina. Concentration of the first 200 ml of eluate gave 1.1 g (48%) of 7-chloro-2,3-dihydro-3-methyl-5-phenyl-1H-1,4-benzodiazepine, mp 124–126°, which was identified with an authentic sample[9] by mixture melting point and infrared spectrum.

7-Chloro-2-methyl-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (7).

a. A mixture of 6.4 g (20 mmoles) of 6-chloro-2-chloromethyl-1,2-dihydro-2-methyl-4-phenylquinazoline 3-oxide (**1c**), 200 ml of ethanol, and 20 ml of 1 *N* sodium hydroxide was heated under reflux for 1 hr. The solution was then diluted with 500 ml of water and cooled to give 3.98 g (78%) of crude product, mp 164–168° dec. Recrystallization from ethanol gave colorless needles, mp 163–165° dec; ultraviolet maxima at 222 mμ (ε 28,000), 278 mμ (ε 16,800), and 307 (inflection) mμ (ε 9300); nmr spectrum ($CDCl_3$): singlet at δ 2.5 (3 H), singlet at δ 4.43 (2 H), multiplet at δ 7.4 (*ca.* 8 H).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.48; H, 4.60. Found: C, 67.61; H, 4.74.

b. By Oxidation of 8. A solution of 2.0 g (7 mmoles) of **8** in 100 ml of chloroform was stirred overnight at room temperature with 10 g of activated manganese dioxide. The manganese dioxide was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from ethanol to give 0.68 g (34%) of **7**, mp 167–169° dec, which was identified by mixture melting point and infrared spectrum.

Hydrolysis of 7-Chloro-2-methyl-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (7) to 2-Amino-5-chlorobenzophenone. A solution of 2.0 g (7 mmoles) of **9** in 25 ml of concentrated hydrochloric acid was kept at 25° for 2.5 hr and then poured into 300 ml of ice water. The precipitate was collected. The mother liquor was neutralized with solid sodium bicarbonate and extracted with three 50-ml portions of ether. The solid collected above and 0.2 g of charcoal were added to the ethereal extracts which were then dried over magnesium sulfate and evaporated to leave 1.5 g of a yellow solid. Recrystallization from ether–hexane by boiling off the ether gave a yellow solid, mp 88–95°. An ether solution of this material was filtered through 10 g of alumina and evaporated to leave 0.97 g (4.2 mmoles) of 2-amino-5-chlorobenzophenone, mp 94–97°, undepressed on addition of authentic material. The infrared spectra were also identical.

7-Chloro-2,3-dihydro-2-methyl-5-phenyl-1H-1,4-benzodiazepine 4-Oxide (8). A solution of 35 g (0.124 mole) of 7-chloro-2-methyl-5-phenyl-3H-1,4-benzodiazepine 4-oxide (**7**) in 750 ml of warm methanol was cooled in an ice bath to below 10°. After 7.5 g (0.23 mole) of sodium borohydride had been added, the mixture was stirred in an ice bath for 1 hr. The mixture was neutralized with acetic acid and concentrated *in vacuo* to a small volume. After 48 hr, 33.1 g (94%) of solid, 195–202°, was collected and washed with water. This gave, on recrystallization from ethanol, 26.6 g (75%) of **8**, mp 200–203°. An analytical sample was obtained as off-white prisms, mp 200–202.5°, by three recrystallizations from ethanol; ultraviolet maxima at 240 mμ (ε 26,000), 265 (17,500), 305 (9500), and 380 (4200); nmr spectrum ($CDCl_3$): doublet at δ 1.33 (3 H), multiplet at δ 4.2 (3 H), and multiplet at δ 7.2 (*ca.* 9 H).

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27. Found: C, 66.90, 66.95; H, 5.61, 5.38.

7-Chloro-1,2-dihydro-2-methyl-5-phenyl-3H-1,4-benzodiazepine (11).

a. Reduction of 7-Chloro-2,3-dihydro-3-methyl-5-phenyl-1H-1,4-benzodiazepine 4-Oxide (10) with Phosphorus Trichloride. A solution of 6.1 g (21.5 mmoles) of **8** and 7 ml (80 mmoles) of phosphorus trichloride in 150 ml of chloroform was heated under reflux for 0.5 hr in the presence of 12 g of anhydrous sodium carbonate. The reaction mixture was poured into a mixture of 350 ml of 10% sodium carbonate solution and 150 g of ice and extracted with two 125-ml portions of methylene chloride. The combined organic extracts were washed with 50 ml of 10% sodium carbonate solution and with 100 ml of brine and dried (sodium sulfate). The residue, left on concentrating the solution *in vacuo*, was dissolved in methylene chloride and filtered through 100 g of alumina. The oil eluted with 250 ml of methylene chloride was crystallized from ether to give 2.7 g (*ca.* 50%) of crude **11**, mp 143–147°. An analytical sample was obtained as off-white prisms, mp 146–147.5°, by three recrystallizations from ethyl acetate; ultraviolet maxima at 231 mμ (ε 25,500) and 373 mμ (ε 3000).

Anal. Calcd for $C_{16}H_{15}ClN_2$: C, 70.60; H, 5.58. Found: C, 70.56; H, 5.21.

b. Reduction of 7-Chloro-2-methyl-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (7) with Raney Nickel. A suspension of 28.5 g (0.1 mole) of **7** in 400 ml of ethanol was hydrogenated at atmospheric pressure and room temperature with 64.5 g of wet Raney nickel until 5.5 l. of hydrogen was absorbed (2 molar equiv requires 4.8 l.). The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residual red oil (31.4 g) was dissolved in methylene chloride, and the solution was filtered through 300 g of alumina using 500 ml of methylene chloride as eluent. The residue obtained on evaporation of the methylene chloride solution crystallized on treatment with hexane to give 14 g (52%) of crude **11**, mp 135–142°. Two recrystallizations from ethyl acetate raised the melting point to 144–147°.

c. From 7-Amino-1,2-dihydro-2-methyl-5-phenyl-3H-1,4-benzodiazepine (12). A solution of 2.21 g (8.8 mmoles) of **12** in 20 ml of 6 *N* hydrochloric acid was cooled below 0° in an ice–salt bath and treated with 8.8 ml of 1 *N* sodium nitrite solution. This mixture was stirred in the cold for 15 min and then poured into a solution of 2.5 g of cuprous chloride in 20 ml of 7.5 *N* hydrochloric acid which had been cooled to 10°. This mixture was allowed to warm to 20° in 0.5 hr, warmed to 30–40° for 2 hr, and then left at room temperature for 2 hr. The mixture was diluted with 150 g of ice, neutralized with about 45 ml of concentrated ammonium hydroxide, and extracted with 300 ml of methylene chloride in three portions. The methylene chloride extracts were washed with 100 ml of water and with 100 ml of brine, and dried over sodium sulfate. The methylene chloride solution was concentrated to leave a residue of 2.7 g which was dissolved in methylene chloride and filtered through 30 g of alumina, using a total of 200 ml of methylene chloride to elute the alumina. Concentration of the solution left 1.48 g of red oil which was dissolved in ether and filtered through 40 g of alumina. The material eluted from the alumina with ether and 25% methylene chloride–ether crystallized from hexane to give 0.97 g (40%) of **11**, mp 141–146°. Recrystallization from ethyl acetate–hexane yielded 0.6 g, mp 145–146°, which gave no depression on admixture of **11** prepared as described above. The infrared and ultraviolet spectra were also identical.

7-Amino-1,2-dihydro-2-methyl-5-phenyl-3H-1,4-benzodiazepine (12). A suspension of 4.72 g (15.9 mmoles) of 1,2-dihydro-2-methyl-7-nitro-5-phenyl-3H-1,4-benzodiazepine (**13**) in 100 ml of ethanol was hydrogenated at room temperature and atmospheric pressure with 7.4 g of wet Raney nickel. The hydrogenation was stopped after 105% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue when treated with ether–hexane gave 3.92 g (92%) of crystalline material, mp 185–193° dec, which was recrystallized from ethyl acetate to give 2.2 g (51%) of **12**, mp 192–196° dec. An analytical sample formed yellow-brown needles, mp 190–194° dec. It was obtained by filtering a solution in methylene chloride through alumina and recrystallizing the residue, after removal of the solvent, from ethyl acetate–hexane.

Anal. Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82. Found: C, 76.66; H, 6.37.

2-Methyl-7-nitro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine (13). The residue left after separation of the 3-methyl isomer[9] was treated with methanolic hydrogen chloride and ether and fractionally crystallized to yield the hydrochloride of **11**, mp 276–277°, in 2% yield. The free base was obtained by ether extraction of an aqueous solution of the hydrochloride which had been made basic. The residue left after concentrating the dried extract was recrystallized from ether to give **13** as yellow prisms, mp 152–153°.

Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38. Found: C, 68.24; H, 5.71.

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Alkyl Migration to Electron-Deficient Nitrogen

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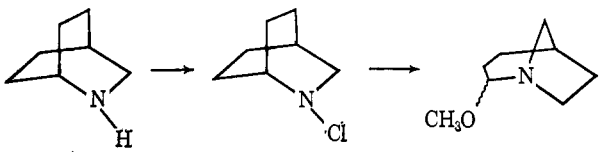
Abstract: Although aryl migration has been well documented in the rearrangement of aryl-substituted N-chloramines, the lack of alkyl migration has remained an anomaly. We have shown that such alkyl migrations can occur in high yield. The N-chloro derivatives of 2-azabicyclo[2.2.2]octane (**1**) and 6-azabicyclo[3.2.1]octane (**2**) have been prepared through the reaction of **1** and **2** with *t*-butyl hypochlorite. The N-chloro derivatives, **3** and **4**, respectively, rearrange with alkyl migration to nitrogen under solvolytic conditions in the presence of silver nitrate. When methanol was the solvent, **3** rearranged to 2-methoxy-1-azabicyclo[3.2.1]octane (**5**) in greater than 60% yield. By comparison, **4** gave the ring cleavage product, 3-(2,2-dimethoxyethyl)piperidine (**6**), on reaction with methanolic silver nitrate. The formation of **6** also requires alkyl migration to nitrogen. The silver ion catalyzed and thermal decompositions of **3** and **4** are compared.

Although the Stieglitz rearrangement of tritylhydroxylamines and the related rearrangement of aryl-substituted N-chloramines have been investigated in some detail, it have been noted[2] that there are no existing examples of such rearrangements involving alkyl migration. In fact, the failure of N-methyl-N-chlorotritylamine to rearrange has been used as evidence for a mechanism which involves initial loss of a proton from the amine followed by loss of chloride ion[2,3] as shown below. It was also proposed[2] that

$$Ar_3\overset{H}{\overset{|}{C}}NCl \xrightarrow{-H^+} Ar_3\bar{C}\overset{+}{N}Cl \xrightarrow{-Cl^-} Ar_2C{=}NAr$$

with N,N-dichloramines the initial step was loss of positively charged chloride. The results discussed below demonstrate: (1) that alkyl migration can occur in rearrangements of N-chloramines, (2) that N,N-disubstituted chloramines do undergo rearrangement and, consequently, (3) that the mechanism of N-chloramine rearrangements can involve loss of chloride anion as the initial step.

Since bicyclic molecules are known to undergo rearrangement with particular ease, our initial efforts in the study of N-chloramine rearrangements have been restricted to the azabicyclic area. Thus, 2-azabicyclo[2.2.2]octane (**1**) was prepared according to the method of Schneider and Dillman[4] and subsequently converted to 2-chloro-2-azabicyclo[2.2.2]octane (**3**) with *t*-butyl hypochlorite. Refluxing of **3** with a methanolic solution of silver nitrate for 2 hr gave a 60% yield of 2-methoxy-1-azabicyclo[3.2.1]octane (**5**).[5]



1 **3** **5**

Compound **5** was a clear, colorless liquid which possessed unusual stability for an α-amino ether. It was completely resistant to acid hydrolysis under conditions which normally cause rapid hydrolysis of α-amino ethers.[6–8] Furthermore, it was stable to reductive conditions such as lithium aluminum hydride described by Eliel and Daignault[9] for the reductive cleavage of α-amino ethers. The unusual stability of **5** may be due to the inability of **5** to yield an intermediate with a double bond to the bridgehead, which would be in violation of Bredt's rule.

In view of the failure of **5** to undergo reactions normally associated with α-amino ethers, it was deemed desirable to prove unequivocally that **5** had the proposed structure. This was accomplished by partial degradation, coupled with synthesis of the degradation products.

The rearrangement product, **5**, was converted to the quaternary methiodide, **7a**, followed by passage of a methanolic solution of **7a** through IRA 400 ion-ex-

(1) Esso Fellow, summer 1964; American Cyanamid Fellow, 1964-1965; Goodyear Foundation Fellow, 1965–1966.
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