THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 21

OCTOBER 20, 1972

Quinazolines and 1,4-Benzodiazepines. LIV.[1] The Base-Catalyzed Rearrangement of 2-Dimethylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-Oxide

NORMAN W. GILMAN,* J. F. BLOUNT, AND LEO H. STERNBACH

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received March 8, 1972

The reaction of 2-dimethylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-oxide (**2**) with the lithium anion of dimethyl sulfoxide followed by quenching with water has been shown to lead to the indoles **3** and **4** and the quinoline **5**. If the reaction mixture is treated with dimethyl sulfate prior to quenching with water, five products are formed. These are the indoles **6**–**9** and the quinoline **5**. The structures of the products were established by spectral data (**3**, **4**, **8**), single-crystal X-ray analysis (**6**, **7**), and by an independent synthesis (**5**, **9**). A reasonable mechanism is proposed which leads to a common intermediate C from which all of the various products can be derived.

The synthesis of 2-methylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-oxide (**1**) has been described by Sternbach and Reeder.[2,3] Subsequently, the treatment of **1** with sodium hydride and methyl iodide was shown to lead to the dimethylamino analog **2**.[4] As was reported, we have found that the methylation reaction proceeds smoothly and in high yield. However, no results have appeared on the further methylation of **2**.

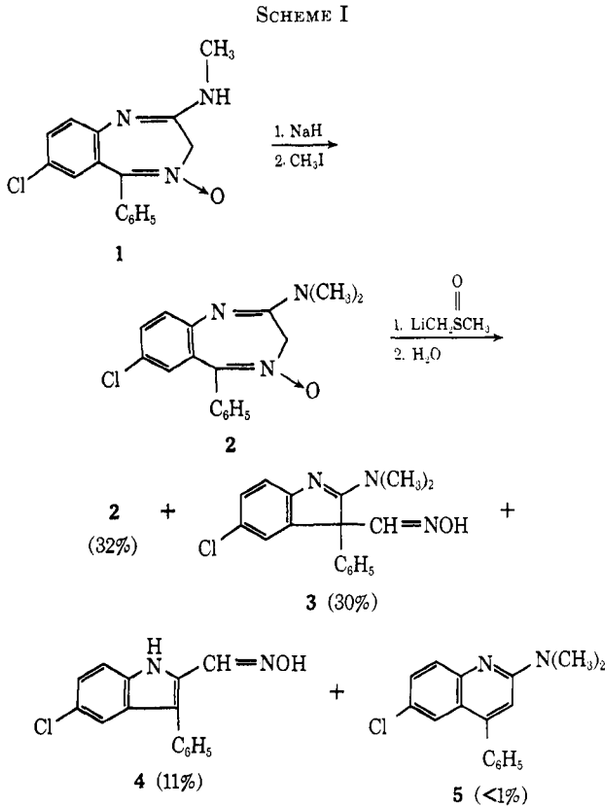
We now wish to report that the reaction of **2** with a strong base followed by a methylating agent does not lead to a simple methylated derivative of **2**, but instead gives only products resulting from a rearrangement.

In order to establish whether this rearrangement was due solely to the base or to a combination of base and methylating agent, we first treated **2** with base only. After treating **2** with the lithium anion of dimethyl sulfoxide (prepared by reaction of dimethyl sulfoxide with *n*-butyllithium) and quenching with water, we found that profound changes had occurred. The isolated reaction products were the indoles **3** and **4** and the quinoline **5**, as outlined in Scheme I. The yields shown are for isolated recrystallized products.

The indole **3** was isolated by trituration of the crude reaction mixture (after work-up) with methylene chloride, and then the products **4** and **5** were separated by preparative thick layer chromatography.

In a reaction, concerned with the methylation, compound **2** was treated with the lithium anion of dimethyl sulfoxide followed by the addition of dimethyl sulfate. The reaction with base yields a deep purple-black solution which turns pale yellow upon addition of dimethyl sulfate in an exothermic reaction. In contrast to the reaction which was quenched with water, the use of dimethyl sulfate as a methylating (and quenching) agent leads to the five rearranged products **5**–**9**. The yields for isolated, purified compounds, which were

SCHEME I



(1) Part LIII: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 2968 (1971).

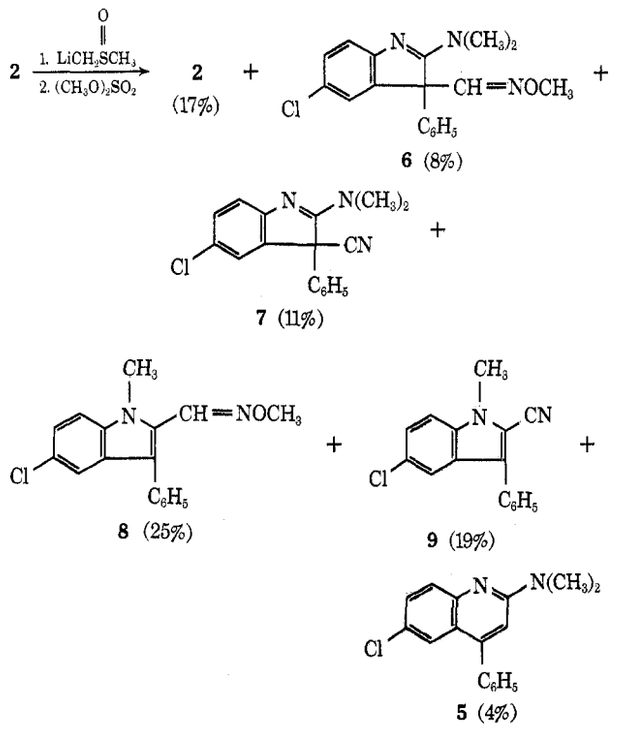
(2) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(3) The generic name is chlordiazepoxide. This compound, as the hydrochloride, is the active component of Librium.

(4) S. Farber, H. M. Wuest, and R. I. Meltzer, *J. Med. Chem.*, **7**, 235 (1964).

determined from one experiment, are given in Scheme II. In repetitive runs, it was sometimes possible to

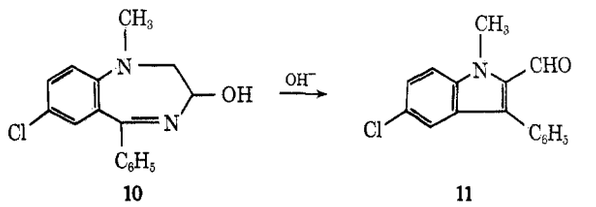
SCHEME II



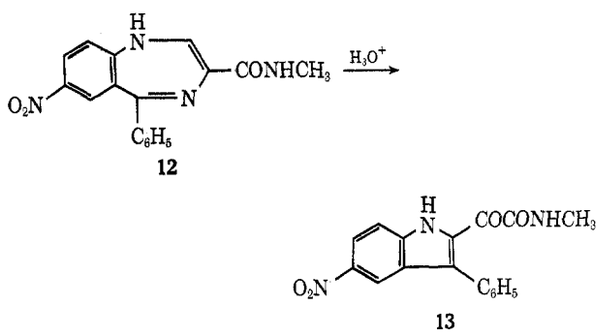
crystallize the crude reaction mixture directly from methanol to yield either **6** or **8**. In most cases, **6** was obtained preferentially but, in all experiments, thin layer chromatography showed the presence of all five products. The relative yields of the products were not determined in every experiment.

As is shown in Schemes I and II, the quinoline **5** is formed in very low yield in both cases. The product **3**, which was obtained by quenching the reaction with water, appears to be related to the indoles **6** and **7**. The methylation of the oxime anion of **3** (before quenching with water) with dimethyl sulfate would yield the indole **6**, which could lose methanol to give **7**. In a similar manner, the oxime anion of **4** upon methylation and loss of methanol would give the indoles **8** and **9**.[5,7]

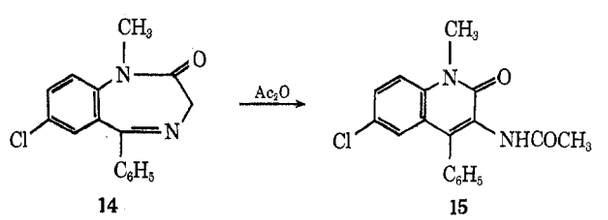
Mechanisms.—Although numerous rearrangements of 1,4-benzodiazepines to other heterocyclic systems have been reported,[8] none of these exactly parallels the complex rearrangement reported for **2**. The formation of indoles was observed in two cases. 5-Chloro-1-methyl-3-phenylindole-2-carboxaldehyde (**11**) was formed from the base treatment of **10**.[9] In an acid-



catalyzed rearrangement, the benzodiazepine **12** has been shown[10] to lead to the indole **13**.



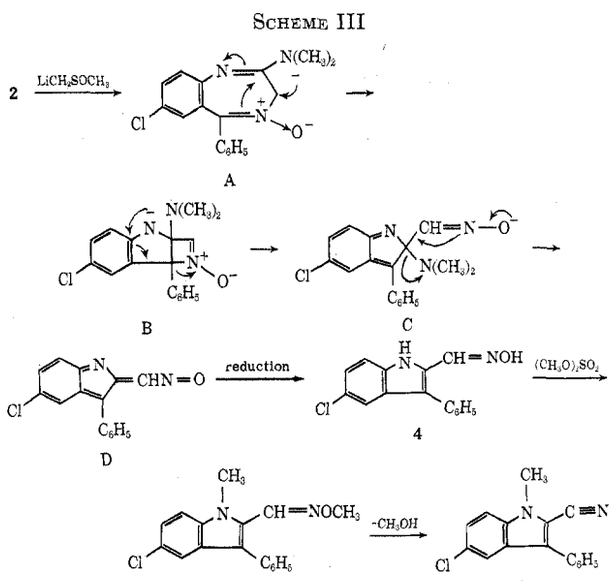
The formation of the quinoline **15** from the benzodiazepine **14** has been reported but with the retention of



the 4-nitrogen.[11] No reports have appeared on the formation of a quinoline from a benzodiazepine in which the 4-nitrogen has been lost, as is the case in the rearrangement of **2** to give **5**.

A plausible mechanism for the base-catalyzed rearrangement of **2** into the indoles **4**, **8**, and **9** is shown in Scheme III.

SCHEME III



(5) The conversion of either **6** to **7** or **8** to **9** was not verified experimentally, although, on the basis of similar reactions, the loss of methanol from either **6** or **8** does have precedence.[6]

(6) For example, the treatment of oximes with mesyl chloride followed by base treatment has been reported to lead to nitriles: T. J. Bentley, J. F. McGhie, and D. H. R. Barton, *Tetrahedron Lett.*, 2497 (1965).

(7) The ratios of the reaction products **3** to **4** and **6** + **7** to **8** + **9** differ in Schemes I and II. This was not further explored, since the data in each case are based on a single experiment. Slight variations in the reaction conditions and in the work-up could well account for these differences.

(8) For a review see R. Ian Fryer, *J. Heterocycl. Chem.*, **9**, 747 (1972).

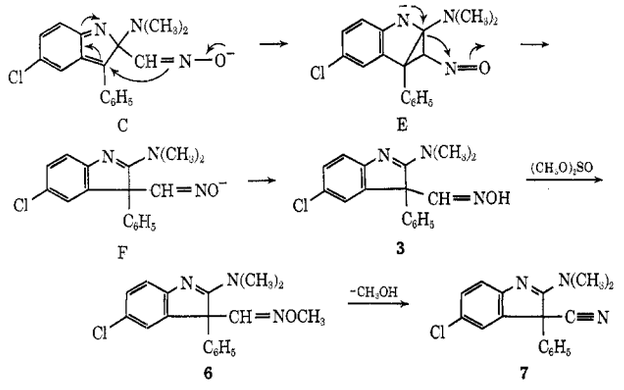
(9) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **29**, 1621 (1964).

(10) R. Ian Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

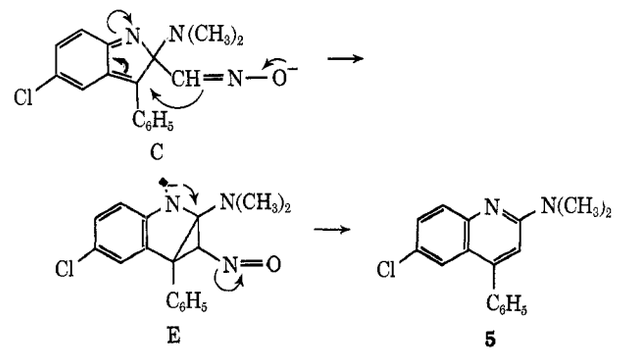
(11) R. Ian Fryer and L. H. Sternbach, *ibid.*, **30**, 524 (1965).

Removal of the proton at the 3 position would give the anion A. Ring closure to B occurs by nucleophilic attack on the amidine rather than the imine–oxide double bond. This might be expected to occur, since the amidine double bond should be more electrophilic. Ring opening of B gives an intermediate C, from which all of the various products can be derived (see also Schemes IV and V). The loss of the dimethyl-

SCHEME IV



SCHEME V



amino group from C would give D which has the gross structure of the products **4**, **8**, and **9**. The exact nature of the reducing agent responsible for the conversion of D into **4** is not known. In the presence of dimethyl sulfate, **4** is methylated to yield **8**, which *via* loss of methanol yields the nitrile **9**.

The formation of **3**, **6**, and **7** also proceeds through the intermediate C, as shown in Scheme IV.

The formation of the cyclopropane intermediate E results from the cyclization of the azomethine bond in C to the 3 position of the indole. Ring opening of E would then give F, which upon protonation yields **3**. The methylation of **3** with dimethyl sulfate gives **6**, which can lose methanol to give **7**.

The formation of the quinoline **5** can also arise from intermediate C, as shown in Scheme V.

The cyclization of C to E proceeds as shown and the quinoline **5** would result from cleavage of the bond bridging the six-membered ring in E with simultaneous loss of nitrous oxide.

Although other possible mechanisms can be envisioned for the rearrangement of **2**, the transformations shown in the preceding schemes are attractive because all of the observed products can be derived from a common intermediate, namely C.

Structure Proof of the Products.—The structures of **6** and **7** were indicated by microanalyses and spectral data, and were confirmed by single-crystal X-ray crystallographic analyses (see crystallography section).

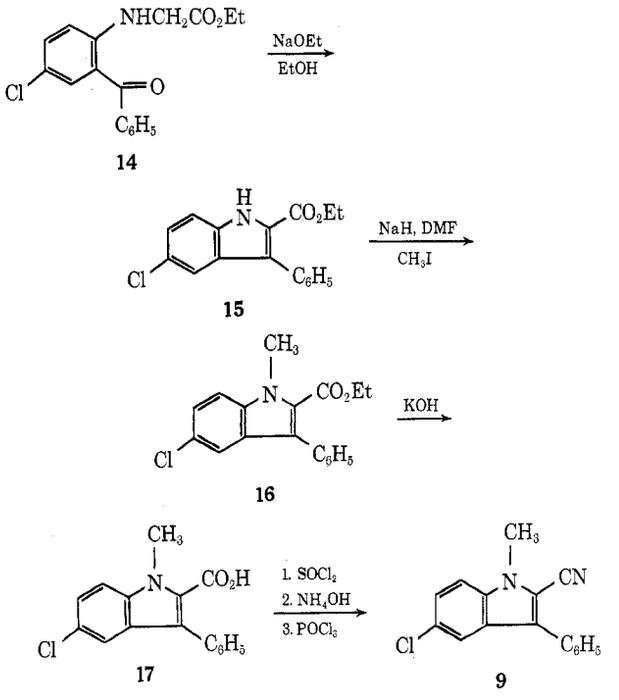
The structures of **5** and **9** were suggested by spectral data and verified by independent synthesis.

Compounds **3**, **4**, and **8** were assigned the structures shown on the basis of microanalyses and spectral data in analogy with the previously determined structures of compounds **6** and **9**. All of the appropriate data for these compounds appear in the Experimental Section.

Synthesis of 5.—The known 2,6-dichloro-4-phenylquinoline[12] was treated with dimethylamine to give 6-chloro-4-phenyl-2-dimethylaminoquinoline (**5**), whose physical properties and spectra were identical with those of the compound which was isolated from the rearrangement of **2**.

Synthesis of 9.—Compound **14** was transformed into **9** as outlined in Scheme VI.

SCHEME VI



The ring closure of **14**[13] to the known indole **15** proceeded smoothly in ethanol with sodium ethoxide as the condensing agent.[14]

The indole **15** was methylated in DMF by treatment with sodium hydride followed by the addition of methyl iodide.[15]

The resulting ester **16** was then converted to the nitrile **9** as described in the literature.[15] All physical properties of this compound were identical with those of the nitrile isolated from the rearrangement of **2**.

Crystallography.—Crystals of **6** are orthorhombic, space group $P2_12_12_1$, with $a = 10.698$ (2), $b = 10.252$ (2), $c = 15.259$ (3) Å, $Z = 4$, $d_{obsd} = 1.30$, $d_{calcd} = 1.299$ g cm^{-3}, $\mu = 20.8$ cm^{-1}. Crystals of **7** are triclinic, space

(12) A. E. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **3**, 359 (1966).

(13) G. A. Archer and L. H. Sternbach, U. S. Patent 3,317,518 (1966); *Chem. Abstr.*, **65**, 16,988 (1966).

(14) For two different synthesis of **15**, see (a) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); (b) S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.*, **19**, 263 (1971).

(15) Compound **16** has also been prepared directly by a Fischer indole synthesis: H. Yamamoto, *et al.*, South African Patent 68,003,041 (1969); *Chem. Abstr.*, **71**, 124519m (1969).

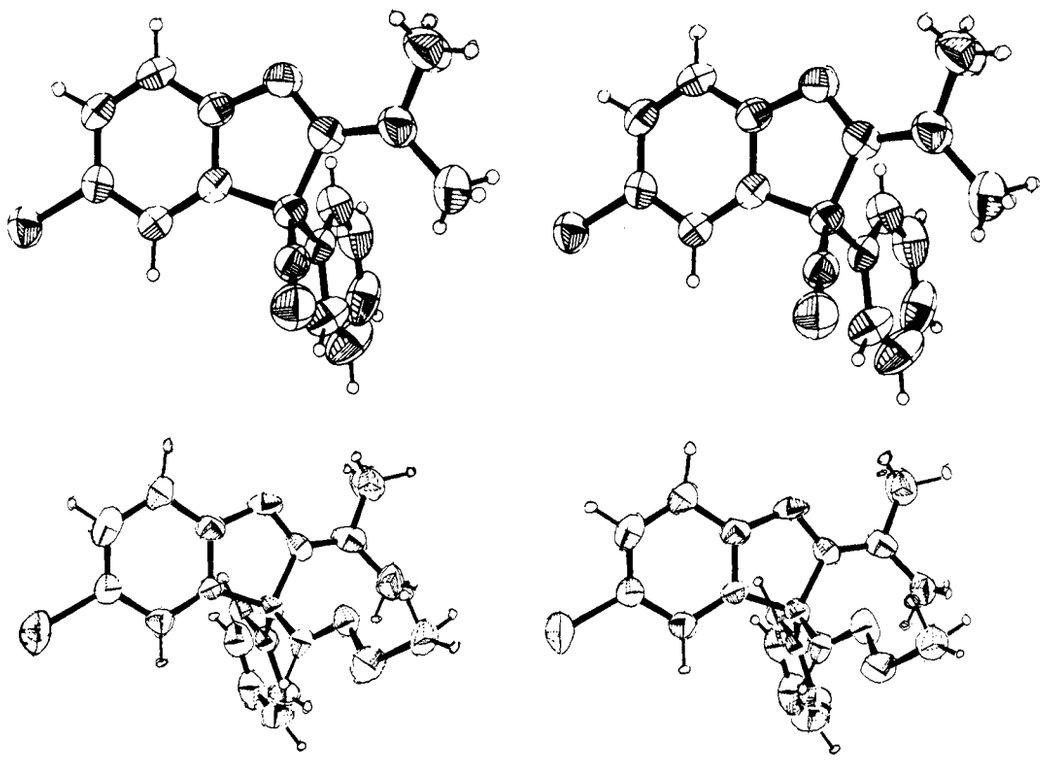


Figure 1.—Stereodrawings of **7** (upper) and **6** (lower). The ellipsoids represent the thermal motions of each atom at the 50% probability level. The two molecules are shown in slightly different orientations in order to reduce overlap of the atoms.

group $P\bar{1}$, with $a = 10.758$ (3), $b = 11.899$ (6), $c = 12.423$ (3) Å, $\alpha = 88.91$ (3), $\beta = 72.41$ (3), $\gamma = 83.08$ (3)°, $Z = 4$, $d_{obsd} = 1.30$, $d_{calcd} = 1.305$ g cm^{-3}, $\mu = 22.0$ cm^{-1}. Intensity data for both compounds were collected on a Hilger-Watts Model Y290 four-circle diffractometer by a moving crystal-moving detector method. Nickel filtered Cu K_α radiation and pulse height discrimination were used. The approximate dimensions of the crystals used for data collection were 0.05 × 0.05 × 0.35 mm (**6**) and 0.25 × 0.25 × 0.20 mm (**7**); no absorption corrections were made. Of the 1801 accessible independent reflections of $\theta > 70°$, only 724 had intensities significantly greater than background and these data were used for the structure analysis of **6** (there were 3920 observed data out of a total of 5040 reflections with $\theta < 70°$ for **7**).

Both structures were solved by the heavy atom method starting with Cl coordinates determined from sharpened Patterson functions. The hydrogen atoms were located from difference Fouriers calculated after partial refinement of the structures. The structure of **6** was refined by full-matrix least squares and the structure of **7** was refined by clock-diagonal least squares with the matrix partitioned into nine blocks. In both cases all atoms except hydrogen were assigned anisotropic thermal parameters. The hydrogen parameters were held fixed for **6** but were refined for **7**.

The quantity minimized was

$$\Sigma w \, ||F_o| - |F_c||^2$$

where $w = 1/(a + |F_o| + c|F_o|^2)$, $a = 13.3$, $c = 0.016$ Å for **6**, $a = 4.5$, $c = 0.012$ Å for **7**.

Standard scattering curves were used for Cl, O, N, C,[16] and H.[17] The Cl curve was corrected for the real and imaginary parts of the anomalous scattering.[18] The refinement was stopped when the shifts of all parameters except those of the hydrogens were less than one-third of the corresponding standard deviations. The difference Fouriers based on the final parameters have no features greater than 0.3 e Å^{-3} in magnitude. The final $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ is 0.048 for **6** and 0.041 for **7**.[19]

The bond lengths and angles in the two structures are in agreement with the expected values. In the $-C_\beta-C_\alpha=NOCH_3$ moiety of **6** the distances and angles are $C_\beta-C_\alpha$, 1.547 (13); $C_\alpha=N$, 1.254 (12); N-O, 1.410 (10); O-CH_3, 1.409 (13) Å; $C_\beta-C_\alpha-N$, 120.5 (9); $C_\alpha-N-O$, 108.7 (8); N-O-CH_3, 108.0 (8)°. Average values for the bond angle and lengths in the $C_\alpha-C\equiv N$ moiety of **7** are $C_\alpha-C$, 1.473 (3); $C\equiv N$, 1.140 (3) Å; $C_\alpha-C-N$, 178.4 (3)°. The conformations of the two crystallographically independent molecules in crystalline **7** are nearly identical and thus a stereoview of only one is shown in Figure 1, together with a stereoview of **6**.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. The ir spectra were determined on a Beckman IR-9 spectrometer in chloroform (3% solutions) unless stated otherwise. The nmr spectra were recorded with a Varian A-60 instrument in deuteriochloroform. Absorption values are given in parts per million downfield from tetramethylsilane added as an internal standard. The mass spectra were determined with a CEC 21-110B instrument.

(16) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).

(17) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

(18) D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).

(19) Listings of structure factors, coordinates, and thermal parameters for **6** and **7** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-37-3201. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Separation of 3, 4, and 5 from the Reaction of 2 with $LiCH_2SOCH_3$ Followed by Water Treatment.—To 150 ml of dry dimethyl sulfoxide, under argon, was added 46.5 ml of 1.6 *M* *n*-butyllithium in hexane. After the evolution of H_2 had ceased, 18.8 g (60 mmol) of **2** was added in one portion. The resulting deep purple-black solution was stirred for 35 min and quenched with 500 ml of water. The color immediately reverted to pale yellow. After extraction with three 400-ml portions of CH_2Cl_2, the organic solutions were combined, washed with 15% NaCl, dried ($MgSO_4$), and concentrated to yield 17.5 g of sticky yellow solid. This residue was triturated with 250 ml of hot CH_2Cl_2, cooled, and filtered to give 5.6 g (30%) of **3**. The filtrate was concentrated and the residue was separated by preparative thick layer chromatography [benzene–ethyl acetate (5:1) as eluent] to give 800 mg (0.5%) of **5** as a high R_f band and 3 g (11%) of **4** as a low R_f band. From the origin, 6 g (32%) of starting material was recovered.

5-Chloro-2-dimethylamino-3-phenyl-3*H*-indole-3-carboxaldehyde Oxime (3).—This oxime was obtained as colorless prisms by recrystallization from benzene: mp 222–223.5°; ir ($CHCl_3$) 3500–2000, 1610, 1560, 1462, 1404, 1310 cm^{-1}; nmr δ 2.93 [s, 6 H, $N(CH_3)_2$], 7.01 (m, 3 H, aromatic), 7.30 (s, 5 H, aromatic), 8.25 (s, 1 H, CH=N), 11.22 (s, 1 H, OH); mass spectrum *m/e* 313 (M^+), 296 ($M^+ - OH$).

Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.05, 64.94; H, 5.23, 5.21; N, 13.29, 13.32.

5-Chloro-3-phenyl-2-indolecarboxaldehyde Oxime (4).—The indole was recrystallized from methanol–water to give colorless prisms: mp 204–206°; ir ($CHCl_3$) 3400, 3350–2250 cm^{-1}; nmr δ 7.24–7.73 (m, 9 H, aromatic and CH=N), 11.75 and 12.15 (br s, 2 H, NH and OH); mass spectrum *m/e* 270 (M^+), 253 ($M^+ - OH$).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.72, 66.75; H, 4.13, 4.16; N, 10.41, 10.43.

6-Chloro-2-dimethylamino-4-phenylquinoline (5).—This compound was recrystallized from methanol to give pale yellow needles: mp 93–95°; ir (KBr) 1610, 1600 cm^{-1}; nmr δ 3.06 [s, 6 H, $N(CH_3)_2$], 6.69 (s, 1 H, aromatic), 7.31–7.80 (m, 8 H, aromatic); mass spectrum *m/e* 282 (M^+), 267, 253, 239.

Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.16; H, 5.42, 5.50; N, 9.97, 9.90.

Preparation and Separation of Compounds 5–9 (General Procedure).—To 150 ml of dry dimethyl sulfoxide, under argon, was added 46.5 ml of 1.6 *M* *n*-butyllithium in hexane. The resulting solution was stirred at room temperature for approximately 15 min until the evolution of hydrogen had ceased. Compound **2** (18.8 g, 60 mmol) was then added in one portion and, after 15 min, 6.3 ml (66 mmol) of dimethyl sulfate was added. The solution was stirred for 18 hr at room temperature, then poured into ice water; the mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The residue, which was a mixture of solid and gummy material, was dissolved in CH_2Cl_2 and chromatographed on 200 g of aluminum oxide (Woelm, activity I) to give 14.1 g of crude products (benzene as eluent) and 3.2 g of starting material (17% recovered **2**) as a final fraction. The first fraction was separated into three fractions on 20 × 20 cm silica gel thick layer plates (approximately 500 mg per plate) in chloroform–heptane (1:1).

The high R_f (0.48)[20] fraction yielded, after recrystallization from methanol, 4.5 g (25%) of **8**.

The medium R_f (0.25) fraction gave, after recrystallization from methanol, 3.0 g (19%) of **9**.

The material remaining at the origin was recovered and rechromatographed on thick layer plates, using benzene–ethyl acetate (3:1) as eluent, to give the other three products.

The high R_f material (0.52) gave 1.5 g (8%) of **6** after recrystallization from methanol. The medium R_f (0.26) spot yielded 2.0 g (11%) of **7** after recrystallization from 2-propanol. The low R_f (0.18) band gave 0.7 g (4%) of **5** after recrystallization from methanol.

The total yield of recovered products, including starting material, was 84%.

5-Chloro-2-dimethylamino-3-methoxyiminomethyl-3-phenyl-3*H*-indole (6).—This compound was obtained as colorless prisms from methanol or from benzene–hexane: mp 173–175°; ir ($CHCl_3$) 1610, 1580 cm^{-1}; uv max (EtOH) 220 mμ (ϵ 26,800), 287 (17,450), 295 (16,800), 320 (sh, 4,200); nmr δ 3.00 [s, 6 H, $N(CH_3)_2$], 3.85 (s, 3 H, OCH_3), 6.81 (t, J = 1 cps, 1 H, aromatic), 7.12 (d, J = 2 cps, 2 H, aromatic), 7.30 (m, 5 H, aromatic), 7.95 (s, 1 H, CH=N); mass spectrum *m/e* 327.1184 (M^+), 296.0978 ($M^+ - OCH_3$, theory 296.0955).

Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found: C, 66.23; H, 5.62; N, 12.93.

6 HBr.—The hydrobromide was prepared in the usual fashion and recrystallized from ethanol–ether to give colorless prisms, mp 237–239°.

Anal. Calcd for $C_{18}H_{18}ClN_3O \cdot HBr$: C, 52.89; H, 4.68; N, 10.28. Found: C, 52.90; H, 4.52; N, 10.51.

The free base could be recovered by treatment of the salt with $NaHCO_3$.

5-Chloro-3-cyano-2-dimethylamino-3-phenyl-3*H*-indole (7).—The pure nitrile was obtained as colorless prisms by recrystallization from methanol: mp 166–168°; ir ($CHCl_3$) 2240, 1620 cm^{-1}; Raman (solid) 2240 cm^{-1}; nmr δ 3.08 [s, 6 H, $N(CH_3)_2$], 7.01 (m, 1 H, aromatic), 7.17 (br s, 2 H, aromatic), 7.36 (s, 5 H, aromatic); mass spectrum *m/e* 295 (M^+).

Anal. Calcd for $C_{17}H_{14}ClN_3$: C, 69.04; H, 4.77; N, 14.21. Found: C, 68.89; H, 4.75; N, 14.06.

5-Chloro-1-methyl-2-methoxyiminomethyl-3-phenylindole (8).—The product was obtained as colorless needles by recrystallization from methanol: mp 145–147°; ir ($CHCl_3$) 1610 cm^{-1}; nmr δ 3.97 (s, 3 H, NCH_3 or OCH_3), 4.01 (s, 3 H, NCH_3 or OCH_3), 7.24 (d, J = 1 cps, 2 H, aromatic), 7.38 (s, 5 H, aromatic), 7.59 (t, J = 1 cps, 1 H, aromatic), 8.16 (s, 1 H, N=CH); mass spectrum *m/e* 298.0897 (M^+, theory 298.0873), 267.0695 ($M^+ - OCH_3$, theory 267.0689).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.10, 68.22; H, 5.07, 5.04; N, 9.31, 9.31.

5-Chloro-2-cyano-1-methyl-3-phenylindole (9).—The indole was recrystallized from methanol to give colorless needles: mp 125–127°; ir ($CHCl_3$) 2220 cm^{-1}; nmr δ 3.80 (s, 3 H, NCH_3), 7.04–7.77 (m, 8 H, aromatic); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 71.59, 71.46; H, 4.17, 4.15; N, 10.44, 10.30.

Ethyl 5-Chloro-3-phenylindole-2-carboxylate (15).—To a solution of sodium ethoxide [from 2.53 g (0.11 mol) of sodium] in 400 ml of ethanol was added 32 g (0.1 mol) of **14**. After refluxing for 2 hr (a large amount of precipitate forms) the mixture was poured into a large volume of water and filtered. The solid was recrystallized from methanol to yield 11.3 g (38%) of **15**, mp 173–174° (lit.[14] mp 172–172.5°).

Ethyl 5-Chloro-1-methyl-3-phenylindole-2-carboxylate (16).—To a suspension of 1.47 g of 57% sodium hydride in mineral oil (35 mmol of sodium hydride) in 100 ml of DMF, under argon at room temperature, was added 10 g (33.4 mmol) of **15**. After approximately 20 min, hydrogen evolution had ceased and 6.2 ml (100 mmol) of methyl iodide was added. After stirring for 4 hr at room temperature, the solution was diluted with water and extracted thoroughly with ether. The ether extracts were combined, washed with water, dried ($MgSO_4$), and concentrated to give 10 g (95%) of **16** as a pale yellow solid, mp 82–84° (lit.[15] mp 88–89°). The product was used without further purification.

5-Chloro-1-methyl-3-phenylindole-2-carboxylic Acid (17).—To a solution of 1.85 g (33 mmol) of potassium hydroxide in 100 ml of warm ethanol was added 10 g (32 mmol) of **16** and the solution was refluxed for 45 min. After concentrating *in vacuo*, the residue was dissolved in water, acidified with 3 *N* HCl, and filtered to give 8.7 g (95%) of the acid as an off-white solid, mp 215–218° (lit.[15] mp 211–213°).

5-Chloro-2-cyano-1-methyl-3-phenylindole (9) from 17.—A solution of 1.0 g (3.5 mmol) of **17** in 5 ml of thionyl chloride was refluxed on the steam bath for 15 min and concentrated *in vacuo*. Ammonium hydroxide (10 ml) was added, and the mixture was heated on the steam bath for 20 min, cooled, and filtered to give 800 mg (80%) of the corresponding amide.

The amide was refluxed with 5 ml of phosphorus oxychloride for 10 min. After cooling, the solution was poured over ice, allowed to warm to room temperature, basified with concentrated ammonium hydroxide, cooled, and filtered. The solid so obtained was recrystallized from methanol–water to give 450 mg (60%) of **9**, mp 128–129° (lit.[14] mp 128.5–130.5°). The spectra (ir, nmr, mass spectrum) were identical with those of the product isolated from the rearrangement of **2**.

(20) The R_f values refer to Merck plates. The thick layer separations were done on laboratory-prepared plates on which the products had slightly higher R_f values.

6-Chloro-2-dimethylamino-4-phenylquinoline (5), Prepared from 2,6-Dichloro-4-phenylquinoline.—The dichloroquinoline was prepared according to the procedure of Drukker and Judd.[12] A mixture of 13 g (47.5 mmol) of 2,6-dichloro-4-phenylquinoline, 100 ml of 25% dimethylamine in water, and 50 ml of ethanol was heated in a Parr bomb at 100–110° for 18 hr. After the solution was concentrated to a small volume, the residue was recrystallized from methanol to yield 12.1 g (90%) of **5** as pale yellow needles, mp 98–100°. The spectral data were identical with those for the compound obtained from the rearrangement of **2**.

Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.24; H, 5.50; N, 9.55.

Registry No.—**2**, 3693-14-9; **3**, 35337-03-2; **4**, 35337-04-3; **5**, 31576-98-4; **6**, 35337-06-5; **6** HBr, 35337-07-6; **7**, 35337-08-7; **8**, 35337-09-8; **9**, 24139-18-2.

Acknowledgment.—The authors wish to thank the following members of our Physical Chemistry Department under the direction of Dr. R. Scott: Dr. F. Scheidl for the microanalysis, Dr. T. Williams for the nmr spectra, Mr. S. Traiman for the ir spectra, Dr. W. Benz for the mass spectra, and Dr. V. Toome for the uv spectra. The skillful technical assistance of Mr. G. Walsh is also appreciated. We wish to thank Professor G. Büchi for his interest and many valuable discussions and suggestions.

Reactions of Epimeric 2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines

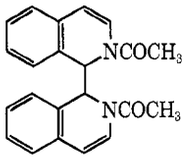
RONALD A. HENRY,* ARNOLD T. NIELSEN, AND DONALD W. MOORE

Chemistry Division (Code 605), Michelson Laboratory, U. S. Naval Weapons Center, China Lake, California 93555

Received April 10, 1972

The title compounds are brominated by NBS to yield epimeric 2,2′-diacetyl-4,4′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines rather than 1,1′-dibromo derivatives as reported previously. Cleavage of the 1,1′ bond characterizes attempts to aromatize these compounds by oxidative methods; *e.g.*, the dibromo derivatives are converted to 4-bromoisoquinoline in 90% yield by 5.3 *N* nitric acid at 30°. *dl*- and *meso*-4,4′-dibenzal-1,1′,4,4′-tetrahydro-1,1′-biisoquinolines are recovered in low yields when the title compounds are heated in ethanol with benzaldehyde and concentrated hydrochloric acid; extensive cleavage of the 1,1′ bond again occurs with the formation of 4-benzal-1,4- (and 3,4-) dihydroisoquinoline. 5,5′-Dinitro- and 5-nitro-1,1′-biisoquinoline are described.

Previously it was reported[1] that both epimers of 2,2′-diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (**1a,b**)

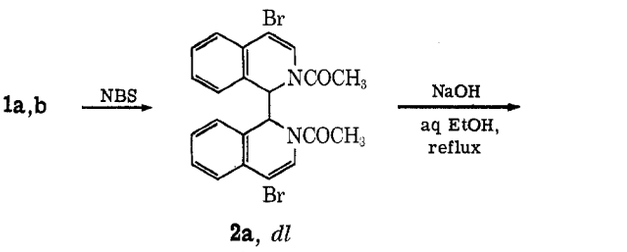


1a, *dl*
b, meso

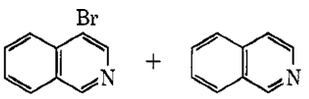
(prepared by the Dimroth reaction from isoquinoline, zinc, and acetic anhydride) and *N*-bromosuccinimide reacted in acetic acid to give epimeric dibromo compounds, $C_{22}H_{18}Br_2N_2O_2$. Alkaline hydrolysis of the latter gave mixtures of isoquinoline and a bromoisoquinoline (approximately equimolar). Based in part on the melting point of the bromoisoquinoline recovered by preparative glc, this compound was considered to be the 1-bromo isomer; the dibromo compounds were then considered to be epimeric 2,2′-diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines.

Subsequent work (mixture melting points, comparison of ir spectra, ^{1}H nmr) has shown that this bromoisoquinoline is actually the 4 isomer. Consequently, the dibromo compounds are reformulated as 2,2′-diacetyl-4,4′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines (**2a,b**). This assignment is confirmed by the proton nmr spectrum[2] on the lower melting, more-soluble, *dl* isomer, **2a**.

Cleavage of the 1,1′ bond with formation of a mixture of isoquinoline and 4-bromoisoquinoline is also observed



2a, *dl*
b, meso



when **2a** and **2b** are oxidized by refluxing nitrobenzene. On the other hand, oxidation of **2a** with 5.3 *N* nitric acid at 30° gives 4-bromoisoquinoline in 90% yield.

Aromatization of **2a** without cleavage of the 1,1′ bond so as to recover 4,4′-dibromo-1,1′-biisoquinoline was attempted by the procedure of Knabe.[3] The latter had demonstrated that laudanosine could be oxidized to *N*-methylpapaverinium and *N*-methyl-3,4-dihydropapaverinium salts by mercuric acetate and disodium ethylenediaminetetracetate in aqueous acetic acid; other oxidation conditions had caused cleavage at the 1-methylene bond. However, even after prolonged heating at 80–85° only partial oxidation of **2a** had occurred; small amounts (<15%) of impure 4-bromoisoquinoline were isolated, suggesting that cleavage was still the preferred route.

The conversion of **1a,b** directly to 1,1′-biisoquinoline or derivatives has been further investigated beyond the results reported previously.[1] Extensive cleavage of the 1,1′ bond again characterizes most of the reactions.

(1) A. T. Nielsen, *J. Org. Chem.*, **35**, 2498 (1970).

(2) ^{1}H nmr for *dl*-2,2′-diacetyl-4,4′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline: τ ($CDCl_3$) 2.42 (dd, 1, J = 7.5, 1.5 Hz, H_5), 2.69 (td, 1, J = 7.5, 1.5 Hz, H_6), 2.94 (s, 1, H_3), 3.15 (td, 1, J = 7.5, 1.5 Hz, H_7), 4.02 (dd, 1, J = 7.5, 1.5 Hz, H_8), 4.15 (s, 1, H_1), 7.83 (s, 3, $COCH_3$).

(3) J. Knabe, *Arch. Pharm. (Weinheim)*, **292**, 416 (1959).