[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES, NORTH CHICAGO, ILL.]

Neighboring Group Reactions. VII. Electrophilic Reactions of 3-(β-Haloethyl)-3-phenyloxindoles. A New Type of Ring–Chain Tautomerism

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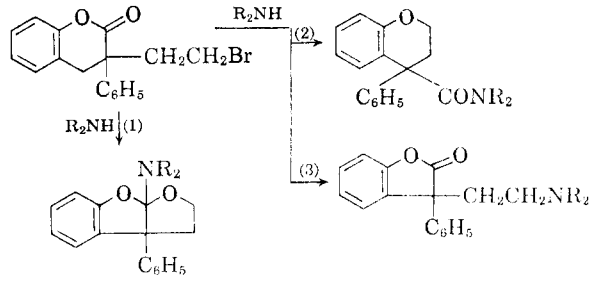
The reactions of several 3-(β-haloethyl)-3-phenyloxindoles with methoxide ion and with amines are described. The chloro- and bromoethyloxindoles II and V add methoxide ion at the carbonyl group before (or during) displacement of the halide ion to give VI (B ⇄ C), an example of a novel type of ring–chain tautomerism. By contrast, the N-methyloxindole analog IX, treated identically, undergoes elimination to give X. Unlike the analogous 2-benzofuranones, the oxindoles II and IX do not add amines at the carbonyl group. Instead, direct displacement of the halogen occurs. Treatment of 1-(β-chloroethyl)-3-phenyloxindole (IV) with sodium hydride produces a new heterocyclic compound III (85% yield). However, the isomeric 3-(β-chloroethyl)-oxindole II, under identical conditions, leads to no detectable quantity of the analogous cyclized product A. These results are interpreted in terms of two possible mechanisms leading to VI, of which the one involving tetrahedral intermediate D is favored.

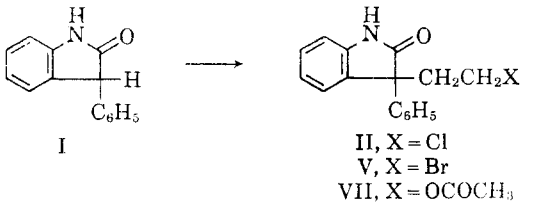
The previous paper of this series[1] described the delicate balance among equilibria in the reaction of 3-(β-bromoethyl)-3-phenyl-2-benzofuranone with secondary amines.



By proper choice of reagent, temperature and solvent it was possible to guide the reaction course predominantly in any one of three directions: (1) addition to the lactone carbonyl group followed by intramolecular nucleophilic bromide ion displacement by the oxygen atom of the tetrahedral intermediate; (2) addition to the carbonyl group followed or accompanied by expulsion of phenoxide ion which then displaces bromide ion intramolecularly; and (3) direct intermolecular bromide ion displacement.

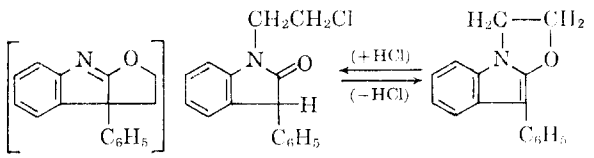
Clearly, it is of interest to determine whether the occurrence of nucleophilic reactions of type 1 can be generalized by providing a substrate with a potential leaving group less stable than phenoxide ion (*i.e.*, less prone to leave and, consequently, less likely to undergo type 2 reaction). The analogous oxindole system meets this requirement. The present paper, therefore, describes the preparation of β-haloethyl derivatives of 3-phenyl- and 1-methyl-3-phenyloxindole and their reactions with nucleophilic reagents.

Alkylation of the sodium derivative of 3-phenyloxindole (I) with 1-bromo-2-chloroethane in dimethylformamide solution gave a mixture from which two products were isolated. The main product (25% yield) was the desired chloroethyl derivative II. The minor product (5% yield) was 1,2-dihydro-4-phenyloxazolo[3,2-a]indole (III), an example of what appears to be a previously unreported heterocyclic system. The assignment of its structure followed from its elemental com-



I

II, X = Cl
V, X = Br
VII, X = OCOCH3



A IV III

position, infrared spectrum, ultraviolet spectrum (consistent with the presence of an indole nucleus[2,3]), and from the fact that in hot concentrated hydrochloric acid it was converted (79% yield) to an oxindole IV ($\lambda_{max}^{C=O}$ 5.85μ; λ_{max} 252 mμ, log ε 3.86)[4] isomeric with II. The structure of IV followed from the observation that, unlike II, it showed no N–H absorption in the infrared.

By treatment with sodium hydride in 1,2-dimethoxyethane or in dimethylformamide, IV was readily reconverted to III (79 and 85% yields, respectively). In contrast, the isomeric chloride II, with sodium hydride in dimethylformamide, gave an intractable halogen-free material which by infrared analysis was shown to contain little, if any, of the expected product A. In 1,2-dimethoxyethane, even though the sodium derivative of II formed readily with sodium hydride, a 65% yield of unreacted II was recovered after hydrolytic work-up.

By alkylation of 3-phenyloxindole with 1,2-dibromoethane in the usual way, the bromo analog (V) of II was obtained in poor yield (< 20%).

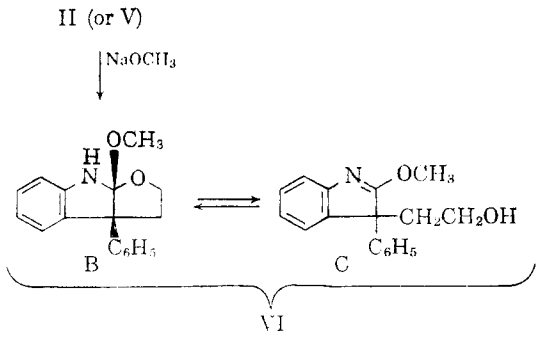
When either the chloro derivative II or its bromo analog V was refluxed with sodium methoxide in methanol for several days, a halogen-

(1) H. E. Zaugg, F. E. Chadde and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567 (1962).

(2) R. B. Carlin, J. G. Wallace and E. E. Fisher, *ibid.*, **74**, 990 (1952).

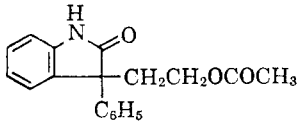
(3) G. F. Smith, *J. Chem. Soc.*, 3844 (1954).

(4) Compare E. Wenkert, A. K. Bose and T. L. Reid, *J. Am. Chem. Soc.*, **75**, 5514 (1953).



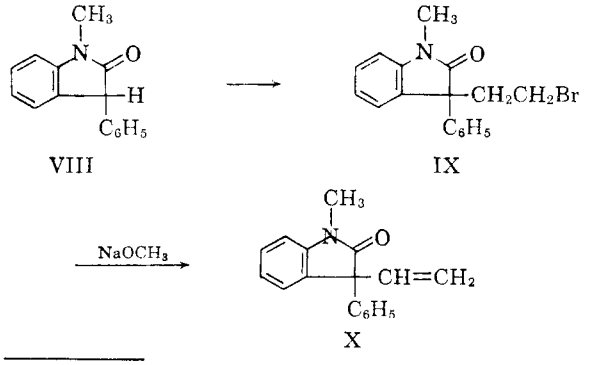
free product, m.p. 98–99°, was obtained in fair yield (65–70%). Its molecular weight and elemental composition corresponded to the replacement of bromide ion by methoxide ion. Yet its infrared spectrum was devoid of carbonyl absorption characteristic of the oxindole ring. Furthermore, both N–H and O–H absorption were clearly evident. This seemingly conflicting evidence was reconciled by the n.m.r. spectrum (Table I) which is consistent with assignment VI, comprising an equilibrium (in deuteriochloroform at room temperature) of about 20–30% of the cyclized form B with 70–80% of its open chain tautomer C. The sharp melting point of VI suggests that in the crystalline state it exists entirely in one of the two tautomeric forms. Unfortunately, the infrared spectrum of the solid (in Nujol mull) equivocates this point.

As an added check on its structure,[5] VI was subjected to acid decomposition. Hydrobrominolysis gave the bromide V in 84% yield and acetolysis led to the acetoxy derivative VII in 91% yield.

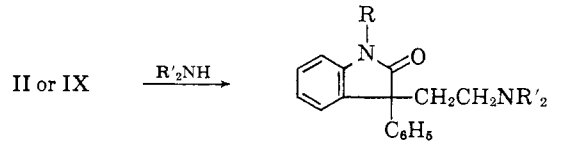


VII

In an attempt to prepare the N-methyl derivative of B, in which tautomerization would be blocked, 1-methyl-3-phenyloxindole (VIII) was converted to the corresponding bromoethyl derivative IX in the usual way (87% yield). However, addition of methoxide ion to the carbonyl group of IX could not be effected. Instead, elimination occurred to give the vinyl derivative X in 91% yield.



To complete the comparison with the analogous benzofuranone series, the chloroethyloxindole II and the bromoethyl-N-methyloxindole IX were treated with several amines.



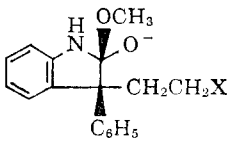
XI, R = H, NR'_2 = morpholino
XII, R = H, NR'_2 = benzylamino
XIII, R = CH_3, NR'_2 = morpholino
XIV, R = CH_3, NR'_2 = cyclopropylamino

In all cases direct displacement of the halogen occurred to give the aminoethyloxindoles XI–XIV in yields ranging from 54 to 78% (the structure of XI was proved by independent synthesis). Although reactions of the chloro derivative II required elevated temperatures (90–100°), the bromo derivative IX underwent reaction (with morpholine) at room temperature. However, it was inert to liquid ammonia (−33°).

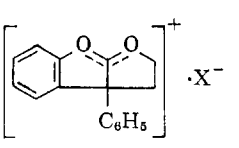
Discussion

By converting the oxindole II (or V) to the tautomeric substance VI, the original expectation of the present work was realized. Unfortunately, the failure of the N-methyloxindole derivative IX to behave analogously equivocates identification of the mechanism by which VI may be formed. Thus, a scheme alternative to the one which clearly operates in type 1 reactions in the benzofuranone series may here involve initial proton abstraction from the oxindole nitrogen to produce an ambident anion. The oxygen atom of this ion then displaces halide ion intramolecularly to give A, and addition of the elements of methanol to A finally yields the tautomeric system VI. Since the N-methyloxindole IX (which cannot form an ambident anion) did not react analogously, this mechanism cannot be disregarded.

Nevertheless, aside from its formal similarity to the type 1 process in the benzofuranone series, there is reason to believe that the mechanism leading to the tautomeric system VI may proceed through the tetrahedral intermediate D, rather than through A. Evidence for this view lies in the plainly demonstrated inability to obtain any of the



D



E

intermediate A from the 3-chloroethyloxindole II under the same conditions which led to good yields of cyclized product III from the isomeric 1-chloro-

(5) Unlike the analogous reactions in the benzofuranone series,[6] raised temperatures and longer times were required for successful reaction of methoxide ion with the oxindoles II and V. These relatively drastic reaction conditions suggested the possibility of the occurrence of unexpected rearrangements.

(6) H. E. Zaugg, R. W. DeNet and R. J. Michaels, *J. Org. Chem.*, **26**, 4821 (1961).

ethyloxindole IV.[7] The structural feature which A possesses in common with the carboxonium ion E, namely, two five-membered rings fused by atoms in different states of hybridization (one sp^2 and one sp^3), suggests that the elusive character of both derives from the same source and that A, like E, is an unlikely intermediate for any reaction scheme.[8]

Experimental[14]

3-(β-Chloroethyl)-3-phenyloxindole (II) and 1,2-Dihydro-4-phenyloxazolo[3,2-a]indole (III).—To a stirred solution of 3-phenyloxindole (I,[15] 104.5 g., 0.5 mole; $\lambda_{max}^{CHCl_3}$ 2.91 μ (NH), 5.83 μ (C=O); $\lambda_{max}^{CH_3OH}$ 252 mμ, log ε 3.905) in dry dimethylformamide (500 ml.), sodium hydride (13.2 g., 0.55 mole) was added portionwise over a period of 1 hr. maintaining the temperature below 50°. After stirring and heating for another 3 hr. at 50°, the mixture was cooled to room temperature, 1-bromo-2-chloroethane (78.5 g., 0.55 mole) was added in one portion, and stirring without heating was continued overnight. After heating the stirred mixture on the steam-bath for 3 hr., the solvent was removed by distillation under water-pump vacuum, the cooled residue was partitioned between ether and water, and the ether extract was dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a thick glassy residue, a sample (25 g.) of which was distilled *in vacuo*, b.p. 190–210° (0.5–1.0 mm.). Trituration of the distilled amber colored glassy material with warm cyclohexane resulted in a crystalline product which could be used as seed material for isolation of the bulk of the product. By an involved fractional crystallization using hexane and methanol separately as solvents, the product was separated into two pure fractions. The less soluble one consisted of the desired product II (34 g., 25%), m.p. 139–140°, $\lambda_{max}^{CHCl_3}$ 1.48, 2.92 μ (N—H), 5.84 μ (C=O); $\lambda_{max}^{CH_3OH}$ 252 mμ (log ε 3.859).

Anal. Calcd. for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.76; H, 5.39; N, 4.98.

The more soluble fraction consisted of the by-product III (6 g., 5%), m.p. 140–141°; $\lambda_{max}^{CHCl_3}$ 6.15(s), 6.25(s), 6.32(s)μ (C_6H_5C=C), no NH or C=O absorption; $\lambda_{max}^{CH_3OH}$ 228mμ (log ε 4.344), 280 mμ (log ε 4.305).

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.56; N, 5.96. Found: C, 81.59; H, 5.62; N, 5.24.

A mixture of approximately equal amounts of II and III melted at 110°.

1-(β-Chloroethyl)-3-phenyloxindole (IV).—A suspension of 1.20 g. (0.0051 mole) of 1,2-dihydro-4-phenyloxazolo-[3,2-a] indole (III) in 75 ml. of concentrated hydrochloric acid was refluxed for 3 hr. From the cooled reaction mixture an oil separated. The aqueous acid was separated by decantation and the oil was triturated with water. The solid product (1.4 g., m.p. 107–108°) which resulted was collected at the filter, washed with water, dried, and recrystallized from methanol to give 1.1 g. (79% yield) of pure IV, m.p. 110–111°; $\lambda_{max}^{CHCl_3}$ 5.85 μ (C=O), no N–H absorption at 2.9 μ; $\lambda_{max}^{CH_3OH}$ 252 mμ (log ε 3.859).

Anal. Calcd. for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.64; H, 5.15; N, 5.45.

A mixture of IV and II melted at 77–80°.

When the 1.1 g. (0.004 mole) of IV was heated on the steam-bath for 4 hr. with a suspension of 0.12 g. (0.005 mole) of sodium hydride in dimethylformamide (25 ml.) and then worked up in the usual manner (see above), III, m.p. 139–140°, was recovered in 85% yield (0.8 g.). When 1,2-dimethoxyethane was substituted for dimethylformamide as solvent and the mixture was refluxed for 6 hr., a 79% yield of III was obtained.

3-(β-Bromoethyl)-1-methyl-3-phenyloxindole (IX) was prepared from 1-methyl-3-phenyloxindole (VIII)[16] by alkyla-

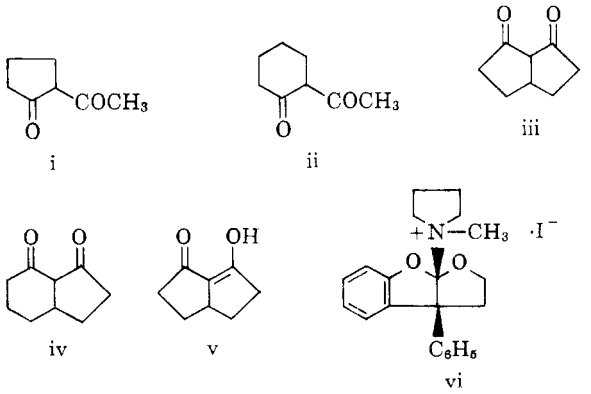
(7) Although the halogen of II reacted completely with sodium hydride *in dimethylformamide*, the presence of the intact oxindole ring (NH and CO in the infrared spectrum) in the intractable product suggests either that dehydrohalogenation occurred followed by polymerization of the resulting 3-vinyloxindole, or the sodium derivative reacted with solvent in some manner involving the halogen atom. The results obtained in 1,2-dimethoxyethane support the latter view.

(8) H. E. Zaugg and R. J. Michaels, *Tetrahedron*, **18**, 893 (1962), found that 3-(β-chloroethyl)-3-phenyl-2-benzofuranone would react neither with silver perchlorate nor with antimony pentachloride to give the carboxonium salt E (X^- = ClO_4^- and $SbCl_6^-$, respectively).[9] As the reason for this it was suggested that the strain resulting from the two five-ring fusion atoms possessing different geometry (one trigonal and one tetrahedral) over-compensates for stabilization gained through charge delocalization in the cation.[10]

(9) Compare H. Meerwein, K. Bodenbenner, P. Bonner, F. Kunert and K. Wunderlich, *Ann.*, **632**, 38 (1960).

(10) A quantitative estimate of this strain in a simple bicycloöctane ring system is available: the free energy of enolization of i is only 480 cal./mole greater than that of ii.[11] On the other hand, the free energy of enolization of iii is 3460 cal./mole greater than that of iv.[12] The difference, 3 kcal./mole, represents the maximum strain energy that can be ascribed to the formation of the enol v, involving the mixed hybrid fusion of the two five-membered rings.[13]

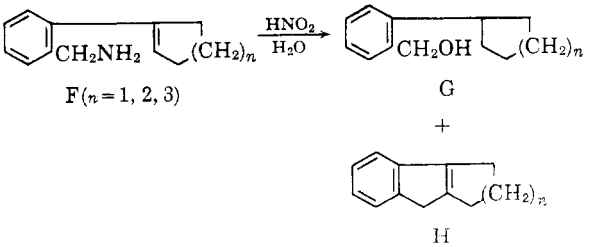
The magnitude of this strain may appear insufficient to account for some of the phenomena that have been ascribed to it [certainly the fact that the quaternary salt vi can be isolated,[1] suggests that a barrier greater than 3 kcal./mole prevents it from cleaving to E (X^- = I^-) and N-methylpyrrolidine]. However, it is reasonable to assume that substitution of the bulky phenyl group at the sp^3 ring juncture renders any approach to coplanarity considerably more difficult than in the unsubstituted enol of the simple bicycloöctane system.



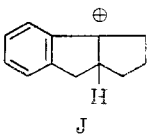
(11) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1044 (1944).

(12) H. Stetter, I. Kruger-Hansen and M. Rizk, *Chem. Ber.*, **94**, 2702 (1961).

(13) Since a 3 kcal. increase in the free energy of an unstable intermediate or a 3 kcal. increase in free energy of activation decreases the corresponding observed rate of a reaction by a factor greater than 10^3, this magnitude of strain can easily account for some recent findings of W. E. Parham, C. D. Wright and D. A. Bolon, *J. Am. Chem. Soc.*, **83**, 1751 (1961).



In a study of the foregoing reaction they found that the cycloheptene and cyclohexene homologs of F (n = 2,3) gave significant amounts (10–55%) of H (n = 2,3) in addition to the expected product G. However, the cyclopentene homolog F (n = 1) gave G to the exclusion of H. Formation of the latter would have required the intermediacy of J and the mixed hybrid fusion of two five-membered rings.



J

(14) Melting points are uncorrected.

(15) J. Meisenheimer and H. Meis, *Ber.*, **57**, 289 (1924).

(16) (a) G. Palazzo and V. Rosnati, *Gazz. chim. ital.*, **82**, 584 (1952); (b) M. E. Speeter, U. S. Patent 2,759,935 (1956).

tion of its sodium derivative with 1,2-dibromoethane in dimethylformamide solution essentially as described for the preparation of II. From an 0.5-mole run, pure IX was secured in an 87% yield, m.p. 112–113°; $\lambda_{max}^{CHCl_3}$ 5.85 μ, no N–H absorption at 2.9μ.

Anal. Calcd. for $C_{17}H_{16}BrNO$: C, 61.83; H, 4.88; N, 4.24. Found: C, 62.11; H, 5.20; N, 4.06.

However, when the sodium derivative of 3-phenyloxindole (I) was alkylated in the same way with 1,2-dibromoethane, there was obtained only a poor yield (< 20%) of **3-(β-bromoethyl)-3-phenyloxindole (V)**, m.p. 145–146°; $\lambda_{max}^{CHCl_3}$ 2.94 μ (NH), 5.85 μ (C=O).

Anal. Calcd. for $C_{16}H_{14}BrNO$: C, 60.77; H, 4.47; N, 4.43. Found: C, 60.77; H, 4.70; N, 4.61.

When the dimethylformamide was replaced by 1,2-dimethoxyethane or by benzene as solvent the alkylation reaction was less nearly complete (in dimethylformamide, titration showed that reaction had progressed to within 10% of completion) and no V at all could be isolated.[17]

Reaction of 3-(β-Chloroethyl)-3-phenyloxindole (II) with Sodium Methoxide. Preparation of VI.—Compound II (5.4 g., 0.02 mole) was refluxed for 48 hr. with a solution of sodium methoxide [prepared from 0.85 g. (0.037 g.-atom) of sodium] in dry methanol (60 ml.). The methanol was removed by distillation and the residue was partitioned between ether and water. Separation and drying (anhydrous magnesium sulfate) of the ether layer followed by removal of the ether by distillation gave a thick glassy residue (6.0 g.) which resisted crystallization. However, vacuum distillation gave 4.0 g. of a colorless glass, b.p. 165–175° (0.3 mm.). Trituration with and recrystallization from cyclohexane gave pure VI (3.0 g., 56%), m.p. 98–99°; $\lambda_{max}^{CH_3OH}$ 258 mμ (log ε 3.769); $\lambda_{max}^{CCl_4}$ (μ)1.40 (OH), 1.51 (NH); $\lambda_{max}^{CH_2Cl}$ (μ) 2.74(w), 2.92(w), 3.30(m), 6.18(m), 6.31(s), 6.67(m), 6.84(m), 7.17(w), 7.38(m), 7.58(m), 7.88(m), 8.73(m), 9.61(m), 10.04(m), 10.85(w), 11.45(w), 14.43(m); for the n.m.r. spectrum, see Table I.

TABLE I

N.M.R. DATA FOR COMPOUND VI[a]

Chemical shift[b]	Assignment	Rel. area[c]
433.8, 402.1	Aromatic H's	9.0
292.2	—N—*H*	0.32
237.0	=C—OC*H*$_3$	2.5
252.0, 225.0, 201.0	—OC*H*$_2$—	1.7[d]
179.0	—C—OC*H*$_3$	0.80
155.0	—C—C*H*$_2$—C—O	1.8[d]
116.0	—C—OH	0.89

[a] At 60 megacycles in deuteriochloroform solution (*ca.* 6%). [b] In c.p.s. from tetramethylsilane used as an internal standard. [c] Assuming 9 aromatic protons. [d] The total area for the two methylene groups is admittedly low—3.5 observed *vs.* 4.0 theoretical. It is believed, however, that the remainder of the area (0.5 proton) is situated under several very weak peaks noted in the vicinity of 252.0 and 225.0 c.p.s. The integral supports this interpretation, but it is not conclusive.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; O, 11.97; mol. wt., 267. Found: C, 76.60; H, 6.55; N, 5.10; O, 12.04; mol. wt., 260 (Rast), 268 (by cryoscopy in benzene).

In subsequent runs it was possible to avoid distillation of the product by trituration of the crude glass with ether in the presence of a few seed crystals. In this way yields of 65–70% were obtainable. When the reaction was allowed to take place at room temperature for 4 weeks, only starting chloro derivative II was recovered (70%). When the bromoethyloxindole V was substituted for the chloro analog II in the above procedure, VI (identified by m.p., mixed m.p. and infrared spectrum) was obtained in a 50% yield.

When the chloroethyl derivative II (2.7 g., 0.01 mole) was heated on the steam-bath for 4 hr. with a suspension of sodium hydride (0.36 g., 0.015 mole) in dimethylformamide (50 ml.) and then was worked up in the usual way, an amorphous halogen-free product (2.6 g., m.p. 90–120°) was obtained. It could not be purified, but the infrared spectrum (strong peak at 5.84 μ and N–H absorption at 1.48 μ) indicated that the oxindole ring remained undisturbed. Hence, compound A was not a major product.

When II was refluxed for 6 hr. with an equivalent quantity of sodium hydride in 1,2-dimethoxyethane, a clear solution resulted indicating formation of the sodium derivative of II. However, treating the reaction mixture with cold water and working up in the usual way gave a 65% recovery of unreacted II and no indication of the formation of A.

Reactions of Compound VI. A. Hydrobrominolysis.—A mixture of VI (1.5 g., 0.00561 mole), 48% hydrobromic acid (10 ml.) and glacial acetic acid (30 ml.) was refluxed for 12 hr. and then concentrated to dryness. The residue was partitioned between ether and water and recovered in the usual way (see above). Crystallization from an ethyl acetate–hexane mixture gave 3-(β-bromoethyl)-3-phenyloxindole (V) (1.5 g., 84%), m.p. 142–143°, identified by mixed melting point and infrared spectrum.

B. Acetolysis.—A mixture of VI (1.0 g., 0.00374 mole), 5% sulfuric acid (3 ml.) and glacial acetic acid (10 ml.) was refluxed overnight and then worked up as in the foregoing procedure. Trituration of the oil thus obtained with cyclohexane gave crude VII, m.p. 82–85° (1.0 g., 91%). Two recrystallizations from aqueous isopropyl alcohol produced pure **3-(β-acetoxyethyl)-3-phenyloxindole (VII)**, m.p. 98–99°; $\lambda_{max}^{CCl_4}$ 1.48 (NH); $\lambda_{max}^{CHCl_3}$ 5.74μ (ester C=O), 5.84 μ (lactam C=O).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.81; N, 4.74. Found: C, 73.25; H, 5.91; N, 4.70.

1-Methyl-3-phenyl-3-vinyloxindole (X).—3-(β-Bromoethyl)-1-methyl-3-phenyloxindole (IX) (9.9 g., 0.03 mole) was treated with an equivalent quantity of sodium methoxide exactly as described above for the preparation of VI. The crude product isolated in the usual manner was an oil (7.5 g). which was distilled to give 6.8 g. (91%), b.p. 145–147° (0.4 mm.), $n^{25}D$ 1.6081. The distillate solidified, m.p. 80–81°. One recrystallization from cyclohexane gave 4.5 g. of pure X, m.p. 85°; $\lambda_{max}^{CHCl_3}$ 1.63 μ (terminal C=C), 5.86μ (C=O).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.07; N, 5.62. Found: C, 81.92; H, 5.95; N, 5.66.

The product rapidly absorbed bromine from solution in carbon tetrachloride.

When the bromo compound IX was refluxed and stirred with an equivalent amount of sodamide in toluene, 80% of it was recovered unchanged. No other product could be isolated.

3-(β-Morpholinoethyl)-3-phenyloxindole hydrochloride XI. A. From II.—A mixture of 3-(β-chloroethyl)-3-phenyloxindole (II) (5.4 g., 0.02 mole) and morpholine (25 ml.) was heated on the steam-bath for 4 hr. The morpholine was removed by distillation at the water-pump using a rotating evaporator. The residue was taken up in ether and extracted with 10% hydrochloric acid. From the neutral ether layer 3.0 g. of unchanged II was recovered. The acid extract was made alkaline with aqueous potassium hydroxide, the resulting oil was taken up in ether, washed with water and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oily base which could not be crystallized. It was then taken up in dry ether and treated with ethereal hydrogen chloride. The resulting salt (2.5 g., 35% conversion, 78% yield), m.p. 160–165°, was recrystallized from an ethanol–ether mixture to give pure XI (2.1 g.), m.p. 165–167°; $\lambda_{max}^{CHCl_3}$ 2.75, 2.94, 5.83μ.

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2$: C, 66.94; H, 6.46; N, 7.81. Found: C, 66.63; H, 6.74; N, 7.68.

When this reaction was allowed to take place at room temperature for 4 weeks, 80% of the chloro compound II was recovered and no product XI could be isolated.

(17) Compare H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961).

B. From I.—The sodium derivative prepared from 3-phenyloxindole (I) (11 g., 0.05 mole) and sodium hydride (0.06 mole) in dry benzene was refluxed and stirred overnight with 4-(β-chloroethyl)-morpholine (0.06 mole). Isolation of the product in the foregoing manner gave 8.6 g. (48%) of pure XI, m.p. 165–167°, identical (mixed m.p. and infrared spectrum) with the sample obtained from II.

3-(β-Benzylaminoethyl)-3-phenyloxindole Hydrochloride (XII).—3-(β-Chloroethyl)-3-phenyloxindole (II) (5.4 g., 0.02 mole) was heated overnight on the steam-bath with excess benzylamine (25 ml.). The mixture was worked up in the usual way (see preparation of XI) to give 5.2 g. (68%) of pure XII, m.p. 235–237° (from isopropyl alcohol); λ_{max}^{Nujol} 3.11, 5.83μ.

Anal. Calcd. for $C_{23}H_{23}ClN_2O$: C, 72.91; H, 6.12; N, 7.39. Found: C, 72.93; H, 6.33; N, 7.44.

1-Methyl-3-(β-morpholinoethyl)-3-phenyloxindole (XIII) (Base).—A solution of 3-(β-bromoethyl)-1-methyl-3-phenyloxindole (IX) (9.9 g., 0.03 mole) in morpholine (30 ml.) was allowed to stand at room temperature for 48 hr. and then worked up in the usual way (see preparation of XI). In this case, however, the base solidified (5.5 g., m.p. 76–79°, 54%) and was recrystallized from cyclohexane to give pure XIII, m.p. 81–82°, $\lambda_{max}^{CHCl_3}$ 5.85 μ.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.99; H, 7.19; N, 8.33. Found: C, 75.00; H, 7.20; N, 8.54.

3-(β-Cyclopropylaminoethyl)-1-methyl-3-phenyloxindole Hydrochloride (XIV).—A solution of IX (0.03 mole) in cyclopropylamine (30 ml.) and benzene (25 ml.) was refluxed for 48 hr. and worked up as usual to give 7.3 g. (71%) of XIV, m.p. 202–203° (from ethanol); $\lambda_{max}^{CHCl_3}$ 1.63 μ (cyclopropyl-CH_2), 5.86 μ (C=O).

Anal. Calcd. for $C_{20}H_{23}ClN_2O$: C, 70.07; H, 6.77; N, 8.18. Found: C, 70.25; H, 6.68; N, 8.13.

When the bromo compound IX was stirred with liquid ammonia for 24 hr. it was quantitatively recoverable.

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Application of Mass Spectrometry to Structure Problems. VIII.[1] Quebrachamine[2,3]

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Quebrachamine was shown to have structure I by comparison of its mass spectrum with the one of Ia, prepared from asipdospermine IIIa. The presence of the same carbon skeleton in both compounds is revealed by these spectra making it unnecessary to remove chemically the methoxyl group of II to prove identity. It was shown that (−)-quebrachamine and (−)-aspidospermine, both occurring in *Aspidosperma quebracho blanco*, have the same absolute configuration at C-5.

The first detailed investigation of the alkaloids of *Aspidosperma quebracho blanco* Schlecht. by Hesse[4] led to the isolation of six alkaloids: aspidospermine, quebrachine (= yohimbine), quebrachamine, aspidospermatine, and two amorphous bases, hypoquebrachine and aspidosamine. Quebrachamine was found in an amount too small to permit its elemental composition to be established, but the alkaloid was later reisolated by Field[5] and shown to have the composition $C_{19}H_{26}N_2$. The presence of one basic tertiary nitrogen was established, and a number of color reactions made it very probable that quebrachamine is an indole derivative. Attempts of oxidative degradation under various conditions failed to yield any actual information.

The problem of the structure of quebrachamine remained dormant for over three decades and only comparatively recently has this alkaloid again received more detailed attention, when Witkop[6] confirmed the presence of an indole moiety on the basis of the ultraviolet spectrum of quebrachamine and reported a number of experiments aimed at the elucidation of the structure of this alkaloid. These consisted of various oxidation and dehydrogenation experiments of which only zinc dust distillation led to products for which definite structures were suggested. When this reaction was carried out fifty times using 50 milligrams of quebrachamine for each experiment, there was obtained from the pooled crude products a basic fraction, a non-basic, steam-volatile fraction, and a non-basic non-volatile fraction. The basic fraction gave a picrate of m.p. 180–181°, identical with the material obtained from aspidospermine on similar treatment[7] and believed to be the picrate of 3,5-diethylpyridine contaminated with some 3-methyl-5-ethylpyridine. The steam-volatile, non-basic fraction was also converted to a mixture of picrates which on repeated recrystallization, raising the melting point from 104° to 132°, gave an analysis indicating a C_3-indole, and was suggested to be a mixture of β-methyl and β-ethylindole picrates contaminated with higher homologs. It is of interest to note that a further recrystallization raised the melting point to 143°, but the amount was insufficient for analysis. Finally, the non-steam-volatile portion was suggested to be a mixture of carbazole and some homolog on the basis of elemental analysis and color reactions.

These findings seemed to establish two points, namely, that quebrachamine may be related to aspidospermine and that in both molecules there is present the carbon skeleton of 3,5-diethylpyridine.

The occurrence of an α,β-substituted indole system in quebrachamine was finally established by its n.m.r. spectrum, which, however, did not offer any additional structural information.[8]

(1) Part VII: K. Biemann, A. L. Burlingame and D. Stauffacher, *Tetrahedron Letters*, **No. 12**, 527 (1962).

(2) For a preliminary communication on this work see K. Biemann and G. Spiteller, *ibid.*, **No. 9**, 299 (1961).

(3) This investigation was supported by a grant (G-5051) from the National Science Foundation.

(4) O. Hesse, *Ann.*, **211**, 249 (1882).

(5) E. Field, *J. Chem. Soc.*, **125**, 1444 (1924).

(6) B. Witkop, *J. Am. Chem. Soc.*, **79**, 3193 (1957).

(7) B. Witkop, *ibid.*, **70**, 3712 (1948).