[Contribution from the Research Department of Ciba Pharmaceutical Products, Inc.]

The Alkaloids of *Tabernanthe iboga*. Part VI.[1] The Synthesis of the Selenium Dehydrogenation Products from Ibogamine

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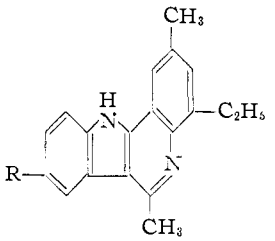
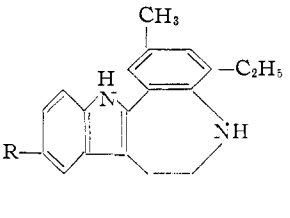
4-Ethyl-2,6-dimethyl-11H-indolo[3,2-c]quinoline (Ib) and 4-ethyl-5,6,7,12-tetrahydro-2-methylindolo[3,2-d][1]benzazepine (IIb) have been synthesized. A comparison of the physical properties of these substances with those of the two selenium dehydrogenation products from ibogamine showed their identity and thus established the structure of these iboga alkaloid degradation products.

Paper IV of this series[2] described the selenium dehydrogenation of the iboga alkaloids ibogaine and ibogamine, and gave a discussion of the reasoning which led to the proposed structures (Ia and IIa) for the two products derived from ibogaine. Proof also was presented that, as had been considered previously, ibogamine was desmethoxybogaine. Hence, its degradation products would in all probability be the desmethoxy analogs Ib and IIb of those from ibogaine. As such they



Ia, R = OCH_3
Ib, R = H



IIa, R = OCH_3
IIb, R = H

would be simpler to synthesize and we were, therefore, requested to devise a method of preparation for these compounds. The ultimately successful route is given in Chart I.

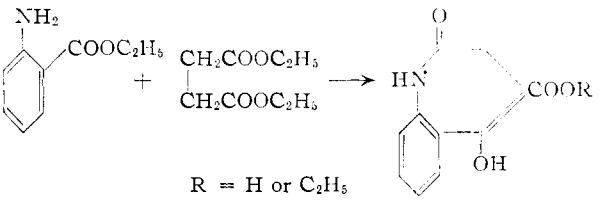
The most logical starting point for the synthesis of the desired substances appeared to be 2-ethyl-4-methylaniline (III) which was prepared by Willgerodt and Brandt[3] by the direct alkylation of *p*-toluidine. These authors also presented a convincing proof of structure for their product, an essential point for the starting material of a synthetic project such as this. The substance also had been prepared by Hill and Graf[4] by the reduction of 2′-acetamido-2-chloroacetophenone. Although we obtained the same material by both methods, we found the direct alkylation method more adaptable to larger scale preparation.

Synthesis of the Indolobenzazepine

In reviewing the literature on benzazepine derivatives it was found that Astill and Boekelheide[5] had reported that they were unable to cyclize 4-(N-*p*-tolylsulfonylanilino)-butyric acid by the application of the usual conditions for the Friedel–Crafts reaction. We also were unsuccessful in applying this procedure to our synthesis in spite of repeated attempts with known model compounds and a wide variety of reagents.

These same authors further showed that the desired compound could be made by a Dieckmann cyclization of the appropriately N-substituted methyl anthranilate. Accordingly, the anthranilic acid V was prepared from III *via* the isatin IV. However, all attempts to synthesize the N-γ-carboethoxypropyl substituted ester by either direct alkylation or from the corresponding tolylsulfonamide were unsuccessful. A similar alkylation of methyl N-*p*-tolylsulfonylanthranilate and its cyclization has since been reported.[6]

In another series of experiments with model substances it was shown that ethyl anthranilate reacted with ethyl succinate in the presence of sodium hydride to yield a product of the structure shown



R = H or C_2H_5

Both the ultraviolet and infrared spectra indicate that the product does not exist in the keto form but is enolic. It is interesting to note that in both the free acid and the ester a strong band appears at 1623 and 1545 cm.$^{-1}$, respectively. This is apparently due to the enhanced —C=C— vibration in the system O—C=C—COOR.

Repeated attempts to effect decarboxylation of the acid were all unsuccessful and, hence, this approach was abandoned.

We next turned to a method which necessitated the synthesis of the substituted indole IX. Kiang, Mann, Prior and Topham[7] had successfully prepared 2-(*o*-aminophenyl)-indole by a Fischer indole synthesis on 2′-aminoacetophenone. Various attempts to make the aminoacetophenone VIII directly from the anthranilic acid V met with little success in spite of the use of several N-protecting groups previous to the necessary preparation of the acid chloride. In all cases we obtained uncharacterized high melting products which apparently resulted from the self condensation of two molecules. Therefore, the amino group was oxidized with pertrifluoroacetic acid to the nitro acid VI. This readily was converted to the acetophenone VII.

(1) Part V, W. I. Taylor, *Experientia*, **13**, 454 (1958).

(2) M. F. Bartlett, D. F. Dickel and W. I. Taylor, This Journal, **80**, 126 (1958).

(3) C. Willgerodt and L. Brandt, *J. prakt. Chem.*, [2] **69**, 433 (1904).

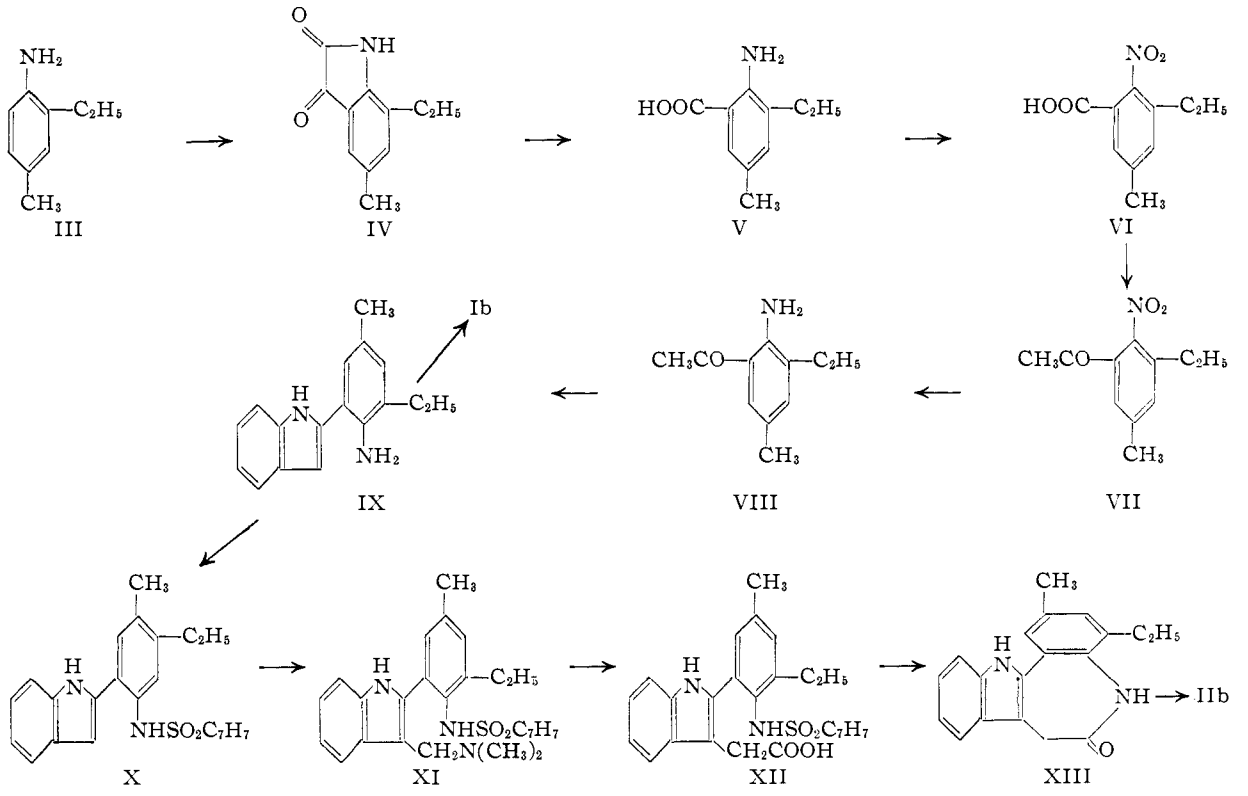
(4) A. J. Hill and L. E. Graf, This Journal, **37**, 1839 (1915).

(5) B. D. Astill and V. Boekelheide, *ibid.*, **77**, 4079 (1955); see also G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302 (1957); J. T. Braunholtz and F. G. Mann, *ibid.*, 4174 (1957).

(6) G. R. Proctor and R. H. Thomson, *ibid.*, 2312 (1957).

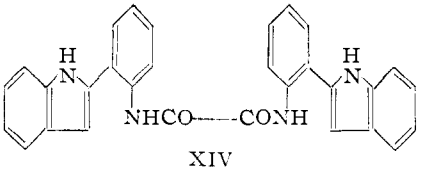
(7) A. K. Kiang, F. G. Mann, A. F. Prior and A. Topham, *ibid.*, 1319 (1956).

CHART I

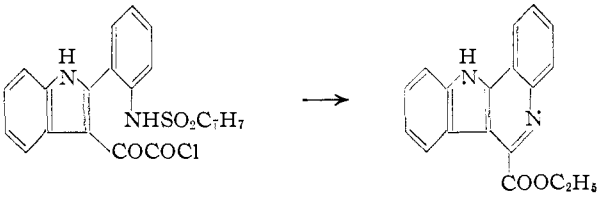


Since it was desirable to retain the nitro group until a later stage in the synthesis, model experiments were carried out using 2′-nitroacetophenone in the Fischer indole procedure and good yields were obtained with polyphosphoric acid. However, when this same method was applied to VII only black tars resulted.[8] The nitro group was, therefore, reduced back to amino and the resulting compound VIII readily was transformed to the desired indole IX.

It was now necessary to elaborate a two-carbon side chain on the 3-position of the indole moiety in such a manner that cyclization to the seven membered ring would take place. In a preliminary experiment 2-(*o*-aminophenyl)-indole was treated with oxalyl chloride[9] in the hope that the seven membered ring would be formed directly. However, the infrared spectrum of the resulting product indicated that it was probably the oxamide XIV. The amino group was, therefore, protected by tosylation. Reaction with oxalyl chloride now produced the acid chloride XV in good yield. Treatment of this substance with alcoholic hydrogen chloride to esterify and to remove the blocking



XIV



tosyl group produced a substance to which we have assigned the structure XVI on the basis of the analytical data. The infrared spectrum supports this conclusion in that the strong band at 1740 cm.$^{-1}$, which is higher than normally expected for conjugated esters, appears to be indicative of a 2-quinolinecarboxylic ester and also no other oxygen function is indicated.

The desired side chain was successfully built up by means of the usual gramine synthesis from the tolylsulfonamide X yielding XI in acceptable yield. The 3-acetic acid XII then was produced by treatment of XI with potassium cyanide followed directly by hydrolysis of the crude product. On removal of the tosyl group with hydrobromic acid–acetic acid, cyclization apparently took place during the reaction. The only product isolated, although not further characterized, had an infrared spectrum consistent with the lactam structure XIII. Reduction of this material with $LiAlH_4$ at the temperature of boiling *n*-butyl ether gave the desired final product IIb. The synthetic material proved to be identical with the weakly

(8) Prof. E. Wenkert, Iowa State College, has suggested that in this case the steric crowding due to the diortho substitution of the nitro group may be sufficient to cause it to undergo interaction, possibly in an oxidative–reductive manner, with the neighboring hydrazino intermediates in the Fischer reaction.

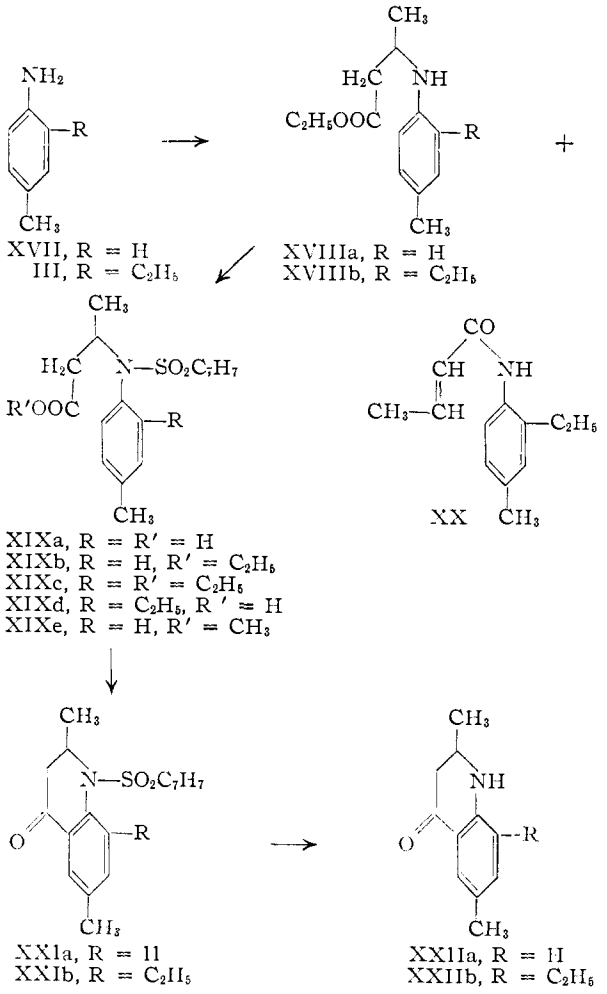
(9) M. E. Speeter and W. C. Anthony, THIS JOURNAL, 76, 6208 (1954).

basic selenium dehydrogenation product from ibogamine.

Synthesis of the Indoloquinoline

At the same time that the early part of the work described above was being carried out, a synthesis of Ia was attempted by a method based essentially on the procedure described by Johnson, Woroch and Buell[10] for the preparation of 4-quinolones.

CHART II



This is shown in Chart II. Addition of ethyl crotonate to the anilines III and XVII gave the corresponding β-anilinobutyric esters XVIIIa and XVIIIb in moderate yield. The reaction time had to be greatly prolonged as compared with the addition of aniline to methyl acrylate[10] and even then both starting compounds could be partly recovered. Still more drastic conditions did not improve the yield but led to an increase in residual material on distillation. No advantage was found in a preparation in which *p*-toluidine hydrochloride was heated with an excess of ethyl β-pyrrolidino-*n*-butyrate. From the reaction with III the crotonic anilide XX was obtained as a side product. Tosylation of either amino ester gave no crystalline products and the crude oils were directly hydrolyzed to the corresponding acids XIXa and XIXd. In both instances extensive β-elimination was observed and demonstrated to arise from treatment with base, by preparation of a crystalline methyl ester XIXe and treatment of this pure compound under the same conditions. Intramolecular acylation led to the N-tosyltetrahydroquinolones XXIa and XXIb from which the free amines XXIIa and XXIIb were obtained by acid hydrolysis. Fischer indole synthesis with *p*-methoxyphenylhydrazine produced only a small amount of product which, although ill-defined, did have ultraviolet and infrared absorption spectra similar to Ia and showed identical behavior on paper chromatography.

At about this time the synthesis outlined in Chart I had progressed to the point where compound IX was available. When this was treated with acetaldehyde in the presence of acid, the salt of Ib was formed readily. Both this hydrochloride and the free base were found to be identical in all respects with the more basic selenium dehydrogenation product of ibogamine[2] and its corresponding salt. Thus the structure of both degradation products has been established.

Acknowledgments.—We wish to express our appreciation to Dr. E. Schlittler for his interest in this work and to Dr. E. Wenkert for his many suggestions. We are indebted to Mr. B. Korzun and his colleagues for paper chromatographic analyses which greatly aided our progress, to the staff of the Analytical Section for the ultraviolet and infrared spectra and for the microanalyses, and to Mr. G. Moll of the High Pressure Laboratory for assistance in the pressure reactions. We also are grateful to Dr. G. A. Jeffrey, University of Pittsburgh, for the X-ray comparison. Finally, we especially wish to thank Mr. L. Dorfman for his spectral interpretations and for his valued help throughout this work.

Experimental[11]

2-Ethyl-4-methylaniline (III).[3]—A mixture of 330 g. of *p*-toluidine, 180 ml. of anhydrous ethanol and 420 g. of anhydrous zinc chloride was placed in a Pyrex glass liner and heated in a stainless steel autoclave at 275° for 8 hours. The maximum pressure reached in a number of experiments was 610 p.s.i. After cooling to 100–125° the system was vented with nitrogen and the charge removed. It was poured into an excess of aqueous ammonia (approximately 1 liter) and the oil which separated was extracted with three 400-ml. portions of ether. After drying over sodium sulfate, the ether was removed *in vacuo* leaving a mixture of crude amines. Five such batches were combined and distilled *in vacuo* collecting everything boiling below 170° at 15–16 mm. This material was twice fractionated at atmospheric pressure in a 24-inch column of glass helices. A quantity of *p*-toluidine was recovered boiling 200–201° which could be reused in subsequent runs. Intermediate fractions boiling below 222° were collected and saved for refractionation with later batches. The main fraction boiling 222–230° (320 g.) contained the 2-ethyl-4-methylaniline.

The crude amine was purified by conversion to its N-acetyl derivative with 410 ml. of acetic anhydride. The mixture became quite warm and on cooling to room temperature deposited a quantity of crystals. These were augmented by the addition of an equal volume of petroleum ether. The total precipitate was filtered and well washed with petroleum ether giving 144 g. of product, m.p. 121–

(10) W. S. Johnson, E. L. Woroch and B. G. Buell, This Journal, 71, 1901 (1949).

(11) Melting points are uncorrected and were determined in capillary tubes. Unless otherwise noted the ultraviolet absorption spectra were measured in ethanol and infrared spectra taken in Nujol mulls.

128°. Concentration of mother liquor yielded an additional 56 g. for a total of 200 g. (36.7%) of material which was used directly in the next step. A small sample was further recrystallized from ethanol, m.p. 130–133° (lit.[12] 132°).

Hydrochloride.—A mixture of 75 g. of the above 2′-ethyl-4′-methylacetanilide and 600 ml. of concentrated hydrochloric acid was refluxed for 2 hours and then chilled and the crystalline material filtered. After air-drying overnight in the hood 66.0 g. (91%) of product was obtained, m.p. 207–212°. This was used directly in the next preparation.

7-Ethyl-5-methylisatin (IV).—To a solution of 68.6 g. of chloral hydrate in 916 ml. of water were added in order 522 g. of anhydrous sodium sulfate in 464 ml. of water, 66.0 g. of the above hydrochloride in 600 ml. of water and 84.2 g. of hydroxylamine hydrochloride in 384 ml. of water.[13] The mixture was stirred and heated to boiling over a period of 55 minutes and then cooled. The gum which precipitated was recrystallized from methanol yielding 93 g. of the crude isonitrosoacetanilide.

The above material was added portionwise to 224 ml. of concentrated sulfuric acid which was stirred and maintained at 60–70° during the addition. When this was complete the solution was heated to 80° for 10 minutes and then it was poured into 2.4 l. of crushed ice. Stirring the mixture produced red crystals of the isatin. This was recrystallized from methanol and yielded 41.6 g. (60.6%) of product, m.p. 182–185°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H. 5.86; N, 7.40. Found: C, 69.73; H, 5.74; N, 7.47.

3-Ethyl-5-methylanthranilic Acid (V).—To a solution of 48.3 g. of sodium hydroxide in 384 ml. of water was added 36.97 g. of 7-ethyl-5-methylisatin and the mixture cooled to 20°. A solution of 48.3 ml. of 30% hydrogen peroxide in 193 ml. of water was added dropwise over a period of 1 hour during which time the temperature was kept at 25–30°. After stirring the solution for 3 hours at room temperature, 1 g. of Darco was added and the stirring continued for an additional 5 minutes.[14] After filtration and chilling the 3-ethyl-5-methylanthranilic acid was precipitated by the dropwise addition of 170 ml. of cold hydrochloric acid (2:1). The product was filtered and recrystallized from ethanol and yielded 30.68 g. (87.6%), m.p. 150–153°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.74; H, 7.18; N, 7.74.

Reaction of Ethyl Anthranilate with Ethyl Succinate.—A mixture of 14.7 g. of ethyl succinate, 10.3 g. of ethyl anthranilate and 2.14 g. of sodium hydride in 140 ml. of dry toluene was stirred and refluxed for 3 hours. It was allowed to stand overnight and then 75 ml. of 10% hydrochloric acid was added slowly. The precipitate which formed was filtered and recrystallized three times from ethanol yielding 4.5 g. (29.5%) of material, m.p. 210–213°; infrared: 1673 $cm.^{-1}$ (conjugated ester), 1648 $cm.^{-1}$ (amide), 1623 cm^{-1} (C=C); $\lambda_{max}^{ethanol}$ 228–229 mμ, ε 29,260; 239 mμ, ε 19,580 (shoulder); 293–296 mμ, ε 12,200.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.31; H, 5.45; N, 5.78.

Hydrolysis.—The above compound, 1.0 g., was dissolved in 10 ml. of ethanol containing 3 ml. of 20% sodium hydroxide solution and the mixture was refluxed for 90 minutes. The major part of the alcohol was removed by distillation and then 10 ml. of 20% sulfuric acid was added and the acid suspension heated on the steam-bath for 2 hours. The solid material was filtered from the hot solution and after recrystallization from ethanol melted at 322–323° dec.; yield 820 mg. (93%).

Anal. Calcd. for $C_{11}H_9NO$: C, 60.27; H, 4.14. Found: C, 60.77; H, 4.46.

3-Ethyl-5-methyl-2-nitrobenzoic Acid (IV).—To a well-stirred mixture of 7.40 ml. of 90% hydrogen peroxide and 130 ml. of methylene chloride in an ice-bath was added dropwise 34 ml. of trifluoroacetic anhydride while the temperature was maintained below 10°. A slurry of 11.36 g. of the aminobenzoic acid in 70 ml. of methylene chloride was then added in portions so that the temperature was maintained at 5–6°.[15] The solution was allowed to stand in the ice-bath 1 hour and then to warm up to room temperature. It was washed with three 30-ml. portions of water and then dried with magnesium sulfate. After concentrating the solution *in vacuo* at room temperature to 30 ml., crystals formed. These were filtered and recrystallized from ethanol yielding 8.12 g. (59%) of nitro acid, m.p. 199–201°.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.36; H, 5.51; N, 6.88.

3′-Ethyl-5′-methyl-2′-nitroacetophenone (VII).—A mixture of 1.18 g. of magnesium turnings, 2.4 ml. of anhydrous ethanol and 9 drops of carbon tetrachloride was refluxed for 5 minutes and then 36.2 ml. of anhydrous ether added. To this was added dropwise a solution of 7.85 ml. of ethyl malonate in 14.4 ml. of dry ether and 2.4 ml. of anhydrous ethanol. This mixture was refluxed for 3 hours until the magnesium was all in solution.[16]

The acid chloride of 3-ethyl-5-methyl-2-nitrobenzoic acid was prepared by refluxing a mixture of 9.60 g. of acid and 96 ml. of thionyl chloride for 90 minutes. The excess reagent was removed by vacuum distillation and the remaining acid chloride dissolved in 35 ml. of dry ether. This solution was added dropwise to the stirred refluxing magnesium malonate solution mentioned above. Refluxing was continued for 15 minutes after the addition was complete. The mixture was then chilled and to it was added 5.6 ml. of concentrated sulfuric acid in 45 ml. of water. The layers were separated and the aqueous phase extracted with ether. The organic phases were combined, washed with water and the solvents removed leaving a red oil weighing 16.6 g. This material was refluxed for 4 hours in a solution of 13.5 ml. of glacial acetic acid, 9 ml. of water and 1.7 ml. of concentrated sulfuric acid. The mixture was then cooled, made basic with 20% sodium hydroxide solution and then the product was extracted with ether. The extract was washed with water, dried with sodium sulfate and the solvent removed. The resulting brown oil crystallized and was purified by distillation at 0.1 mm., b.p. 115–118°, and yielded 8.59 g. (90.5%) of product, m.p. 43–45°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.94; H, 6.39; N, 6.62.

2-(*o*-Nitrophenyl)-indole.—A mixture of 8.43 g. of 2′-nitroacetophenone,[7] 7.0 ml. of phenylhydrazine and 1.0 ml. of glacial acetic acid in 16.8 ml. of ethanol was refluxed for 6 hours. On standing overnight in the refrigerator orange crystals separated. These were filtered, washed with a small amount of ethanol and dried, m.p. 80–81° (yield 11.0 g., 84.5%).

A suspension of 10.0 g. of the above phenylhydrazone (well pulverized) in 150 g. of polyphosphoric acid was heated on the steam-bath until bubbling appeared (65°). The temperature was then very gradually raised to 75–80° and the now fluid mixture held at this temperature for 20 minutes. After cooling it was poured into ice-water and the product extracted with ether after a uniform aqueous suspension had been obtained. The ether extract was washed with water, dried and the solvent removed leaving a red-brown solid. This was recrystallized from ethanol and yielded 6.7 g. (72%) of the indole, m.p. 140–141°. It was positively identified by catalytic reduction of a small sample to yield an aminophenylindole identical with that prepared by the method of Kiang, *et al.*[7]

2′-Amino-3′-ethyl-5′-methylacetophenone (VIII).—A mixture of 7.3 g. of the nitroacetophenone VII and 32.6 ml. of concentrated hydrochloric acid was stirred on the steam-bath while 13.1 g. of granular tin was added portionwise over a period of 1 hour.[7] The heating and stirring were continued for 30 minutes after the addition was complete. The solution was then cooled in an ice-bath and made alkaline with a 30% sodium hydroxide solution. The product was removed by steam distillation. The distillate was extracted with ether and the ethereal extract dried with anhydrous potassium carbonate. After removal of the solvent there remained 4.5 g. (72%) of yellow oil which was not further characterized but was used directly in the next preparation.

2-(2-Amino-3-ethyl-5-methylphenyl)-indole (IX).—A

(12) G. T. Morgan and A. E. J. Pellet, *J. Chem. Soc.*, 418 (1934).

(13) C. S. Marvel and G. S. Hires, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 327.

(14) S. Archer and C. M. Suter, THIS JOURNAL, 74, 4296 (1952).

(15) W. D. Emmons, *ibid.*, 76, 3471 (1954).

(16) G. A. Reynolds and C. R. Hauser, *Org. Syntheses*, 30, 70 (1950).

mixture of 4.5 g. of the above aminoacetophenone VIII, 9.45 ml. of anhydrous ethanol, 0.6 ml. of glacial acetic acid and 4.72 ml. of freshly distilled phenylhydrazine was refluxed for 6 hours. The solution was then concentrated *in vacuo* and the residue taken up in benzene, the solution dried with sodium sulfate and the benzene removed by distillation leaving an oil which could not be crystallized.

The oily hydrazone was well mixed with 100 g. of polyphosphoric acid and the thick mass heated slowly to 37–42° and kept at this temperature for 25 minutes during which time it was periodically mixed with a glass rod. At the end of this time the temperature was raised to 75° for 3–4 minutes and then allowed to return to room temperature. About 200 ml. of ice and water was added and the gum was stirred until it became crystalline. The mixture was made neutral with 20% sodium hydroxide solution and extracted with ether. The ether extracts were washed, dried and on evaporation of the solvent 7.9 g. of brown oil was obtained which gave 4.3 g. (68%) of crystals from ethanol. After recrystallization from this solvent a m.p. of 136–138° was obtained.

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.67; H, 7.23; N, 11.24.

Reaction of 2-(*o*-Aminophenyl)-indole with Oxalyl Chloride.—To a solution of 100 mg. of 2-(*o*-aminophenyl)-indole[7] in 50 ml. of dry ether was added 0.5 ml. of oxalyl chloride. The clear solution immediately turned yellow and after 1–2 minutes crystals were deposited. After standing at room temperature for 15 minutes the crystals were filtered and washed with ether. The product, 83 mg. (71.3%), m.p. 285–286°, could not be recrystallized because of its insolubility in any of the solvents tried. The infrared absorption spectra had a typical oxamide band at 1683 cm.$^{-1}$.

2-[*o*-(*p*-Tolylsulfonamido)-phenyl]-indole.—A mixture of 2.0 g. of 2-(*o*-aminophenyl)-indole and 1.95 g. of *p*-toluenesulfonyl chloride in 25 ml. of dry pyridine was allowed to stand 1 hour at room temperature and then it was heated an additional hour on the steam-bath. At the end of this time it was poured into ice-water and the product extracted with ether. The ether solution was washed with 10% hydrochloric acid and water and, after drying, the solvent was removed. The resulting glass crystallized upon the addition of methanol. After recrystallization from this solvent 2.38 g. (68.5%) of material was obtained, m.p. 138–139°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2S$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.95; H, 5.14; N, 7.77.

2-[*o*-(*p*-Tolylsulfonamido)-phenyl]-3-indoleglyoxyl Chloride (XV).—To a solution of 2.0 g. of the compound described above in 100 ml. of dry ether was added 0.5 ml. of oxalyl chloride in 10 ml. of dry ether. After standing at room temperature for 4 hours the crystals were filtered and washed with ether. In this way 2.3 g. (96.5%) of chloride was obtained, m.p. 135–136°.

Anal. Calcd. for $C_{23}H_{17}ClN_2O_4S$: C, 61.00; H, 3.75; N, 6.19. Found: C, 59.92; H, 3.44; N, 5.93.

Ethyl 11-H-Indolo[3,2-c]quinoline-6-carboxylate (XVI).—Two grams of the above chloride was refluxed for 1 hour in 50 ml. of anhydrous ethanol containing 10% hydrogen chloride. The alcohol was concentrated hot to one-third the volume and on cooling crystals separated. These were redissolved in warm ethanol and the solution made alkaline with ammonium hydroxide. On dilution with water crystals precipitated. These were filtered and recrystallized from a small volume of ethanol yielding 830 mg. (62%) of product, m.p. 215–217°; infrared, 1749 cm.$^{-1}$ (conjugated ester), 1652 cm.$^{-1}$ (C=N).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.20; H, 5.18; N, 9.85.

2-[3-Ethyl-5-methyl-2-(*p*-tolylsulfonamido)-phenyl]-indole (X).—To a solution of 4.2 g. of the phenylindole IX in 42.4 ml. of dry pyridine was added 3.6 g. of *p*-toluenesulfonyl chloride. The mixture was allowed to stand overnight at room temperature and was then heated on the steam-bath for 1 hour. After cooling it was poured into 50 ml. of cold water. The gum crystallized on rubbing with a glass rod. It was filtered and recrystallized from ethanol, yielding 5.42 g. (80.7%) of product, m.p. 187–188°.

Anal. Calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.41; H, 6.02; N, 6.79.

3-Dimethylaminomethyl-2-[3-ethyl-5-methyl-2-(*p*-tolylsulfonamido)-phenyl]-indole (XI).—To a mixture of 2.0 ml. of glacial acetic acid, 0.5 ml. of 37% formaldehyde solution and 1.1 ml. of 25% aqueous dimethylamine solution was added 1.21 g. of tosylate X. The suspension was allowed to stand at room temperature for 24 hours during which time the material went into solution. It was then poured into 50 ml. of 30% aqueous acetic acid and enough glacial acetic acid added to make the solution acid to congo paper. After thoroughly shaking the suspension, the insoluble material was removed by filtration and the clear filtrate neutralized with concentrated ammonium hydroxide. The white granular precipitate was filtered, washed with cold water and recrystallized from ethanol to give 980 mg. (69.5%) of product, m.p. 194–198° dec. The analytical sample was prepared by twice recrystallizing this material from ethyl acetate, m.p. 199–201° dec.

Anal. Calcd. for $C_{27}H_{31}N_3O_2S$: C, 70.26; H, 6.77; N, 9.11. Found: C, 69.97; H, 6.80; N, 8.95.

2-[3-Ethyl-5-methyl-2-(*p*-tolylsulfonamido)-phenyl]-3-indoleacetic Acid (XII).—To a solution of 930 mg. of the gramine XI in 12 ml. of ethanol was added 1.4 g. of sodium cyanide in 3 ml. of water. The mixture was refluxed for 40 hours, cooled and diluted with 25 ml. of water. Concentrated hydrochloric acid then was added until the solution was acid to congo paper. The precipitated material was extracted with ether and the ethereal solution washed with water, dilute sodium hydroxide solution and finally again with water. After drying, the solvent was removed leaving a crystalline product (850 mg.). An infrared spectrum showed this material to be a mixture of nitrile and amide.

It was, therefore, hydrolyzed by dissolving it in 10 ml. of 20% alcoholic potassium hydroxide solution and refluxing the mixture for 23 hours. The solvent was then removed and the residue dissolved in water. The aqueous solution was extracted with ether and then acidified with 50% hydrochloric acid. The crystalline precipitate was filtered, washed with water and recrystallized twice from ethanol–water; yield 550 mg. (59%), m.p. 172–174°; infrared, 1708 cm.$^{-1}$ (-COOH).

Anal. Calcd. for $C_{26}H_{26}N_2O_4S$: C, 67.52; H, 5.67. Found: C, 67.77; H, 5.79.

4-Ethyl-5,6,7,12-tetrahydro-2-methylindolo[3,2-d][1]benzazepine (IIb).—A mixture of 620 mg. of the acid XII, 620 mg. of phenol and 6.5 ml. of glacial acetic acid containing 30% hydrogen bromide was refluxed for 20 minutes. The solution was poured into 50 ml. of dry ether and the precipitated material was collected by filtration and recrystallized from ethanol yielding 60 mg. of crude product (XIII) m.p. 220–250°; infrared: 1645 cm.$^{-1}$ (lactam). The product was not further characterized.

To 20 ml. of *n*-butyl ether containing 250 mg. of lithium aluminum hydride was added 50 mg. of the above lactam. The mixture was refluxed for 22 hours and then the excess of hydride decomposed by the cautious addition of ethyl acetate, water and finally 10% sulfuric acid. The product was extracted with ether and the ether solution washed with 5% sodium hydroxide solution and water. After drying, the solvent was removed leaving 30 mg. of brown crystalline material. Recrystallization from ethanol yielded a substance, m.p. 170–180°. It was further purified by sublimation *in vacuo* (0.03–0.04 mm.) and again recrystallized from ethanol. The analytical data indicated solvation and, hence, the product was resublimed yielding 8 mg. (17.5%) of pure product, m.p. 186–187°.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29. Found: C, 82.46; H, 7.17.

The above material was shown to be identical with the weakly basic selenium degradation product of ibogamine[2,11] by the fact that a mixture of the substances showed no depression of m.p., and by the fact that their infrared (KBr) and ultraviolet absorption spectra were identical. Their identity was confirmed beyond any doubt by X-ray data on single crystal specimens.

Ethyl 3-*p*-Toluidinobutyrate (XVIIIa).—A mixture of 37.2 g. of *p*-toluidine, 42.6 g. of ethyl crotonate and 1.0 ml. of glacial acetic acid was refluxed (about 160°) under nitrogen for two days. The pale yellow reaction mixture was

(17) In paper II of this series (W. I. Taylor, THIS JOURNAL, **79**, 3298 (1957)) the m.p. of this material was erroneously reported to be 214°. Actually the correct material melts at 187°.

then distilled, giving 6.0 g. of recovered *p*-toluidine as forerun and 43.0 g. (56%) of product, b.p. 128–129° (1 mm.), $n^{20}D$ 1.5195. The balance of material consisted of a viscous residue.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.66; N, 6.33. Found: C, 70.73; H, 8.56; N, 6.30.

3-[N-(*p*-Tolylsulfonyl)-*p*-toluidino]-butyric Acid (XIXa).—To a solution of 43.0 g. of the amine XVIIIa in 260 ml. of dry pyridine, 77.0 g. of *p*-toluenesulfonyl chloride was added with cooling in ice. The reaction was left at room temperature for 48 hours (or heated on a steam-bath for 15 minutes) and then worked up by pouring it into water and extracting thoroughly with ether. The combined extracts were washed well with 10% hydrochloric acid, 0.5% potassium hydroxide and finally with water and saturated salt solution. After drying over magnesium sulfate and evaporating of the solvent, 71.0 g. of a pale yellow oil remained, which could not be crystallized and was not readily purified by distillation (b.p. about 180° (10^{-3} mm.) in a jacketed flask); crude yield 95%. No *p*-toluenesulfonamide of *p*-toluidine could be isolated or detected.

Hydrolysis was carried out by dissolving the crude oil in 310 ml. of methanol, adding 78 ml. of water and 137 ml. of 10% aqueous potassium hydroxide and stirring for 48 hours at room temperature. The solution was then poured into 1 l. of water, acidified and extracted well with ether. The combined ether portions were extracted with aqueous sodium bicarbonate until a sample remained clear on acidification. Acidification of the bicarbonate solution and extraction with ether gave, after washing with salt solution, drying over magnesium sulfate and evaporation of the solvent, 20.0 g. of the acid XIXa; after recrystallization from benzene–heptane, 19.0 g. (28%), m.p. 132–134°. A sample recrystallized for analysis melted at 138–139°.

Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.04. Found: C, 62.43; H, 6.13; N, 4.10.

The ether solution remaining from the sodium bicarbonate extraction was washed with water and saturated salt solution, dried over magnesium sulfate and evaporated to give 29.6 g. of *p*-toluidine-*p*-toluenesulfonamide, m.p. 116–117°, identical with an authentic sample.

Methyl 3-[N-(*p*-Tolylsulfonyl)-*p*-toluidino]-butyrate (XIXe).—To a solution of 1.4 g. of XIXa in 30 ml. of ether, cooled in ice, was added an excess of diazomethane in ether. After standing at room temperature for 30 minutes, the excess of diazomethane and the solvent were boiled off and the remaining material taken up in ether. Washing with sodium bicarbonate, water and salt solution, drying over magnesium sulfate and concentration gave 1.4 g. (96%) of the crystalline methyl ester. Recrystallization from ether–heptane gave a pure sample melting at 78–79°.

Anal. Calcd. for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.88. Found: C, 63.33; H, 6.38; N, 4.06.

Hydrolysis: 1.0 g. of the methyl ester was suspended in 5.0 ml. of methanol, 1.2 ml. of water and 2.1 ml. of 10% potassium hydroxide. After stirring for 15 hours at room temperature the reaction was worked up in the same way as the hydrolysis of the crude ethyl ester, described above. Thus 0.40 g. of *p*-toluidine-*p*-toluenesulfonamide and 0.39 g. of the acid XIXa were obtained (39% yield).

2,3-Dihydro-2,6-dimethyl-1-(*p*-tolylsulfonyl)-4-quinolone (XXIa).—The acid XIXa, 6.9 g., was dissolved in 40 ml. of dry carbon disulfide. After addition of 4.2 g. of phosphorus pentachloride the mixture was refluxed under nitrogen for 1 hour, cooled in ice and 3.5 ml. of stannic chloride in 20 ml. of carbon disulfide added. After stirring for 1 hour, 2.0 g. of powdered aluminum chloride was added to the solution from which some yellow complex had started to precipitate. Stirring was continued for 15 hours and the reaction was then poured into dilute hydrochloric acid and extracted with ether. The extracts were washed with sodium carbonate and saturated salt solution, dried over magnesium sulfate and evaporated to give 6.2 g. (94%) of a yellow gum which was used directly in the following step. For characterization a small portion was crystallized from ethanol. After several recrystallizations this material melted at 167–168°.

Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.82; N, 4.26. Found: C, 65.19; H, 5.82; N, 4.33.

A further portion of the crude material was converted to the 2,4-dinitrophenylhydrazone, m.p. 149–150° dec. after recrystallization from methylene chloride–ethanol.

Anal. Calcd. for $C_{24}H_{23}N_5O_6S$: C, 56.57; H, 4.55; N, 13.75. Found: C, 56.37; H, 4.73; N, 13.88.

2,3-Dihydro-2,6-dimethyl-4(1H)-quinolone (XXIIa).—The crude cyclization product XXIa, 4.8 g., was dissolved in 25 ml. of glacial acetic acid and added to 25 ml. of concd. hydrochloric acid and 12 ml. of water. After refluxing for 3 hours under nitrogen, the clear solution was cooled, poured into water, made basic with sodium hydroxide and extracted thoroughly with ether. The extracts were washed with 5% sodium hydroxide, water and saturated salt solution. Drying over magnesium sulfate and evaporation gave an oil from which 0.80 g. (33%) of the yellow amine could be crystallized with ether–heptane. Recrystallization gave a pure sample, m.p. 123–124°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.45; H, 7.65; N, 7.88.

Ethyl 3-(2-Ethyl-*p*-toluidino)-butyrate (XVIIIb).—A mixture of 9.8 g. of 2-ethyl-4-methylaniline, 9.0 g. of ethyl crotonate and 0.3 ml. of glacial acetic acid was heated at gentle reflux under nitrogen for two days. Distillation of the reaction mixture gave a forerun of 8.0 g. of starting materials, b.p. up to 95° (5 mm.) and 7.2 g. of crude product, b.p. 120–123° (0.3 mm.).

Addition of petroleum ether (30–60°) to a solution of this crude product in 20 ml. of ether caused 0.20 g. of the crotonic anilide to crystallize. After recrystallization from benzene–heptane the pure compound melted at 157–158° and showed strong peaks in the infrared (chloroform) at 1670, 1510 cm.$^{-1}$ (amide) and a smaller band at 3370 cm.$^{-1}$ (NH).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.80; H, 8.43; N, 6.89. Found: C, 76.89; H, 8.47; N, 6.87.

After removal of the anilide, distillation of the mother liquor material gave 6.9 g. (38%) of aminobutyric ester, b.p. 120–122° (0.3 mm.), $n^{20}D$ 1.5150.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.24; H, 9.29; N, 5.62. Found: C, 72.47; H, 9.07; N, 5.76.

On heating the 8.0 g. of forerun material again with 8.0 g. of ethyl crotonate, a further 4.9 g. of product and 0.20 g. of the crotonic amide was obtained; over-all yield 66%.

3-[2-Ethyl-N-(*p*-tolylsulfonyl)-*p*-toluidino]-butyric Acid (XIXd).—A solution of 10.8 g. of the amine XVIIIb in 57 ml. of dry pyridine was cooled in ice and 17.2 g. of *p*-toluenesulfonyl chloride added. After standing for 48 hours at room temperature, 200 ml. of water was added and the mixture extracted well with ether. After washing the combined extracts successively with 10% hydrochloric acid, 0.5% potassium hydroxide, water and saturated salt solution, concentration of the dried solution gave 16.1 g. of a yellow oil (crude yield 89%) which was directly subjected to hydrolysis with 68 ml. of methanol, 17 ml. of water and 30 ml. of 10% aqueous potassium hydroxide. After stirring at room temperature for 20 hours, the reaction was poured into water, acidified and extracted well with ether. The combined ether portions were extracted thoroughly with sodium bicarbonate, the latter acidified and extracted with ether. After the usual washing and drying, evaporation of the solvent gave 3.5 g. (22%) of product, crystallized from benzene–heptane. A pure sample melted at 151–152°.

Anal. Calcd. for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.74. Found: C, 64.00; H, 6.81; N, 3.92.

Evaporation of the original ether solution from sodium bicarbonate extraction produced 5.4 g. of the *p*-toluenesulfonamide of 2-ethyl-4-methylaniline, recrystallized from ethanol–water and benzene–heptane; pure sample m.p. 89–90°.

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.55; N, 4.67.

2,3-Dihydro-2,6-dimethyl-4(1H)-quinolone (XXIIb).—Phosphorus pentachloride, 1.1 g., was added to a solution of 2.0 g. of the acid XIXd in 40 ml. of dry carbon disulfide. After refluxing for 1 hour under nitrogen, the mixture was cooled and 0.60 ml. of stannic chloride in 4 ml. of carbon disulfide added. The reaction was stirred at room temperature for 1 hour, turning pale yellow during this period but showing no formation of a complex; 2.0 g. of aluminum chloride was then added, stirring continued for 15 hours and the mixture finally refluxed for 8 hours. After cooling it

was poured into dilute hydrochloric acid and extracted with ether. The extracts were washed with saturated sodium bicarbonate and salt solutions, dried over magnesium sulfate and evaporated to give 1.8 g. of crude cyclization product XXIb (crude yield 94%) which could not be crystallized but was hydrolyzed directly to the amine by refluxing for 15 hours in a mixture of 11 ml. of glacial acetic acid, 5 ml. of water and 11 ml. of concentrated hydrochloric acid. The cooled solution was then poured into water and extracted well with ether. After washing the extracts with bicarbonate and saturated salt solutions and drying over magnesium sulfate, concentration gave 0.56 g. (52%) of a yellow crystalline compound; recrystallized from ether–heptane, m.p. 87–88°. Ether extraction of the original aqueous solution, after making it strongly basic, did not yield any further material.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.80; H, 8.43; N, 6.89. Found: C, 77.09; H, 8.53; N, 7.14.

4-Ethyl-2,6-dimethyl-11H-indolo[3,2-c]quinoline (Ib).—A solution of 100 mg. of the aminophenylindole (IX) in 10 ml. of ethanol containing 1 ml. of an acetaldehyde solution (250 mg./ml.) was allowed to stand at room temperature for 5 minutes. Then 5 ml. of 20% hydrochloric acid was added. This resulted in an immediate red coloration, the precipitation of white crystals and the evolution of heat. After standing at room temperature for 30 minutes, the precipitate was filtered and recrystallized from ethanol yielding 92 mg. (73.5%), m.p. >300°.

Anal. Calcd. for $C_{19}H_{19}ClN_2$: C, 73.41; H, 6.16; N, 9.01. Found: C, 73.14; H, 6.36; N, 9.16.

The above hydrochloride was converted to the base by dissolving 75 mg. of material in about 3 ml. of hot ethanol and adding 10% ammonium hydroxide until the solution was basic. On concentration *in vacuo* crystals separated and these were removed by filtration. After recrystallization from ethanol 52 mg. (76%) of base was obtained, m.p. 194–195°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 83.22; H, 6.56; N, 10.55.

A mixture of the above base with that from the selenium dehydrogenation of ibogamine[2] showed m.p. 195–196°. The infrared and ultraviolet absorption spectra of both bases and their hydrochlorides were identical.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Diuretics. Organomercurials

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The alkoxymercuration of allylic compounds was carried out in fourteen different alcohols and in water. New alkoxy groups were thereby introduced into the basic mercurial diuretic structure. Mercuration of the *ortho*, *meta* and *para* isomers of N-allylcarbamylphenoxyacetic acid yielded anhydro N-(3-hydroxymercuri-2-alkoxypropyl)-carbamylphenoxyacetic acids in the case of the *ortho* and *meta* isomers, but did not give an anhydro derivative with the *para* isomer. The structures of these anhydro derivatives and of anhydro compounds prepared by the mercuration of α,β-unsaturated acids were established by infrared studies.

The presently known mercurial diuretics are all derivatives of β-alkoxyethylmercuric salts. They differ in the type of substituents on the β-carbon of the ethyl group and in the anion of the salt. The β-alkoxy group has, however, been limited in most examples to the methoxy group. In this investigation changes were made in the β-alkoxy group by the alkoxymercuration of olefins in a number of different alcohols.

The methoxymercuration of *o*-(N-allylcarbamyl)-phenoxyacetic acid (I) is reported[1] to yield *o*-(N-3 - acetoxymercuri - 2 - methoxypropylcarbamyl)-phenoxyacetic acid. In this present work when compound I was allowed to react with mercuric oxide in the presence of alcohols the products were not the expected *o*-(N-3-hydroxymercuri-2-alkoxypropylcarbamyl)-phenoxyacetic acids. They were instead dehydrated or anhydro forms of the expected products. Furthermore, the addition of mercuric acetate to the *m*- isomer II, under the conditions of the alkoxymercuration reaction, yielded anhydro *m*-(3-hydroxymercuri-2-alkoxypropylcarbamyl)-phenoxyacetic acids. An anhydro derivative, however was, not obtained from the *p*- isomer III. This latter isomer reacted with mercuric acetate in ethylene glycol to yield *p*-(N-3 - acetoxymercuric - 2 - β - hydroxyethoxypropylcarbamyl)-phenoxyacetic acid (VI). A few examples of the anhydro derivatives of mercurated carboxylic acids are given in the literature. Aliphatic α,β-unsaturated acids are reported to yield four-membered ring anhydrides of β-alkoxy-α-hydroxymercuripropionic acids.[2] The product obtained from the methoxymercuration of I is said to be converted to a 12-membered ring derivative.[3] The assigned structures of these reported anhydro compounds are not supported by findings other than elemental analysis. Since there was no firm basis for assigning these structures and consequently no reason to assign similar structures to the anhydro derivatives prepared here, they were further examined in order to establish the correct anhydro structure.

Evidence for the structures of the anhydro products was obtained by studying their infrared spectra. A moderately intense band for NH at 2.97 μ in the chloroform solution of the *o*-isomer IV (R = $(CH_2)_2OCH_3$) eliminates the possibility of the amide hydrogen having been replaced. Thus, an N–Hg bond is not present. Intense bands for amide at 6.10 and 6.53 μ also support the *mono*-substituted amide IV. Absence of a band for the carboxyl group suggests a zwitterion structure or internal salt between the carboxylate group and the positive mercury. The carboxylate absorption of mercuric acetate in chloroform solution consists primarily of two bands of medium intensity at 6.13 and 6.21 μ. Although a band at 6.20 μ

(1) M. Bockmühl and A. Schwarz, United States Patent 1,693,432; W. H. Feinstone, United States Patent 2,581,397.

(2) F. C. Whitmore, "Organic Compounds of Mercury," The Chemical Catalog Co. (Reinhold Publ. Corp.), New York, 1922, pp. 137–153.

(3) K. O. Möller, *Arch. Exp. Path. Pharm.*, **153**, 111 (1930).