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OXINDOLYLALANINE

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The recent reports (1–3) of several successful syntheses of oxindolylalanine, *i.e.*, hydroxytryptophan, prompts us to place on record some experiments which were conducted in these laboratories and which were directed towards the same goal. Much of our initial work proceeded along lines similar to those already reported (1–4). In addition our unsuccessful approaches included: the oxidation of N-acetyl-L-tryptophan with various peroxyacids (5); an attempt to convert 1-methyl-2-methoxy-3-hydroxymethylindole to the corresponding chloride prior to condensation with diethyl acetamidomalonate; the attempted condensation of 1-methyl-2-methoxyindole-3-aldehyde with hippuric acid, hydantoin, diketopiperazine, and diethyl malonate; the attempted condensation of 2-acetamido- and 2-diacetimido-phenylacetonitrile with β-chloroacetal prior to hydrolysis to the aldehyde and a subsequent Strecker synthesis; and the attempted condensation of 1-methyloxindole with diethyl methylenemalonate prior to subsequent amination *via* the α-bromo acid Although *o*-nitrotropic acid and *o*-nitrochlorohydratropic acid appeared to be suitable intermediates for the synthesis of oxindolylalanine all attempts to find a practical procedure for the direct *ortho* nitration of the corresponding acids failed. Since oxindole will not undergo a normal Mannich reaction (4) an attempt was made to prepare 3-aminomethyloxindole *via* reduction of isatin cyanohydrin. This reaction also failed principally because of the instability of the cyanohydrin during the attempted reduction. While Cornforth, *et al.* (2) reported the successful condensation of ethyl pyruvate and isatin to give 3-isatylidenepyruvic acid, the condensation of pyruvic acid with isatin, in our hands, gave quinoline-2,4-dicarboxylic acid as the principal reaction product. In a model synthesis in which 1-methyloxindole was condensed with diethyl malonate (6), and the resulting keto ester converted into the corresponding α-oximino-β-keto ester, all attempts to reduce the latter compound were unsuccessful.

When it was found that oxindole could be obtained from the hydrochloride of 2-aminoindole by simply heating an aqueous solution of the latter compound at 170° for five hours the synthesis outlined below was attempted.

2-Aminoindole was prepared from *o*-nitrophenylacetonitrile according to Pschorr (7). A convenient synthesis of the latter compound is described in the experimental section of this communication. 2-Aminoindole was also synthesized by treatment of the azide of 2-indolecarboxylic acid (8) with benzyl alcohol and subsequent hydrogenolysis of the resulting urethan with palladized charcoal. 2-Diacetimidoindole (I) was obtained by reaction of 2-aminoindole with acetic anhydride (7).

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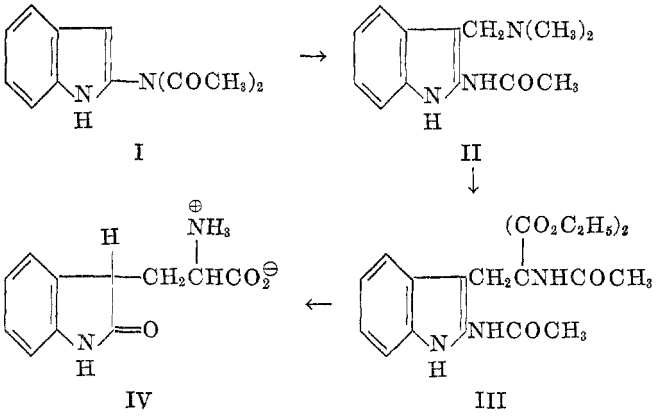
The condensation of 2-diacetimidoindole (I) with formaldehyde and dimethylamine gave 2-acetamido-3-dimethylaminomethylindole (II). II was isolated as such, or more conveniently as the crude methiodide. The latter compound was obtained only as an unstable amorphous powder, *cf.* (9). Condensation of the crude methiodide of II with the sodio derivative of diethyl acetamidomalonate gave ethyl α-acetamido-α-carboethoxy-β-(2-acetamido-3-indole)propionate (III). III was also prepared by the simple fusion of diethyl acetamidomalonate with II, or with 2-acetamido-3-(piperidinomethyl)indole.



The hydrolysis and decarboxylation of III under alkaline conditions, or with concentrated hydrochloric acid, followed by hydrolysis in water at 170°, gave deeply colored products which gave a positive reaction with ninhydrin but from which no crystalline oxindolylalanine (IV) could be obtained. In order to exclude the possibility that, in the preparation of II, aminomethylation had taken place in the 1-position of the indole nucleus giving rise to ethyl α-acetamido-α-carboethoxy-β-(2-acetamido-1-indole)propionate instead of II, III was treated with nitrous acid. A yellow mononitroso derivative was obtained which exhibited properties analogous to those of the N-nitroso derivative of ethyl α-acetamido-α-carboethoxy-β-(3-indole)propionate which was prepared for the sake of the above comparison. The ultraviolet absorption spectra of the nitroso derivatives, and those of their parent compounds, are given in Figures 1 and 2. It will be seen that in both cases conversion of the parent compound into the corresponding mononitroso derivative has caused an increase in the extinction coefficient of the principal maxima and their shift to a region of shorter wave length.

The similarity of the chemical and spectral behavior of the above compounds was taken as evidence in favor of the formulation of II as the product of the Mannich reaction. Final proof of the correctness of this conclusion was obtained in a renewed attempt to cause the hydrolysis of III to IV, this time with 30% aqueous-sulfuric acid.[3] The product so obtained was a yellow-brown powder

[3] Th. Wieland and Schmidt (10) have likewise observed the greater stability of oxindolylalanine in aqueous-sulfuric acid relative to that in hydrochloric acid.

whose behavior was identical with that of authentic IV in that both gave a positive ninhydrin reaction, a deep blue color with the Folin-Denis reagent, and coupled, only after heating with aqueous sodium hydroxide and subsequent diazotization, with β-naphthol to give a red dye (11). There can be no doubt that II is formed from I *via* a normal Mannich reaction.

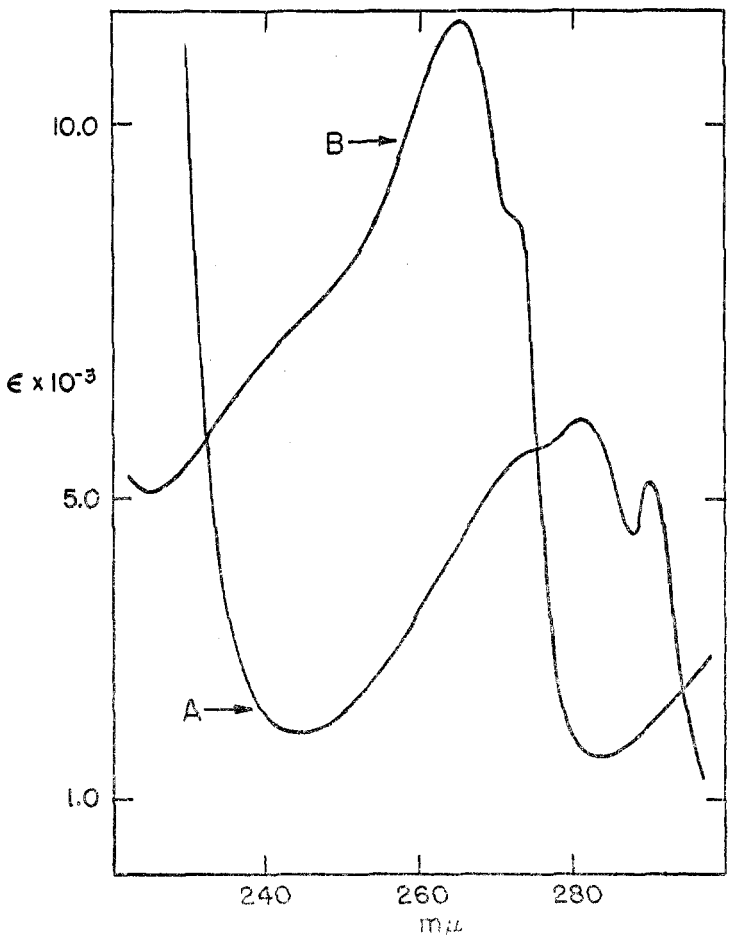


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF: (A) ETHYL α-ACETAMIDO-α-CARBOETHOXY-β-INDOLE-3-PROPIONATE; AND (B) ETHYL α-ACETAMIDO-α-CARBOETHOXY-β-(1-NITROSOINDOLE-3)PROPIONATE. SOLVENT, 95% ETHANOL

Although several attempts to isolate pure IV, or its hydrochloride, from the crude hydrolysis product were unsuccessful further evidence for the conversion of III into IV was obtained by chromatography, on a silicic acid-Celite column (12), of the dinitrophenyl derivatives prepared from the hydrolysis product. The results obtained from these experiments are presented graphically in Figures 3–5. Both authentic crude IV, prepared according to Kotake, *et al.* (1), and the

hydrolysis product described above gave two dinitrophenyl derivatives, *i.e.*, a slow-moving and a fast-moving derivative, whose respective R_F values were in good agreement. In the case of the dinitrophenyl derivatives prepared from crude authentic IV the slow-moving component was present only in trace quantities whereas the same component derived from the hydrolysis product was

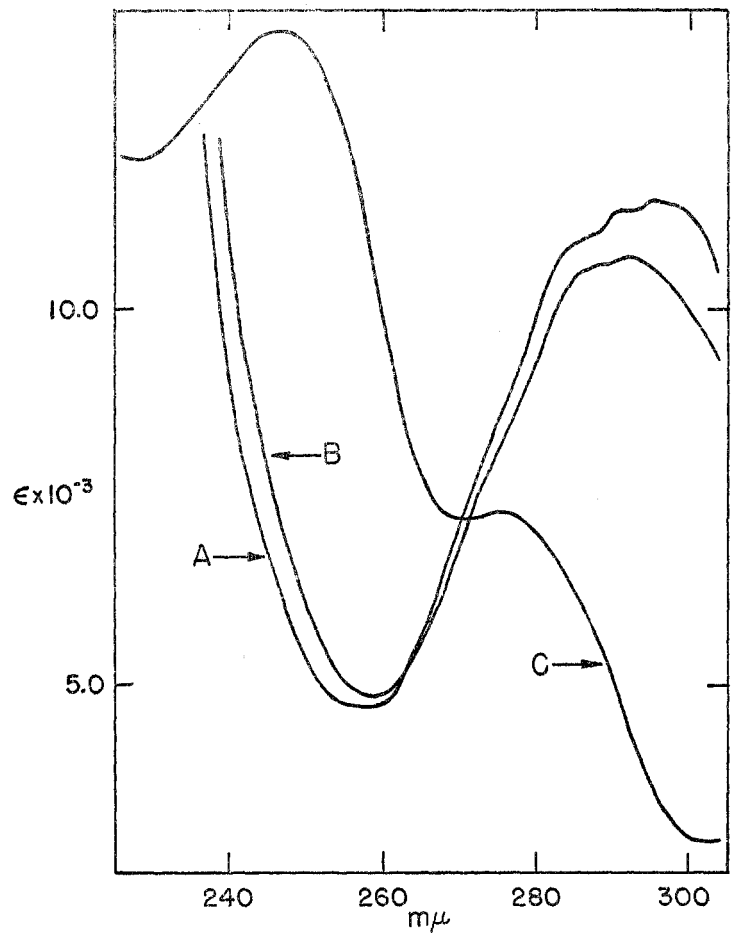


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRA OF: (A) 2-ACETAMIDO-3-(DIMETHYLAMINOMETHYL)INDOLE; (B) ETHYL α-ACETAMIDO-α-CARBOETHOXY-β-(2-ACETAMIDOINDOLE-3)PROPIONATE; AND (C) ETHYL α-ACETAMIDO-α-CARBOETHOXY-β-(1-NITROSO-2-ACETAMIDO-INDOLE-3)PROPIONATE. SOLVENT, 95% ETHANOL

present in significant amounts. Purified authentic dinitrophenyloxindolylalanine gave only a fast-moving component whose chromatographic behavior paralleled that of the fast-moving component found in the derivatives prepared from the hydrolysis product even when several different developers were employed. Thus it is reasonable to conclude that III was converted into IV at least in part.

There is some evidence that the slow-moving component present in the crude preparations may be a bis-dinitrophenyl derivative. When pure authentic IV was boiled for a few minutes with aqueous sodium hydroxide prior to its reaction with dinitrofluorobenzene a product was obtained which, when chromatographed,

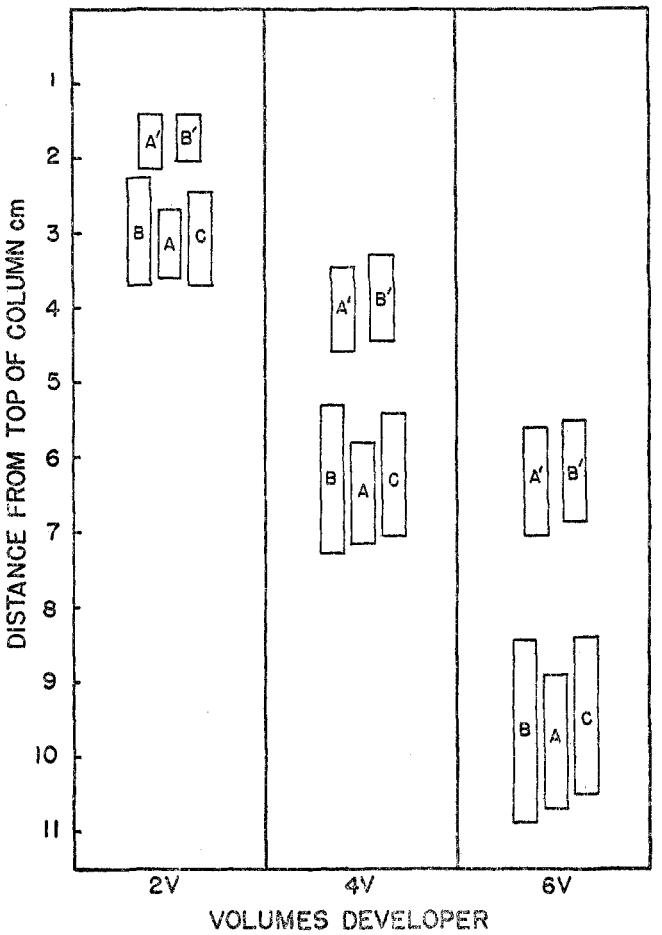


FIG. 3. CHROMATOGRAMS OF α-N-(2,4-DINITROPHENYL)OXINDOLYLALANINES. (A') slow-moving DNP derivative from hydrolysate; (A) fast-moving DNP derivative from hydrolysate; (B') slow-moving component of crude DNP derivative from authentic IV; (B) fast-moving component of crude DNP derivative from authentic IV; (C) purified DNP derivative from authentic IV. Developer; 3% (v/v) acetic acid and 15% (v/v) acetone in ligroin; V = 6.4 ml.

gave a single, though much wider, zone which was, for the most part, concentrated in the region of the slow-moving band observed for the derivatives prepared from the crude samples.

The presence of IV in the crude hydrolysis product derived from III may also

be inferred from the spectroscopic data given in Figures 2 and 6. Although the crude material exhibits a maximum at 255–256 mμ and the authentic sample one at 252 mμ the two curves are very similar and both differ substantially from that of III which presents a minimum at 258–260 mμ and a maximum at 291-292 mμ.

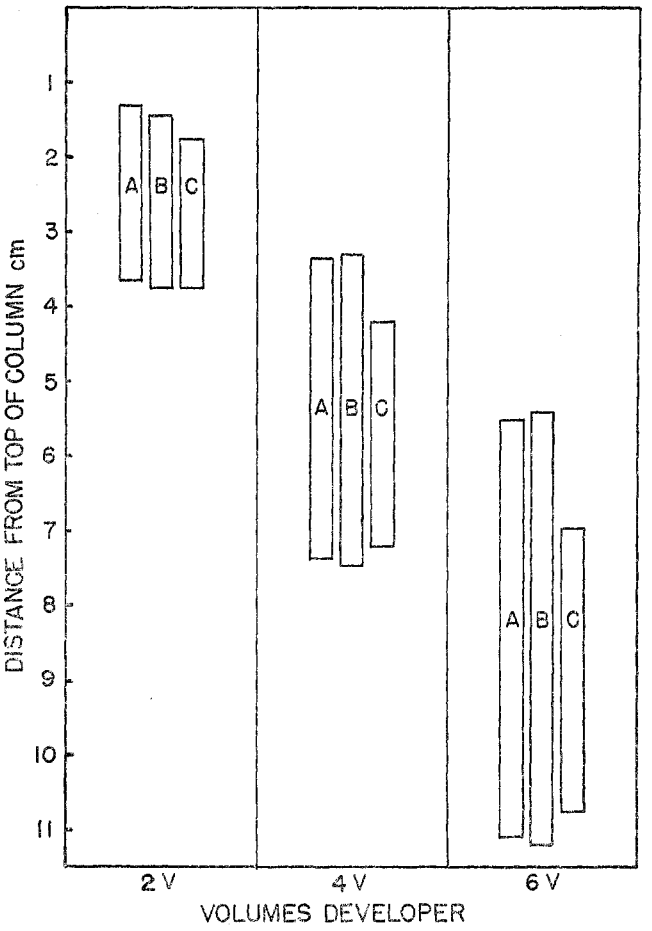


FIG. 4. CHROMATOGRAMS OF α-N-(2,4-DINITROPHENYL)OXINDOLYLALANINES. (A) crude DNP derivative from hydrolysate; (B) DNP derivative from authentic IV after previous treatment with aqueous sodium hydroxide; (C) purified DNP derivative from authentic IV. Developer; 8% (v/v) acetic acid and 15% (v/v) ethyl acetate in ligroin; V = 6.4 ml.

While it is clear that IV was present in the crude hydrolysis product obtained from III no attempt was made to find more favorable conditions for this transformation principally because other, and more attractive, methods for the synthesis of this compound are now available (1–3).

Phalloidin, the toxic peptide isolated from *Amanita phalloides*, from which IV was first obtained by hydrolysis (11) possesses an ultraviolet absorption

spectrum (10, 13) that is very different from that of IV, *cf.* Figure 6, but closely resembles that of III, *cf.* Figure 2. To account for this anomaly Cornforth, *et al.* (2) concluded that IV was formed only on hydrolysis of the peptide and was derived from the fragment V which was assumed to be present in the peptide.

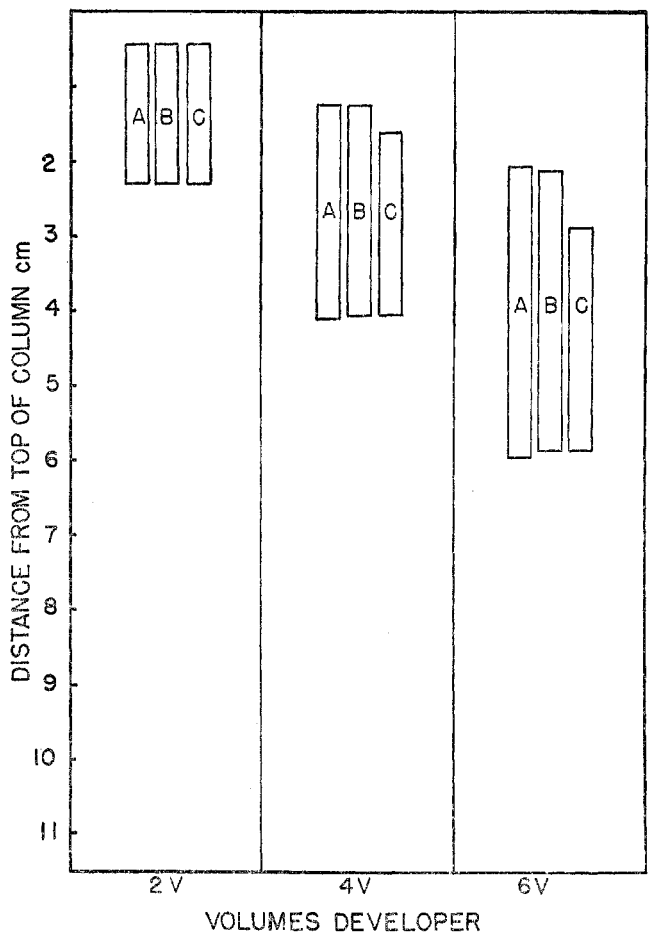


FIG. 5. CHROMATOGRAMS OF α-N-(2,4-DINITROPHENYL)OXINDOLYLALANINES. (A) crude DNP derivative from hydrolysate; (B) crude DNP derivative from authentic IV; (C) purified DNP derivative from authentic IV. Developer; 5% (v/v) acetic acid in benzene; V = 6.4 ml.

In view of the demonstrated conversion of III to IV by a hydrolytic process it is clear that several other possibilities, *e.g.* VI and VII, should also be considered in addition to V, and oxygen analogs thereof, particularly since there appears to be a second molecule of IV that is derived from a structure other than V (10).[4]

The ultraviolet absorption spectrum of the hydrochloride of the socalled

[4] It is of interest to note that the ring system of VI is similar to that of physostigmine.

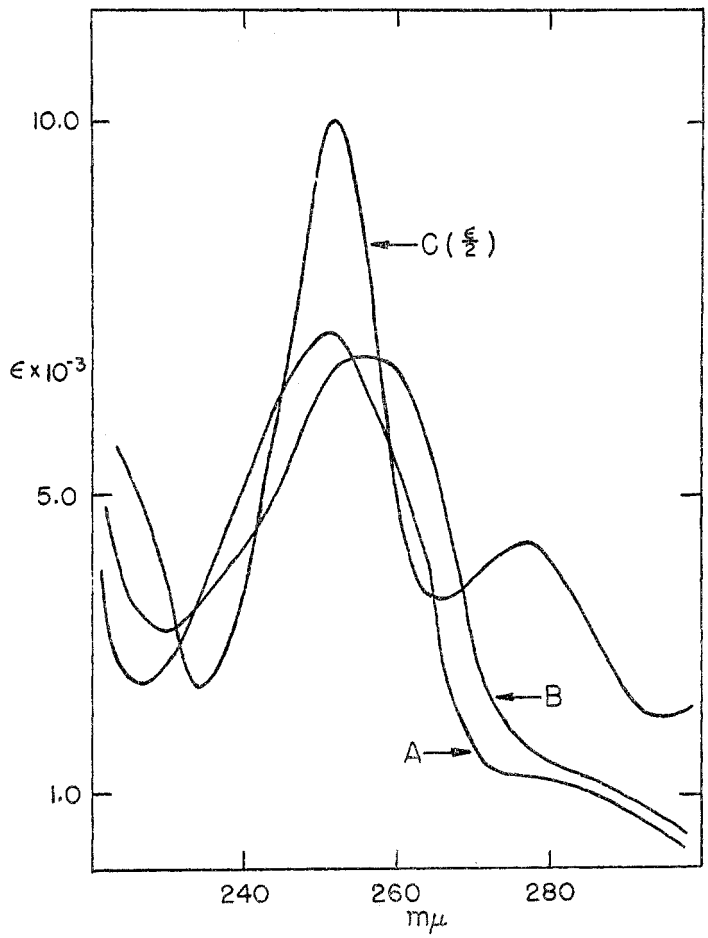
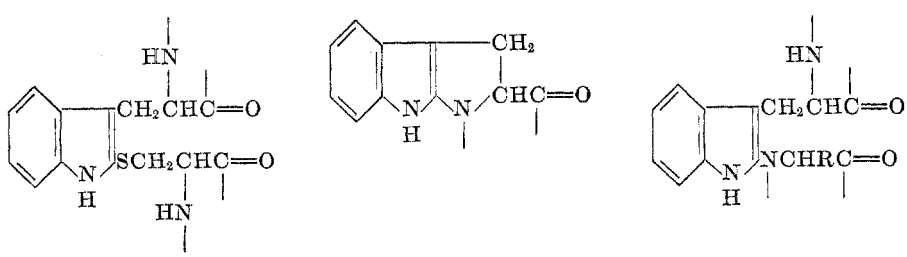


FIG. 6. ULTRAVIOLET ABSORPTION SPECTRA OF: (A) authentic oxindolylalanine hydrochloride; (B) crude hydrolysis product; (C) 2-iminoindoline hydrochloride. Solvent, 95% ethanol



V VI VII

2-aminoindole, *cf.* Figure 6, is similar to that of oxindole and very different from those of the 2-acetamidoindoles given in Figure 2. Therefore it appears that the former compound should be considered to be 2-iminoindoline hydrochloride.

EXPERIMENTAL[5, 6]

N-Benzyloxindole (2). Oxindole, 4.0 g., was added, with stirring, to a solution of 0.69 g. of sodium in 15 ml. of absolute ethanol, the mixture was heated to boiling under a reflux condenser, 3.34 ml. of benzyl chloride was added over a period of 3 hours, and the reaction mixture was heated for an additional 2 hours. The precipitated sodium chloride was removed from the cooled reaction mixture, and the filtrate was acidified with dilute hydrochloric acid, diluted with water, extracted repeatedly with chloroform, and the chloroform extract dried over sodium sulfate. The dried extract was freed of solvent, and the red oily residue was taken up in ethanol and fractionally crystallized to give a colorless crystalline product, m.p. 199.5–202.5°. This product was recrystallized three times from ethanol to give 20% of N-benzyloxindole, m.p. 205–206°.

Anal. Calc'd for $C_{15}H_{13}ON$ (223.3): C, 80.7; H, 5.9; N, 6.3.
Found: C, 80.6; H, 6.0; N, 6.3.

From the mother liquors there was obtained a small amount of tribenzyloxindole, m.p. 112–113°, after three recrystallizations from ethanol.

Anal. Calc'd for $C_{29}H_{25}NO$ (403.5): C, 86.3; H, 6.2; N, 3.5.
Found: C, 86.2; H, 6.1; N, 3.5.

Ethyl α-oximino-β-keto-3-(1-methyloxindolyl)propionate. Ethyl β-keto-3-(1-methyloxindolyl)propionate (6), 7.9 g., was added, with rapid stirring, to a hot solution of 0.69 g. of sodium in 65 ml. of absolute ethanol. To the orange-colored reaction mixture, cooled to 0°, there was added dropwise over a period of 20 minutes, 4.6 ml. of freshly distilled isoamyl nitrite; then the reaction mixture was stirred an additional 45 minutes at 25°, heated briefly to 70° and the clear solution cooled to −10° to effect crystallization of the orange-colored sodio-derivative which was collected in a pre-cooled centrifuge tube by centrifugation at 2500 r.p.m. for 10 minutes. The solid was dissolved in 100 ml. of cold water, the solution was acidified with dilute aqueous sulfuric acid in the presence of ice, the mixture extracted three times with 100 ml. of chloroform, and the chloroform extract was dried over sodium sulfate. The solvent was removed and the residual oil was dissolved in hot aqueous-ethanol and cooled to give yellow needles, initial m.p. 108–113°, resolidification at 120–130°, final m.p. 159–160°. Repeated recrystallization of this product from a mixture of ethanol, ether, and 60°-ligroin gave needles, initial m.p. 110–115°, resolidification above 120°, final m.p. 160–161°.

Anal. Calc'd for $C_{14}H_{14}N_2O_5 \cdot H_2O$ (308.3): C, 54.6; H, 6.2; N, 9.1.
Found: C, 55.2; H, 5.2; N, 8.8.

Carbobenzoxy-2-aminoindole. The azide of 2-indole-carboxylic acid (8), 10 g., was added in small portions to a boiling mixture of 20 ml. of benzyl alcohol and 100 ml. of toluene and the reaction mixture was heated, under refluxing conditions, for 30 minutes after the vigorous evolution of nitrogen had subsided. The precipitate that formed on cooling, probably bis-2-indolylurea, was discarded, the filtrate evaporated to dryness, and the residue recrystallized from methanol to give 6.4 g. of the urethan. Evaporation of the mother liquors and recrystallization of the residue from two 175-ml. portions of 90–120° ligroin gave an additional 2.6 g. of product. The crude product was twice recrystallized from methanol to give almost colorless carbobenzoxy-2-aminoindole, m.p. 139–140°.

Anal. Calc'd for $C_{16}H_{14}N_2O_2$ (252): C, 72.2; H, 5.3; N, 10.5.
Found: C, 71.6; H, 5.3; N, 10.4.

2-Aminoindole. A solution of 2.6 g. of the above urethan in 50 ml. of ethanol containing 0.8 ml. of concentrated hydrochloric acid was shaken in a stream of hydrogen with 0.5 g. of palladized carbon, prepared from 0.5 g. of carbon and 10 ml. of 5% aqueous palladium chloride, until the evolution of carbon dioxide had ceased. The catalyst was removed, the filtrate was evaporated to dryness, the residue dissolved in ethanol, filtered, the filtrate again evaporated to dryness, and this process repeated until the residue obtained upon

[5] All melting points are corrected.

[6] Microanalyses by Dr. A. Elek.

evaporation of the solvent was completely soluble in hot ethanol. Sufficient ether was added to the warm ethanol solution to produce a turbidity and the solution cooled to give 1.35 g. of 2-aminoindole hydrochloride, m.p. 222–224° after repeated recrystallization from a mixture of ethanol and acetone.

Anal. Calc'd for $C_8H_8N_2 \cdot HCl$ (168.6): C, 57.0; H, 5.4; N, 16.6.
Found: C, 57.1; H, 5.2; N, 16.3.

Hydrolysis of 2-aminoindole to oxindole. 2-Aminoindole hydrochloride, 0.1 g., was heated in a sealed tube with 25 ml. of water for 5 hours at 150–170°, the solvent was removed, and the residue was recrystallized from 60–70° ligroin to give 0.06 g. (76%) of oxindole, m.p. 123–125°.

o-Nitrophenylacetonitrile. The method described below was found to be more convenient and to give better yields than that of Rousseau and Lindwall (14) from which it was derived. The crude oxime of *o*-nitrophenylpyruvic acid (20 g.), obtained in a 64% yield by a procedure very similar to that described by Rousseau and Lindwall (14), was heated for 90 minutes, under refluxing conditions, with a mixture of 200 ml. of water and 10 ml. of acetic acid. The crystalline material which separated when the reaction mixture was cooled was collected and dried to give 12.4 g. (85%) of crude α-nitrophenylacetonitrile, m.p. 79–84°. Purification was effected by distillation at *ca.* 1 mm., b.p. 137–139°.

2-Acetamido-3-(dimethylaminomethyl)indole. 2-Diacetimidoindole, 3.0 g., prepared according to Pschorr (7) was dissolved in 12 ml. of acetic acid, the solution was cooled in an ice-bath, and 2.2 ml. of 33% aqueous dimethylamine was added; and then, slowly and with shaking, 1.2 ml. of 37% aqueous formaldehyde was dropped in. The temperature of the reaction mixture was kept below 35° until only a small amount of insoluble material remained; it was then heated briefly to 60°, the solution decanted from the residue, and the former added to an ice-cold solution of 20 g. of sodium carbonate in 150 ml. of water. After the addition of ice to the reaction mixture 10 *M* aqueous sodium hydroxide was added until the solution was alkaline to phenolphthalein; the precipitated solid was taken up in ether, the ethereal extract washed with a small amount of cold water, dried over sodium sulfate, the solvent removed, and the residue recrystallized from acetone to give 1.6 g. of the Mannich base, m.p. 161°.

Anal. Calc'd for $C_{13}H_{17}N_3O$ (231.3): C, 67.5; H, 7.4; N, 18.2.
Found: C, 67.6; H, 7.5; N, 18.2.

Reaction of the above base with methyl iodide gave a methiodide, m.p. 155–156°, which was too unstable to be recrystallized from the usual solvents.

2-Acetamido-3-(piperidinomethyl)indole. 2-Diacetimidoindole, 3.0 g., was condensed with piperidine and formaldehyde, as described in the preparation immediately above, to give 3.9 g. of crude Mannich base. Recrystallization from ethanol gave a product, m.p. 144–146°.

Anal. Calc'd for $C_{16}H_{21}N_3O$ (271.3): C, 70.8; H, 7.8; N, 15.5.
Found: C, 71.1; H, 7.9; N, 15.4.

Ethyl α-acetamido-α-carboethoxy-β-(2-acetamidoindole-3-)propionate. (*A*). Ethyl acetamidomalonate, 0.64 g., was added to 6.8 ml. of a solution of 1.0 g. of sodium in 100 ml. of ethanol; 1.1 g. of the crude methiodide of 2-acetamido-3-(dimethylaminomethyl)indole was then added and the mixture was heated under refluxing conditions for 6–7 hours. The solvent was removed, and the residue taken up in water, extracted with chloroform, the chloroform extract washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, evaporated to dryness and the residue recrystallized from ethanol to give 0.38 g. of product, m.p. 205–206°. Repeated recrystallization from ethanol gave colorless crystals, m.p. 208°.

Anal. Calc'd for $C_{20}H_{25}N_3O_5$ (403.4): C, 59.6; H, 6.2; N, 10.4.
Found: C, 59.9; H, 6.0; N, 10.1.

(*B*). An intimate mixture of 0.46 g. of 2-acetamido-3-(dimethylaminomethyl)indole and 0.44 g. of ethyl acetamidomalonate was heated at 150–170° for 15 minutes. After the oily reaction product had solidified it was recrystallized from ethanol to give 0.53 g. (66%) of product, m.p. 205–208°, and whose m.p. was not depressed when mixed with the preparation obtained in (*A*) above.

Ethyl α-acetamido-α-carboethoxy-β-(1-nitroso-2-acetamidoindole-3)propionate. A concentrated aqueous solution containing 0.15 g. of sodium nitrite was added dropwise to an ice-cold solution of 0.15 g. of ethyl α-acetamido-α-carboethoxy-β-(2-acetamidoindole-3)propionate in 1.5 ml. of glacial acetic acid. The mixture was then poured into 15 ml. of ice-water, and the yellow precipitate was recovered, dried over phosphorus pentoxide, and recrystallized from benzene to give 0.08 g. of the N-nitroso compound, fine yellow needles, m.p. 232–233°.

Anal. Calc'd for $C_{20}H_{24}N_4O_7$ (432.4): N, 13.0. Found: N, 12.8.

Ethyl α-acetamido-α-carboethoxy-β-(1-nitrosoindole-3)-propionate. Ethyl α-acetamido-α-carboethoxy-β-indole-3-propionate (15) was treated with sodium nitrite in acetic acid as described in the preceding preparation. The yellow product thus obtained was recrystallized from a mixture of benzene and 60–70° ligroin to give the N-nitroso compound, m.p. 145° with decomposition.

Anal. Calc'd for $C_{18}H_{21}N_3O_6$ (375.4): C, 57.6; H, 5.6; N, 11.2.
Found: C, 58.1; H, 5.7; N, 11.0.

Both the above and the preceding nitroso derivative appeared to decompose during recrystallization.

Oxindolylalanine. (*A*). Oxindolylalanine hydrochloride was prepared according to Kotake, *et al.* (1) and was found to exist in two allotropic modifications; one, m.p. 208°, with decomposition as reported (1), and the other, m.p. 234°, with decomposition.

Anal. Calc'd for $C_{11}H_{12}N_2O_3 \cdot HCl$ (256.7): C, 51.5; H, 5.1; N, 10.9.
Found: C, 51.8; H, 5.1; N, 10.6.

(*B*). Ethyl α-acetamido-α-carboethoxy-β-(2-acetamidoindole-3)propionate, 0.35 g., was heated, under refluxing conditions and in a stream of nitrogen, with 3.5 ml. of 30% aqueous sulfuric acid for 22 hours. The dark brown reaction mixture was cooled, diluted with water, carefully neutralized with aqueous barium hydroxide, and the precipitated barium sulfate repeatedly washed with water. The filtrate and washings were combined, the solvent removed, and the residue dried over concentrated sulfuric acid to give 0.1 g. of an ochre colored powder, m.p. *ca.* 221°, with decomposition. Like authentic oxindolylalanine this material gave a purple color with ninhydrin, a strong positive reaction with the Folin-Denis reagent (16), and a red dye when heated with aqueous sodium hydroxide followed by diazotization and reaction with β-naphthol. When the preliminary heating with aqueous sodium hydroxide was omitted only a transient orange coloration of the reaction mixture was observed. All attempts to obtain crystalline oxindolylalanine by recrystallization of the above powder were unsuccessful as was an experiment in which purification was attempted *via* the water-insoluble mercury complex.

α-N-(2,4-Dinitrophenyl)oxindolylalanine. To a solution of 0.02 g. of oxindolylalanine hydrochloride and 0.05 g. of sodium bicarbonate in 0.5 ml. of water there was added 0.05 g. of 2,4-dinitrofluorobenzene in 1 ml. of ethanol and the mixture was shaken under an atmosphere of nitrogen for 2 hours. The solvent was removed by evaporation in a stream of nitrogen, the residue taken up in water, and the excess dinitrofluorobenzene removed by extraction with ether. The aqueous phase then was acidified with 5 *N* hydrochloric acid, and the yellow precipitate collected, washed twice with water, dried *in vacuo* over concentrated sulfuric acid, and recrystallized several times from ethyl acetate to give α-N-(2,4-dintrophenyl)oxindolylalanine, m.p. 223°, with decomposition.

Anal. Calc'd for $C_{17}H_{14}N_4O_7$ (386.3): N, 14.5. Found: N, 14.4.

Spectra. All measurements were made at *ca.* 25° with a Beckman model DU spectrophotometer equipped with 1-cm. quartz cells.

Chromatographic experiments. The procedure described by Green and Kay (12) was employed throughout. The chromatographic tubes were *ca.* 200 mm. in length and 9 mm. in diameter, and were packed with *ca.* 150 mm. of a 3:1 mixture of silicic acid (Merck No. 40446) and Celite (Johns-Mansville No. 545). The dinitrophenyl derivatives, prepared essentially as described above, were dissolved in ethyl acetate and sufficient 60–70° ligroin was added to produce a faint turbidity prior to being placed on the column.

SUMMARY

Evidence is presented that oxindolylalanine can be obtained from 2-diacetimidoindole *via* a normal Mannich reaction to 2-acetamido-3-(dimethylaminomethyl)indole followed by condensation with ethyl acetamidomalonate and subsequent hydrolysis and decarboxylation of this reaction product. This reaction sequence and the fact that iminoindoline hydrochloride can be hydrolyzed to oxindole lends support to an interpretation of the origin of the second molecule of oxindolylalanine found in phalloidin hydrolysates. An account of a number of unsuccessful attempts to synthesize oxindolylalanine is also given.

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