[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

SYNTHESES OF 7-SUBSTITUTED INDOLINE DERIVATIVES[1, 2]

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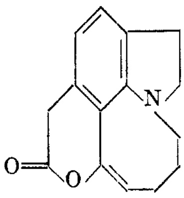
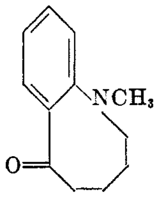
Treatment of β-erythroidine with strong acid gives a compound known as apo-β-erythroidine which is believed to have structure I (1). Preliminary studies using model compounds but directed toward the synthesis of apo-β-erythroidine or a closely related derivative have recently been reported (2, 3). In this work it was shown that methyl anthranilate could be converted readily to structure II and, presumably, a similar sequence of reactions starting with either 7-cyano- or 7-carbomethoxyindoline would yield a compound containing the tricyclic nucleus of apo-β-erythroidine. The present paper describes several attempts which were made to prepare such 7-substituted indoline derivatives and indicates some of the difficulties encountered.



I



II

Although the preparation of 7-substituted indolines would appear to be a rather simple task, investigation of the literature revealed that relatively few such indoline or indole derivatives have been reported. The limitations of the usual indole syntheses are such that they were of little use for the purpose at hand. The routes chosen for investigation therefore stemmed from indoline as starting material.

Electrophilic substitution reactions with N-acylindolines lead primarily to the introduction of a substituent at the 5-position and secondly to a substituent at the 7-position. To place a substituent at the desired 7-position it was therefore necessary to block the more readily substituted 5-position. The two ways in which this was done are illustrated in the reaction sequence below.

In the first instance, N-acetylindoline (III) was brominated to give 5-bromo-N-acetylindoline (IV) and this, in turn, was nitrated to yield VII in excellent over-all yield. Catalytic hydrogenation of VII over a palladium-on-charcoal catalyst resulted in removal of bromine as well as reduction of the nitro group and gave 7-amino-N-acetylindoline (IX) directly in good yield. However, the conversion of 7-amino-N-acetylindoline to 7-cyano-N-acetylindoline (XIII) by

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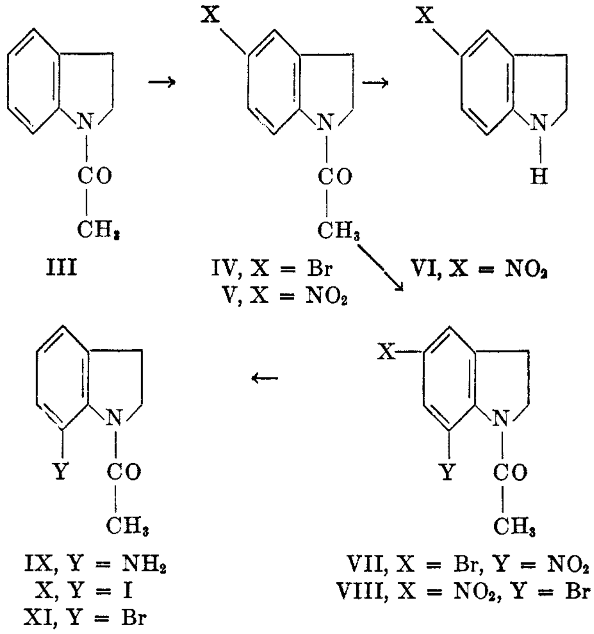
[1] Aided in part by a grant from the United Cerebral Palsy Association, Inc.

[2] Paper XIII in this series, for the preceding communication see ref. 3.

means of the Sandmeyer reaction failed completely. Although the analogous replacement of the amino group by iodine did occur under the conditions of the Sandmeyer reaction and it was possible to prepare 7-iodo-N-acetylindoline (X) in this way, the yield in this step was extremely low and it was impractical to continue this approach.



III

IV, X = Br
V, X = NO_2

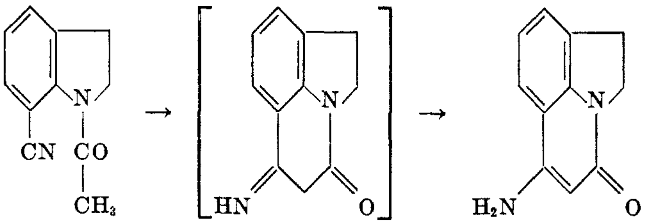
VI, X = NO_2

IX, Y = NH_2
X, Y = I
XI, Y = Br

VII, X = Br, Y = NO_2
VIII, X = NO_2, Y = Br

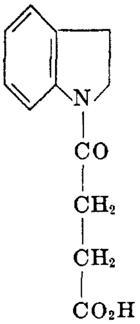
To overcome these difficulties the same general reaction scheme was repeated but the order of introduction of substituents was reversed. Thus, nitration of N-acetylindoline occurred readily to give 5-nitro-N-acetylindoline (V). Since this compound resisted bromination, the acetyl group was removed by hydrolysis and the resulting 5-nitroindoline was brominated in good yield. Reacetylation of the bromo derivative then gave the desired 5-nitro-7-bromo-N-acetylindoline (VIII). By the use of Adams' catalyst, the hydrogenation of VIII could be controlled to effect reduction of the nitro group without loss of bromine. The resulting 5-amino-7-bromo-N-acetylindoline after conversion to the corresponding diazonium derivative then was deaminated using hypophosphorous acid according to the procedure of Kornblum (4) to give the final product, 7-bromo-N-acetylindoline (XI). Although the yields in all of the reactions in this series are excellent, the fact that six steps are required to convert N-acetylindoline to 7-bromo-N-acetylindoline illustrates the tedious nature of the problem of preparing simple indoline derivatives.

It was anticipated that 7-bromo-N-acetylindoline on being subjected to the conditions of the von Braun reaction (5) would undergo replacement of bromine by the cyano group to give XII. Unfortunately, the reaction takes a different course. Although the product to be isolated had the correct composition for 7-cyano-N-acetylindoline (XII), its physical and chemical properties were not in accord with those to be expected for this structure. To account for the properties of the product—its high melting point, solubility in acid and resistance to hydrolysis—we propose that its structure is actually that of 4-amino-1, 8-ethano-2-quinolone (XIII). In this postulation it is assumed that the initial product is actually the cyano derivative (XII) but that under the conditions of the reaction this spontaneously cyclizes to give XIII, as illustrated below. Finally the spectral data strongly support XIII, rather than XII, as the correct structure. In the infrared a strong band occurs in the 3.05 to 3.15 μ region usually attributed to an N—H grouping, while in the ultraviolet the over-all absorption is quite similar to that of a quinolone (2) showing a broad peak in the 300 to 350 mμ region beyond where a simple indoline derivative should absorb.

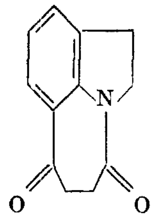


XII XIII

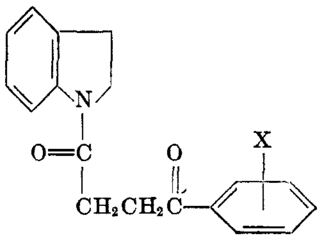
When it became apparent that the proposed schemes were not yielding the desired 7-substituted indoline derivatives, a number of alternate approaches were investigated. Of these, the attempts to cyclize N-succinoylindoline (XIV) perhaps deserve mention. In this instance a successful cyclization would yield in one step compound XV containing the desired tricyclic system. However, the usual conditions for cyclization of acids were without effect. When XIV was converted to the corresponding acid chloride and treated with aluminum chloride, reaction occurred but with the solvent to give a N-(β-benzoylpropionyl)indoline (XVI).



XIV



XV



XVI

EXPERIMENTAL[3]

N-Acetyl-5-bromoindoline (IV). To a mixture of 46.4 g. of N-acetylindoline (2, 6) in 300 ml. of acetic acid there was added dropwise with stirring 14 ml. of bromine. The reaction mixture was allowed to stand for a few minutes and then was poured into 2.5 l. of cold water. After the stirred suspension was treated with sodium bisulfite to remove the excess bromine, the solid was collected by filtration. Recrystallization of this solid from methanol gave 58.8 g. (85%) of colorless crystals, m.p. 118–119°.

Anal. Calc'd for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.18.
Found: C, 49.94; H, 4.31.

N-Acetyl-5-nitroindoline (V). To a mixture of 80 ml. of conc'd nitric acid in 250 ml. of conc'd sulfuric acid there was added 5-g. portions N-acetylindoline while maintaining the temperature of the mixture between 10 and 20° until a total of 120 g. of N-acetylindoline had been added. The reaction mixture was held at 5 to 10° for 12 hours and then was poured slowly into 2 l. of cold water with stirring. The precipitate was collected, washed thoroughly with water, and recrystallized from ethanol. This gave 121 g. (80%) of yellow needles, m.p. 173.5–175.5°.

Anal. Calc'd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89.
Found: C, 58.14; H, 5.15.

5-Nitroindoline (IV). A solution of 120 g. of N-acetyl-5-nitroindoline and 70 ml. of ethanol in 500 ml. of 6 *N* hydrochloric acid was boiled under reflux for 30 min. After filtration to remove traces of solid, the solution was made basic with aqueous ammonia and the solid precipitate was collected. This, after recrystallization from methanol, gave 76 g. (80%) of orange crystals, m.p. 92–93°.

Anal. Calc'd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91.
Found: C, 58.26; H, 5.14.

5-Nitro-7-bromoindoline. To a solution of 76 g. of 5-nitroindoline in 650 ml. of acetic acid there was added dropwise with stirring 22 ml. of bromine. After the addition was complete, the solution was poured into 3 l. of cold water containing 1.0 g. of sodium bisulfite. The precipitated solid was collected and recrystallized from ethanol to give 81 g. (72%) of orange crystals, m.p. 149–151°.

Anal. Calc'd for $C_8H_7BrN_2O_2$: C, 39.53; H, 2.90.
Found: C, 39.64; H, 3.17.

N-Acetyl-5-bromo-7-nitroindoline (VII). To a cold mixture of 9.7 ml. of fuming nitric acid, 50 ml. of acetic acid, and 62 ml. of conc'd sulfuric acid there was added in small portions with stirring 41.5 g. of N-acetyl-5-bromoindoline. During addition the reaction mixture was maintained between 0 and 5° and it was held at this temperature for another 15 hours. At the end of this time the mixture was poured onto cracked ice and the precipitated solid was collected, washed with water, and dried. Recrystallization of the resulting material from benzene gave 40.0 g. (78%) of yellow crystals, m.p. 197–198°.

Anal. Calc'd for $C_{10}H_9BrN_2O_3$: C, 42.12; H, 3.18.
Found: C, 41.71; H, 3.38.

N-Acetyl-5-nitro-7-bromoindoline (VIII). A mixture of 81.0 g. of 5-nitro-7-bromoindoline, 50.0 g. of acetyl chloride, and 400 ml. of acetic acid was boiled under reflux until hydrogen chloride was no longer evolved. The mixture then was cooled and poured into 3 l. of cold water. After the precipitate had been collected, it was washed carefully with water and dried. Recrystallization from a benzene-methanol mixture gave 70.0 g. (74%) of yellow crystals, m.p. 173.5–175.5°.

Anal. Calc'd for $C_{10}H_9BrN_2O_3$: C, 42.12; H, 3.18.
Found: C, 42.38; H, 3.31.

N-Acetyl-7-aminoindoline (IX). A suspension of 11.6 g. of N-acetyl-5-bromo-7-nitro-

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[3] Analyses by Miss C. King and Miss V. Williams. All melting points are corrected.

indoline and 5.0 g. of a 10% palladium-on-charcoal catalyst in 150 ml. of ethanol was subjected to hydrogenation at 3 atmospheres pressure and room temperature. After 30 min. hydrogen absorption was complete and the catalyst and solvent were removed. The residual solid, the amine hydrobromide, was dissolved in water and treated with solid sodium carbonate to liberate the free amine. When the product was collected and recrystallized from water, there resulted 6.3 g. (90%) of colorless crystals, m.p. 159–160°. The catalyst was recovered and used again without loss of activity.

Anal. Calc'd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86.
Found: C, 68.43; H, 7.22.

N-Acetyl-7-iodoindoline (X). A solution of 1.76 g. of N-acetyl-7-aminoindoline in 10 ml. of water containing 0.65 ml. of conc'd sulfuric acid was diazotized by adding a solution of 0.72 g. of sodium nitrite in 1.5 ml. of water dropwise with stirring. The resulting solution was acidified by adding 0.2 ml. of conc'd sulfuric and then 2 g. of potassium iodide in 2 ml. of water was added, the temperature of the mixture being maintained at 0°. Then, 10 mg. of copper-bronze was added and the mixture was warmed until nitrogen evolution ceased. The black oil, which separated, was extracted with chloroform, washed with sodium thiosulfate, and concentrated. To insure the presence of the acetyl group, the residual oil was warmed with acetic anhydride and then was poured into cold aqueous sodium carbonate solution. The brown solid, which separated, was collected and recrystallized from methanol. This gave 200 mg. (7%) of colorless crystals, m.p. 119–120°.

Anal. Calc'd for $C_{10}H_{10}INO$: C, 41.83; H, 3.51.
Found: C, 42.36; H, 3.71.

When the above experiment was repeated using potassium cyanide in place of potassium iodide, nothing useful could be isolated from the reaction mixture. Likewise, the use of cuprous cyanide under various conditions, as employed in the Sandmeyer action, was not helpful.

N-Acetyl-5-amino-7-bromoindoline. A solution of 22.0 g. of N-acetyl-5-nitro-7-bromoindoline in 75 ml. of ethanol containing 500 mg. of platinum oxide catalyst was subjected to hydrogenation at 70° and 3 atmospheres pressure. As soon as the solution became colorless the hydrogenation was interrupted and the solvent and catalyst were removed. Crystallization of the residue from methanol gave 14.5 g. (74%) of colorless crystals m.p. 188–190°.

Anal. Calc'd for $C_{10}H_{11}BrN_2O$: C, 47.08; H, 4.35.
Found: C, 47.22; H, 4.91.

N-Acetyl-7-bromoindoline (XI). A solution of 17.7 g. of N-acetyl-5-amino-7-bromoindoline in 60 ml. of 6 *N* hydrochloric acid was cooled to $-5°$ and diazotized by the dropwise addition with stirring of a solution of 5.1 g. of sodium nitrite in 12 ml. of water. Then 125 ml. of a cold solution of 50% hypophosphorous acid was added and the mixture was stored overnight at 5°. The solid, which separated, was collected and recrystallized from ethanol to give 11.0 g. (66%) of light tan crystals, m.p. 113–115.5°. A sample for analysis was further purified by treatment with charcoal and recrystallization from methanol and was obtained as colorless crystals, m.p. 116–117°. A mixture of this material and N-acetyl-5-bromoindoline, prepared by the bromination of N-acetylindoline, showed a marked depression of melting point.

Anal. Calc'd for $C_{10}H_{10}BrNO$: C, 50.02; H, 4.18.
Found: C, 50.25; H, 4.52.

4-Amino-1,8-ethano-2-quinolone (XIII). A mixture of 2.0 g. of N-acetyl-7-bromoindoline and 1.5 g. of cuprous cyanide plus small amounts of *p*-tolunitrile and copper sulfate was heated at 250° for 25 min. A vigorous reaction appeared to occur as evidenced by effervescence and blackening. The mixture, after cooling, was finely powdered, placed in a Soxhlet and extracted continuously with acetone for 3 days. After removal of the acetone, the residue was sublimed at 250° and 0.5 mm. to give 260 mg. (17%) of a yellow crystalline solid. This, on recrystallization first from acetic acid and then from ethanol, gave yellow prisms, m.p. 324–326°, dec. These crystals were insoluble in most organic solvents, although sparingly soluble in ethanol. They dissolved in acid but not in base. Attempts to effect hydrolysis with acid or base under the usual conditions for a nitrile or amide group gave unchanged starting material.

Anal. Calc'd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05.

Found: C, 70.53; H, 5.55; N, 15.03.

N-Succinoylindoline (XIV). A mixture of 12.2 g. of powdered succinic anhydride and 14.5 g. of indoline in 130 ml. of chloroform was boiled under reflux for 3 hours. The solution was extracted with 5% sodium carbonate solution and the alkaline extracts were acidified. The solid, which separated, was recrystallized from absolute ethanol to give 22.5 g. (85%) of colorless crystals, m.p. 163–164°.

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98.

Found: C, 65.53; H, 6.13.

Treatment of N-succinoylindoline with hydrogen fluoride or sulfuric acid led either to unchanged starting material or resulted in hydrolysis giving indoline and succinic acid. In one experiment, 1.8 g. of N-succinoylindoline, 1.0 g. of zinc chloride, and 6 ml. of acetic anhydride in 9 ml. of acetic acid was boiled under reflux for one hour. When the mixture was poured into 50 ml. of cold water a solid separated. This was collected, washed with a sodium carbonate solution, and then crystallized from ethanol. There was obtained 1.3 g. (84%) of colorless crystals, m.p. 229–232°. That this material was succinindolide was shown from its composition and also by independent synthesis. When a mixture of succinic anhydride and two equivalents of indoline was heated at 150°, a sample of identical properties resulted.

Anal. Calc'd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29.

Found: C, 75.03; H, 6.26.

N-(β-Benzoylpropionyl)indoline (XVI, X = H). A mixture of 1.0 g. of N-succinoylindoline and 1.0 g. of phosphorus pentachloride in 5 ml. of benzene was warmed until hydrogen chloride evolution ceased and a clear yellow solution resulted. The solution then was concentrated *in vacuo* at room temperature and a mixture of 10 ml. of benzene and 10 g. of anhydrous aluminum chloride was added. After the resulting mixture had boiled under reflux for 30 min., it was hydrolyzed by pouring it onto a mixture of hydrochloric acid and cracked ice. The benzene layer was separated, washed with an aqueous sodium carbonate solution, and concentrated. The resulting solid was recrystallized from a benzene-heptane mixture to give 250 mg. (27%) of colorless crystals, m.p. 141–142°. That these crystals had ketonic properties was shown by the formation of a 2,4-dinitrophenylhydrazone derivative (m.p. 227–229°).

Anal. Calc'd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.14; N, 5.01.

Found: C, 77.20; H, 6.30; N, 5.06.

A similar experiment in which 20 ml. of chlorobenzene was substituted for the benzene as solvent led to the isolation of 0.96 g. (60%) of yellow plates, m.p. 148–149°, after recrystallization from ethanol. The composition of this material indicated that it was an N-(β-chlorobenzoylpropionyl)indoline (XVI, X = Cl). The position of the chlorine atom was not determined but, by analogy with similar Friedel-Crafts reactions with chlorobenzene as solvent (7), it probably is *para* to the carbonyl group.

Anal. Calc'd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14.

Found: C, 69.05; H, 5.28.

SUMMARY

The preparation of a number of 7-substituted indolines is described. Although these derivatives have interest as possible precursors for the tricyclic system present in apo-β-erythroidine, attempts to accomplish such a conversion were unsuccessful.

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On and after September 1, 1955, the Journal will accept *Notes*; the Journal will accept *Communications to the Editor* received on or after November 1, 1955 for publication in Volume 21. See revised Notice to Authors for details.

Effective with Volume 21, the Journal will use a double column format with a page size approximately 6½″ by 9″. Authors should consider this in connection with graph sizes, and table compositions.