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The Synthesis of 5-Keto-1,3,4,5-tetrahydrobenz[cd]indole. A Synthesis of 4-Substituted Indoles

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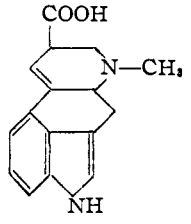
The alkaloids isolated from *Claviceps purpurea* have been shown to be substances of polypeptide nature derived from certain α-amino acids of relatively low molecular weight combined through amide linkage with a characteristic,complex indole derivative, lysergic acid.[1] More recently, the tetracyclic structure originally postulated on the basis of degradation studies for this characteristic ampholyte has been confirmed by the total synthesis of dihydro-*dl*-lysergic acid.[2] The unprecedented *ergoline* ring system[3] encountered as this expression in the ergot alkaloids represents the only example of an indole derivative condensed in the 3,4-position to other nuclei which has been observed in nature or obtained by synthesis. Hitherto, the sole synthetic route to this novel type of structure has involved the sodium–butanol reduction of appropriately substituted naphthostyril derivatives and benzo[f]quinoline lactams. This procedure, while feasible in certain cases with simple derivatives, fails, or at best affords the indole in yields of less than ten per cent. in the case of naphthostyrils substituted with highly reactive functional groups, and attempts to synthesize lysergic acid by procedures involving reduction to the indole stage as one of the final steps have appeared most unpromising. New methods of approach to the synthesis of the ergoline type of ring structure are accordingly required to facilitate study of the chemistry of these interesting and unique indole derivatives, as well as to provide intermediates for the eventual synthesis of the alkaloids themselves.



Lysergic acid

Simple indoles substituted in the 4-position have been rarely reported in the literature, inasmuch as the only methods available for their synthesis have been those (such as the Fischer synthesis from meta-substituted phenylhydrazones) which give a mixture of the 4- and 6-isomers which are difficult to separate and identify, or those which with few exceptions yield compounds with substituents in the hetero-ring not readily eliminated in subsequent reactions.[4] A procedure has now been developed by which it is possible to prepare directly and in pure form, free from isomers, indoles substituted only in the 4-position in the benz-nucleus. The synthesis leads directly to the 4-chloro- and 4-cyanoindoles, and further functions are obtained by operation upon these groups. This new method has been extended to the preparation of β-(4-carboxy-3-indole)-propionic acid (VII), and ring closure under specific conditions has led to the synthesis of the tricyclic 5-keto-1,3,4,5-tetrahydrobenz[cd]indole (VIII).

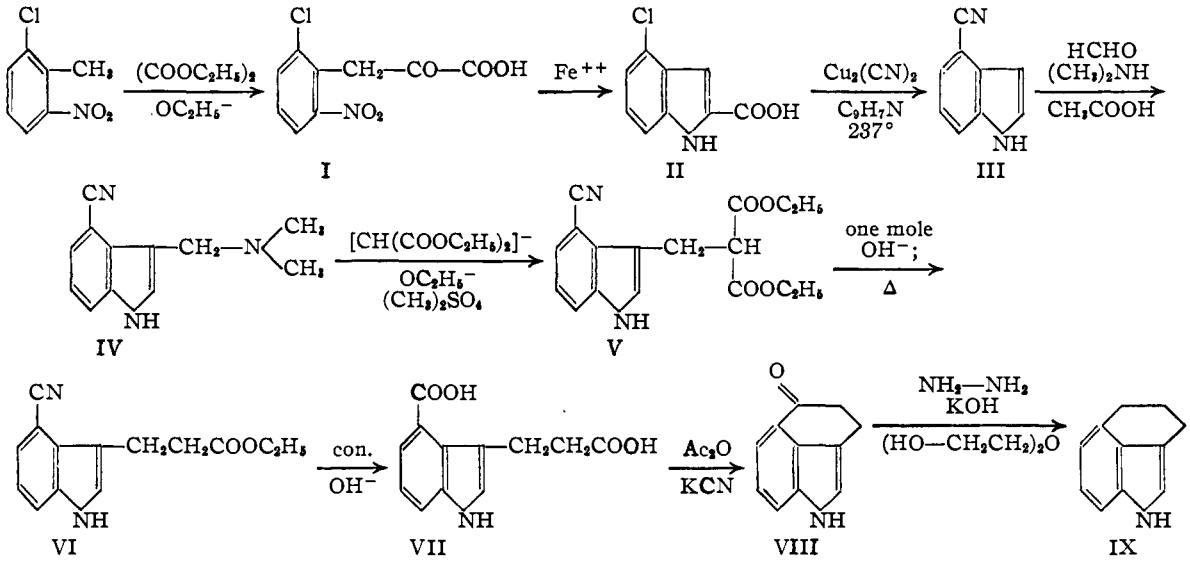
The starting material chosen for the synthetic sequence, the readily available dyestuff intermedi-

(1) For example, four of the principal alkaloids yield the following hydrolysis products, respectively: ergotamine—lysergic acid, *d*-proline, *l*-phenylalanine, pyruvic acid, and ammonia; ergosine—lysergic acid, *d*-proline, *l*-leucine, pyruvic acid, and ammonia; ergocornine—lysergic acid, *d*-proline, *l*-valine, isobutyrylformic acid, and ammonia; ergonovine—the least complex of the series—lysergic acid and *d*-2-aminopropanol.

(2) Uhle and Jacobs, *J. Org. Chem.*, **10**, 176 (1945).

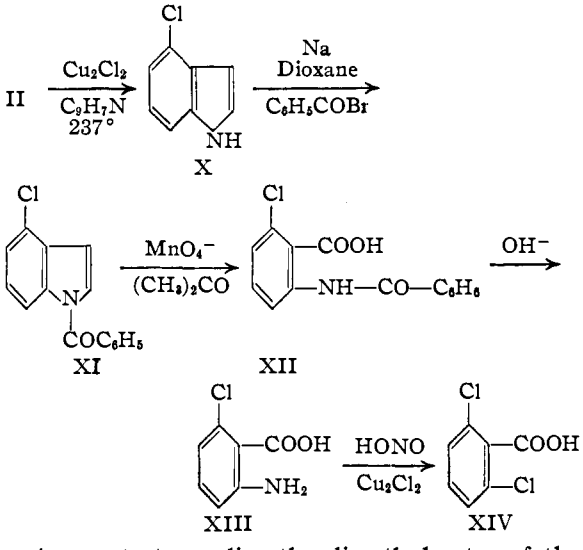
(3) Ring Index No. 2439.

(4) Marion and Oldfield, *Can. J. Res.*, **25B**, 1 (1947).

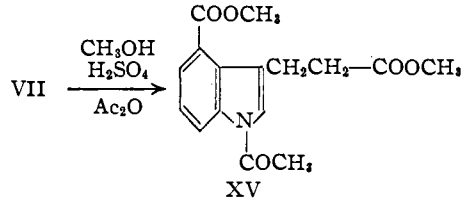


ate, 2-nitro-6-chlorotoluene, was condensed with ethyl oxalate, and the pyruvic acid derivative (I) reduced with ferrous hydroxide to 4-chloro-2-indolecarboxylic acid (II). Decarboxylation, as well as metathetical replacement of the halogen substituent occurred with cuprous cyanide in refluxing quinoline, and the 4-cyanoindole (III) isolated in good yield and characterized as 4-indolecarboxylic acid was converted through the Mannich base (IV) and the malonic ester derivative (V) to β-(4-carboxy-3-indole-)-propionic acid (VII).

The position of the substituent in the benz-nucleus was confirmed by the degradation of 4-chlorindole (X), obtained by decarboxylation of (II) with cuprous chloride in quinoline, to the known 6-chloroanthranilic acid (XIII) and 2,6-dichlorobenzoic acid (XIV).



Attempts to cyclize the dimethyl ester of the acid (VII) under the conditions of the Dieckmann condensation, using a wide variety of experimental variations and solvents, failed to give evidence of the formation of the desired tricyclic β-keto ester. Reaction with the metal occurred under some conditions leading to condensations involving presumably the indole nitrogen, but the products were difficult to isolate in a state of purity. N-Acetyl methyl-β-(4-carbomethoxy-3-indole)-propionate (XV) when allowed to react with sodium in re-

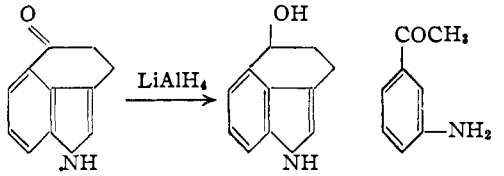


fluxing *p*-cymene gave no evidence of reaction. Ethyl β-(4-cyano-3-indole)-propionate (VI) likewise failed to exhibit tendency toward intramolecular condensation. Pyrolysis of the calcium or barium salt of β-(4-carboxy-3-indole)-propionic acid (VII) was not successful, and pyrolysis of the free dicarboxylic acid (VII) at 300° under diminished pressure led to decarboxylation of the nuclear carboxyl group, giving as the sublimate β-(3-indole)-propionic acid in low yield.

It was eventually found, however, that when a dilute solution of β-(4-carboxy-3-indole)-propionic acid (VII) in acetic anhydride containing a catalytic quantity of potassium cyanide was maintained at reflux temperature for an extended period and the reaction product hydrolyzed with alkali, a beautifully crystalline ketone was isolable in excellent yield. Uncyclized dicarboxylic acid was recovered from the alkaline filtrate, accounting for essentially the entire quantity of the compound used. The lemon-yellow keto-compound gave the usual carbonyl reactions and was characterized as the semicarbazone and as the *p*-nitrophenylhydrazone. A modified Wolff–Kishner

type reduction with hydrazine and potassium hydroxide in diethylene glycol, as well as a Clemmensen reduction, led to the formation of a compound which proved to be identical with 1,3,4,5-tetrahydrobenz[cd]indole (IX), prepared by sodium–butanol reduction of naphthostyril. The structure of the ketone is accordingly indicated to be 5-keto-1,3,4,5-tetrahydrobenz[cd]indole (VIII).

Hydrogenation of (VIII) by means of lithium aluminum hydride in ether solution gave 5-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (XVI) in excellent yield. Reduction of the carbonyl function in anhydrous isopropyl alcohol in the presence of aluminum isopropoxide led to the formation of a derivative with properties and analytical data which indicated it to be the isopropyl ether (XVII) of the alcohol (XVI).[5]



VIII XVI XVIII

The ultraviolet absorption spectrum[6] of the ketone (VIII), Fig. 1, exhibits maxima at 245 and 325 mμ and a minimum at 267 mμ, values suggesting those given by lysergic acid, which shows peaks at 230 and 315 mμ and a minimum at 270 mμ.[7] *m*-Aminoacetophenone (XVIII) gives a curve of similar form with maxima at 235 and 340 mμ and a minimum at 285 mμ. The 5-hydroxy compound (XVI) prepared by lithium aluminum hydride hydrogenation of the ketone (VIII), the isopropyl ether (XVII) formed in the Meerwein reduction, and the 1,3,4,5-tetrahydrobenz[cd]-indole (IX) prepared by hydrazine reduction of the ketone (VIII) as well as by sodium–butanol reduction of naphthostyril, gave practically superimposable curves with maxima at 230 and 280 mμ and a minimum at 254 mμ in conformity with data previously observed for certain indoles and for heterocyclic compounds derived from the indole nucleus.[7,8]

Additional reactions and properties of (VIII) and its utilization in further synthetic work, as well as an extension of the general methods, will be reported in subsequent communications.

Experimental[9]

2-Nitro-6-chlorophenylpyruvic Acid (I).—To a solution of 23 g. (1.0 mole) of sodium in 350 ml. of absolute ethanol was added 146 g. (1.0 mole) of ethyl oxalate and 171.6 g. (1.0 mole) of 2-nitro-6-chlorotoluene and the mixture maintained at reflux temperature for forty minutes. The dark red solution was diluted with water and distilled with steam until starting material no longer collected in the distillate. The aqueous residue from the distillation was clarified by filtration and acidified with hydrochloric acid. The heavy precipitate which separated was collected by filtration and recrystallized from benzene. The compound gave the characteristic deep red color with alkali and a dark green color with ferric chloride solution. The yield was 102 g. (42%), and 70 g. (41%) of 2-nitro-6-chlorotoluene was recovered unchanged; m. p. 114–115°.

Anal. Calcd. for $C_9H_6NO_5Cl$: C, 44.38; H, 2.48. Found: C, 44.39; H, 2.84.

The semicarbazone was prepared in dilute ethanol and recrystallized from ethanol; m. p. 204–205°.

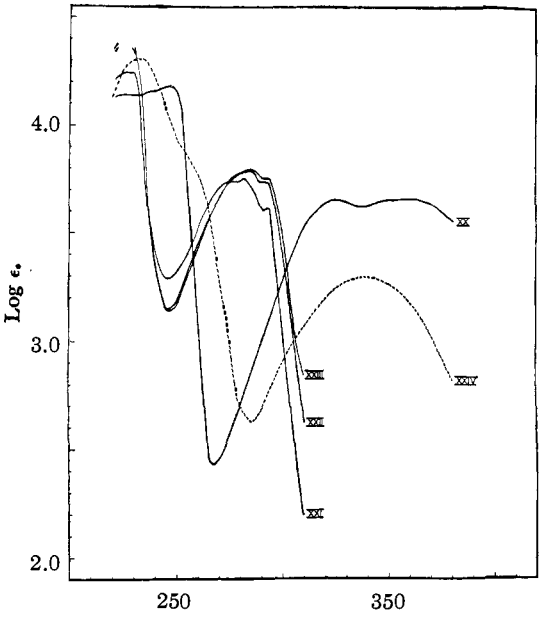
Anal. Calcd. for $C_{10}H_9N_4O_5Cl$: C, 39.95; H, 3.01. Found: C, 39.92; H, 3.05.

4-Chloro-2-indolecarboxylic Acid (II).—A solution of 81 g. (0.33 mole) of 2-nitro-6-chlorophenylpyruvic acid in dilute ammonium hydroxide solution was added to a suspension of ferrous hydroxide prepared from 560 g. (2.0 moles) of ferrous sulfate heptahydrate and 230 ml. of concentrated ammonium hydroxide solution in two liters of water and the mixture maintained at the boiling point for five minutes. The ferric hydroxide was separated by filtration, washed repeatedly with dilute ammonium hydroxide solution and water, and the filtrate acidified with dilute hydrochloric acid solution. The precipitate was recrystallized from a mixture of ethanol and water; yield 60 g. (92%); m. p. 259–260°.

Anal. Calcd. for $C_9H_6NO_2Cl$: C, 55.27; H, 3.09. Found: C, 55.38; H, 3.08.

The methyl ester was prepared by maintaining under reflux a solution of 3 g. of the acid in a mixture of 30 ml. of methanol and 3 ml. of concentrated sulfuric acid for fifteen hours. The solution was concentrated under diminished pressure, extracted with ether and aqueous sodium bicarbonate solution, and the residue from evaporation of the ether recrystallized from ethanol; yield 2.8 g. (87%); m. p. 146–147°.

Anal. Calcd. for $C_{10}H_8NO_2Cl$: C, 57.30; H, 3.84. Found: C, 57.42; H, 3.87.



Wave length in millimicrons.

Fig. 1.—Ultraviolet absorption spectra.

(5) Ether formation under the conditions of the Meerwein–Pondorff–Verley reduction has been observed in a few cases, Adams, *et al.*, "Org. Reactions," Vol. II, p. 190.

(6) The ultraviolet absorption spectra were determined on a Beckmann quartz spectrophotometer using a hydrogen discharge tube as a source of radiation, solvent, absolute ethanol; $\epsilon = 1/cd \log I/I_0$, $c = 0.0001$ molar, $d = 1$ cm.

(7) Jacobs, Craig and Rothen, *Science*, **83**, 166 (1936).

(8) Ward, *Biochem. J.*, **17**, 891 (1923).

(9) All melting points are micro melting points. Microanalyses by Stephen Nagy of the Massachusetts Institute of Technology.

4-Chloroindole (X).—A mixture of 49 g. (0.25 mole) of 4-chloro-2-indolecarboxylic acid, 75 g. (0.125 mole) of cuprous chloride and 150 g. of quinoline was maintained under reflux for eight hours. The hot mixture was poured into ice and hydrochloric acid and repeatedly extracted with ether. The ether solution was washed with hydrochloric acid, water and sodium bicarbonate solution, dried over magnesium sulfate, and the residue from the distillation of the ether submitted to fractionation *in vacuo*. The yield of colorless oil was 30 g. (77.5%); b. p. 143° (10 mm.); d^{20}_{20} 1.2485; $n^{20}D$ 1.6254; M_D calcd. 42.43; M_D found 42.93.

Anal. Calcd. for C_8H_6NCl: C, 63.38; H, 4.00. Found: C, 63.95; H, 4.15.

The picrate was prepared in ethanol solution and recrystallized from the same solvent; m. p. 171–173°.

Anal. Calcd. for $C_{14}H_9N_4O_7Cl$: C, 44.16; H, 2.38. Found: C, 44.31; H, 2.52.

N-Benzoyl-4-chloroindole (XI).—To a suspension of 1.15 g. (0.05 mole) of sodium sand in 20 ml. of dioxane was added 7.6 g. (0.05 mole) of 4-chloroindole and the mixture maintained under reflux for two hours to complete formation of the sodium derivative. A solution of 9.25 g. (0.05 mole) of benzoyl bromide in 5 ml. of dioxane was then added and the mixture maintained at reflux temperature for fifteen hours. The dioxane was distilled under diminished pressure, the residue extracted with a mixture of ether and water and the residue from the dried ether solution recrystallized from absolute ethanol; yield 6.2 g. (49%); m. p. 130–131°.

Anal. Calcd. for $C_{15}H_{10}NOCl$: C, 70.46; H, 3.94. Found: C, 70.36; H, 4.13.

N-Benzoyl-6-chloroanthranilic Acid (XII).—To a solution of 2.56 g. (0.01 mole) of N-benzoyl-4-chloroindole in 100 ml. of acetone was added, in portions, 10 g. (0.063 mole) of finely powdered potassium permanganate and the mixture stirred for fifteen hours. Fifty milliliters of ethanol was added and when the purple color had been discharged the manganese dioxide was separated by filtration and washed repeatedly with ethanol. The combined filtrates were concentrated to dryness under diminished pressure, dilute sodium hydroxide solution was added, 0.30 g. (14%) of unchanged starting compound removed by filtration, the filtrate acidified with hydrochloric acid, and the precipitate recrystallized from a mixture of ethanol and water; yield 1.38 g. (50%); m. p. 188–190°.

Anal. Calcd. for $C_{14}H_{10}NO_3Cl$: C, 61.00; H, 3.66. Found: C, 61.10; H, 3.79.

6-Chloroanthranilic Acid (XIII).—A solution of 1.38 g. (0.005 mole) of N-benzoyl-6-chloroanthranilic acid in 25 ml. of 10% sodium hydroxide solution was maintained under reflux for five hours, cooled, and acidified with dilute hydrochloric acid. The benzoic acid which separated weighed 500 mg. (82%). The filtrate was neutralized to *p*H 4 with solid sodium acetate and a solution of cupric acetate added dropwise. The copper salt which separated was collected by filtration, suspended in water, decomposed with hydrogen sulfide, and the filtrate from the copper sulfide concentrated to dryness *in vacuo*. The residue was recrystallized from benzene; yield 350 mg. (41%); m. p. 153–154°.[10]

Anal. Calcd. for $C_7H_6NO_2Cl$: C, 49.00; H, 3.52. Found: C, 49.10; H, 3.66.

The N-acetyl derivative was prepared by stirring a solution of 50 mg. of the sodium salt in 2 ml. of water with 0.5 ml. of acetic anhydride. The precipitate which separated after the solution had been chilled was recrystallized from water; m. p. 215–216°.[10]

2,6-Dichlorobenzoic Acid (XIV).—To a suspension at 0° of 86 mg. of 6-chloroanthranilic acid obtained from the oxidation of N-benzoyl-4-chloroindole in 1 ml. of 20% hydrochloric acid was added 35 mg. of sodium nitrite and the solution of the diazonium salt poured into a solution of 50 mg. of cuprous chloride in 20% hydrochloric acid and the solution allowed to come to room temperature. The precipitate was recrystallized from a mixture of equal quantities of benzene and ligroin; yield 72 mg. (76%); m. p. 143–144°.[11]

4-Cyanoindole (III).—A mixture of 9.78 g. (0.05 mole) of 4-chloro-2-indolecarboxylic acid (II), 6.7 g. (0.0375 mole) of cuprous cyanide, and 35 g. of quinoline was maintained at the reflux temperature of 237° for twenty hours. The hot dark-brown solution was poured into a mixture of 25 ml. of concentrated hydrochloric acid and ice and the well stirred precipitate collected by filtration and washed with water. The filtrate and precipitate were repeatedly extracted with ether, the ether solutions combined and washed with hydrochloric acid solution and water, dried over magnesium sulfate and concentrated under diminished pressure. The crystalline compound which remained was recrystallized from a large volume of water from which it separated in long, white silken needles; yield 3.6 g. (51%); m. p. 120–121°.

Anal. Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 75.94; H, 4.27; N, 19.53.

The picrate was prepared in methanol and recrystallized from the same solvent; m. p. 164–165°.

Anal. Calcd. for $C_{15}H_9N_5O_7$: C, 48.52; H, 2.44. Found: C, 48.32; H, 2.60.

4-Indolecarboxylic Acid.—A suspension of 1 g. of 4-cyanoindole in 10 ml. of 20% potassium hydroxide solution was maintained at reflux temperature for twenty hours. The alkaline solution was extracted with ether, the aqueous phase acidified with dilute hydrochloric acid solution and the precipitate recrystallized from water; yield 0.90 g. (80%); m. p. 213–214°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38. Found: C, 66.95; H, 4.57.

The methyl ester was prepared by maintaining at reflux temperature a solution of the acid in a mixture of 1 ml. of concentrated sulfuric acid in 10 ml. of methanol. The solution was concentrated under diminished pressure, extracted with ether and with dilute sodium bicarbonate solution and the residue from the ether recrystallized from methanol; m. p. 146–147°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.20; H, 5.13.

4-Cyanogramine (IV).—To a solution of 71.0 g. (0.5 mole) of 4-cyanoindole in 250 ml. of acetic acid was added 41 g. (0.5 mole) of a 36.5% aqueous solution of formaldehyde and 90 g. (0.5 mole) of a 25% aqueous solution of dimethylamine and the mixture allowed to stand at room temperature for twelve hours. The acetic acid was distilled under diminished pressure, 500 ml. of water was added, the solution clarified by filtration, and the filtrate alkalinized with dilute sodium hydroxide solution. The crystalline base which separated was collected from the cold solution by filtration and recrystallized from acetone; yield 94.5 g. (95%). The compound appears to be somewhat unstable at elevated temperature but melts abruptly between 175 and 180° if the melting point is approached rapidly.

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.32; H, 6.57. Found: C, 72.25; H, 6.83.

Ethyl α-Carbethoxy-β-(4-cyano-3-indole)-propionate (V).—To a solution of 2.30 g. (0.1 mole) of sodium in 150 ml. of absolute ethanol was added 16.0 g. (0.1 mole) of diethyl malonate, and 9.96 g. (0.05 mole) of 4-cyanogramine, and, while the mixture was cooled externally, 12.6 g. (0.1 mole) of dimethyl sulfate was added dropwise. The homogeneous solution was maintained at reflux temperature for five hours and the ethanol distilled *in vacuo*. Water and ether were added to the residue, and the product from the dried ether extract was stirred with petroleum ether. The crystalline solid which remained was recrystallized from ethanol; yield 10.2 g. (65%); m. p. 110–111°.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77. Found: C, 64.67; H, 5.61.

(10) Cohn, *Monatsh.*, **22**, 473 (1901).

(11) Norris and Bearse, THIS JOURNAL, **62**, 956 (1940).

α-Carboxy-β-(4-cyano-3-indole)-propionic Acid.—To a solution of 31.4 g. (0.1 mole) of ethyl α-carbethoxy-β-(4-cyano-3-indole)-propionate (V) in 250 ml. of ethanol was added a solution of 24 g. (0.4 mole) of potassium hydroxide in 25 ml. of water and the mixture maintained at reflux temperature for one-half hour. The solution was diluted with water, the ethanol removed under diminished pressure, the aqueous residue clarified by filtration, acidified with hydrochloric acid, and the precipitate collected by filtration and recrystallized from water; yield 24.6 g. (95%); m. p. 210–212°.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90. Found: C, 60.06; H, 4.01.

β-(4-Cyano-3-indole)-propionic Acid.—(a) The malonic acid derivative was maintained at the melting point until the evolution of carbon dioxide had ceased and the crystalline residue recrystallized from a mixture of ethanol and water. (b) To a solution of 2.42 g. (0.01 mole) of ethyl β-(4-cyano-3-indole)-propionate (VI) in 20 ml. of ethanol was added 7 ml. of 10% sodium hydroxide solution and the mixture maintained under reflux for one hour. The ethanol was removed under diminished pressure, the residue extracted with ether, and the aqueous solution acidified with dilute hydrochloric acid. The precipitate was recrystallized from a mixture of ethanol and water; yield 2.0 g. (93.5%); m. p. 205–207°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.27; H, 4.70. Found: C, 67.17; H, 4.75.

The methyl ester was prepared by maintaining under reflux a solution of the acid in a solution of 1 ml. of concentrated sulfuric acid in 10 ml. of methanol. The ester was recrystallized from methanol; m. p. 138–139°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30. Found: C, 68.36; H, 5.35.

Ethyl β-(4-Cyano-3-indolepropionate (VI).—A solution of 15.7 g. (0.05 mole) of ethyl α-carbethoxy-β-(4-cyano-3-indole)-propionate (V) in a mixture of 18 ml. (0.05 mole) of 10% sodium hydroxide solution, 50 ml. of ethanol and 50 ml. of water was maintained under reflux for five hours. The ethanol was removed under diminished pressure, the aqueous solution extracted with ether and the acid precipitated by the addition of dilute hydrochloric acid, filtered and dried. The yield was 12.2 g. (85%). The acid was decarboxylated by maintaining at 200° for five minutes. The ester which crystallized when the melt had been allowed to cool was recrystallized from a mixture of ethanol and water, yield 9.8 g. (95%); m. p. 153–154°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.38; H, 5.96.

β-(4-Carboxy-3-indole)-propionic Acid (VII).—To 20 ml. of 30% potassium hydroxide solution was added 2.42 g. (0.01 mole) of ethyl β-(4-cyano-3-indole)-propionate (VI) and the mixture was maintained under reflux for fifty hours by which time the evolution of ammonia had nearly ceased. The solution was brought to the neutral point with hydrochloric acid, clarified with Norite, and the filtrate acidified with hydrochloric acid. The precipitate was collected by filtration and recrystallized from water; yield 2.1 g. (90%); m. p. 188–189°; molecular weight calcd. 233.22; found, by neut. equiv., 233.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80, H, 4.76. Found: C, 61.65; H, 4.94.

Methyl β-(4-Carbomethoxy-3-indole)-propionate.—A solution of 2.33 g. (0.10 mole) of β-(4-carboxy-3-indole)-propionic acid (VII) in a mixture of 3 ml. of concentrated sulfuric acid and 30 ml. of methanol was maintained under reflux for fifteen hours. The solution was concentrated under diminished pressure, extracted with ether and sodium bicarbonate solution, and the crystalline residue from the ether extract recrystallized from ethanol; yield 1.96 g. (75%); m. p. 84–85°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.37; H, 5.79. Found: C, 64.30; H, 6.02.

The N-acetyl derivative (XV) was prepared by maintaining under reflux for ten hours an acetic anhydride solution of the ester, concentrating to dryness under diminished pressure, and recrystallizing from ethanol; m. p. 105–106°.

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.65. Found: C, 63.12; H, 5.53.

5-Keto-1,3,4,5-tetrahydrobenz[cd]indole (VIII).—A solution of 2.33 g. (0.01 mole) of β-(4-carboxy-3-indole)-propionic acid (VII) and 0.20 g. of potassium cyanide in 100 ml. of acetic anhydride was maintained at reflux temperature for twenty hours. The acetic anhydride was distilled under diminished pressure, the residue dissolved in a mixture of 40 ml. of 10% potassium hydroxide solution and 40 ml. of ethanol and the solution maintained under reflux for one hour. The ethanol was distilled under diminished pressure and the crystalline product which separated was extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid and 0.21 g. (9%) of unchanged dicarboxylic acid was collected by filtration. The washed and dried ether solution was concentrated and the crystalline residue recrystallized from ethanol; yield 1.37 g. (80%); m. p. 165–166°.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.96; H, 5.37; N, 8.21.

The semicarbazone was prepared in aqueous ethanol and recrystallized from ethanol; m. p. 215–216°.

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.14; H, 5.31. Found: C, 63.21; H, 5.30.

The *p*-nitrophenylhydrazone was prepared in ethanol and recrystallized from the same solvent; m. p. 235–236°.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61. Found: C, 66.68; H, 4.83.

1,3,4,5-Tetrahydrobenz[cd]indole (IX).—A mixture of 510 mg. (0.003 mole) of the ketone (VIII), 0.4 ml. of 85% hydrazine hydrate, 560 mg. of potassium hydroxide, and 4 ml. of diethylene glycol was maintained at 200° for four hours. The dark brown solution was poured into 10 ml. of water and extracted with ether. The residue from the washed ether extract was recrystallized from a mixture of ethanol and water. The glistening white plates melted at 55–56° and a mixed melting point with a sample of 1,3,4,5-tetrahydrobenz[cd]indole[12] prepared by sodium–butanol reduction of naphthostyril[13] was 55–56°; yield 300 mg. (64%).

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.21; H, 7.11; N, 9.04.

The picrate was prepared in ethanol and recrystallized from the same solvent. The melting point was 164–166° and a mixed melting point with a sample prepared from the indole obtained by sodium–butanol reduction of naphthostyril was 164–166°.

Anal. Calcd. for $C_{17}H_{14}N_4O_7$: C, 52.85; H, 3.65. Found: C, 52.80, H, 3.64.

5-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (XVI).—To a solution of 227 mg. (0.006 mole, twice the theoretical quantity) of lithium aluminum hydride in 30 ml. of absolute ether was added dropwise a solution of 1.03 g. (0.006 mole) of the ketone (VIII) in 20 ml. of absolute ether. The yellow color was at once discharged and the metal complex separated as a flocculent white precipitate. After the mixture had been maintained under reflux for ten minutes, water was added dropwise and the ether solution washed with 20% sulfuric acid, water, and sodium bicarbonate solution, and dried over magnesium sulfate. The crystalline residue from the ether was recrystallized from water; yield 780 mg. (75%); m. p. 126–127°.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40. Found: C, 76.50; H, 6.63.

The *p*-nitrobenzoate was prepared with *p*-nitrobenzoyl chloride in pyridine and was recrystallized from methanol; m. p. 140–141°.

Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38. Found: C, 66.80; H, 4.28.

(12) Ring Index No. 1681.

(13) Jacobs and Gould, *J. Biol. Chem.*, **120**, 141 (1937).

5-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole Isopropyl-Ether (XVII).—To a solution of 50 mg. of aluminum in 10 ml. of absolute isopropyl alcohol was added 171 mg. (0.001 mole) of the ketone (VIII) and the mixture maintained at reflux temperature for four hours. The isopropyl alcohol was distilled under diminished pressure and the residue extracted with ether and 10% sodium hydroxide solution. The residue from the washed and dried ether solution was recrystallized from a mixture of ethanol and water; yield 138 mg. (64%); m. p. 131–132°. The compound did not react with *p*-nitrobenzoyl chloride or with phenyl isocyanate.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.11; H, 7.96. Found: C, 78.11; H, 7.91.

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Summary

A synthesis of 4-substituted indoles has been developed. 4-Cyanoindole has been converted through the Mannich base to β-(4-carboxy-3-indole)-propionic acid, and cyclization of the dicarboxylic acid has afforded a new synthesis of the tricyclic 1,3,4,5-tetrahydrobenz[cd]indole ring system.

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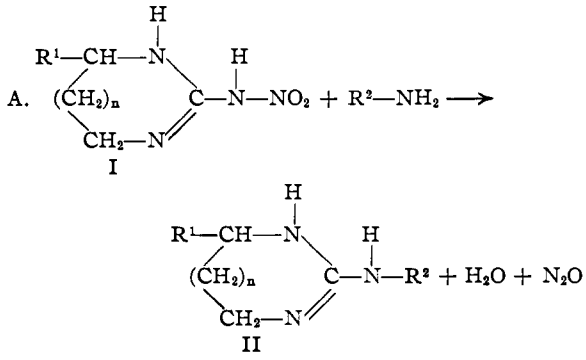
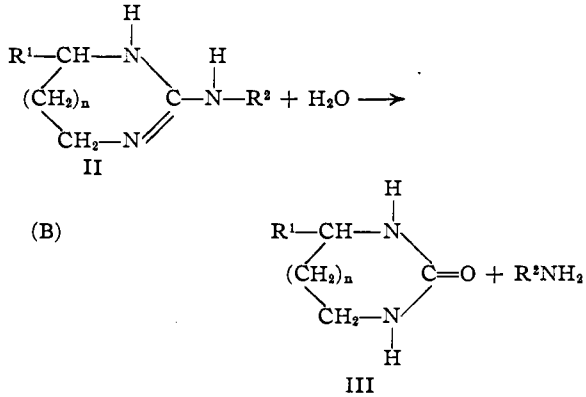
The Reaction of Primary Amines with 2-Nitramino-Δ^2-1,3-diazacycloalkenes

BY A. F. MCKAY, M. N. BUCHANAN AND GORDON A. GRANT

When 2-nitramino-Δ^2-1,3-diazacycloalkenes[1] I are heated in the presence of primary amines a rapid evolution of gas occurs and the nitramino group is replaced by a substituted amino group. This reaction is analogous to the one described by Davis and Elderfield[2] in the preparation of *sym*-dibutylguanidine from N-butyl-N¹-nitroguanidine and butylamine in the presence of water. On the other hand, N-methyl-N¹-nitroguanidine and N-ethyl-N¹-nitroguanidine on heating with aqueous methylamine and aqueous ethylamine respectively gave the corresponding alkylureas. This would be expected because of the large volumes of water used by these authors. A. W. Hofmann[3] found that *sym*-triethylguanidine monohydrate on distillation decomposed into ethylamine and *sym*-diethylurea. Therefore, in order to eliminate the formation of cyclic ureas the 2-nitramino-Δ^2-1,3-diazacycloalkenes I were heated with the anhydrous amines (reaction A). Water, however, is produced during this reaction in sufficient quantities to effect hydrolysis of part of the product II by reaction B.





R^1 = CH_3 or H; R^2 = alkyl or aralkyl; n = 0 or 1

The 1,3-diazacyclopentene-2 I (n = 0) compounds displayed less tendency to form urea derivatives than the 1,3-diazacyclohexene-2 I (n = 1) compounds. On heating 2-nitramino-Δ^2-1,3-diazacyclopentene or 2-nitramino-Δ^2-1,3-diazacyclohexene with a primary amine until gas evolution ceased the former compound gave 4–8% 1,3-diazacyclopentanone-2 III (n = 0, R′ = H) while the latter gave a 22% yield of 1,3-diazacyclohexanone-2 III (n = 1; R^1 = H). These yields of cyclic ureas were decreased considerably by using a large excess (2–10 mole equivalents) of the amine which was slowly distilled during the course of the reaction. This excess amine on slow distillation carried with it the water produced during the reaction. The 2-alkylamino- and 2-aralkylamino-Δ^2-1,3-diazacycloalkenes prepared in this manner are recorded along with their properties in Table I.

The formation of cyclic urea derivatives by the reaction of water with the 2-alkylamino- or 2-aralkylamino-Δ^2-1,3-diazacycloalkenes II rather than with the corresponding 2-nitramino-Δ^2-1,3-diazacycloalkenes I was verified by refluxing

(1) A. F. McKay and G. F. Wright, THIS JOURNAL, **70**, 430 (1948).
(2) T. L. Davis and R. C. Elderfield, *ibid.*, **55**, 731 (1933).
(3) A. W. Hofmann, *Jahresber. Fortschr. Chem.*, 516 (1861).