Synthesis of 1,2,3,4-Tetrahydro-2,3-disubstituted 10-Hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles

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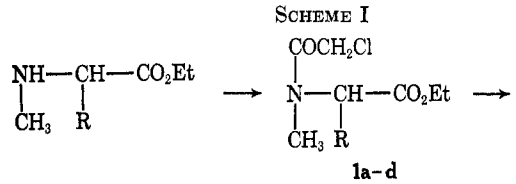
1,2,3,4-Tetrahydro-2,3-disubstituted 10-hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles have been prepared by two methods: cyclization of the corresponding *dl*-*o*-carbomethoxyphenylglycyl-N-methylamino acid esters in the presence of sodium methoxide, and from 3-methoxyindole-2-carboxylic acid by acylation of N-methylamino acid esters followed by spontaneous base-catalyzed cyclization and demethylation in the last stage.

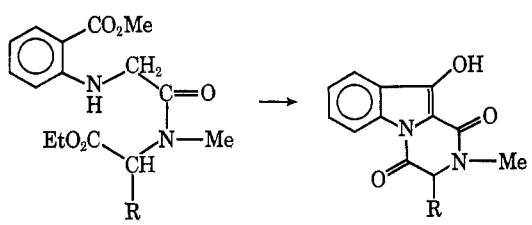
Synthesis of 1,2,3,4-tetrahydro-2,3-dimethyl-10-hydroxy-1,4-dioxopyrazino[1,2-*a*]indole (**3a**) was carried out in connection with studies on the structure of anhydrodethiogliotoxin,[1] one of the degradation products of the mold antibiotic gliotoxin. The above 10-hydroxypyrazinoindole was selectively reduced with sodium amalgam to the 10:11-dihydro derivative, which was eventually shown by spectral analysis and other evidence to be different from anhydrodethiogliotoxin.[2,3]

However, the 10-hydroxy-1,4-dioxopyrazinoindole ring system with its closed peptide structure is interesting enough in itself to stimulate a rational synthesis. Two independent syntheses of 1,2,3,4-tetrahydro-2,3-disubstituted 10-hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles have been worked out in Schemes I and II.

SCHEME I



1a-d

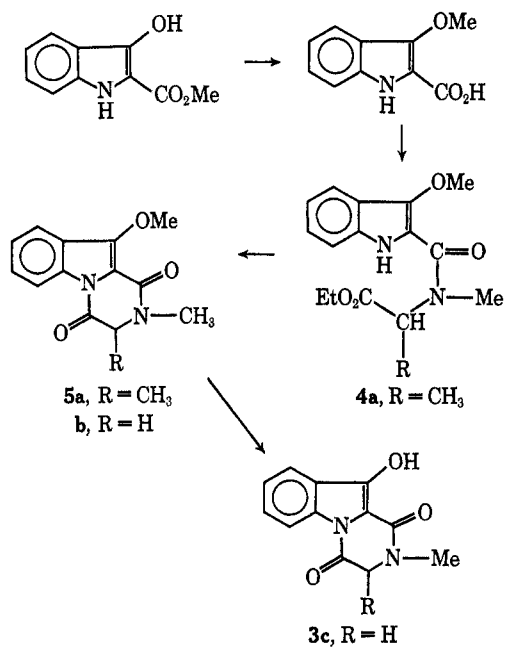


2a-d **3a-d**

a, R = CH_3
b, R = CH_2CH_3
c, R = H
d, R = $CH_2C_6H_5$

In Scheme I, *dl*-N-methyl-α-amino acid esters were chloroacetylated, and the chloroacetyl derivatives (**1**) were condensed with methyl anthranilate by heating them either in alcoholic solution[4] or neat to give *dl*-*o*-carbomethoxyphenylglycyl-N-methylamino acid esters (**2**). In both cases, the condensation proceeded without formation of amides, polymerization, or intramolecular cyclization to form the pyrazine ring. *dl*-*o*-Carbomethoxyphenylglycyl-N-methylamino acid esters (**2**) were cyclized in the presence of sodium methoxide to give 10-hydroxypyrazinoindoles (**3**). Our findings regarding this base-catalyzed cyclization are in agreement with earlier reports[5,6] that this cyclization takes place only if there is no active hydrogen on the amide nitrogen.

SCHEME II



5a, R = CH_3 **4a**, R = CH_3
b, R = H

3c, R = H

In Scheme II, N-methylamino acid esters were condensed with preformed indoxylic acid. Fusion of methyl 3-hydroxyindole-2-carboxylate with sodium hydroxide at 300°[7] resulted in extensive decarboxylation and subsequent oxidation to indigo. The ester was hydrolyzed smoothly in 30% sodium hydroxide at 60°.

Since direct condensation of indoxylic acid with N-methylamino acid esters in the presence of N,N′-dicyclohexylcarbodiimide (DCCI) was not possible because of the strongly phenolic nature of the 3-hydroxy group, the latter had to be suitably protected. Acylation of indoxylic acid leads preferably to N-acyl derivatives.[4] Choice of benzyl group was not very fortunate. Alkaline hydrolysis of methyl 3-benzyloxyindole-2-carboxylate invariably led to decarboxylation. The ester was eventually hydrolyzed in

(1) J. R. Johnson and A. R. Kidwai, unpublished observations; doctoral thesis, Cornell University, 1950.
(2) J. R. Johnson and L. R. Harper, unpublished observations; doctoral thesis, Cornell University, 1954.
(3) M. R. Bell, J. R. Johnson, B. S. Wildt, and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 1001 (1958).
(4) J. R. Johnson and J. H. Andreen, *ibid.*, **72**, 2862 (1950).
(5) J. R. Johnson, J. H. Andreen, and A. D. Holley, *ibid.*, **69**, 2370 (1947).
(6) J. D. Dutcher, J. R. Johnson, and W. F. Bruce, *ibid.*, **66**, 617 (1944).
(7) A. Baeyer, *Ber.*, **14**, 1741 (1881).

the presence of concentrated sulfuric acid,[8] but the carboxyl group in 3-benzyloxyindole-2-carboxylic acid was too hindered sterically to condense effectively with amino acid esters in the presence of DCCI. On treatment with thionyl chloride, the acid was recovered unchanged at low temperatures and was decarboxylated under more stringent conditions. Consequently, methyl 3-hydroxyindole-2-carboxylate was methylated, the product was hydrolyzed, and 3-methoxyindole-2-carboxylic acid was condensed with N-methylamino acid esters either in the presence of DCCI or after conversion to the acid chloride. In the presence of a slight excess of amino acid esters, the 3-methoxyindole-2-carboxylamino acid esters formed first cyclized spontaneously to the corresponding pyrazinoindoles in high yields. Other basic catalysts like triethylamine and pyridine gave lower yields. Demethylation of 10-methoxypyrazinoindoles was affected with hydriodic acid and red phosphorus.[6]

Experimental Section

Melting points were taken in capillary tubes on Gallenkamp melting point apparatus. All melting and boiling points are uncorrected. Ir spectra were taken on Perkin-Elmer Infracord and uv spectra on a Perkin-Elmer 220.

1,2,3,4-Tetrahydro-2,3-dimethyl-1,4-dioxo-10-hydroxypyrazino[1,2-a]indole (3a). (a) ***dl*-Chloroacetyl-N-methylalanine Ethyl Ester (1a).**—An ethereal solution of *dl*-N-methylalanine ethyl ester prepared from 10 g (0.097 mol) of *dl*-N-methylalanine was treated with freshly distilled chloroacetyl chloride, (5.4 g, 0.048 mol) in 30 ml of dry ether under anhydrous conditions. The reaction mixture was allowed to stand in an ice bath for 2 hr. Half of the ester was converted into its hydrochloride which separated as a liquid. The *dl*-N-chloroacetyl-N-methylalanine ethyl ester remaining in the ether solution was washed free of unreacted ester and chloroacetyl chloride. It distilled at 119–125° (2 mm under N_2), $n^{20}D$ 1.47, yield 7.5 g (75% on the basis of chloroacetyl chloride used).

Anal. Calcd for $C_8H_{14}ClNO_3$: C, 46.3; H, 6.7; N, 6.7. Found: C, 46.2; H, 6.7; N, 6.5.

(b) ***dl*-*o*-Carbomethoxyphenylglycyl-N-methylalanine Ethyl Ester (2a).**—Methyl anthranilate (40.7 g, 0.27 mol) and 1a (14 g, 0.0675 mol) were heated on a steam bath for 8 hr when a large quantity of methyl anthranilate hydrochloride separated. Dry benzene (150 ml) was added and the hydrochloride was filtered off. After removing benzene under reduced pressure, the reaction mixture was heated for another 8 hr and the hydrochloride was separated as before. Further heating resulted in separation of only a negligible quantity of the ester hydrochloride. In all 11.6 g of methyl anthranilate hydrochloride was collected (theoretical 12.6 g). Unreacted methyl anthranilate was distilled off from the residual mass at 110–111° (2–3 mm under N_2) keeping the bath temperature at 165°. The residue (25.5 g) was crystallized from benzene and recrystallized from absolute alcohol, mp 89–90°, yield 15 g (69%). Another crystallization from 1-butanol raised the melting point to 89.5–90°; ir (KBr) 3375 (NH), 1750, 1700, 1675 (amide, ester and NH), 1262, 1225 cm^{-1} (C–O–C); uv max (EtOH) 345, 253, 225 mμ.

Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.6; H, 6.9; N, 8.7. Found: C, 59.8; H, 6.85; N, 8.7.

(c) **1,2,3,4-Tetrahydro-2,3-dimethyl-1,4-dioxo-10-hydroxypyrazino[1,2-a]indole (3a).**—A solution of 10 g of 2a in 50 ml of dry benzene was added to a suspension of sodium methoxide (prepared from 0.7 g of sodium) in dry benzene, and the mixture was heated slowly on a steam bath under anhydrous conditions. First a turbidity appeared and within 10 min a yellow gelatinous precipitate of the sodium salt started separating. The reaction mixture was heated for 1 hr and cooled, 100 ml of dry ether was added, and the sodium salt was filtered, washed with ether, and dissolved in ice-cold water. The aqueous solution was filtered and the 10-hydroxypyrazinoindole was quickly precipitated by adding solid carbon dioxide. After washing with dilute acetic acid and water, the crude, dry product weighed 4 g. Carbon dioxide saturated filtrate on saturation with sodium chloride gave an additional 500 mg. The crude product was crystallized from methanol (leaving 200 mg of an insoluble residue which darkens at 255° and decomposes at 265°), yield 3.25 g (42%), mp 137–139°. For further purification the product was dissolved in cold 1% sodium hydroxide, reprecipitated with solid carbon dioxide, and washed as before. After one crystallization from ethanol and another from 1-butanol, the pure product weighed 2.2 g, mp 138–139°. It gives a dark green color with alcoholic ferric chloride: ir (KBr) 3250 (broad, chelated OH), 1700 (indole NC=O), 1625 cm^{-1} (amide C=O); uv max (EtOH) 302 mμ.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.95; N, 11.45. Found: C, 64.0; H, 4.9; N, 11.3.

The carbon dioxide saturated mother liquor left after removal of the 10-hydroxypyrazinoindole gave a precipitate on acidifying with HCl, which was crystallized from ethanol. It weighed 1.55 g, melted to a red liquid at 195–200°, and gave a red color with alcoholic ferric chloride. This is probably the acid formed by hydrolysis of the pyrazine ring.

1,2,3,4-Tetrahydro-2-methyl-3-ethyl-1,4-dioxo-10-hydroxypyrazino[1,2-a]indole (3b). (a) ***dl*-Chloroacetyl-N-methyl-α-aminobutanoic Acid Ethyl Ester (1b).**—Chloroacetylation of *dl*-N-methylaminobutanoic acid ethyl ester gave 1b in 53.6% yield, bp 140° (4 mm under N_2), $n^{30}D$ 1.40.

Anal. Calcd for $C_9H_{16}ClNO_3$: C, 48.7; H, 7.2; N, 6.3. Found: C, 49.1; H, 7.4; N, 6.1.

(b) ***dl*-*o*-Carbomethoxyphenylglycyl-N-methyl-α-aminobutanoic Acid Ethyl Ester (2b).**—This was prepared by condensation of 1b with methyl anthranilate in 68% yield. It crystallized from absolute alcohol, mp 83°.

Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.1; N, 8.3. Found: C, 60.6; H, 7.1; N, 8.3.

(c) **1,2,3,4-Tetrahydro-2-methyl-3-ethyl-1,4-dioxo-10-hydroxypyrazino[1,2-a]indole (3b).**—2b cyclized to 3b in 40% yield in the presence of sodium methoxide. 3b was crystallized from absolute alcohol in white prisms: mp 146°; ir (KBr) 3250 (broad), 1700, 1625 cm^{-1}; uv max (EtOH) 302 mμ.

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.6; N, 10.8. Found: C, 65.2; H, 5.6; N, 10.6.

1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-hydroxypyrazino-[1,2-a]indole (3c). (a) **Chloroacetyl-N-methylglycine Ethyl Ester (1c).**—Chloroacetylation of N-methylglycine ethyl ester gave 1c in 46% yield, bp 145° (2 mm under N_2), $n^{30}D$ 1.472.

Anal. Calcd for $C_7H_{12}ClNO_3$: C, 43.4; H, 6.2; N, 7.2. Found: C, 43.2; H, 6.3; N, 7.3.

(b) **1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-hydroxypyrazino-[1,2-a]indole (3c).**—The above chloroacetyl derivative (1c) was condensed with methyl anthranilate to give 2c. The latter failed to crystallize, and therefore it was dried (P_2O_5) and cyclized as such with sodium methoxide to give 3c in 33% yield. 3c crystallized from absolute ethanol: mp 215° dec; ir (KBr) 3250 (broad), 1700, 1620 cm^{-1}; uv max (EtOH) 300 mμ.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.6; H, 4.4; N, 12.2. Found: C, 62.3; H, 4.3; N, 11.9.

1,2,3,4-Tetrahydro-2-methyl-3-benzyl-1,4-dioxo-10-hydroxypyrazino[1,2-a]indole (3d).—*dl*-Chloroacetyl-N-methylphenylalanine ethyl ester (1d) obtained by chloroacetylation of *dl*-N-methylphenylalanine ethyl ester did not distil even at 200° (2 mm). Above this temperature it started decomposing; therefore, it was condensed as such with methyl anthranilate to give 2d, which was cyclized in the presence of sodium methoxide to give 3d in 23% yield. 3d crystallized from alcohol: mp 148°; ir (KBr) 3100 (broad), 1670, 1620 cm^{-1}; uv max (EtOH) 304 mμ.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.2; H, 5.0; N, 8.7. Found: C, 71.0; H, 5.0; N, 8.2.

Indoxylic Acid.—A solution of 5 g of methyl 3-hydroxyindole-2-carboxylate[4,5] in 25 ml of 30% sodium hydroxide solution was warmed on a water bath at 60° for 1 hr. The cold reaction mixture was acidified with hydrochloric acid to give 4 g (87%) of indoxylic acid, which was dried (P_2O_5), mp 123°.

Methyl 3-Benzyloxyindole-2-carboxylate.—Methyl 3-hydroxyindole-2-carboxylate (19.1 g, 0.1 mol) was benzylated with freshly distilled benzyl chloride (12.65 g, 0.1 mol) over anhydrous potassium carbonate (10 g) in dry acetone using potassium iodide as a catalyst. It crystallized from ethyl acetate–petroleum ether (bp 40–60°): mp 95–96°; yield 19.7 g (70%).

(8) H. P. Treffers and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1708 (1937).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.6; H, 5.3; N, 5.0. Found: C, 72.2; H, 5.3; N, 4.85.

3-Benzyloxyindole-2-carboxylic Acid.—Methyl 3-benzyloxyindole-2-carboxylate (8.43 g, 0.03 mol) was finely powdered and dissolved completely in 30 ml of concentrated sulfuric acid; the solution was poured into a large amount of crushed ice with vigorous stirring. The precipitated acid was extracted with ether, the ethereal layer was washed, the ether was evaporated off under reduced pressure at room temperature, and the residue crystallized from ethanol, mp 120°, yield 7 g (87%).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.9; N, 5.2. Found: C, 72.3; H, 5.0; N, 4.9.

Methyl 3-Methoxyindole-2-carboxylate.—Methyl 3-hydroxyindole-2-carboxylate (16 g, 0.083 mol) was methylated with dimethyl sulfate (10.5 g) over anhydrous potassium carbonate in 200 ml of dry acetone. It crystallized from ethyl acetate, mp 106°, yield 13.7 g (80%).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4; N, 6.8. Found: C, 64.0; H, 5.3; N, 7.1.

3-Methoxyindole-2-carboxylic Acid.—A solution of methyl 3-methoxyindole-2-carboxylate (20 g, 0.096 mol) in 200 ml of 1 *N* methanolic potassium hydroxide was refluxed for 3 hr in a water bath. Methanol was distilled off and the acid precipitated from cold aqueous solution of the sodium salt with hydrochloric acid. It crystallized from dry benzene, mp 135° dec, yield 16 g (86%).

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.8; H, 4.7; N, 7.3. Found: C, 62.9; H, 4.9; N, 6.9.

1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-methoxypyrazino-[1,2-*a*]indole (5b).—An ethereal solution of 3-methoxyindole-2-carboxylic acid (5.7 g, 0.03 mol) was treated with thionyl chloride (7.1 g, 0.06 mol). After it was maintained for 1 hr at room temperature, ether and thionyl chloride were removed *in vacuo* without external heating. The residual acid chloride was flushed with fresh lots of dry ether to remove traces of thionyl chloride. The slightly pigmented semicrystalline residue was dissolved in dry ether and treated with an ethereal solution of N-methylglycine ethyl ester (prepared from 8 g, 0.09 mol, of N-methylglycine). The reaction mixture warmed up slightly and was left at room temperature overnight. The ester hydrochloride was filtered off. The ethereal filtrate was washed well with distilled water, the ether was evaporated, and the solid residue was crystallized from aqueous methanol: mp 155°; yield 5.2 g (72%); ir (KBr) 1700, 1640, 1250, 1089 cm^{-1} (=COMe); uv max (EtOH) 296 mμ.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.9; N, 11.6. Found: C, 64.2; H, 5.2; N, 11.2.

1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-hydroxypyrazino-[1,2-*a*]indole (3c).—**5b** (732 mg, 0.003 mol) was demethylated by boiling gently for 3 hr with red phosphorus (1.4 g) and a mixture of acetic anhydride (5 ml) and hydriodic acid (4 ml, sp gr 1.7). The demethylated product was worked up in the usual way. It crystallized from ethanol, mp 215° dec, yield 600 mg (87%), mmp with **3c** 215° dec: uv and ir spectra were also identical with **3c**.

3-Methoxyindole-2-carboxyl-*dl*-N-methylalanine Ethyl Ester (4).—An ethereal solution of 3-methoxyindole-2-carbonyl chloride prepared from 3.6 g (0.019 mol) of 3-methoxyindole-2-carboxylic acid was treated with an ethereal solution of *dl*-N-methylalanine ethyl ester prepared from 4 g (0.038 mol) of *dl*-N-methylalanine. The reaction mixture was left at room temperature for 2 hr; the ethereal layer was decanted from the precipitated ester hydrochloride and washed with 1 *N* HCl, 1 *N* $KHCO_3$, and water. After evaporating ether, the residue was crystallized twice from ethanol: mp 113°; yield 4 g (70%); ir (KBr) 3250 (indole NH), 1740 (ester C=O), 1600 (amide C=O), 1250, 1089 cm^{-1} (=COMe); uv max (EtOH) 295 mμ.

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 62.7; H, 6.6; N, 9.3.

1,2,3,4-Tetrahydro-2,3-dimethyl-1,4-dioxo-10-methoxypyrazino[1,2-*a*]indole (5a).—A methanolic solution of **4** (0.5 g, 0.0016 mol) was treated with 5 ml of an ethereal solution of *dl*-N-methylalanine ethyl ester containing approximately 0.002 mol of the ester. The mixture was left at room temperature overnight. When concentrated and cooled, 10-methoxypyrazinoindole crystallized out in colorless crystals, mp 116°, yield 0.3 g (75%).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.4; N, 10.8. Found: C, 64.8; H, 5.4; N, 10.5.

Direct Condensation of 3-Methoxyindole-2-carboxylic Acid with N-Methylglycine Ethyl Ester.—3-Methoxyindole-2-carboxylic acid (1 g, 0.005 mol) in dry ether was added to a dry ethereal solution of N-methylglycine ethyl ester (prepared from 0.89 g, 0.01 mol, of N-methylglycine) containing DCCI (1 g, 0.005 mol). The reaction mixture was left at room temperature for 24 hr. Dicyclohexylurea was filtered, yield 1 g (theoretical 1.08 g). 1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-methoxypyrazino[1,2-*a*]indole was crystallized from aqueous methanol, mp 155°, mmp with **5b** 155°; uv ir spectra were also identical with **5b**.

Registry No.—**1a,** 24463-58-9; **1b,** 24515-52-4; **1c,** 24515-53-5; **2a,** 24463-59-0; **2b,** 24463-60-3; **3a,** 24463-61-4; **3b,** 24463-62-5; **3c,** 24463-63-6; **3d,** 24463-64-7; **4,** 24463-65-8; **5a,** 24463-66-9; **5b,** 24463-67-0; methyl 3-benzyloxyindole-2-carboxylate, 24463-68-1; 3-benzyloxyindole-2-carboxylic acid, 24463-69-2; methyl 3-methoxyindole-2-carboxylate, 21716-59-6; 3-methoxyindole-2-carboxylic acid, 21598-04-9.

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