[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE SYNTHESIS AND REACTIONS OF METHOXYINDOLE COMPOUNDS

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Received March 8, 1948

A number of methoxy- and hydroxy-indole derivatives have been isolated by many investigators in connection with studies of the "toad poisons" and the Harmala alkaloids. Many of the simpler methoxyindole compounds and a few hydroxyindoles have been synthesized.

The synthetic approach has been continued in this research with the purpose of preparing and characterizing additional methoxyindoles and investigating their conversion to hydroxyindoles.

For the preparation of 2-carboxy-5-methoxyindole, the procedures of Blaikie and Perkin (1), and Wieland, Konz, and Mittasch (2), which are based on Reissert's work (3), are greatly inferior to that of Koelsch (4). Following essentially the procedure of the latter author we were able to convert *m*-cresol successively to a 2-nitroso-5-hydroxytoluene (nearly quantitatively); 2-nitro-5-hydroxytoluene (80%); 2-nitro-5-methoxytoluene (89%); 2-nitro-5-methoxyphenylpyruvic acid (57%), and 2-carboxy-5-methoxyindole (I), (60%). Thus the over-all yield from *m*-cresol is near 25%. The ethyl ester (II), of this compound can be obtained conveniently (in 52% yield) from the *p*-methoxyphenylhydrazone of ethyl pyruvate, which is readily available through the Japp-Klingemann reaction (5, 6), following the general procedure of Hughes, *et al.* (7). By saponification of the ester, the acid (I), may be obtained in excess of 90% yield, the over-all yield from *p*-anisidine being 47%.

Entry into the 7-methoxyindole series was accomplished solely by means of ring-closure of *o*-methoxyphenylhydrazones, prepared by the Japp-Klingemann reaction. The yield of 2-carboethoxy-7-methoxyindole (III) was 30% from *o*-anisidine, and the conversion to the acid (IV) proceeded in 85% yield.

In confirmation of the work of Späth and Brunner (8), the *o*-methoxy- and *p*-methoxy-phenylhydrazones of acetone gave no indole compounds which could be isolated using the normal Fischer procedure, *i.e.*, zinc chloride at 180°, with or without tetrahydronaphthalene as a solvent. Using the modified procedure of the above mentioned authors ($ZnCl_2$, 110°, under vacuum), approximately 20% yields (about one-half of that reported) of 2-methyl-5-methoxyindole (V), were obtained from the *p*-methoxyphenylhydrazone of acetone. Attempts at ring closure of the *o*- and *p*-methoxyphenylhydrazones of acetone using (a) ethyl alcohol saturated with HCl, or (b) ethyl alcohol containing 10% sulfuric acid, or (c) 50% glacial acetic acid-50% concentrated HCl, all failed.

The *p*-methoxyphenylhydrazone of diethyloxalyl acetate, on warming with

[1] We are indebted to the Squibb Institute for Medical Research for the Fellowship which supported this work.

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10% sulfuric acid gave 1-(*p*-methoxyphenyl)-3-carboxypyrazolone-5 (VI), and not 2,3-dicarboethoxy-5-methoxyindole. This is not surprising, however, since this is the basis of a well known pyrazolone synthesis. When the N-methyl-*p*- and *o*-methoxyphenylhydrazones of diethyloxalyl acetate were treated with alcoholic HCl, the corresponding N-methyl-2,3-dicarboethoxy-5-methoxyindole and its 7-methoxy analog, respectively, were presumably formed. Unfortunately, it was not possible to crystallize these two compounds. On saponification with 30% KOH, each yielded an α-carboxylic acid, (VII and VIII), not the 2,3-dicarboxylic acid which might have been expected on the basis of Reif's (9) similar preparation of 1-methylindole-2,3-dicarboxylic acid. This

TABLE I

ANALYSES

COMPOUND NUMBER	FORMULA	CALCULATED			FOUND		
		C	H	N	C	H	N
VI	$C_{11}H_{10}N_2O_4$	56.4	4.27	12.0	56.6	4.55	12.1
VIII	$C_{11}H_{11}NO_3$	64.4	5.37	6.83	64.5	5.62	7.01
IX*	$C_{16}H_{14}N_4O_8$	49.2	3.59	14.4	49.5	3.75	14.6
XIII	$C_{13}H_{18}N_2O$	71.6	8.28	12.8	71.8	8.55	13.0
XIV	$C_{12}H_{16}N_2O$	70.6	7.84	13.7	70.9	7.12	13.9
XV	$C_{15}H_{20}N_2O_3$	65.2	7.25	10.2	65.5	7.27	9.96
XXVI	$C_{15}H_{20}N_2O_3$	65.2	7.25	10.2	65.4	7.50	10.4
XVII*	$C_{20}H_{20}N_6O_7$	52.6	4.39	18.4	52.8	4.23	18.3
XXVIII	$C_{13}H_{16}N_2O_3$	62.9	6.45	11.3	63.1	6.69	11.2
XXIX	$C_{13}H_{16}N_2O_3$	62.9	6.45	11.3	63.0	6.71	11.4
XX	$C_{15}H_{16}N_2O_3$	66.2	5.88	10.3	66.2	6.01	10.3
XXI	$C_{15}H_{16}N_2O_3$	66.2	5.88	10.3	66.3	6.05	10.4
XXII	$C_{14}H_{14}N_2O_2$	69.4	5.78	11.6	69.6	5.65	11.6
XXIII	$C_{13}H_{13}NO_5$	59.3	4.94	5.32	59.4	5.01	5.36
XXIV	$C_{13}H_{13}NO_5$	59.3	4.94	5.32	59.5	5.19	5.47
XXV	$C_{12}H_{11}NO_4$	61.8	4.72	6.01	61.9	4.85	6.07
XXVII	C_9H_9NO	73.5	6.12	9.52	73.6	6.28	9.59
XXVIII	C_9H_9NO	73.5	6.12	9.52	73.8	6.44	9.49

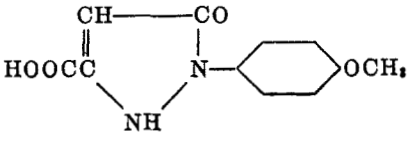
(* Picrate)

observation is similar to that of Diels and Reese (10), who obtained only indole-α-carboxylic acid upon saponifying the monoethyl ester of the 2,3-dicarboxylic acid.

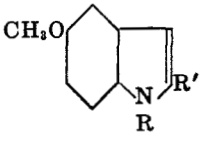
1-Methyl-2-carboxy-5-methoxyindole (VII), has been decarboxylated to yield 1-methyl-5-methoxyindole (IX), an uncrystallizable liquid which forms a well defined picrate.

A number of 3-dimethylaminomethyl derivatives of 5-methoxy- and 7-methoxy-indole were prepared, with the possibility in mind that basic methoxyindole compounds might possess interesting pharmacological properties. The experimental procedures were based on those of previous investigators (11, 12, 13), who utilized the Mannich reaction for the introduction of the dimethylaminomethyl group.

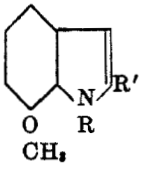
The synthesis of 2-methyl-3-dimethylaminomethyl-5-methoxyindole (XIII), was quite unsatisfactory because of the very marked tendency of 2-methyl-5-



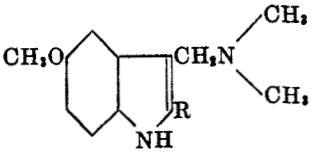
VI



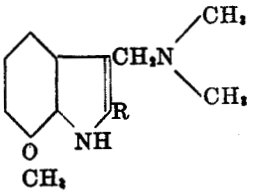
VII R = CH_3, R′ = COOH
IX R = CH_3, R′ = H
XX R = CH_2CH_2CN, R′ = $COOC_2H_5$
XXIII R = CH_2CH_2COOH, R′ = COOH



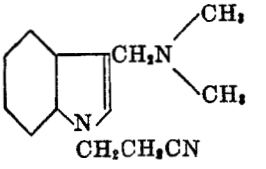
VIII R = CH_3, R′ = COOH
XXI R = CH_2CH_2CN, R′ = $COOC_2H_5$
XXIV R = CH_2CH_2COOH, R = COOH



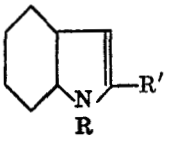
XII R = H
XIII R = CH_3
XV R = $COOC_2H_5$
XVIII R = COOH



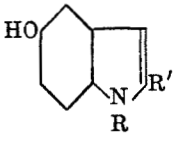
XIV R = H
XVI R = $COOC_2H_5$
XIX R = COOH



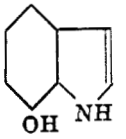
XVII



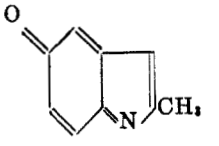
XXII R = CH_2CH_2CN, R′ = $COOC_2H_5$
XXV R = CH_2CH_2COOH, R′ = COOH



XXVI R = H, R′ = H
XXVII R = H, R′ = CH_3
XXVIII R = CH_3, R′ = H



XXIX



XXX

methoxyindole (8) to give resinous condensation products in the presence of formaldehyde. Several early attempts gave no Mannich products whatsoever.

This would appear to be due to the combined activating influence of the 2-methyl group and the 5-methoxyl group on the indole nucleus. It should be noted that while Supniewski and Serafin-Gajewski (12) apparently had no difficulty in obtaining an 88% yield of 2-methylgramine, our experience and that of Brehm (11), was that the use of 2-methylindole derivatives invariably gave some resinous material and our yields of 2-methylgramine by the above authors' procedure (12) were near 50%. Although the 5-methoxy- and 7-methoxyindole have a greater tendency to form resinous products in the Mannich reaction than indole itself, they are less reactive in this respect than 2-methylindole, and fair yields are obtained without great difficulty. The combined influence of both the methyl and methoxyl groups, however, resulted in an 8% yield, at best, of 2-methyl-3-dimethylaminomethyl-5-methoxyindole (XIII). 2-Carboethoxy-5-methoxyindole and 2-carboethoxy-7-methoxyindole react smoothly in the Mannich reaction and these animo esters may, with care, be hydrolyzed to the amino acids.

It has also been possible to prepare N-cyanoethyl derivatives (XX and XXI) of 2-carboethoxy-5-methoxy- and 2-carboethoxy-7-methoxy-indole, and from these to prepare the corresponding dibasic acids (XXIII and XXIV). The procedures employed in this connection were substantially those of Blume and Lindwall (14). 2-Carboethoxyindole was also cyanoethylated (XXII) and the product was then hydrolyzed to the dibasic acid (XXV) for purposes of comparison.

The cyanoethylation of gramine (13) yielded 1-cyanoethyl-3-dimethylaminomethylindole, (XVII), an uncrystallizable syrup, which could not be satisfactorily hydrolzyed to the amino acid in either acid or alkaline solution. Following the attempted hydrolysis, no product precipitated at *p*H 5–7. The same compound (XVII) was prepared by a Mannich reaction on 1-cyanoethylindole (14), the identity of the two compounds being established by comparison of the picrates.

Considerable difficulty was encountered in attempting to dealkylate representative methoxyindoles to yield the corresponding hydroxyindoles. Both $AlCl_3$ and N-methylaniline hydrobromide were used as dealkylating agents. It was found essential to operate in an atmosphere of nitrogen to protect the hydroxyindoles from oxidation. Even with this precaution, the yields were poor. In addition to 5-hydroxyindole (XXVI), the preparation of which (by a different and superior method) has been reported (15), 2-methyl-5-hydroxyindole (XXVII), 1-methyl-5-hydroxyindole (XXVIII), and 7-hydroxyindole (XXIX), have been prepared. Except for the 7-hydroxyindole there seems to be no doubt concerning the identities of the products. In the latter case, however, the compound was obtained in such low yield and questionable purity that only the demonstration of the presence of a phenolic hydroxyl group was possible.

There seems to be little choice between $AlCl_3$ and N-methylaniline hydrobromide as dealkylating agents as far as yield is concerned, although the isolation of the product is somewhat easier with latter.

Demethylation of 2-methyl-5-methoxyindole (V) in the presence of air by

both procedures gave a violet solid from which no hydroxy compound could be sublimed. The product was practically insoluble in water, soluble in alcohol and ether. The melting point was not sharp, but sintering began at about 200°. The nitrogen analysis was unacceptable for the expected 2-methyl-5-pseudoindolone (XXX).

EXPERIMENTAL

1-p-Methoxyphenyl-3-carboxypyrazolone-5 (*VI*). In a little dilute acetic acid, 1.38 g. (0.01 mole) of *p*-methoxyphenylhydrazine [m. p.63–64°, 45% yield, (1)] was dissolved and mixed with 1.88 g. (0.01 mole) of diethyloxalacetic acid (freed from 2.10 g. of its sodium enolate in alcohol with 1 ml. of acetic acid). Sodium acetate (1 g.) was then dissolved in the mixture. The oil which separated on standing resisted attempts to induce crystallization, and was dissolved in 20 ml., of 10% H_2SO_4 and warmed for a few minutes on the steam-bath. A solid separated which was crystallized from aqueous alcohol. There was obtained 2.04 g. (87.2%) of small, light tan crystals which melted with decomposition at 250–251°.

1-Methyl-2-carboxy-5-methoxyindole (*VII*). *Procedure A*. Seven and six-tenths grams (0.05 mole) of (unsym.) methyl-*p*-methoxyphenylhydrazine (prepared from N-methyl-*p*-anisidine) and 4.4 g. (0.05 mole) of freshly-distilled pyruvic acid were added to a mixture of 4 g. of glacial acetic acid in 20 ml. of water and warmed on the steam-bath for a few minutes. After the addition of 50 ml. of concentrated HCl, the mixture was again warmed on the steam-bath (fifteen minutes) and set in the ice-box overnight. The granular solid was crystallized from aqueous alcohol as a light tan powder melting at 215–216°, with decomposition [Kermack and Telrich (16) report 216°]; yield, 3.4 g. (33.2%).

The preparation of 1-methyl-2-carboxy-7-methoxyindole (VIII), melting with decomposition at 199–201°, from N-methyl-*o*-anisidine, was accomplished in the same manner but the yield was very poor [89 mg. from 12.5 g. of (unsym.) N-methyl-*o*-methoxyphenylhydrazine].

Procedure B. To 7.6 g. (0.05 mole) of (unsym.) methyl-*p*-methoxyphenylhydrazine dissolved in a little dilute acetic acid, was added 9.4 g. (0.05 mole) of diethyloxalacetic acid (freed from 10.5 g. of its sodium enolate in alcohol with 4 ml. of acetic acid). Sodium acetate (5 g.) was dissolved in the mixture by warming. The oil which appeared on standing was separated and dissolved in 50 ml. of saturated alcoholic HCl. After warming for a few minutes on the steam-bath, the solution was cooled and diluted to twice its volume with water. The viscous syrup which separated could not be crystallized and was refluxed for one hour with 30% KOH. The cooled solution was made acid to Congo Red and, after chilling in the ice-box, the solid was recrystallized from aqueous alcohol. There was thus obtained 1.18 g. (11.5%) of a nearly white, granular powder melting at 215–216°, with decomposition. A mixed melting point with the known product from *Procedure A* gave no depression.

Application of the same procedure gave a poor yield (54 mg. from 12.5 g. of the hydrazine) of 1-methyl-2-carboxy-7-methoxyindole (VIII), m.p. 200–201°. A mixed melting point with the sample prepared by *Procedure A* showed no depression.

1-Methyl-5-methoxyindole (*IX*). Two and five-hundredths grams (0.01 mole) of 1-methyl-2-carboxy-5-methoxyindole was heated at 200° until the liquid melt no longer gave off CO_2. The 1.15 g. (71.5%) of straw colored liquid could not be induced to crystallize. A picrate melting at 97–98° was obtained, however, which crystallized from aqueous alcohol in red-orange needles.

Similarly, 5-methoxyindole (X), m.p. 54–55°, (65% yield) was prepared from (I), (Reference 1, 55°) and 7-methoxyindole (XI) m.p. picrate 155–156°, (53% yield) from IV (Reference 1, 156°).

3-Dimethylaminomethyl-5-methoxyindole. (*5-Methoxygramine*) (*XII*). To avoid loss of

the volatile amine, 5 g. (0.0367 mole) of 33% aqueous dimethylamine was added beneath the surface of 15 ml. of glacial acetic acid, then 3.5 g. (0.0238 mole) of 5-methoxyindole (X) was dissolved in the solution, which then was cooled to 0°; 3.2 g. (0.0394 mole) of 37% aqueous formaldehyde (which had previously been cooled to 0°) was added dropwise to the above solution in an ice-bath during one-half hour and it was allowed to stand at room temperature overnight. On dilution to four times its volume with water, the solution remained clear. When the reaction was not thoroughly cooled in the initial stage, a considerable amount of high-melting, resinous material separated on standing or on dilution; the solution then required filtration and the yield was poorer. The solution was made alkaline with NH_4OH until there was no further precipitation. The white solid was crystallized from very dilute acetone, dilute alcohol, or petroleum ether. There was obtained 3.5 g. (72%) of fine, white needles, melting at 127.5–128°.

[It should be noted that this compound has been prepared in 10% yield by Wieland and Hsing (17) who treated 5-methoxyindolemagnesium iodide with dimethylaminoacetonitrile.]

By the same procedure were prepared: 2-methyl-3-dimethylaminomethyl-5-methoxyindole (XIII), in 8% yield, m.p. 112–114°; 3-dimethylaminomethyl-7-methoxyindole (XIV), in 53% yield, m.p. 105–106°; 2-carboethoxy-3-dimethylaminomethyl-5-methoxyindole (XV), in 76% yield, m.p. 123.5–124.5°; 2-carboethoxy-3-dimethylaminomethyl-7-methoxyindole (XVI), in 62% yield, m.p. 110–112°; and 1-cyanoethyl-3-dimethylaminomethylindole (XVII), in 79% yield, m.p. of picrate 140–142°.

2-Carboxy-3-dimethylaminomethyl-5-methoxyindole XVIII. The hydrolysis of 1.38 g. (0.005 mole) of 2-carboethoxy-3-dimethylaminomethyl-5-methoxyindole (XV), was accomplished by refluxing for a few minutes with 30 ml. of 20% NaOH until all the ester dissolved. The reaction mixture was cooled immediately and made just acid to litmus with acetic acid. The slightly pinkish precipitate was crystallized from aqueous alcohol or alcohol and isopropyl ether. The white amorphous solid (440 mg., 35.5%) which was obtained melted with decomposition at 197–198°.

When the hydrolytic treatment was carried on for two hours no product resembling an amino acid could be isolated.

The corresponding 2-carboxy-3-dimethylaminomethyl-7-methoxyindole (XIX) was similarly obtained in 28% yield; m.p. 196–197°.

1-Cyanoethyl-2-carboethoxy-5-methoxyindole (XX). To a solution of 2.19 g. (0.01 mole) of 2-carboethoxy-5-methoxyindole in 30 ml. of dioxane, 0.6 g. (.0113 mole) of acrylonitrile was added, followed by 0.3 ml. of trimethylbenzylammonium hydroxide solution (Triton B). The reaction mixture was warmed at 50°, for thirty minutes and permitted to stand at room temperature overnight. Water, containing a little acetic acid, was then added to increase the volume to 150 ml. The white needles which separated were crystallized from alcohol. A yield of 2.25 g. (82.7%) of fine white needles melting sharply at 112° was obtained.

The following were prepared in similar fashion: 1-cyanoethyl-2-carboethoxy-7-methoxyindole (XXI), m.p. 110–112°, in 72% yield; 1-cyanoethyl-2-carboethoxyindole (XXII), in 90% yield, m.p. 86–87°; and 1-cyanoethyl-3-dimethylaminomethylindole (XVII), in 90% yield, m.p. of picrate 140–142°. Compound XVII is identical with the product obtained by the Mannich reaction on N-cyanoethylindole.

The hydrolysis of XX, XXI, and XXII with 40% KOH gave β-(2-carboxy-5-methoxyindolyl-1)propionic acid (XXIII), in 88% yield, m.p. 208–209°; β-(2-carboxy-7-methoxyindolyl-1)propionic acid (XXIV), in 81% yield, m.p. 200–201°; and β-(2-carboxyindolyl-1) propionic acid (XXV), in 92% yield, m.p. 215°, respectively. Attempts to hydrolyze (XVII) to the amino acid were unsuccessful and destructive.

5-Hydroxyindole (XXVI). Procedure A. A solution of 1 g. (0.0068 mole) of 5-methoxyindole (X), in 10 ml. of dry benzene with 2.5 g. (0.0235 mole) of anhydrous $AlCl_3$ was refluxed gently for ten hours in an atmosphere of nitrogen. The reaction mixture was decomposed with 20 ml. of ice-water and the aqueous solution was extracted with two additional 10-ml. portions of warm benzene. The combined benzene portions were evaporated to dryness under nitrogen. The residue (390 mg.) was warmed with petroleum ether, filtered and con-

centrated to a small volume. The impure tan solid which separated melted at 103–107°, (180 mg., 20%) and was most successfully purified by sublimation under vacuum, which yielded 55 mg. (6.1%) of white solid melting at 107–108°. Bergel and Morrison (15) reported 107–109°.

Using the above procedure, 2-methyl-5-methoxyindole (8) (V), (m.p. 85–86°) gave 2-methyl-5-hydroxyindole (XXVII), m.p. 134–136°, in 14% yield.

Procedure B. A mixture of 1 g. (0.0068 mole) of 5-methoxyindole with 3 g. (0.016 mole) of N-methylaniline hydrobromide was melted in an oil-bath for one-half hour at 220°, in an atmosphere of nitrogen. On cooling, trituration with 20 ml. of water and addition of a few drops of HCl, a brown solid separated, which when dried in a vacuum and sublimed in a vacuum gave 146 mg. (16%) of white solid melting at 107–108°. This product was identical (mixed melting point) with the product from *Procedure A*.

In a similar manner XXVII was prepared in 21% yield. 1-Methyl-5-methoxyindole (IX) gave a 15% yield of 1-methyl-5-hydroxyindole (XXVIII), m.p. 42–45°. An attempt to convert 7-methoxyindole (XI) to 7-hydroxyindole (XXIX) by this procedure gave a 3% yield of a light yellow viscous liquid, which gave a low nitrogen analysis.

A dilute solution of $FeCl_3$ gave a deep purple color with XXVI, XXVII, and XXIX, while XXVIII gave a red color which slowly became purple. All gave a pink color with Ehrlich's reagent.

SUMMARY

1. A number of 5-methoxy- and 7-methoxy-indole derivatives have been prepared.

2. Methoxyindoles have been found to undergo the Mannich reaction and cyanoethylation.

3. Hydrolysis of 1-methyl-2,3-dicarboethoxy-5-methoxyindole and the 7-methoxy analog yielded only the α-carboxylic acids.

4. Demethylation of a few 5-methoxyindoles to 5-hydroxyindoles has been accomplished.

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