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Some 3-Dialkylaminomethylindoles and 3,3'-Diindolylmethanes

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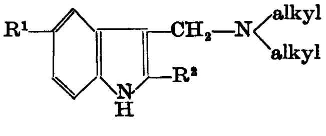
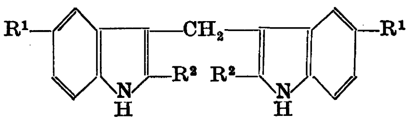
A number of 3-dialkylaminomethylindoles have been prepared by the Mannich reaction. In some cases 3,3'-diindolylmethanes were obtained as by-products. 3,3'-diindolylmethanes could also be prepared from an indole and formaldehyde or from an indole and a Mannich indole base. By the latter method unsymmetrical diindolylmethanes could also be prepared.

In the course of some studies in the indole series, the primary object of which was the synthesis of potential antagonists to serotonin (5-hydroxytryptamine), a number of new 3-dialkylaminomethylindoles were prepared which are reported in this paper.

The indoles, which were of type I ($R^1 = H, CH_3, CH_3O, Cl$; $R^2 = CH_3, C_6H_5$), were easily obtained by the Mannich reaction. In some cases when diethylamine was used as the amino component neutral by-products were isolated which were shown to be 3,3'-diindolylmethanes (II).



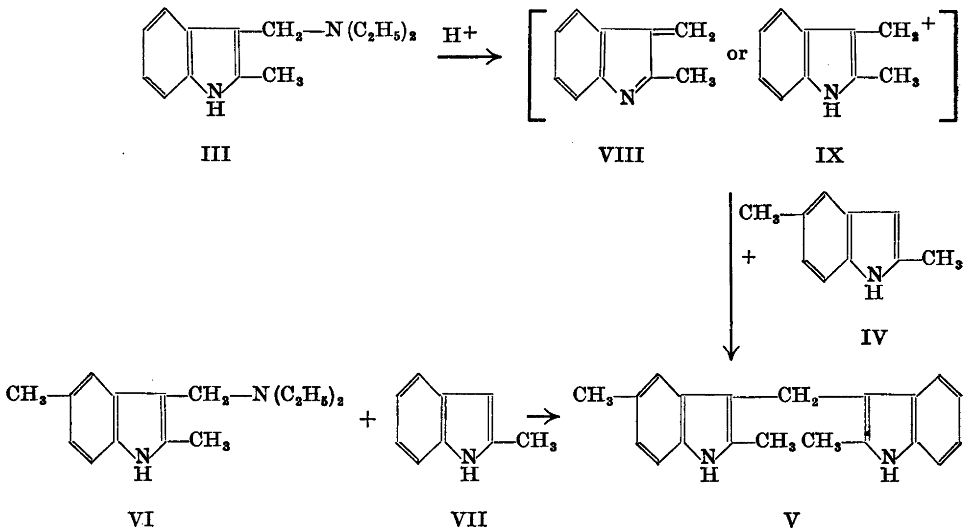
I



II

The formation of diindolyl compounds seemed to be promoted by insufficient cooling in the initial stage of the reaction. Small amounts of by-products have been reported to be formed in the Mannich reaction with indoles [1-5], but the constitutions of these compounds have only occasionally been subject to investigation [3,4]. However, diindolylmethanes have been found as by-products when tertiary Mannich indole bases and their quaternary salts were used as alkylating agents [6]. The diindolyl compounds could also be obtained from the starting indoles and formaldehyde. They were also prepared in good yields by the reaction between an indole unsubstituted in the 3-position and a Mannich indole base under the same experimental conditions as in the Mannich synthesis. Using the last named method unsymmetrical diindolylmethanes could also be obtained. Finally it was observed that salts of the Mannich bases gradually decomposed in aqueous solution giving diindolyl compounds.

The mechanism of the formation of the diindolylmethanes is not clear and may be different under different conditions. Their formation as by-products in the Mannich reaction may be due to a direct reaction between the starting indole and formaldehyde but they may also be formed by alkylation of the starting indole by the formed Mannich indole base. However, the formation of unsymmetrical diindolylmethanes is rather elucidative both with regard to the constitution of the product and to the reaction mechanism. Thus, the reaction between 3-diethylaminomethyl-2-methylindole (III) and 2,5-dimethylindole (IV) affords the same product (V) as the reaction between 3-diethylaminomethyl-2,5-dimethylindole (VI) and 2-methylindole (VII). This seems to confirm that the indole nuclei are connected in 3,3'-position. If the reaction mechanism had been a reverse Mannich reaction followed by the reaction of the thus formed formaldehyde with an indole, the reaction product would most probably consist of a mixture of three different diindolyl compounds, two symmetrical and one unsymmetrical. It is more reasonable to adapt the mechanism proposed by Snyder and Eliel [7] for alkylations with gramine and its salts: Amine elimination from the Mannich base (III) gives an unsaturated intermediate (VIII) or a carbonium ion (IX) which reacts with an indole unsubstituted in the 3-position.



On the other hand, the formation of diindolyl compounds in aqueous solutions of salts of 3-diethylaminomethylindoles cannot be explained in this way, no indole unsubstituted in the 3-position being present. In this case it seems necessary to postulate the first step to be a reverse Mannich reaction followed by recombination of the formaldehyde and the indole fragments or an alkylation of the indole with the Mannich base according to the mechanism outlined above.

The 3-dialkylaminomethylindoles have been investigated pharmacologically by Professor B. Uvnäs and his collaborators of the Department of Pharmacology, Karolinska Institutet, Stockholm. The results will be published elsewhere.

EXPERIMENTAL

3-Dialkylaminomethylindoles

2-Methylindole [8], 5-chloro-2-methylindole [9], 2,5-dimethylindole [10], 5-methoxy-2-methylindole [11], and 2-phenylindole [12] required as starting material were prepared according to procedures described in the literature.

3-Diethylaminomethyl-2-methylindole. To a cooled mixture of diethylamine (2.78 g, 0.038 mole), and 30 % formaldehyde (1.6 ml) in glacial acetic acid (2.5 ml) was added 2-methylindole (2.5 g, 0.019 mole) and the mixture was allowed to stand overnight at room temperature. Next day the orange solution was poured into water giving a solid product (A) which was filtered off. The filtrate was made alkaline with sodium hydroxide giving the desired Mannich base (2.1 g, 51 %); m.p. 89—90° after recrystallisation from 80 % methanol. (Found: C 78.3; H 9.40; N 13.05. $C_{14}H_{20}N_2$ requires C 77.7; H 9.32; N 12.95). The by-product (A) (1.2 g) was recrystallised twice from ethanol; m.p. 236—237.5°. Analysis indicated that the product had the composition $C_{19}H_{18}N_2$ (Found: C 82.9; H 6.52; N 10.2. $C_{19}H_{18}N_2$ requires C 83.2; H 6.61; N 10.2). Mixed m.p. with a sample of *2,2′-dimethyl-3,3′-diindolylmethane*, prepared from 2-methylindole and formaldehyde according to the directions of von Walther and Clemen [13], showed no depression.

By essentially the same procedure the following Mannich bases were prepared:

3-Pyrrolidinomethyl-2-methylindole. M.p. 139—140° (from ethanol). Yield 98 %. (Found: C 78.6; H 8.65; N 13.2. $C_{14}H_{18}N_2$ requires C 78.5; H 8.46; N 13.1).

3-Diethylaminomethyl-5-chloro-2-methylindole. M. p. 105—106° (from 80 % methanol). Yield 74 %. (Found: C 66.9; H 7.12. $C_{14}H_{19}ClN_2$ requires C 67.0; H 7.64).

As a by-product a small amount of *5,5′-dichloro-2,2′-dimethyl-3,3′-diindolylmethane*, m. p. 234—235° (from ethanol), was obtained.

3-Piperidinomethyl-5-chloro-2-methylindole. M. p. 165—166° (from ethanol). Yield 99 %. (Found: C 68.9; H 7.26. $C_{15}H_{19}ClN_2$ requires C 68.55; H 7.29).

3-Dimethylaminomethyl-2,5-dimethylindole. M. p. 160—162° (from ethanol). Yield 86 %. (Found: C 77.1; H 8.71. $C_{13}H_{18}N_2$ requires C 77.2; H 8.97). The synthesis of this compound has also been described in a recent paper by Qvadbeck and Röhm [14].

3-Diethylaminomethyl-2,5-dimethylindole. M. p. 107—108° (from ethanol). Yield 63 %. (Found: C 78.0; H 9.53. $C_{15}H_{22}N_2$ requires C 78.2; H 9.63).

As a by-product *2,2′,5,5′-tetramethyl-3,3′-diindolylmethane*, m. p. 252—253° (from ethanol), was obtained. Yield 32 % calc. on 2,5-dimethylindole.

3-Piperidinomethyl-2,5-dimethylindole. M. p. 173—174° (from ethanol). Yield 89 %. (Found: C 79.6; H 9.19. $C_{16}H_{22}N_2$ requires C 79.3; H 9.15).

3-Pyrrolidinomethyl-2,5-dimethylindole. M. p. 167—168° (from ethanol). Yield 76 %. (Found: C 79.0; H 8.79. $C_{15}H_{20}N_2$ requires C 78.9; H 8.83).

3-Diethylaminomethyl-5-methoxy-2-methylindole. M. p. 84—85.5° (from 80 % methanol). Yield 73 %. (Found: C 72.5; H 8.75; N 11.2. $C_{15}H_{22}N_2O$ requires C 73.1; H 9.00; N 11.4).

3-Piperidinomethyl-5-methoxy-2-methylindole. M. p. 143—144° (from ethanol). Yield 97 %. (Found: C 74.4; H 8.64. $C_{16}H_{22}N_2O$ requires C 74.4; H 8.58).

3-Dimethylaminomethyl-2-phenylindole. M. p. 128—129° (from 80 % ethanol). Yield 93 %. (Found: C 81.1; H 6.98; N 11.1. $C_{17}H_{18}N_2$ requires C 81.6; H 7.24; N 11.2).

3-Piperidinomethyl-2-phenylindole. The *acetate* of this compound separated directly from the reaction mixture in 98 % yield; m. p. 157—158° (from benzene). (Found: C 75.1; H 7.88; N 8.00. $C_{22}H_{26}N_2O_2$ requires C 75.4; H 7.47; N 7.99).

The *base* was obtained on treatment of an aqueous suspension of the acetate with sodium carbonate; m. p. 117—118° (from 80 % methanol). (Found: C 83.0; H 7.90; N 9.34. $C_{20}H_{22}N_2$ requires C 82.7; H 7.63; N 9.64).

3,3′-Diindolylmethanes

2,2′-Dimethyl-3,3′-diindolylmethane. (*a*) This compound was obtained as a by-product in the reaction between 2-methylindole, formaldehyde and diethylamine as described above. It had earlier been prepared by von Walther and Clemen[13] and by Voisenet[15] from 2-methylindole and formaldehyde.

(*b*) It could also be obtained from 2-methylindole and 3-diethylaminomethyl-2-methylindole in the following way.

A mixture of 3-diethylaminomethyl-2-methylindole (0.25 g, 0.00115 mole), 2-methylindole (0.15 g, 0.00115 mole), and glacial acetic acid (0.3 ml) was heated on the water-bath for a few minutes until a clear solution was obtained. The mixture was then kept at room temperature for three hours. The separated crystals were collected (0.15 g, 48 %) and recrystallised from ethanol; m. p. 236—237°, undepressed on admixture with the product prepared according to von Walther and Clemen[13] and by the by-product obtained in the Mannich synthesis.

(*c*) An aqueous solution of 3-diethylamino-2-methylindole hydrochloride (0.5 %, pH 4) was kept at room temperature for 20 days. A small amount of solid material was gradually formed which was collected and recrystallised from ethanol; m. p. 236—237°, undepressed by the products described above.

2,2′,5-Trimethyl-3,3′-diindolylmethane. The reaction of 3-diethylaminomethyl-2-methylindole was reacted with 2,5-dimethylindole in acetic acid was carried out as described under (*b*) above. M. p. 209—210° (from ethanol). Yield 39 %. (Found: C 82.8; H 6.96; N 9.47. $C_{20}H_{20}N_2$ requires C 83.3; H 6.99; N 9.71). This compound could also be prepared in the same way from 3-diethylaminomethyl-2,5-dimethylindole and 2-methylindole.

2,2′,5,5′-Tetramethyl-3,3′-diindolylmethane. (*a*) This compound was obtained as described above as a by-product in the Mannich reaction between 2,5-dimethylindole, formaldehyde and diethylamine.

(*b*) A mixture of 2,5-dimethylindole (0.5 g), 30 % formaldehyde (0.3 ml), glacial acetic acid (0.4 ml) and ethanol (5 ml) was heated on the water-bath for a few minutes. The reaction product began to crystallise almost immediately. After cooling it was collected (0.4 g, 78 %) and recrystallised from ethanol-acetone (1:1); m. p. 252—253°, undepressed by the by-product from the Mannich reaction. (Found: C 82.9; H 7.56; N 9.47. $C_{21}H_{22}N_2$ requires C 83.4; H 7.33; N 9.26).

5-Chloro-2,2′-dimethyl-3,3′-diindolylmethane. Prepared in 96 % yield from 3-diethylaminomethyl-2-methylindole and 5-chloro-2-methylindole in acetic acid in the usual way; m. p. 180—181° (from ethanol). (Found: C 74.2; H 5.27; N 8.90. $C_{19}H_{17}ClN_2$ requires C 73.9; H 5.55; N 9.07).

5,5′-Dichloro-2,2′-dimethyl-3,3′-diindolylmethane. (*a*) A small amount of this compound was obtained as a by-product in the Mannich reaction between 5-chloro-2-methylindole, formaldehyde and diethylamine.

(*b*) It was also prepared in the usual way from formaldehyde and 5-chloro-2-methylindole in 48 % yield; m. p. 234—235° (from ethanol). (Found: C 65,8; H 4.99; N 8.17. $C_{19}H_{16}Cl_2N_2$ requires C 66.5; H 4.70; N 8.16).

2-Methyl-2′-phenyl-3,3′-diindolylmethane. Prepared from 3-diethylamino-2-methylindole and 2-phenylindole in 70 % yield; m. p. 205—207°, after recrystallisation from ethanol-acetone (3:1). (Found: C 85.4; H 6.09; N 8.08. $C_{24}H_{20}N_2$ requires C 85.7; H 5.99; N 8.32).

2,2′-Diphenyl-3,3′-diindolylmethane. Prepared from formaldehyde and 2-phenylindole. Yield 58 %; m. p. 184—185° (from ethanol). (Found: C 86.9; H 5.71; N 7.11. $C_{29}H_{22}N_2$ requires C 87.4; H 5.56; N 7.03).

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