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1-METHYL-3-HYDROXYMETHYLINDAZOLE

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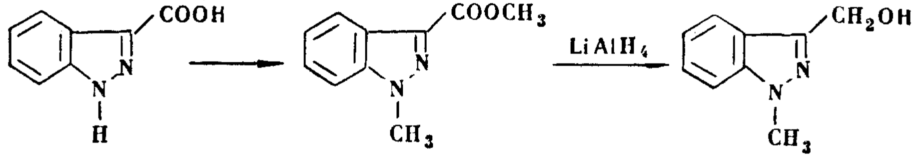
1-Methyl-3-hydroxymethylindazole is prepared by reducing methyl 1-methylindazole-3-carboxylate with lithium aluminum hydride. It is readily acetylated and with thionyl chloride gives 1-methyl-3-chloromethylindazole. The latter reacts with secondary amines to give 1-methyl-3-dialkylaminomethylindazoles, characterized as their methiodides.

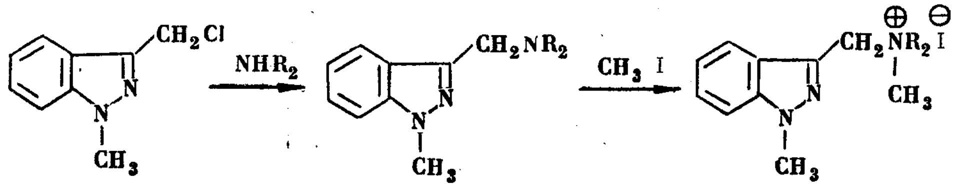
It was previously shown that reaction of indazole and its derivatives with formaldehyde gives 1-hydroxymethylindazoles, which readily undergo exchange reactions involving the hydroxyl group [1]. It was considered of interest to study the analogous reactions of 3-hydroxymethyl derivatives of indazoles. The present investigation is concerned with the properties of 1-methyl-3-hydroxymethylindazole and some of its transformation products.

Because of the inability of position 3 in indazole to undergo hydroxymethylation [2], the route chosen for preparing 1-methyl-3-hydroxymethylindazole from indazole-3-carboxylic acid was via the methyl ester, followed by reduction of the latter with $LiAlH_4$.



I

It was shown that, unlike 1-hydroxymethylindazole, 1-methyl-3-hydroxymethylindazole does not condense with secondary aliphatic or heterocyclic amines when boiled with them, but readily undergoes acylation and smoothly exchanges the hydroxyl group for a chlorine atom when treated with thionyl chloride. While 3-chloromethylindazole gives a polycondensation product [2] and can be prepared only by observing a number of precautions [3], 1-methyl-3-chloromethylindazole is stable enough. Reaction of 1-methyl-3-chloromethylindazole with excess of secondary amines gives good yields of the corresponding aminomethyl derivatives. Reaction of the latter with methyl iodide gives the quaternary salts



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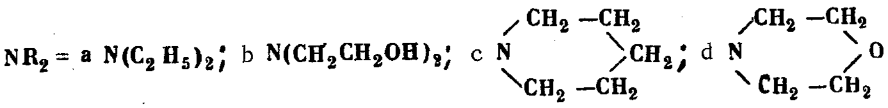


The absorption graphs for 1-methyl-3-hydroxymethylindazole and the products of transforming the hydroxyl group (see figure) show close correspondence with the curves given by 1-alkyl- [4] and 1-aralkylindazoles [5], indicating that the hydroxymethyl, chloromethyl, and aminomethyl groups at position 3 only slightly affect the UV spectra of 1-substituted indazoles.

EXPERIMENTAL

1-Methyl-3-hydroxymethylindazole (I). 20 g of methyl 1-methylindazole-3-carboxylate in 100 ml dry ether are added with stirring to 4 g lithium aluminum hydride in 125 ml dry ether, the rate of addition being adjusted so that the ether slowly boils. Then the reaction mixture is refluxed for 2 hr more and left overnight, and 40 ml water are added dropwise with stirring. The ether layer is separated and dried over sodium sulfate.

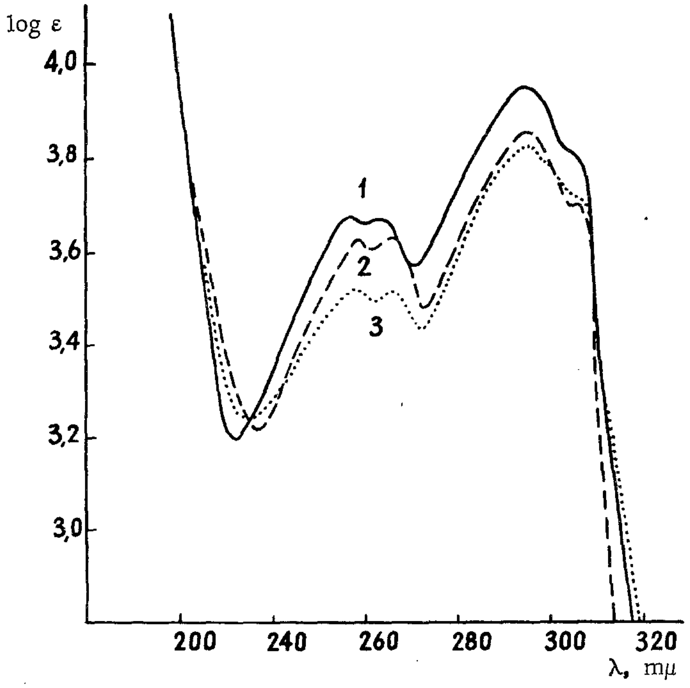
The oily substance remaining after distilling off the ether was fractionally distilled in a vacuum. Yield 12 g (70%), b.p. 150-160° (8 mm). Crystallization from a petroleum ether-chloroform mixture gives colorless crystals m.p. 92-93°. Found: C 66.48, 66.53; H 6.17; 6.24%. Calculated for $C_9H_{10}N_2O$: C 66.65; H 6.21%.

1-Methyl-3-chloromethylindazole (II). 6 ml thionyl chloride are added dropwise to 8 g I in 20 ml dry benzene, and the mixture refluxed 30 min. The benzene and excess thionyl chloride are then distilled off, and the residue vacuum-distilled. Yield 7 g (79.5%) b.p. 156-157° (4 mm), m.p. 54-55° (from petroleum ether). Found. C 60.10, 60.03; H 5.40, 5.16%. Calculated for $C_9H_9ClN_2$: C 59.83; H 5.02%.

1-Methyl-3-diethylaminomethylindazole (IIIa). A mixture of 1 g II and 5 ml diethylamine are heated for 1 hr at 95-100°. The reaction mixture is treated with 10 ml 5% sodium hydroxide solution, and the oily substance separating is extracted with ether. The residue remaining after distilling off the ether from the ether extract is vacuum-distilled. Yield 0.8 g (66.6%), b.p. 151° (4 mm). Found: C 71.74, 71.66; H 8.79, 8.74%. Calculated for $C_{13}H_{19}N_3$: C 71.84; H 8.82%.

1-Methyl-3-diethylaminomethylindazole methiodide (IVa). Equimolecular amounts of IIIa and methyl iodide are mixed in dry benzene. After 2 hrs the precipitate of quaternary salt is filtered off. Colorless crystals melt at 171-172° (from alcohol-ether). Yield quantitative. Found: C 46.90, 46.87; H 6.34, 6.30%. Calculated for $C_{14}H_{22}IN_3$: C 46.80; H 6.17%.

1-Methyl-3-diethanolaminomethylindazole (IIIb). I g II and 1 g diethanolamine are slowly heated together to 175°, and then the reaction mixture is vacuum-distilled, the fraction boiling at 156-158° (4 mm) being collected. The colorless crystalline substance melts at 48-49°. Yield 0.85 g (61.5%). Found: C 62.55, 62.84; H 7.38, 6.32%. Calculated for $C_{13}H_{19}N_3O_2$: C 62.65; H 7.68%.



Absorption spectra:
1. 1-Methyl-3-hydroxymethylindazole; 2. 1-Methyl-3-chloromethylindazole; 3. 1-Methyl-3-diethylaminomethylindazole

1-Methyl-3-piperidinomethylindazole (IIIc). A mixture of 1 g compound II and 1 ml piperidine are heated for 1 hr at 110-115°. The reaction mixture is treated with 10 ml dilute sodium hydroxide solution and extracted with ether. The ether is distilled off, and the residue vacuum-distilled. Yield 0.85 g (67.3%), b.p. 162° (4 mm). Found: C 73.28, 73.19; H 8.47, 8.40%. Calculated for $C_{14}H_{19}N_3$: C 73.32; H 8.36%.

1-Methyl-3-piperidinomethylindazole methiodide (IVc). Colorless crystals m.p. 210-211° (from alcohol-ether). Yield quantitative. Found: C 48.23, 48.38; H 6.29, 6.14%. Calculated for $C_{15}H_{22}IN_3$: C 48.52; H 5.97%.

1-Methyl-3-morpholinomethylindazole (IIId). 1 g II and 1 g morpholine are heated together for 30 min at 125-130°. After vacuum-distilling the reaction mixture, a 1.2 g (93%) yield was obtained, b.p. 171° (4 mm), m.p. 59-60° (from petroleum ether). Found: C 67.38, 67.45; H 7.56, 7.38%. Calculated for $C_{13}H_{17}N_3O$: C 67.55; H 7.35%.

1-Methyl-3-morpholinomethylindazole methiodide (IVd). Colorless crystals (from alcohol+ether), m. 204-205°. Found: C 44.98, 44.93; H 5.56, 5.57%. Calculated for $C_{14}H_{20}IN_3O$: C 45.05; H 5.40%.

1-Methyl-3-acetoxymethylindazole. 1 g I and 4 ml acetic anhydride are refluxed for 1 hr, and the product is vacuum-distilled. Two distillations give a colorless oil, b.p. 152° (4 mm). Found: C 64.68, 64.69; H 5.86, 5.86%. Calculated for $C_{11}H_{12}N_2O_2$: C 64.69, H 5.92%.

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