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# PHYSIOLOGICALLY ACTIVE INDANAMINES. III. THE SYNTHESIS OF THE CYCLIC ANALOG OF EPHEDRINE

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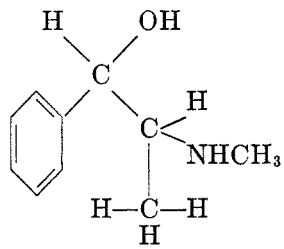
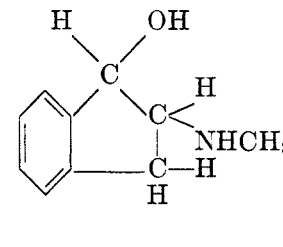
A number of indanamines reported previously from this laboratory (1, 2) have shown promising bronchodilator activity. The present paper describes the synthesis of the cyclic form of ephedrine (I), namely, 2-methylaminoindanol (II). By the Sollmann and von Oettingen perfused lung method this compound has been found to possess somewhat greater bronchodilator activity than ephedrine.[1] The corresponding benzyl ether (IV) appears to be considerably more potent than II.



I.



II.

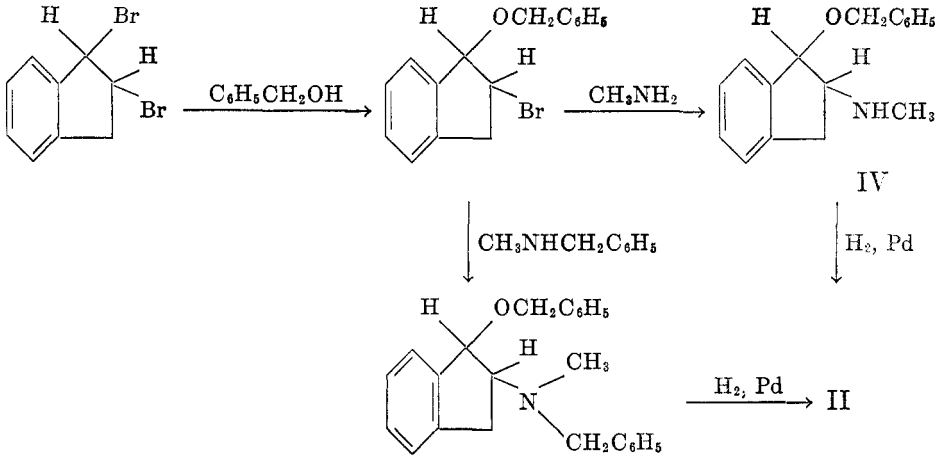
Earlier efforts (1) to prepare 2-methylaminoindanol by the Becker-Decker alkylation of 2-aminoindanol were unsuccessful. von Braun and Weissbach (3) reported isolation of traces of the compound as the picrate by selective demethylation of its methyl ether. In the current studies, attempts to alkylate methylamine and benzylmethylamine with 2-bromoindanone, followed by reduction of the carbonyl group and debenzylation, gave unsatisfactory results.[2] Another approach to the problem was based on a report by Manske and Johnson (4) that 1-phenylpropanedione-1,2 on reductive amination with methylamine gave ephedrine, and by Koelsch and le Claire (5) that the $\beta$-keto group of indandione-1,2 was the more reactive. Several attempts at catalytic reductive amination of indandione with methylamine failed to give a characterizable compound. Likewise efforts to reduce this Schiff base with lithium aluminum hydride (6) were unsuccessful, a very dark solution being formed as soon as the amine

[1] Assays were carried out under the direction of B. E. Graham of our Pharmacology Department.

[2] Since this attempt was made, a statement was found in German Patent 598,142 that bromoindanone with ammonia, methylamine, hexamethylenetetramine, potassium phthalimide, and the potassium salt of N-methyltoluenesulfonamide gave only coupling to indanonylbromoindanone. This has been verified, but it is of interest that with substituted bromoindanones, such as 5,6-dimethoxybromoindanone, such colored self-condensation products are not formed on reaction with amines, and the expected secondary or tertiary aminoindanones are produced.

and ketone were mixed. 2-*p*-Toluenesulfonamidoindanol-1 (III) could be methylated under very limited conditions, but subsequent attempts to cleave the tosyl group with metallic sodium and liquid ammonia (7) met with failure.

The synthesis of II was achieved by the method summarized in the accompanying chart:




This approach consisted of the conversion of 1,2-dibromoindane through indene-bromohydrin benzyl ether into 1-benzyloxy-2-methylaminoindane (IV), followed by reductive debenzylation. It has been shown (3) that reaction of 1,2-dibromoindane with methanol gives 1-methoxy-2-bromoindane in good yield, but when ethanol is used the yield is much poorer (8). In the present work the corresponding benzyl ether was obtained in about 45% yield, but reaction of this with methylamine under pressure gave at best 20% yields of the N-methyl benzyl ether.[3] Catalytic hydrogenation with palladium removed the benzyl group to give the desired cyclic analog of ephedrine (II).

## EXPERIMENTAL

*Sulfonamide alkylations.* *p*-Toluenesulfonamidoindanol (III) was prepared by the addition of 2.10 g. (0.011 mole) of *p*-toluenesulfonyl chloride in three portions to a solution of 1.85 g. (0.01 mole) of 2-aminoindanol hydrochloride in 25 cc. of pyridine. The solution was heated on the steam-bath for fifteen minutes, cooled, poured into ice and excess concentrated hydrochloric acid, and chilled overnight. The brown gummy product was spread on a porous plate to dry and purified by recrystallization from toluene, then dilute alcohol, giving pure white crystals, m.p. 137–138°.

*Anal.* Calc'd for $C_{16}H_{17}NO_3S$: C, 63.50; H, 5.65; N, 4.62.
Found: C, 63.60; H, 5.77; N, 4.59.

*Alkylation* of the sulfonamide (III) was attempted without success using benzyl chloride, benzyl iodide, and methyl iodide. The sodium, potassium or silver salts of III could not be prepared by standard methods employed for sulfonamides (9), since the free sulfonamide reprecipitated in all cases, even from a cooled solution in excess alkali. The sodium salt was prepared by the following method. Two and five tenths grams (0.008 mole) of *p*-toluenesulfonamidoindanol (III) was dissolved in purified dioxane and the solution added dropwise

[3] This is to be expected from the relative unreactivity of 2-bromoindanes (8).

to a hot, well-stirred suspension of 0.19 g. (0.008 mole) of powdered sodium in 75 cc. of dioxane. Usually a purple color formed almost at once, but in a few cases it was very slight. After addition was complete, the solution was heated under reflux an additional hour and allowed to stand at room temperature. After several days there began to form beautiful white rosettes which were removed and redissolved in hot dioxane. After one or two days the rosettes which formed were collected and dried. They left an ash on ignition, and on addition of water the free sulfonamide was liberated (m.p. 139°). The sodium salt could also be prepared using sodamide in liquid ammonia.

Attempted *alkylations* of the *sodium salt* were unsuccessful under the following conditions: (a) addition of methyl iodide to the liquid ammonia solution without isolation of the sodium salt; (b) heating the sodium salt and methyl iodide in a sealed tube at 150° for seven hours, 140° for fifteen hours or 125° for sixty-three hours; (c) heating the sodium salt under reflux with methyl iodide in benzene, toluene or dioxane. The above alkylation was repeated using a ten-fold excess of methyl iodide in dry xylene under reflux for twenty-two hours. The xylene was chilled, the suspended matter removed by filtration and the filtrate concentrated *in vacuo* to a red-brown gum. This was dissolved in excess hot benzene, decolorized with charcoal, and concentrated to a small volume. On standing overnight there crystallized a white product insoluble in hot alkali. Recrystallization from alcohol gave 0.60 g. (from 1.8 g. of sodium salt) of white crystals (III), m.p. 132.5–133.5°.

*Anal.* Calc'd for $C_{17}H_{19}NO_3S$: C, 64.34; H, 6.03; N, 4.41.

Found: C, 64.17; H, 6.06; N, 4.42.

The material originally filtered from the cold xylene on extraction with hot benzene yielded considerable quantities of elementary iodine.

*Indene dibromide* (10). Bromination was carried out by adding an equivalent of bromine dropwise to a solution of indene in ether at 0°. The ether was evaporated at low temperature and the indene dibromide distilled *in vacuo*; b.p. 111° (1.2 mm.); yield, 78%; $n_D^{25}$ 1.6282 [reported (8), 1.6290].

*1-Benzyloxy-2-bromoindane.* Indene dibromide was stirred for three hours under nitrogen on the steam-bath with one equivalent of benzyl alcohol. The theoretical amount of pyridine (8) was added, the mixture poured into water, and the oil separated, dried, and distilled. Yield, 40%; b.p. 155° (0.22 mm.); $n_D^{25}$ 1.5930.

*Anal.* Calc'd for $C_{16}H_{15}BrO$: C, 63.36; H, 4.95; Br, 26.40.

Found: C, 63.01; H, 4.92; Br, 25.85.

A reaction between sodium benzylate and indene dibromide yielded only low-boiling products, one fraction, b.p. 77–90° (3 mm.), of which corresponded in boiling point to that reported (8) for 2-bromoindene.

*Aminations.* When 1-benzyloxy-2-bromoindane was shaken for forty hours at room temperature with a 35% solution of methylamine in benzene no reaction occurred. However, when the reaction was carried out in a sealed tube at an elevated temperature the desired product was isolated in yields up to 20%. Variation of time and temperature indicated the optimum conditions to be approximately 115° for about twenty hours. The methylamine hydrobromide was washed out with water, the benzene and excess methylamine removed *in vacuo* and the residue (IV) converted to its hydrochloride, m.p. 173°. Difficulty was encountered in removing the last traces of methylamine hydrochloride from the product, causing it to have a low carbon and high nitrogen content.

*Anal.* Calc'd for $C_{17}H_{20}ClNO$: C, 70.46; H, 6.90; N, 4.83.

Found: C, 69.85; H, 6.94; N, 5.05.

Preparation of this compound was also attempted by heating 1-benzyloxy-2-bromoindane with benzylmethylamine and sodium carbonate in a nitrogen atmosphere at 150° for four hours, but without success.

*2-Methylaminoindanol hydrochloride* (II). Reductive debenzylation of the above benzyl ether was carried out in absolute ethanol with 10% palladium-Norit catalyst. Hydrogen uptake was slow and a crystalline product was isolated by filtering and evaporating the resulting solution to dryness. The *hydrochloride* was recrystallized from ethanol-ether; m.p. 162°.

*Anal.* Calc'd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.02.
Found: C, 60.34; H, 7.23; N, 7.00.

The *picrate*, on recrystallization from absolute ethanol, melted at 169–169.5° [reported m.p., 171° (3)].

SUMMARY

Synthesis of 2-methylaminoindanol, a cyclic analog of ephedrine, is described. Preliminary pharmacological tests indicate that the compound, as well as its corresponding benzyl ether, possesses bronchodilator activity.

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