[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

SYNTHESIS OF 1-(3,4-DIHYDROXYPHENYL)-1-AMINO-2-PROPANOL

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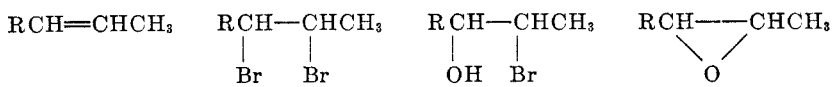
The present paper describes the synthesis of 1-(3,4-dihydroxyphenyl)-1-amino-2-propanol (VI), which is isomeric with the pharmacologically very active 1-(3,4-dihydroxyphenyl)-2-amino-1-propanol (VIII) (1). It was desired to obtain information concerning the connection between the structural change and the change in activity. According to the animal experiments, the 1-(3,4-dihydroxyphenyl)-1-amino-2-propanol loses its blood pressure activity through the change of position of the amino and alcoholic hydroxyl groups.

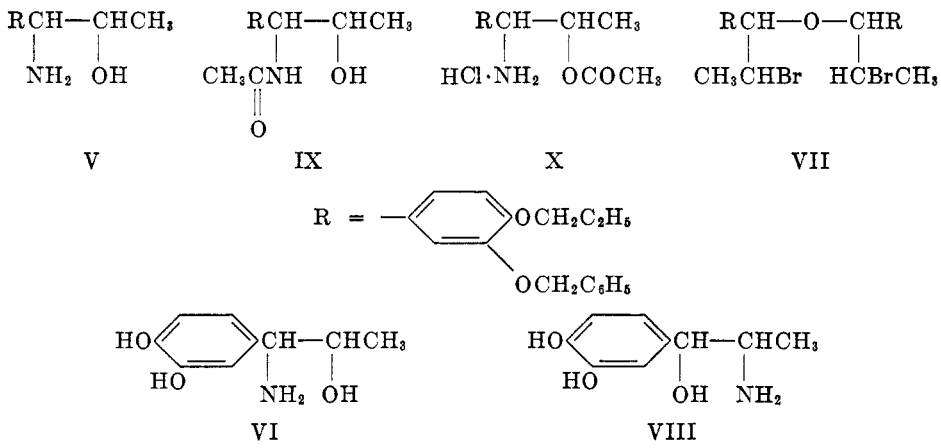
Synthesizing 1-(3,4-dihydroxyphenyl)-1-amino-2-propanol (VI), we started from 3,4-dibenzyloxypropenylbenzene (I), which is readily obtained from safrol in the manner described by Bruckner and Fodor (1) in their "corbasil" synthesis. The two benzyl groups can be easily eliminated by hydrogenolysis.

One can obtain from 3,4-dibenzyloxypropenylbenzene the suitable dibromo derivative (II). This can be converted nearly quantitatively into the corresponding bromohydrin (III) in a manner long known in the literature (2). The bromohydrin can be converted *via* an ethylene oxide derivative (IV) with methanolic ammonia at 150° into the amino alcohol (V). Passage through an intermediate product of the reaction is proved by the fact that the ethylene oxide derivative (IV)—obtained from the bromohydrin (III) with methanolic potassium hydroxide—can be converted with methanolic ammonia into the same amino alcohol (V).

Theoretically the reaction can proceed in two directions, *i.e.*, 1-(3,4-dibenzyloxyphenyl)-2-amino-1-propanol or 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol, and of course each has 2 racemic forms. However we succeeded in isolating, besides an oily reaction product, only the hydrobromide salt of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol (V) of one of the four racemates as the main product. Comparison of the melting point of the hydrochloride of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol (m.p. 189°) with that of the hydrochloride of 1-(3,4-dibenzyloxyphenyl)-2-amino-1-propanol prepared by Bruckner and Fodor (1) (m.p. 169°), does not prove decisively whether the amino and alcoholic hydroxyl groups are arranged according to formula (V), or formula (VIII). As formula (VIII) represents both of the stereoisomer types norephedrine and psi-norephedrine, the above mentioned difference of the melting points can also be explained by assuming the formation of both stereoisomers depending upon the synthesis employed.



I II III IV



We decided the question through acetylation with acetic anhydride in pyridine, and obtained the N-acetylamino compound (IX), m.p. 131°. The compound was treated in the customary manner with phosphorus trichloride in toluene (3); if the arrangement of the hydroxyl and amino groups is as in VIII, we should have obtained the isoquinoline compound, as in the case of 1-(3,4-dibenzyloxyphenyl)-2-acetylamino-1-propanol (m.p. 113°) which under the same conditions cyclizes to 1,3-dimethyl-6,7-dibenzyloxyisoquinoline. Instead of this however a N → O acyl migration took place, and we isolated the hydrochloride of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol acetate (X) (m.p. 174°) from the reaction mixture.

On catalytic debenzylation of the amino alcohol (V) we obtained an amorphous, colorless, hygroscopic residue, which could not be crystallized, as in the case of the isomer corbasil (1). For the pharmacological investigations this amorphous compound (VI) was used.

We wish to add that the bromohydrin (III) must not be kept for long, because on standing, through condensation, an ether (VII) is formed.

EXPERIMENTAL

1-(3,4-Dibenzyloxyphenyl)-1,2-dibromopropane (II). Thirty-three and four-tenths grams of I was dissolved in 100 ml. of abs. chloroform and with cooling 16 g. of bromine in 20 ml. of chloroform was added dropwise. The pale yellow solution was evaporated under reduced pressure, and the crystalline residue was recrystallized from petroleum ether; long needles, m.p. 116°, yield, 40 g. The compound decomposed in light.

Anal. Calc'd for $C_{23}H_{22}Br_2O_2$: C, 56.32; H, 4.8.

Found: C, 56.7; H, 4.8.

1-(3,4-Dibenzyloxyphenyl)-2-bromo-1-propanol (III). Ten grams of II was dissolved in a mixture of 72 ml. of acetone and 18 ml. of water; 1.1 g. of $CaCO_3$ prec. was added, and the solution was warmed for an hour on the steam-bath. The homogeneous pale green solution was evaporated under reduced pressure at 50°. The oily residue was dissolved in ether, shaken with water, and dried with sodium sulfate. The ether yielded a nearly colorless dense oil, yield 7.8 g. This was dried under reduced pressure for a long time before analysis.

Anal. Calc'd for $C_{23}H_{23}BrO_3$: C, 64.7; H, 5.4.

Found: C, 65.2; H, 5.7.

1-(3,4-Dibenzyloxyphenyl)-2-methylethylene oxide (IV). Three and two-tenths grams of bromohydrin (III) was dissolved in 5 ml. of abs. methanol, and 0.45 g. of potassium hydroxide in 10 ml. of abs. alcohol was added to the solution. The potassium bromide separated immediately. After boiling for an hour the reaction mixture was evaporated and the oily residue dissolved in 20 ml. of abs. ether and kept in a desiccator over sulfuric acid and paraffin. The crystallization began soon and the colorless prisms were recrystallized from petroleum ether; m.p. 56°, yield 1.8 g.

Anal. Calc'd for $C_{23}H_{22}O_3$: C, 79.8; H, 6.4.
Found: C, 80.3; H, 6.5.

1-(3,4-Dibenzyloxyphenyl)-1-amino-2-propanol (V). Six grams of 1-(3,4-dibenzyloxyphenyl)-2-bromo-1-propanol (III) was dissolved in 48 ml. of abs. methanol containing 16% ammonia, and heated in a sealed tube for eleven hours at 150°. The pale green solution was evaporated and the oily residue was treated a few times with a small amount of ether. White crystals of the hydrobromide of amino alcohol V were obtained, yield 3.5 g. It was dissolved in alcohol and ether was added to turbidity; the solution soon deposited long needles, m.p. 194°.

Anal. Calc'd for $C_{23}H_{26}BrNO_3$: C, 62.2; H, 5.9.
Found: C, 62.6; H, 6.1.

The free base. Two-tenths gram of the hydrobromide of (V) was dissolved in a mixture of 27 ml. of water and 3 ml. of alcohol and treated to slight alkalinity with 5 *N* sodium hydroxide. An oil soon separated which crystallized in 24 hours. After recrystallization from dil. alcohol long needles were obtained, m.p. 85°.

Anal. Calc'd for $C_{23}H_{25}NO_3$: C, 76.0; H, 6.9.
Found: C, 76.0; H, 7.1.

The amino alcohol (V) prepared above, was dissolved in alcoholic HCl; the *hydrochloride of V* separated soon. It crystallized from a mixture of alcohol and ether in long needles, m.p. 189°.

Nine-tenths gram of IV was dissolved in 12 ml. of methanol containing 19% ammonia and heated in a sealed tube for ten hours at 105°. The pale green solution evaporated *in vacuo* to give a dense, oily residue which was dissolved in 30 ml. of dil. hydrochloric acid. It was shaken with ether a few times and treated with sodium hydroxide to alkalinity. The separated amine (V) crystallized in a yield of 0.4 g. It was converted to hydrochloride in the manner described above, m.p. 189°, not depressed in mixture.

1-(3,4-Dihydroxyphenyl)-1-amino-2-propanol hydrobromide (VI). Five-tenths gram of hydrobromide of V dissolved in 8 ml. of abs. methanol with 0.1 g. of previously hydrogenated 22% Pd charcoal absorbed the theoretical volume of hydrogen; the catalyst-free solution was evaporated at 30° in a hydrogen atmosphere. After the complete removal of the solvent and the toluene there remained a colorless foam. After thorough drying in a desiccator it weighed 0.3 g. (calc'd 0.297 g.). The very hygroscopic, oxidable compound could not be crystallized. It was used for the animal experiments.

1-(3,4-Dibenzyloxyphenyl)-1-acetylamino-2-propanol (IX). Six-tenths gram of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol (V) was dissolved in 3 ml. of abs. pyridine and 0.2 g. of acetic anhydride added under cooling. After standing overnight, it was diluted with 30 ml. of water. The oily acetylated compound separated, and crystallized on standing; this was triturated with dil. sulfuric acid and washed well with water. It crystallized in needles from dilute methanol, (50% water), m.p. 131°, yield 0.6 g.

Anal. Calc'd for $C_{25}H_{27}NO_4$: C, 74.1; H, 6.7.
Found: C, 74.4; H, 6.8.

1-(3,4-Dibenzyloxyphenyl)-1-amino-2-propanol acetate hydrochloride (X). Five-tenths gram of IX was dissolved in 5 ml. of abs. toluene, and after adding 0.5 ml. of phosphorus oxychloride the mixture was boiled one-half hour. On cooling, an oily product separated. The toluene was removed and shaken three times with 5 ml. of water. This aqueous solution was added to the oily product, which crystallized after 24 hours and was washed with ice cold water. It can be crystallized from alcohol-ether in long needles, m.p. 174°, yield 0.24 g.

Anal. Calc'd for $C_{25}H_{28}ClNO_4$: C, 67.9; H, 6.4.
Found: C, 67.7; H, 6.4.

Di-[1,1'-(3,4-dibenzyloxyphenyl)-2,2'-dibromopropyl] ether (VII). 1-(3,4-Dibenzyloxyphenyl)-2-bromo-1-propanol (III), after standing for 10–12 days, was treated with methanol, and became crystalline. After washing with methanol it was crystallized from alcohol or acetone, m.p. 108°.

Anal. Calc'd for $C_{46}H_{44}Br_2O_5$: C, 66.0; H, 5.3.
Found: C, 66.2; H. 5.4.

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