[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

SYNTHESES OF SOME 3-PHENYL-3-*tert*-AMINO-1,2-PROPANEDIOLS

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Although several investigators have reported the preparation of 1-phenyl-2-amino-1,3-propanediols by reacting 1-phenyl-2-bromo-1,3-propanediol (I) with amines, no proof of the position of the amino group of the resulting diols was given (1, 2). Recently, Controulis, *et al.* showed that I gave 3-phenyl-3-amino-1,2-propanediol when treated with ammonia (3). It seemed possible that reaction of I with secondary amines may also have led to 3-phenyl-3-*tert*-amino-1,2-propanediols. It was thus interesting to reinvestigate such reactions.

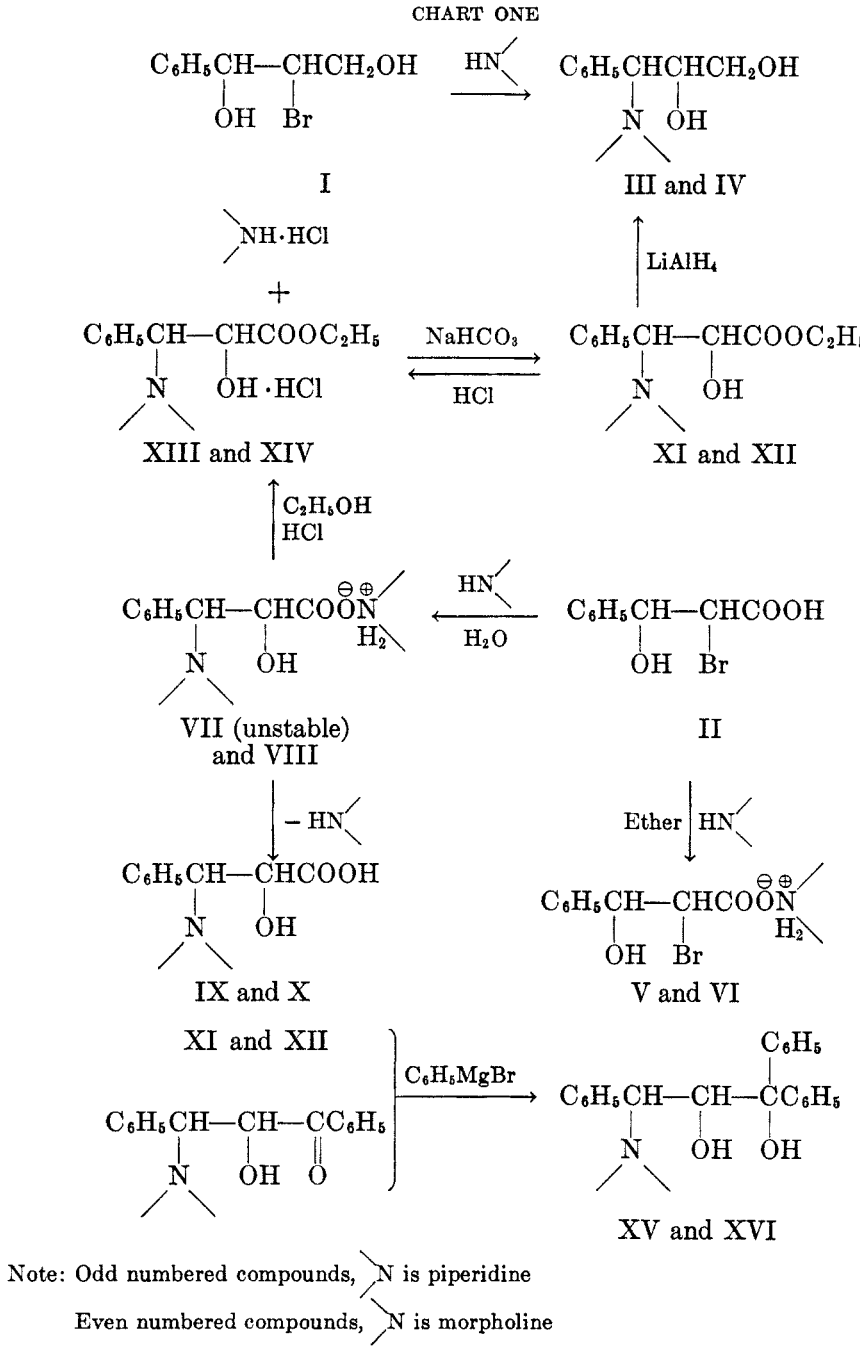
Another possible approach to the synthesis of 1-phenyl-2-*tert*-amino-1,3-propanediols would be through the reduction of α-amino-β-hydroxy-β-phenylpropionic acids by lithium aluminum hydride. Despite the fact that the literature had indicated that both α-amino and β-amino products were possible when α-bromo-β-hydroxy acids were treated with amines (4), the authors were interested in using α-bromo-β-hydroxy-β-phenylpropionic acid (II) (5) as a starting material in order to correlate these two schemes in their reaction mechanisms.

1-Phenyl-2-bromo-1,3-propanediol (I) was prepared in its solid form by using a slightly modified procedure of the early workers (3). On treatment of I with piperidine in water 3-phenyl-3-piperidino-1,2-propanediol (III) was obtained, associated with one mole of piperidine as solvent of crystallization. 3-Phenyl-3-morpholino-1,2-propanediol (IV) was prepared by a similar procedure in low yield.

α-Bromo-β-hydroxy-β-phenylpropionic acid (II) reacted with piperidine and morpholine in ether to give the corresponding amine salts (V and VI) of the starting acid. When II was treated with the amines in aqueous solution, the unstable piperidine salt (VII) of α-hydroxy-β-piperidino-β-phenylpropionic acid (IX) and the morpholine salt (VIII) of α-hydroxy-β-morpholino-β-phenylpropionic acid (X) were isolated. On drying at 100° VII lost piperidine readily to give the free acid (IX). On the other hand, salt VIII was quite stable. Previously Fourneau (6) had reported the preparation of acid IX by reacting piperidine with phenylglycidic ester, and had assigned the position of the amino group by referring to an early work of Erlenmeyer (7) who had assigned the structure from its method of synthesis as analogous to that for phenylisoserine. It seemed to us, however, that a melting point alone could not be the conclusive structural evidence in our investigation. The melting point of IX was found to vary widely by inserting the sample at different temperatures of the melting bath. Therefore, the location of the amino group was still doubtful until the latter part of this investigation.

[1] Abstracted in part from the Ph. D. thesis of Kwan-Chung Tsou, University of Nebraska Regents Fellow, 1948–1949, U. S. Public Health Grant Research Assistant, 1949–1950.

CHART ONE



Note: Odd numbered compounds, ⟩N⟨ is piperidine

Even numbered compounds, ⟩N⟨ is morpholine

Ethyl α-hydroxy-β-piperidino-β-phenylpropionate (XI) and ethyl α-hydroxy-β-morpholino-β-phenylpropionate (XII) were prepared as their hydrochlorides

by esterification of VII and VIII. Reduction of esters XI and XII by lithium aluminum hydride gave again the diols III and IV, respectively.

Nicolet and Shinn had observed that N-diethylaminoethanol, a tertiary hydroxyamine, was not affected by periodic acid (8). Later Leonard and Rebenstorf confirmed the same observation under more strenuous conditions (9). Using a procedure recommended by Siggia (10), we found that diol III consumed about two moles of periodic acid. It was felt, however, that this was not sufficient evidence on which to base the assignment of the amino group since no authentic 1-phenyl-2-*tert*-amino-1,3-propanediol was available for comparison. Hence, the final proof of structure of such diols has rested upon synthesis of the known 1,1,3-triphenyl-3-piperidino-1,2-propanediol (XV) from the reaction of ester XI with phenylmagnesium bromide; the structure of this diol has been established by Cromwell and Starks (11). As a comparison, 1,1,3-triphenyl-3-morpholino-1,2-propanediol (XVI) was synthesized by reaction of ester XII or α-hydroxy-β-morpholinobenzylacetophenone (12) with phenylmagnesium bromide. Such results necessarily confirmed the position of the piperidino group, as well as that of the morpholino group at the carbon holding the phenyl group both in the aminohydroxy esters and in the aminopropanediols. See Chart One for details.

It is thus probable that both starting bromohydrin compounds react *via* an epoxy intermediate followed by a nucleophilic attack of the amine molecule at the carbon atom holding the phenyl group. This carbon atom of the epoxy compound might be expected to accommodate a partial positive charge because of resonance interaction with the phenyl group.[2]

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EXPERIMENTAL[3]

1-Phenyl-2-bromo-1,3-propanediol (I). I was prepared by slightly modifying the procedure given by Controulis, *et al.* (3), using the same amounts of reagents. The addition took about 3½ hours, and at no time was the solution allowed to develop more than a slightly yellow color. The solution was decanted from some tarry material and evaporated under reduced pressure with gentle warming to remove ethanol. The aqueous residue was then saturated with sodium chloride, extracted first with two 50-ml. portions of petroleum ether (b.p. 30–60°), and then with three 150-ml. portions of ether. The combined ether extract was dried and evaporated under reduced pressure to a colorless oil which crystallized on addition of crystalline seeds of I. The yield of crude product was 22.0 g. (95%), m.p. 56–58°. Recrystallization twice from low-boiling petroleum ether (b.p. 30–50°) gave the analytical sample, m.p. 57–59°.

Anal. Calc'd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80.
Found: C, 46.89; H, 4.95.

The piperidine salt (V) *and the morpholine salt* (VI) *of α-bromo-β-hydroxy-β-phenylpropionic acid.* To 0.02 mole of α-bromo-β-hydroxy-β-phenylpropionic acid (II) (5) in 150

[2] The mechanism of the reaction of amines with epoxybenzylacetophenone leading to α-hydroxy-β-aminoketones has been investigated by Barker and Cromwell (to be published soon), and found to be a second order SN_2 reaction.

[3] Microanalyses for carbon, hydrogen, and nitrogen were made by the Clark Microanalytical Laboratory, Urbana, Ill.

ml. of dry ether was added 0.02 mole of piperidine or morpholine dropwise with stirring. The mixture was allowed to stand at room temperature for one hour and the precipitate was recrystallized from absolute ethanol to give V, m.p. 109–110°; or VI, m.p. 126–127°, in 90–95% yield.

Anal. Calc'd for $C_{14}H_{20}BrNO_3$ (V): C, 50.92; H, 6.11; N, 4.24.
Found: C, 50.60; H, 6.08; N, 3.96.

Anal. Calc'd for $C_{13}H_{18}BrNO_4$ (VI): C, 47.00; H, 5.46; N, 4.22.
Found: C, 47.05; H, 5.43; N, 4.05.

α-Hydroxy-β-piperidino-β-phenylpropionic acid (IX). A 16.2-g. sample of II was dissolved in a mixture of 40 ml. of piperidine and 30 ml. of water. The solution was allowed to stand at room temperature for two days. Evaporation under reduced pressure gave a solid residue which was recrystallized from 35 ml. of 90% ethanol to yield 17.0 g. of the unstable piperidine salt (VII) of IX, m.p. 174–176° (decomposed, and partially resolidified). On drying at 100°, VII lost piperidine to yield 12.7 g. (77%) of IX, m.p. 248–249° (dec.). Recrystallization twice from 95% ethanol containing a few drops of glacial acetic acid gave the pure sample which melted at 256° (dec.), when the melting-point tube was inserted at 244° and heated at the rate of 1° per minute. The melting point given by Fourneau (6) is 256°, and by Erlenmeyer, Jr. (7), 255°.

The morpholine salt of α-hydroxy-β-morpholino-β-phenylpropionic acid (VIII). To 4.9 g. of II in 10 ml. of water was added 5.2 g. of morpholine. The solution was allowed to stand at room temperature for one day. Evaporation under reduced pressure gave a solid residue which was recrystallized from 90% ethanol to yield 6.1 g. of a product, m.p. 160–172°. Recrystallization from the same solvent gave 5.8 g. of VIII, m.p. 178–180° (dec.) (85% yield). Recrystallization of VIII from ethanol containing a few drops of acetic acid and ether gave pure VIII unchanged, m.p. 179–180° (dec.).

Anal. Calc'd for $C_{17}H_{26}N_2O_5$: C, 60.33; H, 7.75; N, 8.28.
Found: C, 60.25; H, 7.62; N, 8.26.

An attempt to obtain the acid (X) was made by treating an ethanolic solution of VIII with an equimolar amount of dry hydrogen chloride. The isolated acid was found to be too hygroscopic to handle.

Ethyl α-hydroxy-β-piperidino-β-phenylpropionate (XI) *and ethyl α-hydroxy-β-morpholino-β-phenylpropionate* (XII). A 0.018-mole sample of VII or VIII was suspended in 100 ml. of absolute ethanol and dry hydrogen chloride passed in until the resulting solution was about to boil. On standing at room temperature for 24 hours, the solution was evaporated under reduced pressure to remove ethanol. The residue was treated with sodium bicarbonate solution, and the precipitate was removed. The yield of crude XI was 82%, m.p. 95–97°; that of XII, 58%, m.p. 95–97°. Pure samples of XI, m.p. 96–97.5°, and of XII, m.p. 96–97°, were obtained by recrystallization from ether and petroleum ether (b.p. 30–60°) mixtures.

Anal. Calc'd for $C_{16}H_{23}NO_3$ (XI): C, 69.29; H, 8.36; N, 5.05.
Found: C, 69.37; H, 8.40; N, 5.06.

Anal. Calc'd for $C_{15}H_{21}NO_4$ (XII): C, 64.49; H, 7.58; N, 5.02.
Found: C, 64.62; H. 7.55; N, 5.22.

The hydrochlorides of XI *and* XII. The hydrochlorides were prepared in dry ether solution using dry hydrogen chloride gas and recrystallized from absolute ethanol to give pure XIII, m.p. 196–197°; and pure XIV, m.p. 174–175°.

Anal. Calc'd for $C_{16}H_{24}ClNO_3$ (XIII): Cl, 11.30. Found: Cl, 11.42. Calc'd for $C_{15}H_{22}ClNO_4$ (XIV): C, 57.05; H, 7.02. Found: C, 56.94; H, 6.92.

SYNTHESES OF 3-PHENYL-3-*tert*-AMINO-1,2-PROPANEDIOLS

Method A. 3-Phenyl-3-piperidino-1,2-propanediol (III). A 12.0-g. (0.052 mole) sample of I was treated with 13.6 g. (0.16 mole) of piperidine in 40 ml. of water, with stirring. The mixture was allowed to stand at room temperature for 24 hours and in a refrigerator for two hours. The crystalline precipitate was removed, washed with two 5-ml. portions of water and dried; yield, 14.6 g., m.p. 80–90°. Recrystallization from ethyl acetate gave 10.8

g. of pure III containing one mole of piperidine (65% yield), m.p. 89.5–93°. Further recrystallization from ethyl acetate or chloroform did not change the melting point. This product was investigated to prove that it contained one mole of piperidine as solvent of crystallization:

A sample of the piperidinate was dried to constant weight at room temperature in a vacuum over phosphorus pentoxide.

Anal. Calc'd for $C_{14}H_{21}NO_2$ + 1 $C_5H_{11}N$: N, 8.74. Found: N, 8.52.

To 0.55 g. of the piperidinate (0.0017 mole) in 5 ml. of absolute ethanol was added 0.5 ml. of 3 *N* ethanolic hydrogen chloride (0.0015 mole). Ether was then added to this solution until the precipitation began. On standing at room temperature for two hours, 0.14 g. (0.0011 mole) of piperidine hydrochloride, m.p. 241–243°, was collected and washed with dry ether. A mixed melting point with authentic piperidine hydrochloride (m.p. 243–244°) showed no depression.

A 936.2-mg. sample of the piperidinate was dried at 70–75° *in vacuo* to constant weight. Loss of weight was 241.4 mg. (25.79%). Calc'd for piperidine in the piperidinate, 26.57%.

The dried sample melted at 93–95° and analyzed for pure III. Further recrystallization from ethyl acetate or chloroform did not alter the melting point.

Anal. Calc'd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95.

Found for III: C, 71.28; H, 8.78; N, 5.65.

3-Phenyl-3-morpholino-1,2-propanediol (IV). By using morpholine in a similar procedure to that described above, IV was obtained in 31% yield, m.p. 90–92°. The product was isolated by extracting the reaction mixture with ether. The pure sample, after recrystallizing twice from ethyl acetate, melted at 96–97°.

Anal. Calc'd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90.

Found: C, 65.76; H, 8.17; N, 5.99.

Method B. A 0.01-*M* dry ether solution of XI or XII was added to an ether solution of lithium aluminum hydride (0.01 *M*) with stirring. The mixture was heated gently under reflux for two hours and the excess reducing agent destroyed by the dropwise addition of water (5 ml.). The ether solution was separated by decantation, dried, and evaporated under reduced pressure to give the diol, III m.p. 94–96° (60% yield), or IV m.p. 90–92° (53% yield), respectively. The pure samples were also obtained by recrystallization from ethyl acetate or chloroform. In each case, a mixed melting point with the diol prepared as in *Method A*, showed no depression; whereas a mixed melting point with the starting ester showed 10 to 15 degrees depression.

1,1,3-Triphenyl-3-piperidino-1,2-propanediol (XV). A 2.77-g. sample of ester XI (0.01 mole) in 75 ml. of dry ether was added slowly to a Grignard solution prepared from 1.44 g. (0.06 atom) of magnesium and 9.42 g. (0.06 mole) of bromobenzene in 100 ml. of dry ether. The mixture was then heated gently under reflux for two hours and decomposed with ammonium chloride and ice. The ether layer was separated, washed with water and dried over calcium sulfate. Evaporation of this solution under reduced pressure gave a semi-solid residue which crystallized on the addition of 10 ml. of absolute ethanol; 2.5 g., m.p. 170–173° (65% yield). A mixture with a sample of XV prepared from the reaction of α-hydroxy-β-piperidinobenzylacetophenone and phenylmagnesium bromide (12), was found to melt at 172–174°.

1,1,3-Triphenyl-3-morpholino-1,2-propanediol (XVI). By using a similar procedure XVI was prepared in 83% yield, m.p. 185.5–189°, from ester XII. Recrystallization from absolute ethanol gave pure XVI, m.p. 192–193°.

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99.

Found: C, 77.41; H, 7.20.

A well-pulverized sample of α-hydroxy-β-morpholinobenzylacetophenone (12) (0.01 mole) was reacted with 0.04 mole of phenylmagnesium bromide. The reaction mixture was treated and the product isolated as usual to give 0.7 g. of XVI, m.p. 190–192°, and 0.6 g. of the unreacted starting material, m.p. 154–156°, together with some unidentified oily products. A mixed melting point of XVI with the sample prepared from ester XII showed no depression.

SUMMARY

1. 1-Phenyl-2-bromo-1,3-propanediol has been found to react with the amines, morpholine and piperidine, to yield 3-phenyl-3-*tert*-amino-1,2-propanediols.

2. α-Bromo-β-hydroxy-β-phenylpropionic acid has been found to react with the same amines to give the α-hydroxy-β-amino-β-phenylpropionic acids. The β-morpholino acid was identified as its morpholine salt. The acids were converted to the corresponding ethyl α-hydroxy-β-amino-β-phenylpropionates. Reduction of such esters with lithium aluminum hydride gave the same diols as prepared by the aforementioned method.

3. The assignment of the position of the amino group in the above compounds to the carbon holding the phenyl group has been based upon the syntheses of the 1,1,3-triphenyl-3-*tert*-amino-1,2-propanediols through reaction of the ethyl α-hydroxy-β-amino-β-phenylpropionates with phenylmagnesium bromide. The structure of such diols has been established by Cromwell and Starks (11).

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