[Contribution from the Products Development Laboratories,
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THE PREPARATION OF SEVERAL SUBSTITUTED 1-PHENYL-1,3-PROPANEDIOL AMINES

WILLIAM H. EDGERTON and JAMES R. FISHER

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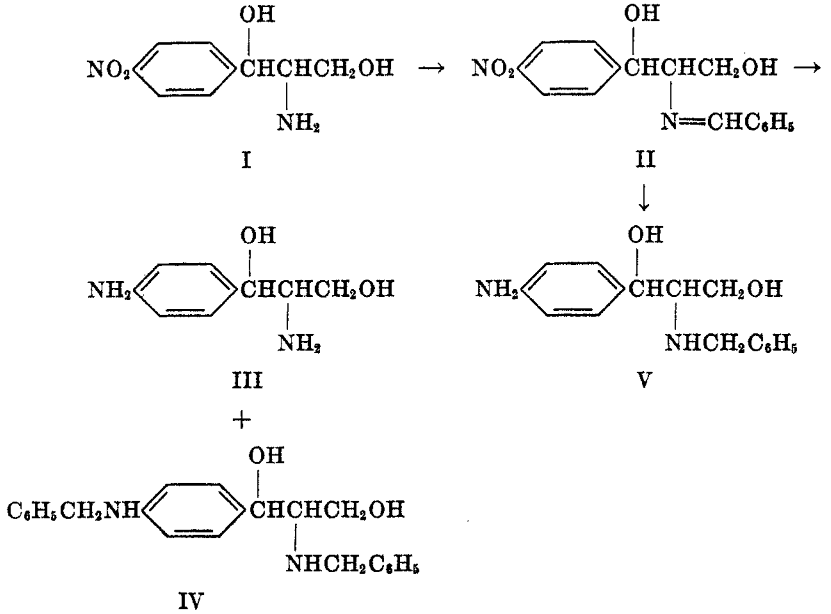
The commercial development of chloramphenicol (Chloromycetin) made 1-phenyl-1,3-propanediol amines readily available. Since such amines are interesting from several medicinal points of view, a series of amines derived from L-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (I, 1) was prepared.

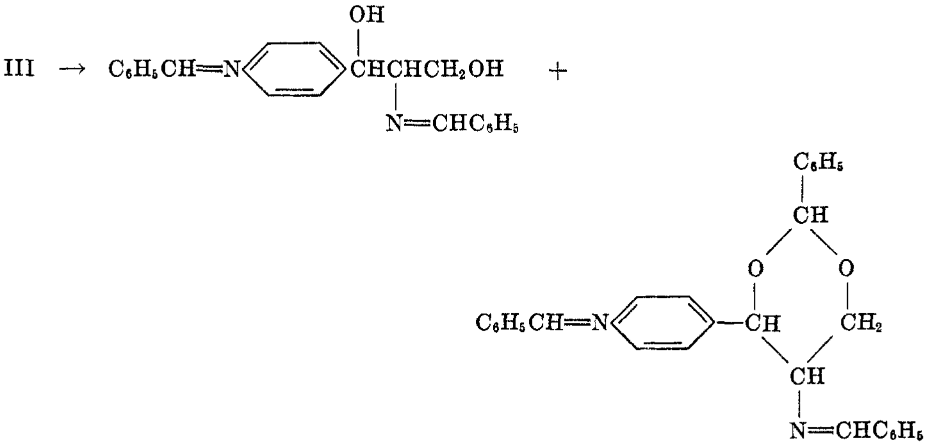


Several attempts at the reductive alkylation (2) of L-*threo*-2-amino-1-*p*-nitrophenyl-1,3-propanediol (I) using benzaldehyde or butyraldehyde resulted in intractable syrups. In order to reduce the possibilities for side reactions, the benzylidene derivative (II) was prepared. The DL-benzylidene derivative has been reported since by two groups of Italian workers (3). Catalytic reduction of II with Adams catalyst and 5% palladium-on-charcoal resulted in the isolation of small amounts of L-*threo*-2-amino-1-(*p*-aminophenyl)-1,3-propanediol (III) and L-*threo*-2-benzylamino-1-(*p*-benzylaminophenyl)-1,3-propanediol (IV). None of the expected product (V) could be isolated.

The reduction of II was attempted using a less vigorous catalyst, Raney nickel (4). The benzylidene compound was purified in order to insure the elimination of adsorbed benzaldehyde. A small amount of the expected product (V) was isolated in addition to the two unusual compounds (III and IV). No toluene was detected. The abnormal reduction products were detected in several different runs using various catalysts.

So far as we know, there is no precedent for such an abnormal reaction in the literature (5). The products isolated could be formed by hydrolysis of the imine yielding benzaldehyde which could then react with the aromatic amino moiety as it is formed during the reduction. A transbenzylation reaction involving a benzyl free radical formed during hydrogenolysis is an improbable possibility.

Catalytic reduction of the *p*-nitrobenzoate (VI) of II proceeded in normal fashion to yield the *p*-aminobenzoate (VII) of the desired compound as a hygroscopic solid.



VIII IX

The reductive alkylation of III also resulted in syrups which could not be purified. The dibenzylidene derivative (VIII) was prepared along with a byproduct which is believed to be L-*threo*-5-benzylideneamino-4-(*p*-benzylideneaminophenyl)-2-phenyl-1,3-dioxane (IX). The infrared spectrum of IX indicated the absence of the strong hydroxyl band at 2.90 μ and the presence of the strong ether band at 9.06 μ, however, the characteristic imine band at 6.10 μ had been dampened. VIII was reduced to IV which was stable as the free base. The dihydrochloride could not be purified and decomposed upon standing.

L-*threo*-2-Amino-1-phenyl-1,3-propanediol (X) was prepared by the deamination method developed independently by H. D. Troutman (6) and G. Fodor, *et al.* (7). L-*threo*-2-Benzylideneamino-1-phenyl-1,3-propanediol (XI) was reduced catalytically with 5% palladium-on-charcoal to L-*threo*-2-benzylamino-1-phenyl-1,3-propanediol (XII) in excellent yield with no trace of debenzylation. The *p*-aminobenzoate (XIV) of XII was also prepared. X was alkylated with various alkyl halides to extend the series to amines of higher molecular weight. The amorphous N-butyl derivative in the "active" series has been since reported by A. Funke and P. Kornmann (8).

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EXPERIMENTAL

All melting points and boiling points are uncorrected.

Commercial grade absolute ethanol was used.

L-*threo-2-Benzylideneamino-1-(p-nitrophenyl)-1,3-propanediol* (II). A solution of 106.0 g. (0.5 mole) of L-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (I) and 58.3 g. (0.55 mole) of freshly-distilled benzaldehyde in 600 ml. of ethanol was heated at reflux for six hours. The solution was filtered, concentrated and cooled in order to separate 140.8 g. (94%) of tan solid, m.p. 141–143°. A sample was recrystallized from ethanol to tan crystals, m.p. 148–149°.

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33.
Found: C, 64.05; H, 5.55; N, 9.44.

Hydrogenation of L-*threo-2-benzylideneamino-1-(p-nitrophenyl)-1,3-propanediol* (II). *Method A.* A solution of 60.0 g. (0.2 mole, m.p. 142–145°) of II in 550 ml. of ethanol with 0.30 g. of platinum oxide was reduced at room temperature at three atmospheres for 20 hours; 0.50 g. of 5% palladium-on-charcoal was added, and the hydrogenation was completed after three hours at 45°.

An aliquot of the alcohol solution (11 g. of base) was evaporated to dryness *in vacuo*. The syrup was taken up in 40 ml. of ethyl acetate. The solution was heated with charcoal, filtered, and diluted with 150 ml. of ether. Cooling produced 2.8 g. of white solid; m.p. 118–123°. Several recrystallizations from ethyl acetate produced white crystals, m.p. 135°, identical with an authentic sample of III.

The ethereal filtrate was evaporated *in vacuo*. The syrup was dissolved in 10 ml. of 5 *N* hydrochloric acid diluted with 35 ml. of water. The solution was treated with charcoal and the syrup was recovered with 5 *N* ammonium hydroxide. The purification was repeated and the syrup was washed with water. An extract in 300 ml. of boiling ether and 50 ml. of petroleum ether was cooled overnight at 5° in order to separate 1.1 g. of white crystals, m.p. 80–105°. The solid was purified by repeated recrystallization from several combinations of solvents and, finally, from ether, benzene and "isoöctane" to white crystals of IV, m.p. 106–108°.

Anal. Calc'd for $C_{23}H_{25}N_2O_2$: C, 76.22; H, 7.23; N, 7.73.
Found: C, 76.60; H, 7.33; N, 7.65.

Method B. A suspension of 15.0 g. (0.05 mole, m.p. 146–147°) of II in 150 ml. of methanol was reduced at 40° with 1 g. of Raney nickel at three atmospheres. The theoretical amount of hydrogen was absorbed. The volatiles were removed *in vacuo*, collected in a Dry Ice-propanol-2 trap, and examined for toluene. None was detected.

The residual syrup was crystallized from ethyl acetate and ether to yield 5.0 g. of white crystals; m.p. 85–115°. This solid was purified by recrystallization from ethyl acetate and propanol-2 to a melting point of 134–136°; no mixture melting point depression with authentic III was observed.

The mother liquor from above was evaporated to a syrup which was extracted with 300 ml. of boiling ether in several portions. The ether was concentrated to 175 ml. and cooled overnight at 5° to yield 3.2 g. of white crystals of V, m.p. 65–75°. This solid was purified by repeated recrystallization from various solvent mixtures and, finally, from ethyl acetate, m.p. 111–112°. A mixture melting point with authentic IV was depressed.

Anal. Calc'd for $C_{28}H_{25}N_2O_2$: C, 70.56; H, 7.40; N, 10.26.
Found: C, 70.14; H, 7.51; N, 10.40.

The ethereal filtrate was concentrated to 100 ml. and diluted with 200 ml. of petroleum ether. Cooling caused the separation of 1.2 g. of white crystals, m.p. 85–103°. After purification by recrystallization from benzene and "isoöctane", the melting point was 109–110° and no mixture melting point depression was observed with authentic IV.

Method C. A third reduction using 5% palladium-on-charcoal at room temperature was carried out. Small amounts of III and IV were isolated and identified. The remainder of the reaction mixture was not investigated.

L-*threo-2-Benzylideneamino-1-(p-nitrophenyl)-1,3-propanediol, 3-(p-nitrobenzoate)* (VI).

A solution of 15.0 g. (0.05 mole) of II and 6 ml. of pyridine in 80 ml. of dimethylformamide was stirred rapidly at room temperature while 9.3 g. (0.05 mole) of *p*-nitrobenzoyl chloride was added. The solution was stirred for five hours and then poured into 500 ml. of water with rapid stirring in order to separate a gummy solid. After washing with water, the solid was recrystallized at once from ethanol; 15.5 g. (69%) of yellow crystals, m.p. 191–192° was obtained. A sample was recrystallized from ethanol to m.p. 194–195°.

Anal. Calc'd for $C_{23}H_{19}N_3O_7$: C, 61.47; H, 4.26.

Found: C, 61.40; H, 4.47.

L-*threo-2-Benzylamino-1-(p-aminophenyl)-1,3-propanediol, 3-(p-aminobenzoate)* (VII). A solution of 7.0 g. (0.0156 mole) of VI in 200 ml. of ethanol was reduced with 5% palladium-on-charcoal. After separation of the catalyst and concentration, cooling produced 3.8 g. (62%) of pink solid, m.p. 110°. One recrystallization from propanol-2 raised the melting point to 112°.

Anal. Calc'd for $C_{23}H_{25}N_3O_3 \cdot 1/2H_2O$: C, 68.98; H, 6.55; N, 10.50; H_2O, 2.25.

Found: C, 69.29, 69.17; H, 6.68, 6.71; N, 10.50; H_2O, 2.85.

L-*threo-2-Benzylideneamino-1-(p-benzylideneaminophenyl)-1,3-propanediol* (VIII). A solution of 18.2 g. (0.1 mole) of III [obtained by the reduction of I with 5% palladium-on-charcoal (9)] and 23.5 g. (0.22 mole) of freshly-distilled benzaldehyde in 125 ml. of ethanol was heated at reflux for 16 hours. The clear solution was concentrated *in vacuo* and cooled to yield brown crystals which were extracted repeatedly with benzene and petroleum ether. The insoluble solid represented 27.8 g. (78%) of the desired compound, m.p. 105–117°. Recrystallization from propanol-2 and a mixture of benzene and petroleum ether raised the melting point to 124–125°.

Anal. Calc'd for $C_{23}H_{21}N_2O_2$: C, 77.07; H, 6.19.

Found: C, 77.10, 77.08; H, 6.54, 6.38.

The benzene-soluble fraction was recovered as 8.2 g. of light crystals, m.p. 138–152°. A sample was recrystallized from propanol-2 to a melting point of 155–156°. This proved to be a tribenzylidene derivative (IX).

Anal. Calc'd for $C_{30}H_{26}N_2O_2$: C, 80.69; H, 5.87; N, 6.29; O, 7.17.

Found: C, 80.84; H, 5.92; N, 6.68; O, 7.24.

L-*threo-2-Benzylamino-1-(p-benzylaminophenyl)-1,3-propanediol* (IV). A solution of 8.1 g. (0.0225 mole) of VIII in 125 ml. of ethanol with 5% palladium-on-charcoal was reduced at room temperature with H_2 at low pressure. Evaporation of the ethanol, after removing the catalyst, resulted in a syrup which crystallized from toluene to yield 4.9 g. (60%) of white crystals, m.p. 94–107°. Recrystallization from several combinations of solvents raised the melting point to 110–111°.

Anal. Calc'd for $C_{23}H_{26}N_2O_2$: C, 76.22; H, 7.23; N, 7.73.

Found: C, 76.19; H, 7.32; N, 7.59.

L-*threo-2-Benzylideneamino-1-phenyl-1,3-propanediol* (XI). A solution of 16.7 g. (0.1 mole) of L-*threo*-2-amino-1-phenyl-1,3-propanediol (X) (6, 7) and 11.7 g. (0.11 mole) of freshly-distilled benzaldehyde in 110 ml. of ethanol was heated at reflux for six hours. Cooling caused the separation of 23.7 g. (93%) of tan solid, m.p. 149–151°. A sample, recrystallized from ethanol, for analysis, melted at 151°.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71.

Found: C, 75.05; H, 6.90.

L-*threo-2-Benzylamino-1-phenyl-1,3-propanediol* (XII). A solution of 23.7 g. (0.093 mole) of XI in 200 ml. of ethanol was reduced with 5% palladium-on-charcoal with low pressure in eight hours. The solution was filtered, concentrated *in vacuo*, and cooled to yield 22.1 g. (93%) of tan solid, m.p. 71–75°. The free base was purified by recrystallization from ether, m.p. 73–75°.

Anal. Calc'd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44.

Found: C, 74.77; H, 7.52.

The *hydrochloride* was prepared by passing dry hydrogen chloride gas into an ether solution of the base and recrystallizing the solid from butanol or propanol-2, m.p. 162–163°.

Anal. Calc'd for $C_{16}H_{19}NO_2 \cdot HCl$: C, 65.41; H, 6.88; N, 4.77.
Found: C, 65.30; H, 7.03; N, 5.14.

L-*threo-2-Benzylideneamino-1-phenyl-1,3-propanediol, 3-(p-nitrobenzoate)* (XIII). This compound was prepared as VI in 30% yield using ethyl acetate rather than ethanol, m.p. 134–135°.

Anal. Calc'd for $C_{23}H_{20}N_2O_5$: C, 68.30; H, 4.99.
Found: C, 68.22; H, 4.95.

L-*threo-2-Benzylamino-1-phenyl-1,3-propanediol, 3-(p-aminobenzoate)* (XIV). This compound was prepared as VII in 62% yield, m.p. 169–170°.

Anal. Calc'd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43.
Found: C, 73.86; H, 6.34.

L-*threo-2-Dibenzylamino-1-phenyl-1,3-propanediol* (XV). A suspension of 12.9 g. (0.05 mole) of XII and 6.9 g. (0.055 mole) of benzyl chloride in 50 ml. of ethanol was heated at reflux for 20 hours. The volatiles were evaporated *in vacuo* to leave a syrup which was washed well with ether and acetone to leave 6.1 g. of XII•HCl. The ethereal filtrate was evaporated and the remaining syrup was taken up in propanol-2. The solution was saturated with hydrogen chloride gas and was diluted with ether to separate a trace of XII•HCl. The syrup, which was obtained by evaporation and washing with 75 ml. of warm water, solidified after stirring under benzene to 6.3 g. (36%) of yellow crystals, m.p. 70–80°. Recrystallization from a mixture of benzene and dioxane then from methyl ethyl ketone raised the melting point to 75–77°. After drying the sample over phosphorus pentoxide *in vacuo* for 20 hours, its melting point was 88–90°.

Anal. Calc'd for $C_{23}H_{25}NO_2 \cdot HCl \cdot 1/2H_2O$: C, 70.30; H, 6.94; N, 3.57.
Found: C, 69.82; H, 7.12; N, 3.65.

A portion of the hydrochloride in water was neutralized with 5 *N* ammonium hydroxide in order to separate a solid which was recrystallized from a mixture of carbon tetrachloride and "isoöctane" to white crystals, m.p. 103–104°.

Anal. Calc'd for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.26; N, 4.03.
Found: C, 79.61; H, 7.44; N, 3.84.

L-*threo-2-Butylamino-1-phenyl-1,3-propanediol* (XVI). A suspension of 33.4 g. (0.2 mole) of X and 27.4 g. (0.2 mole) of *n*-butyl bromide in 100 ml. of ethanol was heated at reflux for 30 hours. The volatiles were removed *in vacuo*. The residual syrup was purified by dissolving in water, heating with charcoal, and neutralizing with sodium carbonate solution. The syrup was extracted with 300 ml. of ether in several portions. Evaporation of the ether left a yellow oil which crystallized to 22.9 g. (51%) of white crystals, m.p. 57–63°. A sample was recrystallized from benzene and "isoöctane" to a melting point of 66–68°.

Anal. Calc'd for $C_{13}H_{21}NO_2$: C, 69.91; H, 9.48.
Found: C, 70.02; H, 9.47.

L-*threo-2-Dibutylamino-1-phenyl-1,3-propanediol* (XVII). A suspension of 33.4 g. (0.2 mole) of X and 27.4 g. (0.2 mole) of *n*-butyl bromide was heated at reflux for four hours. *n*-Butyl bromide (28.6 g., 0.21 mole), 21.6 g. of sodium carbonate, and 40 ml. of water were added. The reaction mixture was heated at reflux with stirring for 35 hours. The aqueous layer was made alkaline with sodium carbonate solution. The ether extract of the aqueous layer was combined with the organic layer of the reaction mixture. The volatiles were removed *in vacuo* from the dried solution to leave 51.2 g. (92%) of brown oil which was vacuum-distilled. A middle cut was redistilled through a column to a clear oil, b.p. 169–170° at 1–2 mm.

Anal. Calc'd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46.
Found: C, 72.73; H, 10.47.

L-*threo-2-Hexylamino-1-phenyl-1,3-propanediol* (XVIII). The hexyl analog was prepared using either *n*-hexyl bromide or *n*-hexyl iodide in 39% or 38% yield; white crystals from "isoöctane", m.p. 55–58°.

Anal. Calc'd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02.
Found: C, 71.71; H, 10.20.

L-threo-2-Hexadecylamino-1-phenyl-1,3-propanediol hydriodide (XIX). The hexadecyl analog as the hydriodide was obtained in 47% yield from propanol-2, m.p. 71-72°.

Anal. Calc'd for $C_{25}H_{45}NO_2 \cdot HI$: C, 57.79; H, 8.92.

Found: C, 58.06; H, 8.89.

SUMMARY

1. The catalytic reduction of L-*threo*-2-benzylideneamino-1-(*p*-nitrophenyl)-1,3-propanediol was studied. An unusual reaction resulted in the isolation of the expected product, L-*threo*-1-(*p*-aminophenyl)-2-benzylamino-1,3-propanediol, as well as two abnormal products, L-*threo*-2-amino-1-(*p*-aminophenyl)-1,3-propanediol and L-*threo*-2-benzylamino-1-(*p*-benzylaminophenyl)-1,3-propanediol.

2. The reduction of L-*threo*-2-benzylideneamino-1-phenyl-1,3-propanediol yielded the normal reduction product in excellent yield.

3. A series of N-mono- and N-di-alkylated L-*threo*-2-amino-1-phenyl-1,3-propanediols was prepared.

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