The base gave a monopicrate which melted at 139–140° after recrystallization from benzene.

Anal. Calcd. for $C_{22}H_{23}O_7SN_5$: C, 52.47; H, 5.00; N, 13.91; S, 6.37. Found: C, 52.39; H, 5.26; N, 14.09; S, 6.43.

The bisuccinate was formed by adding 11 cc. of a saturated alcoholic solution of succinic acid to a solution of 2.328 g. of the base in 10 cc. of ether. The mixture was kept at room temperature overnight, concentrated to a sirup *in vacuo* and crystallized under ether. Recrystallized twice from an ethyl methyl ketone-ether mixture, the salt melted at 99–100°.

Anal. Calcd. for $C_{20}H_{28}O_4SN_2$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.35; H, 7.37; N, 7.15.

Attempted Hydrochloride Formation of Amine 3 and Identification of Decomposition Products.—N^2,N^2-Dimethyl-N^1-phenyl-N^1-(2-thenyl)-1,2-propanediamine, 18.28 g. (0.059 mole) was dissolved in 27 cc. of dry ether, treated with 27.6 cc. of 2.15 *N* ethanolic hydrochloric acid, let stand at room temperature overnight and placed in the refrigerator. After several days the solution was evaporated and the sirupy residue found to have a strong, sweet odor. Water was added to the sirup, the solution made strongly alkaline with sodium hydroxide, the oily layer taken up in ether and the solution dried. After removal of ether the residual oil was fractionated *in vacuo*. Three definite fractions were obtained.

Fraction 1, b. p. 52° (3 mm.), $n^{25}D$ 1.5061, was the sweet smelling component. It was redistilled, b. p. 58.7° (5 mm.). 184–185° (760 mm.), $n^{25}D$ 1.5061 and analyzed.

Anal. Found: C, 58.69; H, 6.79; S, 23.00; N, 0.35.

Disregarding the nitrogen as a trace impurity the analysis indicates an empirical formula of C_7H_8SO or $C_7H_{10}SO$. The analytical and physical data agree reasonably well with that of 2-thenyl ethyl ether,[21] $C_7H_{10}SO$, which has the following constants: b. p. 84–86° (22 mm.), 181–182° (740 mm.), $n^{20}D$ 1.5062, and percentage composition C, 59.12; H, 7.09; S, 22.54.

Fraction 2, b. p. 106–108° (3 mm.), $n^{25}D$ 1.5321, was redistilled (b. p. 111–113° (4 mm.)) with no change in refractive index and gave a monopicrate which melted at 155–156°. This data and the analysis of the base was in good agreement with that of N^2,N^2-dimethyl-N^1-phenyl-1,2-propanediamine (see procedure 1).

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.72. Found: C, 74.33; H, 10.28; N, 15.56.

Fraction 3, b. p. 163–165° (3 mm.), $n^{25}D$ 1.5800. These constants showed that this fraction was recovered tertiary amine.

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Summary

Six new and two previously reported 2-thenyl substituted diamines, $C_4H_3SCH_2(R_1)NR_2B$, have been synthesized in which R_1 is a phenyl or 2-pyridyl radical, R_2 is a straight or branched alkylene chain of two or three carbon atoms and B is a dimethylamino or piperidino group. An interesting decomposition of one of these in the presence of hydrogen halides has been observed, the products identified and a mechanism suggested.

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(21) Leonard, Ph. D. Thesis, University of Michigan, 1946.

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The Resolution of *dl*-Arterenol

BY B. F. TULLAR

Recently the resolution of *dl*-arterenol, α-aminomethyl-3,4-dihydroxybenzyl alcohol, was announced together with a brief description of the physiological characteristics of the active *l*-isomer.[1] The present paper deals with the method of effecting this resolution.

An observation that *dl*-arterenol is almost quantitatively converted to its methyl ether by evaporating *in vacuo* a solution of the hydrochloride in methanol[2] suggested that ether formation might occur during resolution attempts in anhydrous alcohols. Accordingly, aqueous alcohols seemed to offer more promise as resolution solvents.

The presence of water in the resolution mixture afforded an additional advantage since only the *l*-arterenol forms a *hydrated* salt with *d*-tartaric acid. This *l*-arterenol *d*-bitartrate monohydrate possesses greater solubility in aqueous methanol and considerably lower water solubility than does the *non-hydrated* *d*-arterenol *d*-bitartrate, permitting an easy separation of the diastereomers.

The bitartrates were purified by repeated recrystallization from water (*l* isomer) and from 95% methanol (*d* isomer) and converted to the free bases by treatment with ammonium hydroxide. The hydrochlorides were prepared by dissolving the base in isopropanol with slightly more than the calculated amount of concentrated hydrochloric acid and crystallizing by cooling.

d-Arterenol was racemized by heating at 90° for two hours in dilute hydrochloric acid solution with an 83% recovery of the racemic base.

Experimental

Resolution. (a) In Aqueous Methanol.—In a solution of 155 g. of *d*-tartaric acid in 100 ml. of water 169 g. of *dl*-arterenol was dissolved by vigorous stirring. The solution was diluted slowly with methanol to one liter. Crystallization was induced by scratching and after several hours at room temperature there was a nearly solid mass of crystals which was separated and washed with a little 90% methanol. After drying *in vacuo* at

(1) Tainter, Tullar and Luduena, *Science*, **107**, 39–40 (1948).

(2) A similar reaction of epinephrine was described by Öppinger and Vetter, *Med. u. Chemie*, **4**, 343–367 (1942), see *C. A.*, **38**, 5928 (1944). Johnson, *et al.*, THIS JOURNAL, **69**, 2945 (1947), reported alkylation of a hydroxymethylene group under quite similar conditions.

25° the white crystalline *d*-arterenol *d*-bitartrate[3] weighed 110 g., had m. p. 161–163° and $[\alpha]^{25}D$ +31.4° (*C* = 6% water).

d-Arterenol *d*-Bitartrate.—The crystalline fraction was recrystallized twice from 95% methanol. After drying *in vacuo* at 25° the product weighed 58 g. and had m. p. 164–165° (cor.), $[\alpha]^{25}D$ +39.9° (*C* = 1.5% in water). A portion recrystallized from one-half its weight of hot water had the same constants. The solubility of this salt in water is greater than 20% at 25°.

Anal. Calcd. for $C_{12}H_{17}O_8N$: N, 4.40; C, 45.20; H, 5.33. Found: N, 4.30; C, 45.38; H, 5.44.

l-Arterenol *d*-Bitartrate Monohydrate.—The resolution liquor was evaporated to dryness *in vacuo*. The residue was dissolved in 150 ml. of water at 60° and cooled to 2–3° for several hours with occasional stirring and scratching to induce crystallization. The heavy, crystalline precipitate was collected, washed with 95% alcohol and dried *in vacuo* at 25°. The crude salt amounted to 80 g. and had m. p. 90–115°. A portion was converted to base as described below and had $[\alpha]^{25}D$ −20° (*C* = 1.5% in water with 1 equiv. hydrochloric acid).

After three recrystallizations from equal weights of water, drying finally at 50° *in vacuo*, 28 g. of *l*-arterenol *d*-bitartrate monohydrate was obtained with the following constants: m. p. 102–104° (cor.) $[\alpha]^{25}D$ −11° (*C* = 1.6% in water). Recrystallization from 95% ethanol or from water did not change these values. This salt is soluble to more than 20% in water at 25°.

Anal. Calcd. for $C_{12}H_{17}O_8N \cdot H_2O$: H_2O, 5.35; N, 4.15; C, 42.48; H, 5.68. Found: H_2O, 5.34; N, 4.10; C, 42.73; H, 5.65.

(b) Resolution in Water.—The same quantities of *dl*-arterenol and *d*-tartaric acid as in (a) were dissolved in 300 ml. of water. By cooling to 3–5° and inducing crystallization by stirring and scratching there was a heavy precipitate after several hours. This was filtered off, washed with 30 ml. of ice-water and with 2 × 100 ml. of 95% alcohol and air-dried. The product weighed 135 g. and had m. p. 88–95°.

Recrystallization by dissolving in 135 ml. of water at 50° and after decolorizing with charcoal cooling to 2–3° for several hours gave 80 g. of nearly pure *l*-arterenol *d*-bitartrate, m. p. 94–98°. After two more such recrystallizations, 43 g. was obtained having m. p. 102–104.5° (cor.) and $[\alpha]^{26}D$ −10.8°.

From the aqueous resolution liquors by concentration and crystallization from aqueous methanol 110 g. of *d*-arterenol *d*-bitartrate having m. p. 161–165° was recovered.

d-Arterenol.—A solution of 10 g. of the *d*-arterenol bitartrate of maximum rotation in 100 ml. of de-ionized water containing a trace of sodium bisulfite was cooled to 10° and treated slowly while stirring with 4 ml. of ammonium hydroxide solution. After fifteen minutes at 10° the microcrystalline precipitate was collected, washed with water, methanol and finally with ether. After drying *in vacuo* at 25° the colorless base weighed 5.2 g. and had m. p. 215–217°, dec., and $[\alpha]^{26}D$ +37.4° (*C* = 5% in water + 1 equiv. hydrochloric acid).

Anal. Calcd. for $C_8H_{11}O_3N$: N, 8.28; C, 56.75; H, 6.54. Found: N, 8.12; C, 56.77; H, 6.47.

l-Arterenol.—*l*-Arterenol *d*-bitartrate monohydrate of maximum rotation was treated exactly as above. The colorless *l*-arterenol base from 10 g. of the salt amounted to 4.9 g. and had m. p. 216.5–218°, dec., and $[\alpha]^{25}D$ −37.3° (*C* = 5% in water with 1 equiv. hydrochloric acid).

Anal. Calcd. for $C_8H_{11}O_3N$: N, 8.28; C, 56.75; H, 6.54. Found: N, 8.21; C, 56.37; H, 6.61.

(3) When equivalent amounts of *l*-malic acid or of N-benzoyl-*l*-threonine were substituted for tartaric acid the corresponding salts of *d*-arterenol separated in about the same yield and degree of purity.

d-Arterenol Hydrochloride.—To 10 ml. of isopropanol and 1.5 ml. of concentrated hydrochloric acid at 25° was added 1.69 g. of *d*-arterenol. The mixture was stirred until a clear solution was formed and then cooled to −10°. After fifteen minutes the crystalline precipitate was collected, washed with ether and dried *in vacuo* at 25°. The colorless *d*-arterenol hydrochloride weighed 1.4 g. and was very readily soluble in water. It had m. p. 146.8–147.4° and $[\alpha]^{27}D$ +39° (*C* = 6% in water). Recrystallization of this hydrochloride did not raise the melting point or rotation. Exposure of solutions of this salt to elevated temperatures (higher than 50°) during crystallization for even a few minutes lowers the melting point and rotation. This is also true of the *l*-arterenol hydrochloride.

Anal. Calcd. for $C_{11}H_{11}O_2N \cdot HCl$: N, 6.80; C, 46.72; H, 5.88. Found: N, 6.75; C, 46.95; H, 5.99.

l-Arterenol Hydrochloride.—*l*-Arterenol was treated as above. One and sixty-nine one hundredths grams yielded 1.3 g. of colorless *l*-arterenol hydrochloride, having m. p. 145.2–146.4° and $[\alpha]^{25}D$ −40° (*C* = 6% in water).

Anal. Calcd. for $C_8H_{11}O_2N \cdot HCl$: N, 6.80; C, 46.72; H, 5.88. Found: N, 6.73; C, 46.98; H, 5.83.

Racemization of *d*-Arterenol.—One hundred and twenty grams of *d*-arterenol was dissolved in one liter of de-ionized water with 100 ml. of concentrated hydrochloric acid at 90°. After two hours at this temperature in a nitrogen atmosphere the solution was cooled to 20°, treated with Darco and filtered. The filtrate was made alkaline with 80 ml. of concentrated ammonium hydroxide at 10° and let stand until precipitation was complete. The base was collected, washed with water, alcohol and ether and dried *in vacuo* at 25°. One hundred grams of *dl*-arterenol was recovered, m. p. 190–191°, $[\alpha]^{22}D$ +0.6° (*C* = 5% in water as the hydrochloride).

dl-Arterenol Methyl Ether Hydrochloride, [β-(3,4-Dihydroxyphenyl)-β-methoxyethylamine hydrochloride].—One-hundred grams of *dl*-arterenol was suspended in 800 ml. of methanol and hydrogen chloride was passed in with stirring at 10° until a slight excess had dissolved and a clear solution resulted. The solution was concentrated at the water pump at 30–35° to a volume of 300 ml. when heavy crystallization occurred. The precipitate was collected at 0°, washed with cold methanol and ether and dried *in vacuo*, yielding 72 g. of a hydrochloride which was very easily soluble in water and had m. p. 170–171°. A sample of this salt in aqueous solution gave a green coloration with ferric chloride as does arterenol. *dl*-Arterenol hydrochloride has m. p. 141° (dec.).

Anal. Calcd. for $C_9H_{12}O_3N \cdot HCl$: OCH_3, 14.13; N, 6.38. Found: OCH_3, 13.41; N, 6.25.

A portion of the hydrochloride was converted to the free base as described above for *d*-arterenol. The base, which was appreciably soluble in water and methanol, had m. p. 109–112°.

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Summary

1. *dl*-Arterenol has been resolved through the acid tartrates.

2. The *d*- and *l*-base and hydrochloride were prepared.

3. *d*-Arterenol was racemized by heating with dilute acid.

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