bamyl chloride[19] (10.7 g.) in benzene (50 cc.) was added, dropwise, over a period of 20 minutes, to a stirred, refluxing solution of 3-hydroxy-6-methylpyridine[20] (10.7 g.) in a mixture of benzene (500 cc.) and triethylamine (11.5 g.). Stirring under reflux was continued for 6 hours. The triethylamine hydrochloride was then removed by filtration and the filtrate was evaporated *in vacuo*. The residual oil was then distilled through a small column. The product, a pale-yellow oil, b.p. 182–185° (2.5 mm.), crystallized to a white solid m.p. 78–81°; yield 22.2 g. (80%).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: N, 10.13; Cl, 12.83. Found: N, 9.96; Cl, 12.66.

1-Benzyl-3-(dimethylmercapto)-pyridinium Bromide.—Benzyl bromide (2.74 g.) was added to a solution of 3-(dimethylmercapto)-pyridine (2.55 g.) in benzene (10 cc.), and the resulting solution was heated 2 hours under reflux. The yellow solid formed was collected on a filter, washed with benzene and recrystallized twice from a mixture of absolute alcohol and ether. The product, a colorless crystalline solid, melted, at 147–148°; yield 1.6 g. (32%).

Anal. Calcd. for $C_{15}H_{17}BrN_2OS$: N, 7.93; Br, 22.63; S, 9.08. Found: N, 7.77; Br, 22.81; S, 9.37.

1,6-Dimethyl-3-(N-methyl-N-*p*-chlorophenylcarbamyloxy)-pyridinium Bromide.—A solution of 6-methyl-3-(N-methyl-N-*p*-chlorophenylcarbamyloxy)-pyridine (11 g.) in benzene (35 cc.) was added to a solution of methyl bromide (15 g.) in benzene (25 cc.). The solution was allowed to stand at room temperature overnight whereupon a white solid separated out. The crude product was then collected on a filter, washed with benzene and recrystallized from absolute alcohol and ether. Colorless plates m.p. 165–167° were obtained; yield 10.7 g. (72.5%).

Anal. Calcd. for $C_{15}H_{15}BrClN_2O_2$: N, 7.54; Br, 21.51. Found: N, 7.40; Br, 21.46.

(19) See Table III, footnote *h*.

(20) See Table III, footnote *k*.

Acknowledgment.—Technical assistance in experimental work was rendered by Miss Doris Palmer and Mr. A. G. Bilotti.

Summary

3-Pyridol and a number of its derivatives were converted to substituted carbamic esters which, in turn, were quaternized to pyridinium salts. Fifty-three such quaternary salts are reported, embodying successive variations in the ester side-chain, the quaternizing radical and the substituents in the pyridine nucleus.

Several tertiary bases, with α-substituents in the pyridine ring, resisted quaternization; the ortho effect involved is discussed

A number of the pyridinium salts obtained possess physostigmine-like, parasympathomimetic properties and anticholinesterase activity; a brief discussion is presented of the structure–activity relationship.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

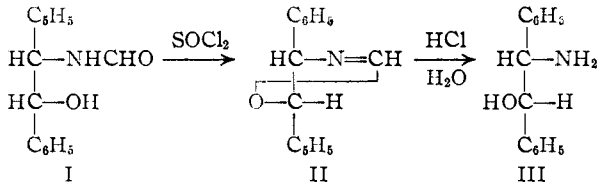
Preparation of the Stereoisomeric α,β-Diphenyl-β-hydroxyethylamines

BY JOHN WEIJLARD, KARL PFISTER, 3RD, EDWARD F. SWANEZY, C. A. ROBINSON AND MAX TISHLER

The preparation of quantities of the stereoisomeric forms of α,β-diphenyl-β-hydroxyethylamine was undertaken in connection with pharmacological study of these compounds as analgesics.[1] Since the literature procedures for the preparation of these compounds are inadequate, we wish to report our experiences in this field.

The high melting racemic modification (m.p. 163°) has been prepared by a number of procedures[2] of which reduction of benzoin oxime appeared most direct. This transformation has been effected in poor yield by sodium amalgam reduction[3] and in better yield by catalytic hydrogenation of the oxime using palladium–sol in dilute ethanol.[4] We prepared this compound in 91% yield by catalytic hydrogenation using palladium-on-charcoal in ethanol containing hydrogen chloride.

The preparation of the lower melting diastereoisomer, known as iso-α,β-diphenyl-β-hydroxyethylamine, was accomplished by inversion of the hydroxyl group *via* oxazoline formation, a procedure successfully applied to the interconversion of threonine and *allo*threonine.[5] In this procedure, N-formyl-α,β-diphenyl-β-hydroxyethylamine (I) is converted to the oxazoline, II, and the latter is hydrolyzed to iso-α,β-diphenyl-β-hydroxyethylamine, III.[6]



No attempt was made to isolate the oxazoline. It is noteworthy that the N-formyl derivative of the iso-α,β-diphenyl-β-hydroxyethylamine (III) did not undergo the inversion reaction under the conditions employed for I. Starting material was mainly recovered in this instance. Under more strenuous conditions, the recovery of starting material was poor but no isomeric hydroxyethylamine, I, was obtained.

The literature on the resolutions of the diastereoisomers of α,β-diphenyl-β-hydroxyethylamine is rather voluminous, particularly so for the lower melting iso racemate. The high melting racemate had been resolved using *d*-oxymethylene camphor

(1) The observation of the morphine-like properties of α,β-diphenyl-β-hydroxyethylamines was made by Dodds, Lawson and Williams, *Nature*, **151**, 614 (1943); *Proc. Roy. Soc. (London)*, **B132**, 119 (1944); *Nature*, **154**, 514 (1944).

(2) Summarized by Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2019 (1948).

(3) Goldschmidt and Polonowska, *Ber.*, **20**, 492 (1887).

(4) Rabe, *ibid.*, **45**, 2166 (1912).

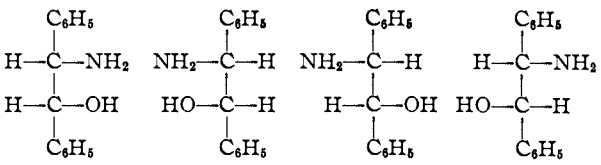
(5) Attenburrow, Elliott and Penny, *J. Chem. Soc.*, 310 (1948); Elliott, *Nature*, **162**, 657 (1948); Pfister, Robinson, Shabica and Tishler, THIS JOURNAL, **70**, 1098 (1948); **71**, 1101 (1949); see also Johnson and Schubert, *ibid.*, **72**, 2187 (1950).

(6) The configuration formulations in this paper are in accord with Fischer's conventions. To effect space economy, only one enantiomorph is given although it should be understood that the second enantiomorph is included when the text refers to the *dl*-form.

and *d*-camphorsulfonic acid,[7] but in our hands the methods were inadequate for large scale preparation. We have found that resolution of the high melting racemate can be effected easily using D-glutamic acid as the resolving agent. The pure levorotatory isomer was obtained from the less soluble glutamate whereas the other enantiomorph was isolated from the more soluble glutamate.

The dextro- and levorotatory forms of the lower melting iso racemate were obtained from the optically active diastereoisomers by application of the same oxazoline inversion procedure. In agreement with the observations of Elliott[8] with the optically active α-amino-β-hydroxybutyric acids, very little or no racemization occurred during the inversion reactions.

Inasmuch as the configurations of the two optically active aminohydrins which form the high melting racemate have been established[9] the transformations of this report allow assignment of the configurations of the remaining two optically active isomers. This assignment of configuration is possible since the inversion during oxazoline formation has been demonstrated to involve only the hydroxyl group.[5] Elliott[8] has applied the same scheme in assigning the configurations of the optically active *allo*threonines. Employing the terms "erythro" and "threo" suggested recently for the racemates,[2] the four optically active isomers have the structures IV through VII.



IV	V	VI	VII
D-*erythro*, m.p. 143°, $[\alpha]^{25}D$ −10°	L-*erythro*, m.p., 143°, $[\alpha]^{25}D$ +10°	D-*threo*, m.p. 116°, $[\alpha]^{25}D$ −124°	L-*threo*, m.p. 116°, $[\alpha]^{25}D$ +124°
DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine, m.p. 163°		DL-*threo*-α,β-diphenyl-β-hydroxyethylamine, m.p. 127°	

Experimental

DL-*erythro*-α,β-Diphenyl-β-hydroxyethylamine (High Melting Racemate).—A mixture of 136 g. of benzoin oxime (0.6 mole), 1120 cc. of ethanol containing 24 g. of hydrogen chloride and 16 g. of 5% palladium-on-charcoal was hydrogenated at 40 lb. pressure. The calculated quantity of hydrogen was absorbed in 2 to 3 hours, and the hydrogenation stopped. To the reaction mixture was added 1000 cc. of water which dissolved the crystalline hydrochloride, and the catalyst was removed by filtration. The filtrate was diluted to 4 l. with water, an excess of concd. ammonia was added, the precipitated base was collected, washed free from chloride with water and dried at 45–50°; yield 117 g. (91.4%), m.p. 163°.

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.83; H, 7.09; N, 6.57. Found: C, 78.64; H, 6.84; N, 6.41.

The hydrochloride was prepared by dissolving the base in hot alcohol, adding a slight excess of alcoholic HCl, and precipitating by adding an equal volume of ether. The yield was nearly quantitative, m.p. 219–220°.

Anal. Calcd. for $C_{14}H_{16}ONCl$: C, 67.33; H, 6.46; N, 5.61. Found: C, 67.22; H, 6.29; N, 5.49.

(7) Read and Steele, *J. Chem. Soc.*, 910 (1927).

(8) Elliott, *ibid.*, 62 (1950).

(9) Weissberger and Bach, *Ber.*, **64**, 1094 (1934); **65**, 63 (1935); McKenzie and Pirie, *ibid.*, **69**, 876 (1936); see also reference 2.

N-Formyl-DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine (I).—A suspension of 5 g. of the hydrochloride in 15 cc. of formamide was heated at 150° for 15 minutes. After cooling, the solution was diluted with 75 cc. of water and the crystalline product was separated and washed with water until free from chlorides; wt. 4.6 g. (96%); m.p. 179–181° (sintering at 175°).[10] The N-formyl derivative (0.5 g.) was hydrolyzed by heating under reflux for 2 hours with 2.5 *N* HCl (10 cc.). The mixture was made alkaline with sodium hydroxide solution and the DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine (0.43 g.) was separated; m.p. 161–162°. A mixed melting point determination showed this material to be identical with the starting material.

D-*erythro*-α,β-Diphenyl-β-hydroxyethylamine-D-glutamate.—A mixture of 134 g. of DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine (0.63 mole) and 93 g. of D-glutamic acid (0.63 mole) was dissolved in 4000 cc. of boiling 50% ethanol. After storage overnight at room temperature, the fine needles were collected, washed with ice-cold 50% ethanol and dried; yield 67 g. (60%); m.p. 215°; $[\alpha]^{25}D$ −50.3° (*c*, 0.65, water).

D-*erythro*-α,β-Diphenyl-β-hydroxyethylamine.—The base was obtained by dissolving the 67 g. of glutamate in 1000 cc. of warm water, precipitating with excess of ammonia, collecting, carefully washing with water and drying; yield 36.0 g (91%), m.p. 143°; $[\alpha]^{25}D$ −10.1° (*c*, 0.59, alc.).

D-*erythro*-α,β-Diphenyl-β-hydroxyethylamine Hydrochloride.—Thirty-two grams of the above base was dissolved in 600 cc. of ethanol, 35 cc. of 23% alcoholic hydrochloric acid was added, and the hydrochloride then precipitated with an equal volume of ether and collected; yield 38.5 g., m.p. 213.5–214.5°; $[\alpha]^{25}D$ −69.5° (*c*, 0.65, water).[11]

Anal. Calcd. for $C_{14}H_{16}ONCl$: C, 67.33; H, 6.46, N, 5.61. Found: C, 67.19; H, 6.21; N, 5.49.

L-*erythro*-α,β-Diphenyl-β-hydroxyethylamine-D-glutamate.—The mother liquor from the D-*erythro*-α,β-diphenyl-β-hydroxyethylamine-D-glutamate was concentrated to 1000 cc., 300 cc. of 95% ethanol was added, and the solution was stored overnight. The crystals were collected, sucked as dry as possible without washing and dried; yield 96 g. of glutamate, $[\alpha]^{25}D$ +24.2°. This crude glutamate was dissolved in 800 cc. of hot 50% ethanol and allowed to stand several hours at room temperature, the heavy, stubby crystals were filtered, washed with ice-cold 50% ethanol and dried; yield 56 g., $[\alpha]^{25}D$ +43.0°. On dissolving this crop in 500 cc. of hot 50% ethanol and allowing to stand overnight at room temperature, 44 g. of pure L-*erythro*-α,β-diphenyl-β-hydroxyethylamine-D-glutamate was obtained (39%), m.p. 195°; $[\alpha]^{25}D$ +45.3° (*c*, 0.65, water).

L-*erythro*-α,β-Diphenyl-β-hydroxyethylamine was obtained as described above, yield 25.4 g. of base from 43 g. of glutamate, m.p. 143°; $[\alpha]^{25}D$ +10.2° (*c*, 0.61, alc.). A mixture of equal quantities of the pure dextro- and levorotatory bases melts at 163°.

L-*erythro*-α,β-Diphenyl-β-hydroxyethylamine hydrochloride was obtained as described above, in almost quantitative yield, m.p. 210–212°; $[\alpha]^{25}D$ +69.6° (*c*, 0.65, water).[7]

Anal. Calcd. for $C_{14}H_{16}ONCl$: C, 67.33; H, 6.46; N, 5.61. Found: C, 67.15; H, 6.45; N, 5.77.

DL-*threo*-α,β-Diphenyl-β-hydroxyethylamine (III).—To 2.5 cc. of thionyl chloride at 5° was added 1.21 g. of N-formyl-DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine (m.p. 179–181°). After 10 minutes at 5°, the temperature was allowed to rise to 22° (0.5 hour). Thirty grams of ice was added to the mixture whereby a white precipitate formed. The mixture was heated under reflux for 2 hours and the clear solution was treated with charcoal and filtered. The colorless solution was made alkaline with 7 cc. of 30% caustic and the resulting solid was collected and washed well with water; wt. 0.96 g.; 91% yield; m.p. 126–128°. Previously reported m.p. 129°.[12]

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.83; H, 7.09. Found: C, 79.01; H, 7.13.

(10) Previously prepared by Söderbaum, *ibid.*, **29**, 1210 (1896), by fusion of the formate; m.p. 182–183° after sintering at 179°.

(11) In agreement with the previously reported value of −69°, McKenzie and Pirie, *ibid.*, **69**, 876 (1936), *cf.* ref. 7.

(12) McPhee and Erickson, THIS JOURNAL, **68**, 624 (1946); also reference (7).

DL-*threo*-α,β-**Diphenyl-β-hydroxyethylamine** hydrochloride was prepared from the base (7.46 g.) by dissolution in ether (950 cc.) followed by addition of ethereal hydrogen chloride until the mixture was acid to congo paper. The product (8.1 g.) melted at 200–201°. It is much more soluble than the diastereoisomeric hydrochloride in mixtures of alcohol and ether.

N-Formyl-DL-*threo*-α,β-diphenyl-β-hydroxyethylamine was prepared from the hydrochloride by treatment with formamide and the product was isolated in the manner described for the *erythro* isomer; m.p. 145–146°; yield 93.5%.

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.71; H, 5.98; N, 5.97.

When boiled with 2.5 *N* HCl for 2 hours and the resulting solution was made alkaline, the free *threo* base was regenerated in high yields.

Attempts to isomerize the N-formyl derivative of the *threo*-hydroxyethylamine under the conditions used for the N-formyl-DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine gave a 70% yield of DL-*threo*-α,β-diphenyl-β-hydroxyethylamine. Boiling the reaction mixture of the N-formyl-derivative and thionyl chloride for 1 and 2 hours followed by the regular work-up procedure gave 60 and 45% yields of the *threo*-hydroxyethylamine. Attempts to isolate the diastereoisomer failed.

N-Formyl-D-*erythro*-α,β-diphenyl-β-hydroxyethylamine was prepared in 88% yield by the formamide procedure. It separated from ethanol as fine needles; m.p. 203–204°. *Anal.* Found: C, 74.81; H, 5.83; N, 6.09.

N-Formyl-L-*erythro*-α,β-diphenyl-β-hydroxyethylamine was prepared in 70% yield (after recrystallization from alcohol) and obtained as lustrous needles from ethanol; m.p. 203–204°. *Anal.* Found: C, 75.00; H, 6.50. A mixture of approximately equal amounts of this product and its enantiomorph melted at 185–189°.

L-*threo*-α,β-**Diphenyl-β-hydroxyethylamine.**—N-Formyl-D-*erythro*-α,β-diphenyl-β-hydroxyethylamine (1.21 g.) was treated with thionyl chloride (2.5 cc.) by the method described for the racemate. The product, isolated in the same manner, melted at 114–115°; 89.6% yield. A solution in ether was converted to the hydrochloride by the addition of an ether solution of hydrogen chloride; m.p. 220–221°; $[\alpha]^{23}D$ +84.7° (*c*, 0.01, water). Treatment of the hydrochloride in water with excess sodium hydroxide precipitated the free base; m.p. 116–116.5°; $[\alpha]^{24}D$ 124° (*c*, 1.18, abs. alcohol).

D-*threo*-α,β-**Diphenyl-β-hydroxyethylamine** was prepared from N-formyl-L-*erythro*-α,β-diphenyl-β-hydroxyethylamine in the manner employed for its enantiomorph. The crude product, m.p. 114–115°, was obtained in 85% yield. By recrystallization from hot benzene, the product was obtained as rods; m.p. 115.2–115.8°; $[\alpha]^{22}D$ −123.7° (*c*, 1.2, abs. ethanol).[13]

Summary

1. The inversion of DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine to DL-*threo*-α,β-diphenyl-β-hydroxyethylamine has been accomplished by treatment of the N-formyl derivative with thionyl chloride followed by acid hydrolysis of the intermediate oxazoline. The same inversion was applied successfully to the optically active forms of the DL-*erythro* series.

2. Configurations have been assigned to the four optically active isomers of α,β-diphenyl-β-hydroxyethylamine.

3. A new procedure for the resolution of DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine using D-glutamic acid as the resolving agent is described.

(13) Read, Campbell and Barker, *J. Chem. Soc.*, 2305 (1929), report m.p. 115.2°, $[\alpha]D$ +133° and −133° for the enantiomorphs. Ingersoll, THIS JOURNAL, **50**, 2264 (1928), reports $[\alpha]D$ +125° and −125.6° for the enantiomorphs.

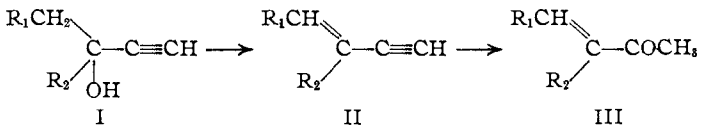
RAHWAY, NEW JERSEY RECEIVED AUGUST 31, 1950

[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

Dehydration and Isomerization of Dimethylethynylcarbinol

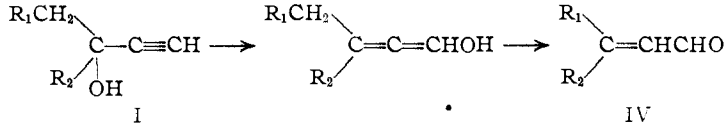
BY ERNST D. BERGMANN

The isomerization of acetylenic carbinols to carbonyl compounds has occupied a number of investigators who reported somewhat contradictory results.[1] It appears now that under the conditions used hitherto, ketones are formed almost exclusively, by dehydration of the tertiary carbinol group and hydration of the triple bond (*i.e.*, not by a true isomerization)[2]



I II III

Recently, Chanley[3] reported that 1-ethynyl-1-cyclohexanol gives a small amount (0.8–6%) of cyclohexylideneacetaldehyde in addition to the α,β-unsaturated ketone, 1-acetylcyclohexene. The mechanism of the aldehyde formation, which involves an allylic shift in a system containing a triple bond would be formulated as



I IV

The experiments reported here and intended to achieve the catalytic vapor phase dehydration of dimethylethynylcarbinol, are believed to shed some light on the phenomenon of its isomerization. It was observed that the dehydration is accompanied by isomerization and that in particular, an aldehyde, β,β-dimethylacrolein, is formed in constant and significant amounts.

Vaughn[4] has studied the **liquid-phase** dehydration of dimethylethynylcarbinol and has found concentrated sulfuric acid satisfactory, giving a 74% conversion and 57% yield, 3-methyl-3-butanol-2-one and methyl isopropenyl ketone (III, R_1 = H, R_2 = CH_3) being formed as by-products. 10% sulfuric acid gave a "quite low yield," phosphoric acid

(1) For a survey of the literature, see E. Bergmann, "Acetylene Chemistry," Interscience Publishers, New York, N. Y., 1948, p. 60 ff.

(2) Hennion, Davis and Maloney, THIS JOURNAL, **71**, 2813 (1949).

(3) Chanley, *ibid.*, **70**, 244 (1948); see also MacGregor, *ibid.*, **70**, 3953 (1948); E. and F. Bergmann, *ibid.*, **59**, 1443 (1937).

(4) Vaughn, U. S. Patent 2,250,558 (*C. A.*, **35**, 7070 (1941)).