sion distillation apparatus to give 35 g. of 1-methyl-5-trifluoromethyltetrazole, b.p. 101–102° (46 mm.). The infrared spectrum was identical with that of the higher boiling fraction (III) obtained from the methylation of sodium 5-trifluoromethyltetrazole.

Anal. Calcd. for $C_3H_3F_3N_4$: C, 23.69; H, 1.99; F, 37.48; N, 36.84. Found: C, 23.69; H, 2.52; F, 38.09; N, 36.05.

N-Chloro-5-trifluoromethyltetrazole (V).—Chlorine gas was passed into an aqueous solution of 5 g. of sodium 5-trifluoromethyltetrazole until approximately 1 ml. of a dense, slightly yellow, liquid separated from the water. The dense liquid, N-chloro-5-trifluoromethyltetrazole, was dried over anhydrous calcium chloride. A weighed sample of the dried liquid was treated with aqueous potassium iodide and the liberated iodine was titrated with standard thiosulfate solution.

Anal. Calcd. for $C_2ClF_3N_4$: Cl, 20.6. Found: Cl, 21.2.

The infrared spectrum shows absorption bands, in microns, at: 6.59, 7.00 (weak), 7.20, 7.40, and 7.60 (weak), 7.92, 8.1–8.7 (broad), 9.09 (weak), 9.70, 10.04, 12.93, 13.16. The spectrum resembles that of 2-methyl-5-trifluoromethyltetrazole in the 6.6, 9–10, and 13-μ regions quite closely.

Caution: N-Chloro-5-trifluoromethyltetrazole is extremely sensitive to shock and heat.

Attempted Reaction of Sodium Azide with Acetonitrile.—Sodium azide (71 g., 1.1 moles) and 150 ml. of acetonitrile were sealed in a pressure vessel. The reaction mixture was heated to 125°, with agitation, for 66 hr. The solid was filtered off, dried, and weighed to give 70 g. of solid. Titration of a weighed sample of the dried solid with standard sodium triiodide (catalyzed with sodium thiosulfate) showed the solid to be sodium azide.

Powdered sodium azide (35 g., 0.55 mole) and 150 ml. of acetonitrile were heated in a pressure vessel to 200°, with agitation, for 18 hr. The sodium azide crystallized from the hot solvent upon cooling depositing a layer of crystals on the inside of the reaction vessel. The solid was filtered from the reaction mixture and dried to give 34.5 g. of material. It required 263 ml. of 1.00 *N* sodium triiodide to react with all the solid. This is equivalent to 0.53 mole, 96%, of the initial amount of sodium azide. Allowing for mechanical losses and the slight solubility in cold acetonitrile this is essentially a quantitative recovery of sodium azide. Sodium 5-methyltetrazole does not react with sodium triiodide in the presence of sodium thiosulfate catalyst.

5-Methyltetrazole.—Sodium azide (33 g., 0.50 mole), 27 g. (0.50 mole) of ammonium chloride, and 150 ml. of acetonitrile were placed in a pressure vessel and heated at 150°, with agitation, for 25 hr. The solids were filtered off, dried, dissolved in 200 ml. of water and 50 ml. of concentrated hydrochloric acid. The water was evaporated and the residue dried at 100°/0.1 mm. pressure. The residue was then extracted with three 100-ml. portions of boiling ethyl acetate. The ethyl acetate was evaporated and the solid sublimed to give 36 g. (100% yield) of 5-methyltetrazole, m.p. 144–146° (lit., m.p.[12] 148–148.5°).

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cis- and *trans*-3-Methyl-2-phenylmorpholine

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The synthesis of racemic *cis*- and *trans*-5-methyl-6-phenyl-3-morpholinone and 3-methyl-2-phenylmorpholine is described.

The first synthesis of an optically active morpholine derivative was achieved by Otto[1b] in 1956 by the acid-catalyzed cyclization of *l*-N-(2-hydroxyethyl)ephedrine to *d*-3,4-dimethyl-2-phenylmorpholine. Subsequently Foltz and Witkop,[2] in commenting on this synthesis, pointed out that whether the ring closure proceeds by a concerted process or *via* a benzyl carbonium ion, the product must have the more stable *trans* configuration. This is apparently the only instance in which the configuration has been assigned to a 2,3-disubstituted morpholine.

We have repeated the acid-catalyzed cyclization reaction using the *N*-(2-hydroxyethyl) derivatives (III and VIII) of racemic norephedrine[3] (I) and nor-ψ-ephedrine[3] (VI), respectively, and in each case racemic *trans*-3-methyl-2-phenylmorpholine (X) hydrochloride[4] was isolated in good yield. A concerted mechanism would have given at least some of the *cis* isomer in the latter case, but there was no evidence of this in the infrared spectrum[5] of the crude product. It is clear from these experiments that the preparation of the *cis* isomer requires a different method, one which does not involve the formation of an intermediate benzyl carbonium ion.

A successful synthesis of *cis*-5-methyl-6-phenyl-3-morpholinone (IV) was achieved when the sodio derivative of norephedrine (I) was treated in benzene solution with ethyl chloroacetate. Subsequent reduction with lithium aluminum hydride resulted in a stereospecific synthesis of *cis*-3-methyl-2-phenylmorpholine (V). Treatment of the sodio derivative of nor-ψ-ephedrine (VI) in a

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(1b) W. G. Otto, *Angew. Chem.*, **68**, 181 (1956).

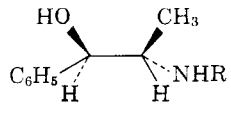
(2) C. M. Foltz and B. Witkop, *J. Am. Chem. Soc.*, **79**, 201 (1957).

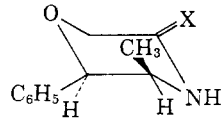
(3) The configurations of norephedrine and nor-ψ-ephedrine have been firmly established and the compounds have been related to the corresponding ephedrines. See H. E. Zimmerman and J. English, Jr., *ibid.*, **76**, 2291 (1954).

(4) Ravensberg G.m.b.H., Belgian Patent 580,045 (1959).

(5) The infrared spectra of the hydrochlorides of the isomers (Nujol mulls) are readily distinguished in the region above 9 μ. In this region intense bands of the *cis* isomer occur at 9.02, 9.24, 13.39, and 14.30 μ while those of the *trans* isomer are found at 9.13, 9.74, 13.27, and 14.44 μ.

similar manner gave *trans*-5-methyl-6-phenyl-3-morpholinone (IX), which on reduction yielded the known *trans*-3-methyl-2-phenylmorpholine (X). These reactions were carried out with racemic compounds, but optically active products would be obtained if the norephedrines were first resolved.[6]

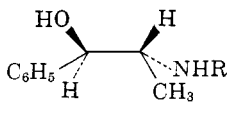


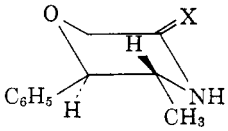


I. R = H
II. R = $COCH_2OOCC_6H_5$
III. R = CH_2CH_2OH

IV. X = O
V. X = H_2

The N-(2-hydroxyethyl) derivatives required for the first part of this work were prepared by reduction of the corresponding benzoylglycolylamides (II and VII) with lithium aluminum hydride The amides were prepared by the reaction of the primary amines with benzoylglycolyl chloride in the presence of triethylamine. This method provides a convenient route for the addition of only one 2-hydroxyethyl group to a primary amine. The benzoylglycolic acid[7] required for this procedure was prepared conveniently by the chromic acid oxidation of ethylene glycol monobenzoate, which in turn was obtained from ethylene chlorohydrin and sodium benzoate.[8]





VI. R = H
VII. R = $COCH_2OOCC_6H_5$
VIII. R = CH_2CH_2OH

IX. X = O
X. X = H_2

Experimental

Benzoylglycolic Acid.—Chromic acid solution[9] (200 ml.) was added over a period of 30 min. to a stirred solution of 63.9 g. of ethylene glycol monobenzoate[8] in 230 ml. of acetone. The temperature of the reaction mixture was maintained at 45° throughout the addition and for 10 min. thereafter by external cooling. The reaction mixture was then cooled and the solvent was decanted from a gummy green precipitate which had formed. The latter was washed well with ether and the combined ether and acetone solutions were extracted, first with a small volume of water and then with a saturated aqueous potassium carbonate solution. The alkaline solution was washed once with ether and then cooled with ice, acidified with concentrated hydrochloric acid, and extracted three times with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to give 47.5 g. of crude product as colorless crystals, m.p. 95–105°. One recrystallization from benzene–ligroin gave 39.6 g. (57.2%) of benzoylglycolic acid, m.p. 112–113° (reported[10] m.p. 112°).

d,l-erythro-**2-Benzoylglycolylamino-1-hydroxy-1-phenylpropane (II).**—A mixture of 5.0 g. (0.028 mole) of benzoylglycolic acid and 10 ml. of oxalyl chloride was refluxed for 30 min. Excess oxalyl chloride was removed *in vacuo* on the steam bath and three successive small portions of benzene were added and removed in a similar manner. The benzoylglycolyl chloride thus prepared was dissolved in 40 ml. of chloroform and the solution added to a stirred solution of 4.2 g. (0.028 mole) of *dl*-norephedrine (liberated from phenylpropanolamine, Merck) and 3.0 g. (0.030 mole) of triethylamine in 140 ml. of chloroform over a period of 1 hr. The reaction mixture, which had become warm, was then refluxed for 1 hr., cooled, washed successively with dilute hydrochloric acid and dilute aqueous sodium carbonate solution, filtered through anhydrous sodium sulfate, and taken to dryness *in vacuo*. The residue, 8.2 g. (94% yield) was a colorless solid, m.p. 133–135°. Several recrystallizations from ethyl acetate–cyclohexane gave an analytical sample, m.p. 134–135°.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.97. Found: C, 69.05; H, 6.22: N, 4.56.

dl-**N-(2-Hydroxyethyl)norephedrine (III).**—A mixture of 5.0 g. of II and 5.7 g. of lithium aluminum hydride in 350 ml. of ether was refluxed with stirring for 16 hr., then cooled with an ice bath and treated in succession with 5 ml. of water, 5 ml. of 15% aqueous sodium hydroxide, and 15 ml. of water. The solids were collected and triturated with two 100-ml. portions of boiling methanol. The solutions were combined and the solvent removed to give 7.0 g. of a yellowish solid. The solid was dissolved in absolute ethanol and the solution made acidic with alcoholic hydrogen chloride. The solution was filtered hot, concentrated to a small volume, and cooled to give 3.1 g. (84% yield) of the hydrochloride of III as colorless crystals, m.p. 163–166° (reported[11] m.p. 166°).

dl-trans-**3-Methyl-2-phenylmorpholine (X).**—A solution of 0.5 g. of the hydrochloride of III in 5.0 ml. of concentrated sulfuric acid was left at room temperature for 17 hr., then poured onto ice and water. The solution was made basic with 50% aqueous sodium hydroxide and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and evaporated to leave an oil which was converted to the hydrochloride salt with anhydrous hydrogen chloride in ether; yield, 0.4 g., m.p. 175–176°. Several recrystallizations from absolute ethanol–ether raised the melting point to 180–181° (reported[4] m.p. 182°).

The picrate salt formed golden yellow crystals from absolute ethanol, m.p. 200–202°.

Anal. Calcd. for $C_{17}H_{16}N_4O_9$: N, 13.33. Found: N, 12.90.

dl-threo-**2-Benzoylglycolylamino-1-hydroxy-1-phenylpropane (VII).**—*dl*-Nor-ψ-ephedrine[12] (6.0 g.) was transformed by a procedure analogous to that described above for II to give 11.8 g. (95% yield) of VII, m.p. 105–110°. A sample for analysis was obtained from ethyl acetate–cyclohexane, m.p. 106–107°.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 5.91; N, 4.46.

dl-**N-(2-Hydroxyethyl)nor-ψ-ephedrine (VIII).**—A mixture of 10.0 g. of VII and 10.0 g. of lithium aluminum hydride in 600 ml. of ether was stirred and refluxed for 15 hr., then cooled and 25 ml. of water added cautiously, followed by about 50 g. of anhydrous sodium sulfate. Methanol (300 ml.) was then added and the solids were collected, trit-

(6) For resolution of the norephedrines see C. Jarowski and W. H. Hartung, *J. Org. Chem.*, **8**, 564 (1943).

(7) The apparently simple procedure of treating glycolic acid with benzoyl chloride [C. Concilio, A. Tezza, and E. Trivellato, *Farmaco* (Pavia) *Ed. sci.*, **12**, 655 (1957); *Chem. Abstr.*, **52**, 4548g (1958)] failed in our hands to give a product that could be recrystallized easily. Other procedures have been described which appeared to us to be less convenient.

(8) H. C. Heim and C. F. Poe, *J. Org. Chem.*, **9**, 299 (1941).

(9) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(10) M. Lederer, *Ann.*, **583**, 29 (1953).

(11) R. H. F. Manske and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1906 (1939). A. Skita and F. Keil, *Ber.*, **63B**, 34 (1930).

(12) Obtained from the hydrochloride, prepared according to H. K. Mueller, *Ann.*, **599**, 211 (1956).

urated with 300 ml. of hot methanol, and again collected. The combined filtrates were acidified with methanolic hydrogen chloride and taken to dryness. When the residual gum did not solidify, it was dissolved in water and the base precipitated with sodium hydroxide and collected to give 6.9 g. of crude product, m.p. 80–90°. Recrystallization from water gave 2.7 g. (28% yield) of VIII, m.p. 118–120°.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.69; H, 8.72; N, 7.18. Found: C, 67.78; H, 8.91; N, 7.04.

A solution of 0.5 g. of VIII in 5.0 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 20 hr. and worked up as before to give 0.5 g. *dl, trans*-3-methyl-2-phenylmorpholine hydrochloride, m.p. 181–183°, undepressed upon admixture with a sample prepared from III.

***dl,cis*-5-Methyl-6-phenyl-3-morpholinone (IV).**—*dl*-Norephedrine (24.0 g., 0.160 mole) was added to a stirred suspension of 4.0 g. (0.172 mole) of sodium hydride (50% dispersion in mineral oil) in benzene at room temperature and stirring was continued for 30 min. The mixture was then cooled in an ice water bath and 20.0 g. (0.160 mole) of ethyl chloroacetate was added during 15 min. Stirring was continued for 1 hr. at room temperature and finally under reflux for 1.5 hr. The solution was cooled, diluted with ether, washed with dilute aqueous hydrochloric acid, dried over anhydrous sodium sulfate, and concentrated to a small volume. Boiling cyclohexane was added and the solution again concentrated and cooled to give 26.6 g. of crude product as colorless crystals, m.p. 120–135°. After three recrystallizations from benzene–cyclohexane the melting point was constant at 142–144°; yield 18.0 g. (59.3%).

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N 7.19.

***dl,cis*-3-Methyl-2-phenylmorpholine (V).**—Ten grams of IV was added in portions to a stirred suspension of 6.6 g. of lithium aluminum hydride in 600 ml. of ether. The mixture was stirred under reflux for 22 hr., then cooled and treated in succession with 6 ml. of water, 9 ml. of 10% aqueous sodium hydroxide, and 15 ml. of water. Anhydrous sodium sulfate was then added and the granular precipitate collected and washed well with ether. The filtrate was evaporated to dryness to 9.1 g. (98% yield) of a colorless oil which was characterized as the hydrochloride, m.p. 152–154° (recrystallized from absolute ethanol–ether).

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.81; H, 7.53; N, 6.55. Found: C, 62.21; H, 7.53; N, 6.64.

The picrate formed brilliant lemon yellow crystals from absolute ethanol, m.p. 210–211°.

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: N, 13.33. Found: N, 13.70.

***dl,trans*-5-Methyl-6-phenyl-3-morpholinone (IX).**—The sodio derivative of *dl*-nor-ψ-ephedrine (8.3 g., 0.055 mole) was prepared and treated with ethyl chloroacetate by the procedure described above for IV. Crystals which had deposited in the benzene solution after standing overnight were redissolved by adding ether and methylene chloride and the solution was then worked up as before to give 9.3 g. (88% yield), m.p. 177–179° (unchanged upon recrystallization from benzene–cyclohexane).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.92; H, 7.00; N, 7.37.

Reduction of 1.00 g. of IX by the procedure described above for the *cis* isomer gave 0.86 g. (43% yield) of X as a colorless oil. The hydrochloride and picrate salts of this oil were identical (melting points, mixture melting points, and infrared spectra) with those of *dl, trans*-3-methyl-2-phenylmorpholine described above.

Acknowledgment.—The author is indebted to Mr. E. Conner of the Physical and Analytical Chemical Research Department for the microanalyses.

Some Substitution Reactions of Isovanillin and Related Compounds[1]

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Bromination of isovanillin results in substitution *ortho* and *para* to the phenolic function, and the reaction conditions determine to a considerable extent that position which undergoes substitution. The action of bromine on isovanillin acetate does not result in simple substitution of halogen for hydrogen, but some 5-bromoguaiacol acetate is formed. 5-Bromoisovanillin has been prepared, and some related reactions have been investigated.

Studies of substitution reactions of vanillin have been rather numerous,[2] but similar investigations involving isovanillin have been limited.[3–5] Several additional observations have now been made of the behavior of isovanillin and related compounds when subjected to bromination (and a nitration reaction has been carried out).

In the vanillin studies, it had been observed that the free phenolic group exerts the principal directive influence: substitution occurs chiefly at position 5 (*i.e., ortho* to the phenolic function). When the phenolic group of vanillin is acylated, the methoxy group exerts greater orienting influence than the acyloxy group, and in bromination reactions, particularly, substitution occurs exclusively at the position *para* to the methoxy group.[6] Nitration of vanillin acetate and of vanillin benzoate takes place *ortho* and *para* (chiefly *ortho*) to the methoxy group.[6b,7]

It was not lack of information concerning sub-

(1) This investigation was supported in part by the Washington State University Research Fund.

(2) See for example: W. B. Bentley, *Am. Chem. J.*, **24**, 171 (1900); H. D. Dakin, *ibid.*, **42**, 493 (1909); L. C. Raiford and J. G. Lichty, *J. Am. Chem. Soc.*, **52**, 4576 (1930); L. C. Raiford and E. H. Wells, *ibid.*, **57**, 2500 (1935).

(3) R. Pschorr and W. Stöhrer, *Ber.*, **35**, 4397 (1902).

(4) T. A. Henry and T. M. Sharp, *J. Chem. Soc.*, 2285 (1930).

(5) L. C. Raiford and M. F. Ravely, *J. Org. Chem.*, **5**, 204 (1940).

(6) (a) L. C. Raiford and W. C. Stoesser, *J. Am. Chem. Soc.*, **49**, 1077 (1927); (b) L. C. Raiford and J. E. Milbery, *ibid.*, **56**, 2727 (1934).

(7) R. Pschorr and C. Sumuleanu, *Ber.*, **32**, 3405 (1899); L. C. Raiford and W. C. Stoesser, *J. Am. Chem. Soc.*, **50**, 2556 (1928); S. F. McDonald, *J. Chem. Soc.*, 376 (1948).