3-Methyl-1-butyn-3-ol–Potassium Hydroxide Reaction Product.—A 42-g. (0.50 mole) sample of methylbutynol and 28.5 g. (0.50 mole) of 98% potassium hydroxide in 800 cc. of diisopropyl ether gave 69.8 g. (99.7% conversion) of adduct.

Anal. Calcd.: KOH, 40.0; C≡CH, 17.9; C, 42.8; H, 6.4. Found: KOH, 38.3; C≡CH, 17.5; C, 42.6; H, 7.8.

2,5-Dimethyl-3-hexyn-2,5-diol–Alkali Hydroxide Adducts.—The method of preparation is identical to the methyl butynol procedure except that a higher reaction temperature (30–35°) is employed with solvents such as diisopropyl ether or toluene. Dimethylhexynediol is dissolved by warming in 300–500 cc. of one of these solvents and then adding the mixture to a 300 cc. slurry of alkali hydroxide in the same solvent. The diol adducts yield a noticeably thicker reaction mass, and dilution with solvent is generally needed to facilitate isolation.

Diol–Potassium Hydroxide Reaction Product.—A 14.2-g. (0.10 mole) sample of dimethylhexynediol and 5.7 g. (98%) of potassium hydroxide in 600 cc. of isopropyl ether gave 19.2 g. of adduct (97% conversion).

Anal. Calcd.: KOH, 28.1; C≡C, 12.1; C, 48.4; H, 7.6. Found: KOH, 27.7; C≡C, 11.1; C, 47.4; H, 8.2.

The average purity based on C and KOH values was 98.1%, and the ethynyl content (C≡CH)[9] was less than 0.05%.

Formation of Methylbutynol–Potassium Hydroxide Adduct from Acetone, Acetylene, and Potassium Hydroxide.—Dry acetylene gas was metered (liters) into a well stirred mixture of 28.5 g. (0.50 mole) of 98% potassium hydroxide in 800 cc. of dry, alcohol-free isopropyl ether at −10 to 0°. The acetylene used was dried successively over granular (0.125 in.) calcium carbide and alumina (F-10), and the 1-l. reactor protected from the atmosphere with alumina towers. The net liters of acetylene absorbed was determined by the use of entrance and exit Weston wet test meters.

When the ether–base slurry was essentially saturated with acetylene (6 l.), the addition of 29.0 g. (0.50 mole) of dry acetone was begun. Acetone addition during 1 hr. was accompanied by the formation of a thick, but stirrable reaction mass. Acetylene was metered into the reaction to a total of 15 l., always maintaining an excess of acetylene over acetone. The reaction product was isolated in the usual manner after a total reaction time of 2 hr., and weighed 61 g. (87% conversion).

Anal. Calcd. (87% pure): KOH, 43.3; C, 37.3; H, 6.58. Found: KOH, 41.5; C, 38.0; H, 6.84.

The product was found by X-ray and infrared examination to be identical with methylbutynol–potassium hydroxide adducts prepared from methylbutynol. It also contained less than 0.05% dimethylhexynediol as determined by internal C≡C value.[11]

Analgesics. Stereoselective Syntheses of α-(+)- and α-(−)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane

A. POHLAND, L. R. PETERS, AND H. R. SULLIVAN

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

Received February 25, 1963

The preparation of α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane has been described.[1] By this procedure the intermediate α-(±)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol was resolved by fractional crystallization of the (+)-camphorsulfonic acid salt and the optically active carbinol was acylated by means of propionic anhydride in pyridine. The α-(+)-isomer, *d*-propoxyphene, has found general acceptance as an analgesic. It was, therefore, of interest to find alternate synthetic routes for the preparation of this compound.

(1) A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.*, **77**, 3400 (1955).

During previous work[2] α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane was hydrolyzed and dehydrated to the stilbene. Ozonization of the stilbene afforded good yields of (−)-β-dimethylamino-α-methylpropiophenone. This optically active amino ketone was found to be surprisingly stable in the salt form and also as solutions of the free base in nonpolar solvents. In light of these observations, it appeared that a stereoselective synthesis of α-(+)-4-dimethylamino - 1,2 - diphenyl - 3 - methyl - 2 - propionoxybutane would be feasible.

β-Dimethylamino-α-methylpropiophenone was resolved by crystallization of the dibenzoyl tartrate salts from acetone solution. The use of dibenzoyl-(−)-tartaric acid yielded the insoluble salt with (−)-dimethylamino-α-methylpropiophenone, while the use of dibenzoyl-(+)-tartaric acid yielded the insoluble salt with the (+)-amino ketone. It is of interest that concentration of the filtrate from the resolution causes racemization of the soluble diastereoisomeric salt and affords a nearly quantitative yield of the insoluble salt of the desired optically active ketone.

(−)-β-Dimethylamino-α-methylpropiophenone was liberated from its dibenzoyl-(−)-tartrate salt by means of base and allowed to react in ether solution with benzylmagnesium chloride in the same manner as described for the racemic ketone.[1] α-(+)-1,2-Diphenyl-3-methyl-4-dimethylaminobutanol-2 was obtained in good yield indicating that little racemization of the amino ketone occurs during the Grignard reaction.

The α-(+)- and α-(−)-aminocarbinols were converted to their propionyl esters by the reported procedures.[1]

Experimental[3]

(−)-β-Dimethylamino-α-methylpropiophenone Acid Dibenzoyl-(−)-tartrate.—A solution of 26 g. (0.65 mole) of sodium hydroxide in 100 ml. of water was added to 122 g. (0.536 mole) of β-dimethylamino-α-methylpropiophenone hydrochloride. The liberated base was taken up in 150 ml. of ether, washed with water, and dried over anhydrous magnesium sulfate. The dry ether solution was concentrated *in vacuo* to yield 101.7 g. (0.53 mole) of β-dimethylamino-α-methylpropiophenone. The oily ketone and 200 g. (0.532 mole) of dibenzoyl-(−)-tartaric acid monohydrate were dissolved in 4 l. of acetone. The resulting solution was allowed to stir at room temperature until crystallization had begun and for an additional 18 hr. The solid was collected on a filter and washed with acetone and dried *in vacuo* to yield 157 g. of product. Successive concentration of the combined filtrate and wash solutions to 1 l., 250 ml., and 100 ml., yielded, respectively, 100.0 g., 12.0 g., and 7.3 g. of additional product. The total yield of product was 276.3 g. (94%); m.p. 112–117°; $[\alpha]^{25}D$ +52.0° (*c* 1, methanol).

A portion was recrystallized four times from acetone solution and melted at 116–117°; $[\alpha]^{25}D$ +57.2° (*c* 1, methanol).

Anal. Calcd. for $C_{12}H_{17}NO \cdot C_{18}H_{14}O_8$: C, 65.56; H, 5.69; N, 2.55. Found: C, 65.04; H, 5.84; N, 2.29.[4]

(+)-β-Dimethylamino-α-methylpropiophenone Acid Dibenzoyl-(+)-tartrate.—This salt was prepared in the same manner using dibenzoyl-(+)-tartaric acid in place of the dibenzoyl-(−)-tar-

(2) H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963).

(3) Melting points are uncorrected. The authors are indebted to W. L. Brown, H. L. Hunter, and G. L. Maciak for the microanalyses.

(4) This salt crystallizes as the hemihydrate and must be dried at 110° *in vacuo* before analysis.

taric acid. After five crystallizations from acetone the product melted at 116–117°; $[\alpha]^{25}D$ −57.3° (*c* 1.5, methanol).[5]

Anal. Calcd. for $C_{12}H_{17}NO \cdot C_{18}H_{14}O_8$: C, 65.56; H, 5.69; N, 2.55. Found: C, 65.48; H, 5.73; N, 2.41.

(−)-β-Dimethylamino-α-methylpropiophenone Hydrochloride.—(−)-β-Dimethylamino-α-methylpropiophenone acid dibenzoyl-(−)-tartrate (156.5 g., 0.285 mole) was treated with 56 ml. of 28% ammonia in 340 ml. of water. The liberated (−)-β-dimethylamino-α-methylpropiophenone was extracted with 1400 ml. of ether, washed with water (85 ml.), and dried with anhydrous magnesium sulfate. The dry ether solution was just acidified with anhydrous hydrogen chloride. The precipitated hydrochloride was filtered, washed with ether, and dried to yield 61.2 g. (94%) of product; $[\alpha]^{25}D$ −42° (*c* 1, water). The crude (−)-β-dimethylamino-α-methylpropiophenone hydrochloride was recrystallized from ethyl acetate–methanol solution to yield 52.9 g of purified hydrochloride which melted at 157–159°; $[\alpha]^{25}D$ −49° (*c* 1, water).[6]

(+)-α-Methyl-β-dimethylaminopropiophenone Hydrochloride.—This hydrochloride, prepared from (+)-β-dimethylamino-α-methylpropiophenone acid dibenzoyl-(+)-tartrate using the same procedure described for the (−)-isomer, melted at 153–155°; $[\alpha]^{25}D$ +47° (*c* 1, water).[7]

α-(+)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.—A solution containing 5.93 kg. (31 moles) of (−)-β-dimethylamino-α-methylpropiophenone in 50 l. of ether was added to a stirred solution of benzylmagnesium chloride prepared from 7.9 kg. (62 moles) of benzyl chloride, 1.9 kg. (78 g.-atoms) of magnesium, and 100 l. of ether. After complete addition the reaction mixture was stirred for 3 hr. and then decomposed by addition of 20 l. of saturated aqueous ammonium chloride solution. The ether solution was decanted from the inorganic material and dried over anhydrous sodium sulfate. The hydrochloride salt was prepared in the usual manner; and after two recrystallizations from methanol–ethyl acetate solution, the product melted at 231–233°; 6.05 kg. (61%). An authentic sample of the product melted at 234–235°; $[\alpha]^{25}D$ +52° (*c* 1, water). The mixture melting point with an authentic sample[1] was not depressed.

α-(−)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.—This compound was prepared from 5.8 g. (0.03 mole) of (+)-β-dimethylamino-α-methylpropiophenone, 7.9 g. (0.062 mole) of benzyl chloride, 1.9 g. (0.078 g.-atom) of magnesium, and 150 ml. of ether following the procedure for the α-(+)-isomer. The product was recrystallized twice from methanol–ethyl acetate solution and melted at 234–235°; $[\alpha]^{25}D$ −53.4° (*c* 1, water); 8.0 g. (69%). The mixture melting point with an authentic sample[1] was not depressed.

(5) S. Ose, Hakamatsu, and Y. Minaki, Japan Patent 4417 (1958) [*Chem. Abstr.*, **53**, 12310b (1958)], report this compound to melt at 122–125°.

(6) Ref. 2 reports the ketone from degradation studies to melt at 153–154°; $[\alpha]^{25}D$ −47 (*c* 1, water).

(7) This compound is not isolated in ref 5. Instead a dilute hydrochloric acid solution of the ketone is reduced to the (−)-aminocarbinol.

The Diphenylhydroxyborane Ester of *o*-Aminophenol[1]

HOWARD K. ZIMMERMAN

Department of Chemistry, University of the Pacific, Stockton, California

Received April 15, 1963

The synthesis of borimidazolines and related substances from aryl dihydroxyboranes and various *o*-arylene diamines is now well known,[2–5] and a new synthesis for some of them, which is useful for certain characterizations and analytical applications, has been pointed out recently.[6] At about the time this class of substances was discovered, it was reported that the corresponding ester amide of *o*-aminophenol, although melting at 99–101° and boiling at 140–145° (2 mm.), was unstable.[7] Thus, the borimidoxolines have remained a relatively unknown class of compounds, and their potential utility has not been realized. The present note reports the preparation of a closely related material which appears to be moderately stable.

Because of extensive experience of the stabilizing effect produced by N–B coordination in the boroxazolidines,[8] it seemed likely that the same principle might be found to operate to permit the preparation of a stable borinic ester of *o*-aminophenol.

The compound obtained did, in fact, appear to be stable over a period of five to ten weeks. However, after several months on the shelf, it was noted that the material had discolored markedly. Nevertheless, the pure substance could be readily recovered from the discolored material merely by repeating the recrystallization. Thus, although the presumed N–B coordination does have the predicted stabilizing effect, its protective influence is distinctly weaker than that observed in any other boroxazolidine or boroxazolidine analog that has yet been studied. This may be a result either of the sharply reduced basicity of the amino group substituent to an aromatic nucleus[9] or of a residual photosensitivity in the aromatic structure.

The question of the strength of the N–B coordination is not yet resolved. Whereas titration of *o*-aminophenol in 9:1 acetone–water gives a very sharp end point, covering eight pH units centering at pH 8.5, the acidic titration of the diphenylhydroxyborane ester in the same solvent gave a flat curve lying at lower pH values than the acidic branch of the curve for *o*-aminophenol itself. This result could be interpreted conveniently to signify an N–B coordination relatively very inert to hydrolysis. However, it might be also a result of extensive buffering action between the basic nitrogen atom and the acidic boron atom subsequent to a facile N–B cleavage, leaving the system to reflect only the acidic property of the phenol function. Available evidence does not now permit a choice between the two alternatives. Our laboratory intends no further work on this problem.

Experimental

Diphenylhydroxyborane ester of *o*-aminophenol was prepared by placing diphenylhydroxyborane from the hydrolysis[10] of 2.0 g. of B,B-diphenylboroxazolidine in 100 ml. of toluene together with 1.2 g. of *o*-aminophenol (Eastman, freshly recrystallized from benzene). The mixture was refluxed through a Dean–Stark trap until no further water could be removed. After distillation

(1) The support of this work by the U. S. Army Research Office (Durham) is gratefully acknowledged.

(2) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3076 (1958).

(3) R. L. Letsinger and S. B. Hamilton, *J. Am. Chem. Soc.*, **80**, 5411 (1958).

(4) E. Nylas and A. H. Soloway, *ibid.*, **81**, 2681 (1959).

(5) R. J. Brotherton and H. Steinberg, *J. Org. Chem.*, **26**, 4632 (1961).

(6) R. Neu, *Tetrahedron Letters*, No. **20**, 917 (1962).

(7) J. M. Sugihara and C. M. Bowman, *J. Am. Chem. Soc.*, **80**, 2443 (1958).

(8) (a) H. K. Zimmerman and H. Weidmann, *Ann.*, **628**, 37 (1959); (b) T. G. Psarras, H. K. Zimmerman, Y. Rasiel, and H. Weidmann, *ibid.*, **655**, 48 (1962); (c) H. K. Zimmerman, D. W. Mueller, and W. F. Semmelrogge, *ibid.*, **655**, 54 (1962); (d) R. K. Stump, H. K. Zimmerman, A. A. Schleppnik, and C. D. Gutsche, *ibid.*, in press.

(9) G. N. Chremos, H. K. Zimmerman, W. Cantrell, R. B. Meyer, and E. H. Zaetsch, *Z. Physik. Chem.* (Frankfurt), **35**, 129 (1962).

(10) G. N. Chremos, H. Weidmann, and H. K. Zimmerman, *J. Org. Chem.*, **26**, 1683 (1961).