Analgesics. The Absolute Configuration of α-(+)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane, *d*-Propoxyphene

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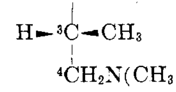
The configuration of *d*-propoxyphene has been determined by chemical transformations to be (2S:3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane (I).

α - (+) - 4 - Dimethylamino - 1,2 - diphenyl - 3-methyl-2-propionoxybutane, *d*-propoxyphene, has been reported to be effective in the relief of pain.[1] Pharmacological studies in rats failed to show the development of tolerance under the same conditions whereby ready tolerance to morphine may be shown.[2] After extensive studies at the Addiction Center in Lexington, Kentucky, Fraser and Isbell reported the addiction potential of *d*-propoxyphene to be substantially less than that of codeine.[3] The demonstration of the absence of physical dependence to repeated oral therapeutic doses using the allyl test has been reported.[4] After nearly five years of general use it has been decided that there has been no evidence of any danger regarding addiction liability.[5] Because of the widespread acceptance of *d*-propoxyphene as an analgesic, it was of interest to determine the absolute configuration of this molecule.

The α-(+)-isomer is the only one of the four optical isomers that possesses analgesic activity.[6] The α-(−)-isomer possesses clinically useful antitussive properties.[7] This paper reports the chemical transformations that permit assignment of the configuration of *d*-propoxyphene as (2S:3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane (I).



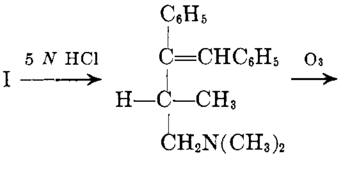
$$\begin{array}{c} OCOC_2H_5 \\ {}^{1}C_6H_5CH_2 \rightarrow {}^{2}C \leftarrow C_6H_5 \\ H \rightarrow {}^{3}C \leftarrow CH_3 \\ {}^{4}CH_2N(CH_3)_2 \end{array}$$

I

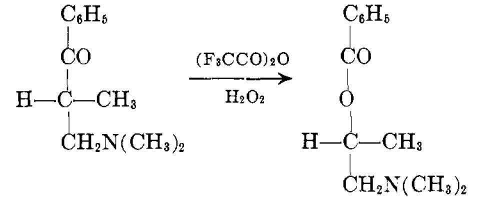
The method employed to relate the configuration of the asymmetric center at carbon-3 involved the degradation to a derivative of D-(−)-1-amino-2-propanol, the configuration of which has been related to D-(+)-glyceraldehyde.[8]

Acid hydrolysis and dehydration of I was accomplished to give 70% of (−)-4-dimethylamino-1.2-diphenyl-3-methyl-1-butene hydrochloride (II). The (+)-isomer of II was prepared from α-(−)-4-dimethylamino - 1,2 - diphenyl - 3 - methyl - 2 - propionoxybutane.

Ozonization of II yielded (−)-β-dimethylamino-α-methylpropiophenone (III) and benzaldehyde. Initial attempts at ozonization of the free base yielded a mixture from which only small amounts of benzoic acid could be isolated. The use of the hydrochloride, however, allowed the facile isolation of III in 43% yield. This (−)-amino ketone was found to be surprisingly stable to racemization either as the hydrochloride salt or the free base and by reaction with benzylmagnesium chloride it affords a stereoselective synthesis of α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol.[9]



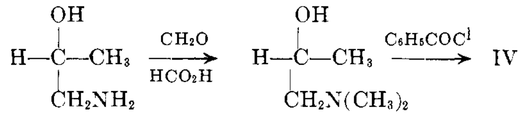
II



III IV D-(−)

The Baeyer–Villiger rearrangement has been shown to proceed with retention of configuration.[10] To the best of our knowledge, amino ketones have not been studied. In order to avoid amine oxide formation, the hydrochloride of III was employed in the rearrangement to yield 32% of (−)-1-dimethylamino-2-propyl benzoate hydrochloride (IV), m.p. 160–161°; $[\alpha]^{25}_D$ −62.8° (*c* 1, water).

D-(−)-1-Amino-2-propanol (V) was prepared according to the procedure of R. L. Clark and co-workers.[11]



V D-(−) VI D-(−)

Methylation with formic acid and formalin yielded D-(−)-1-dimethylamino-2-propanol (VI), which was isolated in crude form as an extremely hygroscopic hydrochloride. Reaction with benzoyl chloride gave crystalline D-(−)-1-dimethylamino-2-propyl benzoate (IV) in 80% yield, m.p. 160–161°; $[\alpha]^{25}_D$ −63.3°,

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[1] C. M. Gruber, Jr., *J. Am. Med. Assoc.*, **164**, 966 (1957).

[2] E. B. Robbins, *J. Am. Pharm. Assoc.*, **44**, 497 (1955).

[3] H. F. Fraser and H. Isbell, *Bull. Narcotics U. N. Dept. Social Affairs*, **12**, 9 (1960).

[4] S. M. Chernish and C. M. Gruber, Jr., *Antibiot. Med. Clin. Therapy*, **7**, 190 (1960).

[5] *Federal Register*, **27**, No. 58, 2770 (1962).

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

[7] H. A. Bickerman, *Med. Clin. N. Am.*, **45**, 805 (1961).

[8] D. E. Wolf, W. H. Jones, J. Valiant, and K. Folkers, *J. Am. Chem. Soc.*, **72**, 2820 (1950).

[9] A. Pohland, L. R. Peters, and H. R. Sullivan, *J. Org. Chem.*, **28**, 2483 (1963).

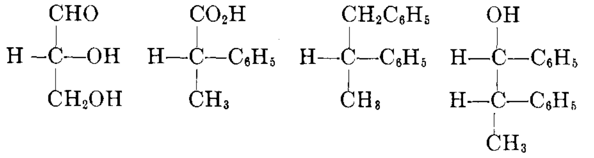
[10] (a) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950); (b) T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950); (c) K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

[11] Robert L. Clark, W. H. Jones, W. J. Raich, and Karl Folkers, *ibid.*, **76**, 3995 (1954).

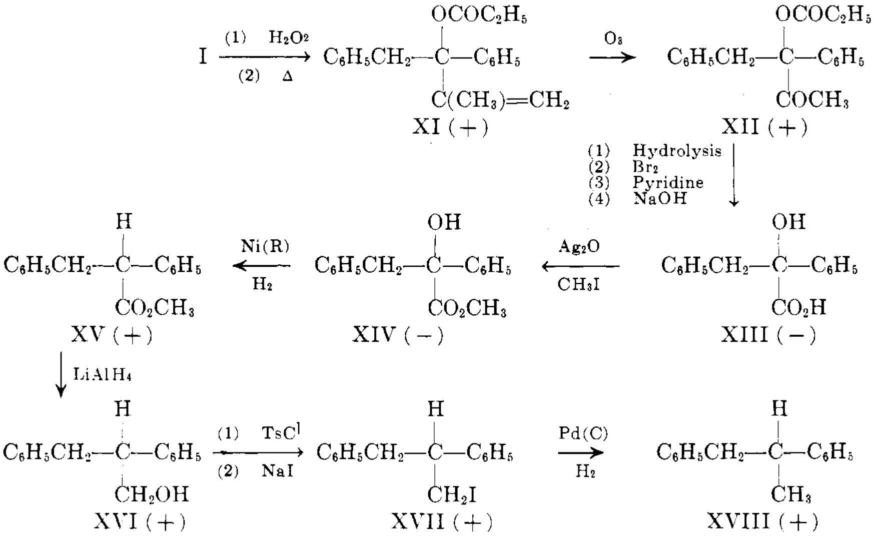
identical with the product obtained from the Baeyer–Villiger rearrangement of (−)-β-dimethylamino-α-methylpropiophenone (III).

The comparison of the sign and magnitude of the rotations of the synthetic product with that from the Baeyer–Villiger rearrangement shows that the oxidation occurs without racemization. The configuration of the 3-carbon center of I is thus related to that of D-glyceraldehyde and has the R-configuration.

In order to relate the configuration of the center at carbon-2, the method employed involved the established correlation between D-(+)-glyceraldehyde (VII) and D-(−)-1,2-diphenylpropane (IX). D-(+)-2-Phenylpropionic acid (VIII) has been related to D-(+)-glyceraldehyde.[12] D-(−)-1,2-Diphenylpropane (IX) has been related to D-(+)-2-phenylpropionic acid by Barnes and Juliano.[13] This compound was prepared by hydrogenolysis of D-(−)-*erythro*-1,2-diphenyl-1-propanol (X)[14] with copper chromium oxide catalyst at 200°. The same authors also prepared the compound by direct hydrogenation of D-(+)-methyldesoxybenzoin[15] with palladium catalyst in glacial acetic acid.



VII D-(+) VIII D-(+) IX D-(−) X D-(−)



The reactions and intermediates involved in the transformation of I to (+)-1,2-diphenylpropane (XVIII) are shown in the sequence XI through XVIII.

The N-oxide of I was prepared by means of hydrogen peroxide in methanol. Pyrolysis under vacuum at 140° afforded (+)-3,4-diphenyl-2-methyl-3-propionoxy-1-butene (XI) in 76% yield, $[\alpha]^{25}\mathrm{D}$ +97° (*c* 1.3, acetone). Ozonolysis of the butene (XI) gave (+)-3,4-diphenyl-3-propionoxy-2-butanone (XII) in 90% yield, $[\alpha]^{25}\mathrm{D}$ +182.7° (*c* 1.1, acetone).

Attempts to oxidize the methyl ketone XII with sodium hypochlorite were unsuccessful. Benzoic acid was the only acid product isolated in small yield from this reaction. Hydrolysis of XII gave (+)-3,4-diphenyl-3-hydroxy-2-butanone in 83% yield, $[\alpha]^{25}\mathrm{D}$ +141.0° (*c* 1.3, ethanol), which was transformed by the Kröhnke degradation[16] to (−)-2,3-diphenyl-2-hydroxypropionic acid (XIII) in 33% yield, $[\alpha]^{25}\mathrm{D}$ −13.7° (*c* 3.5, ethanol).

Hydroxy acid XIII was esterified by means of silver oxide and methyl iodide to give methyl (−)-2,3-diphenyl-2-hydroxypropionate (XIV), $[\alpha]^{25}\mathrm{D}$ −32.4° (*c* 3.4, chloroform).

The first report of the stereospecific hydrogenolysis of benzylic alcohols and ethers was by Bonner and coworkers.[17] Utilizing Raney nickel as the catalyst, methyl D-(−)-2-hydroxy-2-phenylpropionate was hydrogenolyzed to methyl D-(+)-2-phenylpropionate with 86% retention of configuration. Similarly methyl D-(+)-2-methoxypropionate yielded methyl D-(+)-2-phenylpropionate with 72% optical purity.

The hydrogenolysis of (+)-2-hydroxy-2-phenylbutane with Raney nickel was reported by Cram and Allinger[18] to yield (+)-2-phenylbutane (64% optical purity) with retention of configuration.

Barnes and Juliano[13] reported that hydrogenolysis of 1,2-diphenyl-1,2-propanediol with copper chromium oxide catalyst at 200° yielded 1,2-diphenylpropane with only 18% retention of configuration.

A recent investigation has shown the hydrogenolysis of the hydroxyl group of the stereoisomeric 3-phenylcholestanols with W-2 Raney nickel to proceed with greater that 90% retention of configuration.[19]

Initial studies on the hydrogenolysis of (−)-hydroxy ester (XIV) utilizing W-2 Raney nickel catalyst gave only low yields of methyl (+)-2,3-diphenyl-1-propionate (XV) and considerable unchanged starting material was recovered. In subsequent experiments, freshly prepared W-2 catalyst shaken one hour in ethanol with hydrogen at forty pounds pressure was found to give good yields of the desired product. Utilizing this catalyst in refluxing ethanol, the (+)-ester XV was obtained in 81% yield, $[\alpha]^{25}\mathrm{D}$ +90.5° (*c* 4.6, chloroform).

Lithium aluminum hydride reduction of (+)-ester XV gave (+)-2,3-diphenyl-1-propanol (XVI) in 88% yield, $[\alpha]^{25}\mathrm{D}$ +76.3° (*c* 5.3, chloroform). The (+)-propanol XVI was converted to the *p*-toluenesulfonate ester. Reduction of the tosylate with lithium aluminum hydride yielded only the starting alcohol XVI. The tosylate was allowed to react with sodium iodide in anhydrous acetone to yield (+)-2,3-diphenyl-1-iodopropane (XVII), $[\alpha]^{25}\mathrm{D}$ +16.6° (*c* 3.9, ethanol).

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(12) (a) M. L. Wolfrom, R. U. Lemieux, and S. M. Olin, *J. Am. Chem. Soc.*, **71**, 2870 (1949); (b) H. I. Bernstein and F. C. Whitmore, *ibid.*, **61**, 1324 (1939); (c) K. Mislow and M. Heffler, *ibid.*, **74**, 3668 (1952).

(13) R. A. Barnes and B. R. Juliano, *ibid.*, **81**, 6462 (1959).

(14) F. A. Abd Elhafez and D. J. Cram, *ibid.*, **74**, 5846 (1952).

(15) (a) J. B. Conant and G. H. Carlson, *ibid.*, **54**, 4048 (1932); (b) A. McKenzie, R. Roger, and G. O. Wills, *J. Chem. Soc.*, 779 (1926).

(16) F. Kröhnke, *Ber.*, **66**, 604 (1933).

(17) (a) W. A. Bonner, J. A. Zderic, and G. A. Casaletto, *J. Am. Chem. Soc.*, **74**, 5086 (1952); (b) W. A. Bonner, J. A. Zderic, *ibid.*, **78**, 3218 (1956).

(18) D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954).

(19) E. W. Garbisch, *J. Org. Chem.*, **27**, 3363 (1962).

Reduction of XVII in ethanol solution with hydrogen and 5% palladium on carbon as the catalyst gave L-(+)-2,3 diphenyl propane (XVIII) in 68% yield, $[\alpha]^{25}\text{D}$ +76.7° (*c* 2.3, chloroform).

The question of the optical purity of L-(+)-XVIII appeared important enough to warrant further investigation since the D-(−)-isomer XVIII had been reported by Barnes and Juliano[13] to have the optical rotation $[\alpha]^{19}\text{D}$ −63.5° (*c* 2.34, chloroform). It seemed likely that, in their hydrogenolysis of D-(−)-*erythro*-1,2-diphenyl-1-propanol (X) with copper chromium oxide catalyst at 200°, some elimination followed by hydrogenation may have occurred.

Utilizing the catalyst and reaction conditions employed in the conversion of XIV to XV, D-(−)-*threo*-1,2-diphenyl-1-propanol[20] was hydrogenolyzed to D-(−)-1,2-diphenylpropane (IX) in 89% yield, $[\alpha]^{25}\text{D}$ −76.3° (*c* 2.2, chloroform). Therefore, it would appear that the hydrogenolysis of XIV to XV has occurred with a high degree of retention of configuration.

Thus, it can be concluded that the (+)-1,2-diphenylpropane (XVIII) obtained by degradation is related to L-(−)-glyceraldehyde and, therefore, the asymmetric center at carbon-2 in α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane (I) can be assigned the S-configuration. The absolute configuration of the antitussive agent *l*-propoxyphene is, therefore, (2R:3S)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane.

Experimental[21]

(−)-4-Dimethylamino-1,2-diphenyl-3-methyl-1-butene Hydrochloride (II).—A reaction mixture containing 15.0 g. (0.04 mole) of α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride and 135 ml. of 5 *N* hydrochloric acid was refluxed for 2 hr. and then concentrated to dryness *in vacuo*. The solid residue was recrystallized three times from methanol–ethyl acetate solution to yield 8.5 g. (70%) of product melting at 189–190°; $[\alpha]^{25}\text{D}$ −33.7° (*c* 1, water).

Anal. Calcd. for $C_{19}H_{23}N \cdot HCl$: C, 75.60; H, 8.01; Cl, 11.75. Found: C, 75.30; H, 8.16; Cl, 11.76.

(+)-4-Dimethylamino-1,2-diphenyl-3-methyl-1-butene Hydrochloride.—A reaction mixture containing 50 g. (0.133 mole) of α-(−)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride and 450 ml. of 5 *N* hydrochloric acid was refluxed for 6 hr. and then concentrated to dryness *in vacuo*. After three recrystallizations from methanol–ethyl acetate solution, the product melted at 189–190°; 21 g. (54%); $[\alpha]^{25}\text{D}$ +34.3° (*c* 1, water).

Anal. Calcd. for $C_{19}H_{23}N \cdot HCl$: C, 75.60; H, 8.01; Cl, 11.75. Found: C, 75.77; H, 8.17; Cl, 11.81.

(−)-β-Dimethylamino-α-methylpropiophenone Hydrochloride (III).—A solution containing 25.0 g. (0.083 mole) of (−)-4-dimethylamino-1,2-diphenyl-3-methyl-1-butene hydrochloride, 150 ml. of methanol, and 1100 ml. of ethyl acetate was cooled to −20°. Excess ozone was bubbled through this solution during 2 hr., and the reaction mixture was then added with stirring to 250 ml. of ice-water and allowed to stand overnight at room temperature. The methanol and ethyl acetate were removed *in vacuo*. The aqueous residue was washed with 150 ml. of ether and made basic with ammonium hydroxide. The oil was extracted with ether and dried over anhydrous magnesium sulfate. The hydrochloride was prepared using anhydrous hydrogen chloride. After four recrystallizations from methanol–ethyl acetate solution, the product melted at 153–154°; 8.0 g. (43%); $[\alpha]^{25}\text{D}$ −47° (*c* 1, water).

Anal. Calcd. for $C_{12}H_{17}NO \cdot HCl$: C, 63.24; H, 7.97; Cl, 15.57. Found: C, 63.48; H, 8.00; Cl, 15.57.

The ether extract of the reaction mixture was evaporated to yield 7 g. of pale yellow oil having the characteristic odor of benzaldehyde. The 2,4-dinitrophenylhydrazone of a portion of this oil was prepared and melted at 230–232°. Benzaldehyde 2,4-dinitrophenylhydrazone is reported to melt at 237°.[22]

(−)-1-Dimethylamino-2-propyl Benzoate Hydrochloride (IV).—A solution of pertrifluoroacetic acid, prepared by the dropwise addition of 50.8 g. (0.36 mole) of trifluoroacetic anhydride to a solution containing 8.2 ml. (0.31 mole) of 90% hydrogen peroxide in 100 ml. of dichloromethane at 0°, was added dropwise to a mixture consisting of 11.8 g. (0.05 mole) of (−)-β-dimethylamino-α-methylpropiophenone hydrochloride, 130 g. (0.915 mole) of anhydrous disodium phosphate, and 300 ml. of dichloromethane while maintaining the temperature at 0–5° with external cooling in an ice bath. After complete addition, the reaction mixture was allowed to stir for 1 hr. and the temperature was raised to 10°. At this point the mixture thickened and finally solidified. After the mixture stood for 4 hr. at room temperature, 200 ml. of water was added in order to dissolve the solid material. The dichloromethane phase was separated from the aqueous phase and the latter was washed once with 100 ml. of dichloromethane. The combined dichloromethane solution was evaporated to dryness *in vacuo* and the residue dissolved in 100 ml. of 2 *N* hydrochloric acid. The acid solution was washed with 100 ml. of ether and made alkaline with concentrated ammonium hydroxide. The liberated base was taken up in ether and dried over anhydrous magnesium sulfate. The dry ether solution was saturated with anhydrous hydrogen chloride and the (−)-1-dimethylamino-2-propyl benzoate hydrochloride was recrystallized three times from methanol–ethyl acetate solution, m.p. 160–161°; 3.8 g. (32%); $[\alpha]^{25}\text{D}$ −62.8° (*c* 1, water).

Anal. Calcd. for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.13; H, 7.44; N, 5.75; Cl, 14.55. Found: C, 59.00; H, 7.54; N, 5.63; Cl, 14.80.

D-(−)-1-Dimethylamino-2-propanol Hydrochloride (VI).—A reaction mixture consisting of 2.7 g. (0.024 mole) of D-(−)-1-amino-2-propanol hydrochloride,[11] 1.6 g. (0.024 mole) of sodium formate, 8.3 g. (0.18 mole) of 100% formic acid, and 6.7 g. (0.077 mole) of 37% formalin was prepared with liberation of heat and evolution of gas. After the initial reaction had subsided, the solution was heated on the steam bath for 14 hr. and concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml. of 5 *N* hydrochloric acid and again concentrated to dryness *in vacuo*. The oily residue was then dissolved in an ethanol-benzene mixture and evaporated to dryness *in vacuo*. The semisolid residue was digested in ether until crystalline. The D-(−)-1-dimethylamino-2-propanol hydrochloride was extremely hygroscopic and recrystallization for analysis was not possible. The infrared spectrum indicated the presence of a tertiary aminocarbinol with no detectable amount of primary or secondary aminocarbinol; yield, 3.13 g.; $[\alpha]^{25}\text{D}$ −44.5° (*c* 1, methanol).

D-(−)-1-Dimethylamino-2-propyl Benzoate Hydrochloride (IV).—A reaction mixture consisting of 3.13 g. (0.022 mole) of D-(−)-1-dimethylamino-2-propanol hydrochloride, 7.1 g. (0.05 mole) of benzoyl chloride, 25 ml. of triethylamine, and 80 ml. of chloroform was prepared with considerable evolution of heat. After the initial reaction had subsided the mixture was refluxed for 1 hr. on the steam bath and then allowed to stand overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in 200 ml. of 2 *N* hydrochloric acid. The acidic solution was extracted with two 100-ml. portions of ether and made alkaline with concentrated ammonium hydroxide. The basic oil was extracted into ether and dried over anhydrous magnesium sulfate. The hydrochloride salt was prepared using anhydrous hydrogen chloride. The D-(−)-1-dimethylamino-2-propyl benzoate hydrochloride, after three recrystallizations from methanol–ethyl acetate solutions, melted at 160–161°; 4.2 g. (80%); $[\alpha]^{25}\text{D}$ −63.3° (*c* 1, water). The mixture melting point with (−)-1-dimethylamino-2-propyl benzoate hydrochloride from the Baeyer–Villiger rearrangement showed no depression, and the infrared spectra of the two compounds were identical.

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[20] Ref. 14. The authors are indebted to Dr. D. J. Cram for a sample of this compound.

[21] Melting points are uncorrected. The authors are indebted to W. L. Brown, H. L. Hunter, and G. L. Maciak for the microanalyses.

[22] I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. I, Rev. Ed., Oxford University Press, New York, N. Y., 1953, p. 237.

Anal. Calcd. for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.13; H, 7.44; N, 5.75; Cl, 14.55. Found: C, 59.26; H, 7.10; N, 5.98; Cl, 14.68.

α-(+)-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane N-Oxide Hydrochloride.—A solution prepared by the addition of 650 ml. of 30% hydrogen peroxide to 370 g. (1.09 moles) of α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane in 4.5 l. of methanol was allowed to stand at room temperature for 48 hr. The solution was evaporated almost to dryness *in vacuo* in the cold and the residual oil was redissolved in 5 l. of methanol. Platinum oxide, 0.4 g., was cautiously added to the methanol solution to destroy excess hydrogen peroxide. After complete reaction, the catalyst was removed by filtration, and the filtration was evaporated to dryness *in vacuo*. The residual oil was dissolved in 2 l. of ethyl acetate and a solution of 40 g. of anhydrous hydrogen chloride in 1 l. of ethyl acetate was added with stirring. The product crystallized when the solution was cooled and was recrystallized three times from methanol–ethyl acetate solution, m.p. 186–187°; 370 g. (87%); $[\alpha]^{25}D$ +20.2° (*c* 2, methanol).

Anal. Calcd. for $C_{22}H_{29}NO_3 \cdot HCl$: C, 67.42; H, 7.72; N, 3.57. Found: C, 67.20; H, 7.95; N, 3.42.

(+)-3,4-Diphenyl-2-methyl-3-propionoxy-1-butene (XI).—An aqueous suspension of 370 g. of α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane N-oxide hydrochloride in 1500 ml. of water was prepared and solid potassium carbonate was added with stirring until the aqueous phase was saturated. The free base was extracted with chloroform which was concentrated *in vacuo* to dryness to yield 320 g. (0.90 mole). The N-oxide was slowly heated in an oil bath at reduced pressure (0.50 mm.) to 140° and kept at this temperature for 30 min. The residual oil was cooled and dissolved in 2 l. of ether which was washed with 500 ml. of 2 *N* hydrochloric acid, twice with 500-ml. portions of water, and then dried over anhydrous magnesium sulfate. The product distilled at 152° (0.60 mm.); $n^{25}D$ 1.5466; 200 g. (76%); $[\alpha]^{25}D$ +97.0° (*c* 1.3, acetone).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.50; H, 7.56.

The material which collected in the Dry Ice–acetone trap during the pyrolysis was identified as N,N-dimethylhydroxylamine by preparation of its hydrochloride and oxalate salts. The hydrochloride melted at 104–105°. The reported melting point is 106.5–109°.[23] The oxalate salt melted at 147–148°.

Anal. Calcd. for $C_4H_9NO_5$: C, 31.79; H, 6.00; N, 9.27. Found: C, 32.12; H, 6.30; N, 8.91.

(+)-3,4-Diphenyl-3-propionoxy-2-butanone (XII).—A solution consisting of 45.0 g. (0.153 mole) of (+)-3,4-diphenyl-2-methyl-3-propionoxy-1-butene in 1 l. of ethyl acetate was allowed to react with an excess of ozone while maintaining the reaction temperature below −50° with a Dry Ice–acetone bath. Upon the appearance of a characteristic blue color the introduction of ozone was terminated. The reaction mixture was poured into an ice–water mixture and allowed to stand overnight. A dilute solution of sodium bisulfite was added dropwise with stirring until a negative starch–iodide test was obtained. The ethyl acetate layer was separated and the aqueous phase was extracted twice with ether. The organic extracts were combined, washed twice with water, and dried over anhydrous magnesium sulfate. The product distilled at 156–157° (0.50 mm.); 41.0 g. (90%); $[\alpha]^{25}D$ +182.7° (*c* 1.1, acetone).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.17; H, 6.97.

(+)-3,4-Diphenyl-3-hydroxy-2-butanone.—A solution consisting of 32.5 g. (0.11 mole) of (+)-3,4-diphenyl-3-propionoxy-2-butanone, 1 l. of 5 *N* hydrochloric acid and 1 l. of ethanol was refluxed with stirring for 20 hr. The ethanol was removed *in vacuo* and the aqueous solution extracted with three 200-ml. portions of ether. The ether extract was washed once with water and then dried over anhydrous magnesium sulfate. The product distilled at 148° (0.50 mm.); $n^{25}D$ 1.5660; 21.9 g. (83%); $[\alpha]^{25}D$ +141.0° (*c* 1.3, ethanol).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.09; H, 6.78.

(−)-2,3-Diphenyl-2-hydroxypropionic Acid (XIII).—A solution of 45.0 g. (0.28 mole) of bromine in 100 ml. of glacial acetic acid was added dropwise with stirring to a solution of 60.0 g. (0.25 mole) of (+)-1,2-diphenyl-2-hydroxy-3-butanone in 200 ml. of glacial acetic acid. After complete addition the green reaction solution was stirred for 1 hr. at room temperature and then evaporated to dryness *in vacuo*. The residue oil was dissolved in 600 ml. of dry pyridine, and the resulting mixture was heated at steam-bath temperature with stirring for 1 hr. and allowed to cool to room temperature. The pyridine was removed by vacuum distillation at steam-bath temperature, and the residual oil was suspended in a solution containing 60 g. of sodium hydroxide in 900 ml. of water. This mixture was stirred for 2 hr. at steam-bath temperature, cooled, extracted with two 200-ml. portions of chloroform, and then acidified with concentrated hydrochloric acid. The cooled acidic solution was extracted with three 500-ml. portions of ether. The combined ether extract was dried over anhydrous magnesium sulfate. The product after removal of the ether and three recrystallizations from aqueous ethanol solutions melted at 145–146°; 20.0 g. (33%); $[\alpha]^{25}D$ −13.7° (*c* 3.5, ethanol).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.53; H, 5.77.

Methyl (−)-2,3-Diphenyl-2-hydroxypropionate (XIV).—A mixture consisting of 18.0 g. (0.075 mole) of (−)-2,3-diphenyl-2-hydroxypropionic acid, 40.0 g. (0.172 mole) of silver oxide and 200 ml. of methyl iodide was refluxed with stirring for 3 hr. After the mixture had cooled the inorganic material was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The product after three recrystallizations from ether–petroleum ether solutions melted at 102–103°; 15.0 g. (78%); $[\alpha]^{26}D$ −32.4° (*c* 3.4, chloroform).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.29; H, 6.17.

Methyl (+)-2,3-Diphenylpropionate (XV).—Freshly prepared W-2 Raney nickel, 60 g., was shaken for 1 hr. in 200 ml. of absolute ethanol with hydrogen at 40-p.s.i. pressure. A mixture containing the hydrogen pretreated catalyst in ethanol and 8.0 g. (0.031 mole) of methyl (+)-2,3-diphenyl-2-hydroxypropionate was stirred at reflux temperature for 8 hr. The catalyst was removed by filtration of the cooled mixture and the filtrate was evaporated to dryness *in vacuo*. The residual oil was dissolved in 40 ml. of petroleum ether and allowed to crystallize. Filtration yielded 1.40 g. of starting material, methyl (+)-2,3-diphenyl-2-hydroxypropionate, m.p. 102–103°. The filtrate was evaporated to dryness *in vacuo* and the residual oil distilled. The product distilled at 123–124° (0.20 mm.); $n^{25}D$ 1.5518; 6.0 g. (81%); $[\alpha]^{25}D$ +90.5° (*c* 4.6, chloroform).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.98; H, 6.62.

Methyl (+)-2,3-Diphenyl-1-propanol (XVI).—A solution of 10.2 g. (0.0418 mole) of methyl (+)-2,3-diphenyl-2-hydroxypropionate in 40 ml. of anhydrous ether was added dropwise to a suspension of 1.7 g. (0.045 mole) of lithium aluminum hydride in 110 ml. of anhydrous ether at such a rate as to maintain gentle reflux. After complete addition the reaction mixture was refluxed for 3 hr., cooled, and decomposed by careful addition of a saturated ammonium chloride solution. The ether solution was decanted from the inorganic solid and the latter was washed twice with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The product distilled at 128° (0.20 mm.); $n^{25}D$ 1.5742; 7.80 g. (88%); $[\alpha]^{25}D$ +76.3° (*c* 5.3, chloroform).

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.59. Found: C, 85.03; H, 7.66.

(+)-2,3-Diphenyl-1-propyl Tosylate.—A solution consisting of 7.80 g. (0.0368 mole) of (+)-2,3-diphenyl-1-propanol in 200 ml. of dry pyridine was cooled to 0° in an ice bath. *p*-Toluenesulfonyl chloride, 60 g. (0.32 mole), was then added portionwise with stirring while keeping the temperature below 10°. After complete addition the reaction solution was allowed to stand at room temperature for 18 hr. It was then poured into 500 ml. of ice–water, and this mixture was extracted with three 300-ml. portions of ether. The combined ether solution was washed twice with 300-ml. portions of water, once with 300 ml. of 2 *N* hydrochloric acid, once with 300 ml. of 5% sodium bicarbonate solution, and twice with 300-ml. portions of water. The ether solution was dried over anhydrous magnesium sulfate. The solid product after three recrystallizations from acetone–petroleum ether melted at 89–90°; 12.6 g. (93%); $[\alpha]^{25}D$ +40.2° (*c* 2.4, acetone).

Anal. Calcd. for $C_{22}H_{22}O_3S$: C, 72.09; H, 6.05; S, 8.75. Found: C, 71.99; H, 6.01; S, 9.01.

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[23] A. C. Cope, T. T. Foster, and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949).

(+)-2,3-Diphenyl-1-iodopropane (XVII).—A mixture consisting of 7.4 g. (0.02 mole) of (+)-2,3-diphenyl-1-propyl tosylate, 16.5 g. (0.11 mole) of sodium iodide, and 200 ml. of anhydrous acetone was refluxed for 20 hr. with stirring. The precipitated sodium *p*-toluenesulfonate was removed from the cooled mixture by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residual material was suspended in 100 ml. of water, and this mixture was extracted with three 100-ml. portions of ether. The combined ether solution was washed with two 100-ml. portions of water and dried over anhydrous magnesium sulfate. The crystalline product, after two recrystallizations from petroleum ether, melted at 54–55°; 6.35 g. (97%); $[\alpha]^{25}D$ +16.6° (*c* 3.9, ethanol).

Anal. Calcd. for $C_{15}H_{15}I$: C, 55.91; H, 4.69; I, 39.39. Found: C, 56.10; H, 4.72; I, 39.11.

(+)-2,3-Diphenylpropane (XVIII).—A mixture composed of 6.35 g. (0.02 mole) of (+)-2,3-diphenyl-1-iodopropane, 3.0 g. of sodium bicarbonate, and 150 ml. of absolute ethanol was hydrogenated at 25° over 5.0 g. of 5% palladium on carbon. Hydrogen absorption ceased after 10 hr. The catalyst was collected on a filter and the filtrate evaporated to dryness *in vacuo*. The residue was suspended in 100 ml. of water and extracted with two 100-ml. portions of ether. The combined ether solution was washed with 100 ml. of water and dried over anhydrous magnesium sulfate. The product distilled at 85° (0.30 mm.); $n^{25}D$ 1.5558; 2.60 g. (68%); $[\alpha]^{25}D$ +76.7° (*c* 2.3, chloroform).

Anal. Calcd. for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.63; H, 8.29.

The infrared and n.m.r. spectra of this compound were identical with those of (±)-2,3-diphenylpropane [b.p. 119° (2 mm.); $n^{25}D$ 1.5570] prepared by the procedure of Tuot and Guyard.[24]

D-(−)-1,2-Diphenylpropane.—A reaction mixture containing 1.4 g. (0.0066 mole) of (−)-*threo*-1,2-diphenyl-1-propanol,[20] 30 g. of hydrogen pretreated W-2 Raney nickel catalyst as used in the preparation of XV, and 100 ml. of absolute ethanol was heated at reflux temperature for 8 hr. The catalyst was collected on a filter and the filtrate concentrated to dryness *in vacuo*. The residual oil in 50 ml. of ether was washed with 50 ml. of water and dried over anhydrous magnesium sulfate. The product distilled at 88° (0.5 mm.); $n^{25}D$ 1.5553; 1.15 g. (89%); $[\alpha]^{25}D$ −76.3° (*c* 2.2, chloroform).

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[24] M. Tuot and M. Guyard, *Bull. soc. chim. France*, 1087 (1947).

A Synthesis of Quadricyclo[2.2.1.0^{2,6}.0^{3,5}]heptane (Quadricyclene) *via* Photochemical Decomposition of 6,7-Diazaquadricyclo[3.2.1.1^{3,8}.0^{2,4}]non-6-ene.

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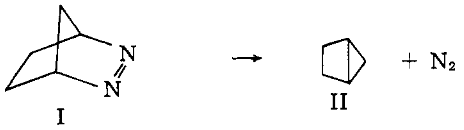
The product of homoconjugate Diels–Alder addition of ethyl azocarboxylate to norbornadiene has been converted by decarboxylation and oxidation to 6,7-diazaquadricyclo[3.2.1.1^{3,8}.0^{2,4}]non-6-ene (V).[1] The ultraviolet, infrared, and nuclear magnetic resonance spectra of this bridged polycyclic azo compound are discussed, and its thermal conversion to norbornadiene is described. Ultraviolet irradiation of V yielded quadricyclene (VI).[2]

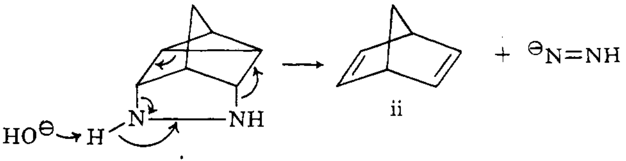
It is known that the thermolysis of cyclic azo compounds proceeds *via* loss of nitrogen with the formation of a diradical.[5] Subsequent reactions of the diradical include fragmentation,[6a] olefin formation,[6b] and intramolecular bond formation.[6c,7] Representative of the last reaction is Criegee's synthesis of bicyclo[2.1.0]pentane (II) from 2,3-diazabicyclo[2.2.1]hept-2-ene (I).[7]



I II

As part of a study aimed at assessing the usefulness of this reaction in the synthesis of other polycyclic fused ring systems, the synthesis of 6,7-diazaquadricyclo[3.2.1.1^{3,8}.0^{2,4}]non-6-ene (V) was undertaken, and its subsequent conversion to quadricyclene (VI) was investigated.

The starting point for synthesis of V was the formation of ethyl 6,7-diazaquadricyclo[3.2.1.1^{3,8}.0^{2,4}]-nonane-6,7-dicarboxylate (III) from the homoconjugate Diels–Alder addition of ethyl azocarboxylate to norbornadiene. It was found in the present study, and also by Cristol, *et al.*,[8] that this reaction yields a 1:1 mixture of adducts III and IIIa which are separable by chromatography on alumina. Decarboxylation of III in methanolic potassium hydroxide gave a low yield (*ca.* 30%) of the corresponding hydrazine IV. Difficulties inherent in this decarboxylation step arose from the instability of the product as evidenced by the concomitant formation of nonnitrogenous hydrocarbons,[9] and from the unfavorable properties of hydrazine IV (it is water soluble, readily air oxidized, and is absorbed on the potassium carbonate formed as the decarboxylation proceeds). Compound IV was characterized as the crystalline N,N-diacetyl derivative IVa. Oxidation of IV was effected either by means of cupric chloride or, more conveniently, by mercuric oxide. With



i ii

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[1] For nomenclature, see S. J. Cristol and R. L. Snell, *J. Am. Chem. Soc.*, **80**, 1950 (1958).

[2] The direct photochemical transformation of norbornadiene into quadricyclene has been reported by Dauben and Cargill[3] and also by Hammond, *et al.*[4]

[3] W. G. Dauben and R. L. Cargill, *Tetrahedron*, **15**, 197 (1961).

[4] G. S. Hammond, N. J. Turro, and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961).

[5] S. G. Cohen and C. H. Wang, *ibid.*, **77**, 3628 (1955).

[6] (a) M. G. Kuzmin, Abstract, Ph.D. thesis, State University of Moscow, U.S.S.R., 1959; (b) S. G. Cohen, S. Hsiao, E. Saklad, and C. H. Wang, *J. Am. Chem. Soc.*, **79**, 4400 (1957); (c) S. G. Cohen, R. Zand, and C. Steel, *ibid.*, **83**, 2895 (1961).

[7] R. Criegee and A. Rimmelin, *Ber.*, **90**, 414 (1957).

[8] S. J. Cristol, E. L. Alfred, and D. L. Wetzel, *J. Org. Chem.*, **27**, 4058 (1962). The structures of III and IIIa are treated in this paper.

[9] The destruction of hydrazine IV in base may involve generation of the diimide anion and norbornadiene (i → ii).