[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Analgesics: α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane-N-methyl-C^{14}

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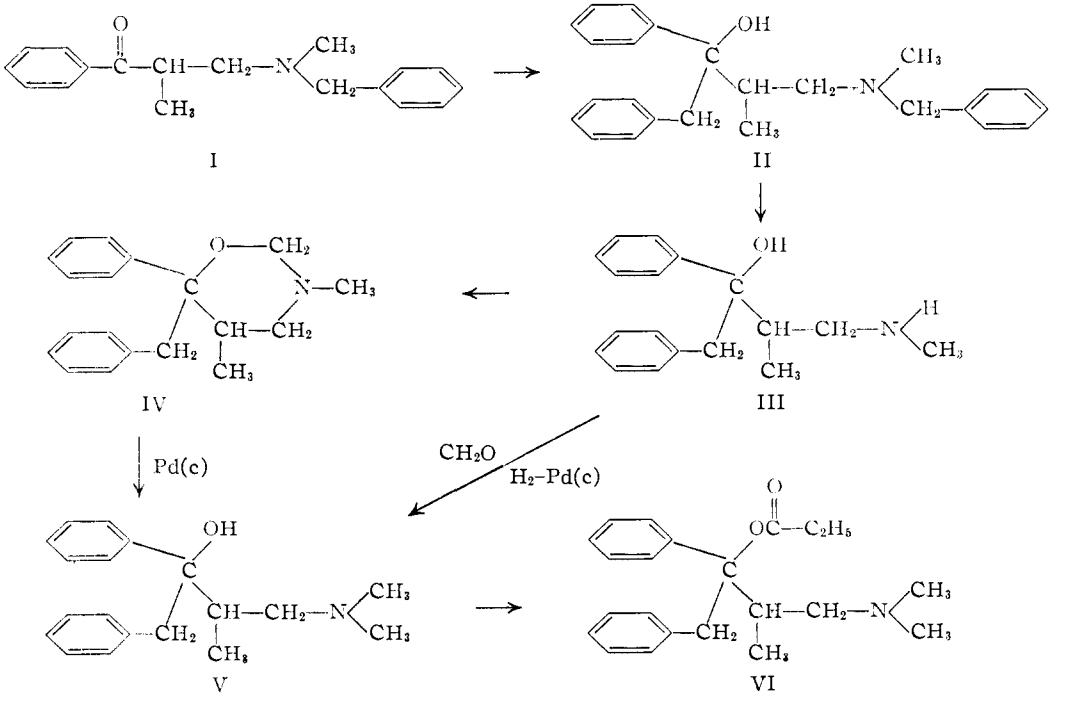
The preparation of α-*dl*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane-N-methyl-C^{14} (VI) is described. β-Benzylmethylamino-α-methylpropiophenone (I) and benzylmagnesium chloride gave both α-*dl*- and β-*dl*-4-benzylmethylamino-1,2-diphenyl-3-methyl-2-butanol (II). Catalytic debenzylation of the α-*dl*-isomer followed by reductive methylation using radio-formaldehyde yielded α-*dl*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol-N-methyl-C^{14}. Acylation with propionic anhydride yielded VI.

α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane has been reported to give analgesic action in animals[1] and in humans.[2] Studies in rats failed to show the development of tolerance under the same conditions whereby ready development of tolerance to morphine may be shown.[3] The α-*d*-isomer was found to possess all of the analgesic activity.[4] The α-*d*-isomer is equivalent to codeine on oral administration to humans with considerably fewer side reactions.[5,6] Administration of therapeutic doses of the α-*dl*- and α-*d*-isomer, for periods up to two years, has shown no development of tolerance to the analgesic effect. Abstinence symptoms were not observed when antipyretic analgesics were substituted.[6] From studies at the Addiction Center in Lexington, Frazier and Isbell estimated that the addiction liability of these isomers is no greater, and is probably less, than that of codeine.[7] These studies are being continued.

In view of these promising results, it was decided to prepare α-*dl*-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane labeled with carbon^{14} in order to facilitate a study of the metabolic fate of this compound. Metabolism studies on known analgesics as well as other drugs have demonstrated that N-demethylation is one of the metabolic pathways for a large number of compounds. A recent review[8] on the metabolic fate of morphine, diacetylmorphine and codeine has appeared. It seemed likely that the most useful compound for this study would be the one containing a carbon^{14} dimethylamino group. α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane-N-methyl C^{14} (VI) was prepared as shown by the accompanying equations.



β-Benzylmethylamino-α-methylpropiophenone and benzylmagnesium chloride gave 25% α-*dl*-4-benzylmethylamino-1,2-diphenyl-3-methyl-2-buta-

(1) A. Pohland and H. R. Sullivan, THIS JOURNAL, **75**, 4458 (1953).
(2) C. M. Gruber, *J. Lab. Clin. Med.*, **44**, 805 (1954).
(3) E. B. Robbins, *J. Amer. Pharm. Assoc.*, **44**, 497 (1955).
(4) A. Pohland and H. R. Sullivan, THIS JOURNAL, **77**, 3400 (1955).
(5) C. M. Gruber, C. Miller, J. Finneran and S. Chernish, *J. Pharmacol. Exptl. Therap.*, in press.
(6) C. M. Gruber, *et al.*, *J. Amer. Med. Assoc.*, in press.
(7) H. F. Frazier and H. Isbell, Addendum to Minutes of the 17th Meeting of the Committee on Drug Addiction and Narcotics, National Research Council, Washington, D. C., January 30–31, 1956, p. 1–13.
(8) H. Peterson, *Bull. Narcotics*, **7**, 23 (1955).

nol (II) and 39% of the β-*dl*-isomer which were separated by fractional crystallization of their hydrochlorides. It is of interest to note that the reaction of β-dimethylamino-α-methylpropiophenone with benzylmagnesium chloride yielded 75% of the α-stereoisomer and 15% of the β-stereoisomer.[1] Catalytic reduction of α-II and β-II in acetic acid solution with 5% palladium-on-carbon catalyst gave, respectively, α- and β-4-methylamino-1,2-diphenyl-3-methyl-2-butanol.

The attempted reductive methylation of α-III by means of formic acid and formalin yielded α-6-benzyl-3,5-dimethyl-6-phenyl-tetrahydro-1,3-oxazine (IV) instead of the expected α-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (V). Catalytic hydrogenation of α-IV in acetic acid solution with 5% palladium on carbon yielded α-V. Thus the stereochemical relationship of the α- and β-benzylmethylaminocarbinols (II) and the α- and β-methylaminocarbinols (III) to the previously reported α- and β-dimethylaminocarbinols[1] (V) is established.

Reductive methylation of α-III with radioformaldehyde and 5% palladium on carbon in ethanol yielded 4-dimethyl-1,2-diphenyl-3-methyl-2-butanol-N-methyl-C^{14} (V). The carbinol hydrochloride (V) was acylated using propionic anhydride and pyridine to yield α-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride N-methyl-C^{14}. The radiochemical yield from formaldehyde-C^{14} was 40%.

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Experimental[9]

β-Benzylmethylamino-α-methylpropiophenone.—A reaction mixture containing 114.8 g. (0.73 mole) of benzylmethylamine hydrochloride, 33.0 g. (1.10 moles) of paraformaldehyde, 98.0 g. (0.73 mole) of propiophenone, 220 ml. of absolute ethanol and 2 ml. of concentrated hydrochloric acid was refluxed for three hours. The reaction solution was cooled, the ethanol removed *in vacuo*, and the oily residue dissolved in 300 ml. of water. After washing with 100 ml. of ether, the aqueous solution was made alkaline with concentrated ammonium hydroxide. An ether solution of the base was dried over anhydrous magnesium sulfate and distilled; b.p. 147–148° (0.5 mm.); $n^{25}D$ 1.5532; 108.0 g. (49%).

Anal. Calcd. for $C_{18}H_{21}NO$: N, 5.24. Found: N, 5.37.

α-*dl*- and β-*dl*-4-Benzylmethylamino-1,2-diphenyl-3-methyl-2-butanol.—Benzylmagnesium chloride was prepared from 83.5 g. (0.66 mole) of benzyl chloride, 41.0 g. (1.70 moles) of magnesium and 1500 ml. of anhydrous ether. The Grignard solution was stirred at room temperature during the dropwise addition of 108.0 g. (0.40 mole) of β-benzylmethylamino-α-methylpropiophenone. The reaction mixture was allowed to stir overnight and then decomposed by addition of 140 ml. of saturated ammonium chloride solution. The ether solution was decanted from the solid and the latter washed twice with 200-ml. portions of ether. The combined ether extract was dried over anhydrous magnesium sulfate and then saturated with anhydrous hydrogen chloride. The mixture of hydrochloride salts was then dissolved in 1.3 l. of hot acetone and chilled to yield the β-*dl*-4-benzylmethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride. After three recrystallizations from methanol–ethyl acetate solution, the product melted at 114–115°; 62.0 g. (39%).

Anal. Calcd. for $C_{25}H_{29}NO{\cdot}HCl$: C, 75.83; H, 7.65; N, 3.54. Found: C, 75.60; H, 7.72; N, 3.60.

(9) All melting points are uncorrected.

The acetone filtrate, upon concentration and dilution with ethyl acetate, yielded the α-*dl*-4-benzylmethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride which, after three recrystallizations from a methanol–ethyl acetate–ether mixture, melted at 176–177°; 40.5 g. (25%).

Anal. Calcd. for $C_{25}H_{29}NO{\cdot}HCl$: C, 75.83; H, 7.65; N, 3.54. Found: C, 75.88; H, 7.85; N, 3.44.

α-*dl*-4-Methylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.—A reaction mixture of 12.0 g. (0.03 mole) of α-*dl*-4-benzylmethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, 100 ml. of glacial acetic acid and 6.0 g. of 5% palladium-on-carbon was reduced with hydrogen at low pressure. After 0.03 mole of hydrogen was absorbed, the catalyst was removed by filtration, and the filtrate concentrated to dryness *in vacuo*. The product, recrystallized twice from methanol–ethyl acetate solution, melted at 157–158°; 7.3 g. (80%).

Anal. Calcd. for $C_{18}H_{23}NO{\cdot}HCl$: C, 70.68; H, 7.91; N, 4.58. Found: C, 70.40; H, 7.81; N, 4.50.

β-*dl*-1,2-Diphenyl-4-methylamino-3-methyl-2-butanol Hydrochloride.—The procedure was the same as for the preparation of the α-*dl*-isomer. The product melted at 214–215°; (88%).

Anal. Calcd. for $C_{18}H_{23}NO{\cdot}HCl$: C, 70.68; H, 7.91; N, 4.58. Found: C, 70.58; H, 7.86; N, 4.66.

α-*dl*-6-Benzyl-3,5-dimethyl-6-phenyltetrahydro-1,3-oxazine Hydrochloride.—A mixture of 4.0 g. (0.013 mole) of α-*dl*-1,2-diphenyl-3-methyl-4-methylamino-2-butanol hydrochloride, 25 ml. of 35–40% formalin and 56 ml. of formic acid was warmed on the steam-bath overnight. The solution was then evaporated *in vacuo* to dryness to give a white solid residue. Addition of dilute ammonium hydroxide yielded the base which was dried in ether solution over anhydrous magnesium sulfate. The hydrochloride was prepared using anhydrous hydrogen chloride. The product, after two recrystallizations, melted at 223–224°; 2.9 g. (71%).

Anal. Calcd. for $C_{19}H_{23}NO{\cdot}HCl$: C, 71.79; H, 7.61; N, 4.41. Found: C, 72.05; H, 7.71; N, 4.15.

β-*dl*-6-Benzyl-3,5-dimethyl-6-phenyltetrahydro-1,3-oxazine Hydrochloride.—The procedure was the same as for the preparation of the α-*dl*-isomer. The product, recrystallized twice from methanol–ethyl acetate, melted at 226–227°; (92%).

Anal. Calcd. for $C_{19}H_{23}NO{\cdot}HCl$: C, 71.79; H, 7.61; N, 4.41. Found: C, 72.04; H, 7.61; N, 4.13.

Hydrogenation of α-*dl*-6-Benzyl-3,5-dimethyl-6-phenyltetrahydro-1,3-oxazine Hydrochloride to α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride.—A reaction mixture of 2.0 g. (0.0065 mole) of α-*dl*-6-benzyl-3,5-dimethyl-6-phenyltetrahydro-1,3-oxazine hydrochloride, 50 ml. of glacial acetic acid and 2.0 g. of 5% palladium-on-carbon was reduced with hydrogen at low pressure. After one equivalent of hydrogen had been absorbed, the catalyst was removed by filtration, and the filtrate concentrated to dryness *in vacuo*. The α-*dl*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride, after two recrystallizations from methanol–ethyl acetate, melted at 231–232° dec.; 1.3 g. (65%). A mixture melting point with an authentic sample was not depressed.

α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride-N-methyl-C^{14}.—The reductive methylation of α-*dl*-1,2-diphenyl-3-methyl-4-methylamino-2-butanol hydrochloride with radio-formaldehyde was carried out by the procedure used for the preparation of N-methyl-C^{14}-erythromycin from des-methylerythromycin.[10] A solution of 520 mg. (1.7 mmole.) of α-*dl*-1,2-diphenyl-3-methyl-4-methylamino-2-butanol hydrochloride and 1.9 mmole. of formaldehyde-C^{14} (1.3 mc.)[11] in absolute alcohol was hydrogenated at 25° and one atmosphere over 500 mg. of 5% palladium-on-carbon. Hydrogen absorption ceased after seven hours. After removal of the catalyst by filtration, the product was recovered by evaporation of the solvent. The yield was quantitative. The crude product, which was not further purified, melted at 229–230°.

α-*dl*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propion-

(10) E. H. Flynn, H. W. Murphy and R. E. McMahon, THIS JOURNAL, **77**, 3104 (1955).

(11) From Baker and Adamson Company.

oxybutane Hydrochloride-N-methyl-C^{14}.—One-half of the crude radioactive *α-dl*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride was converted to its propionyl ester. A reaction mixture containing 272 mg. (0.85 mmole.) of the radioactive carbinol hydrochloride, 1 ml. of propionic anhydride and 0.5 ml. of triethylamine was heated under nitrogen at 82° for 8 hours. To the cooled reaction mixture was added 30 ml. of ether, 10 ml. of water and 700 mg. of sodium bicarbonate. The ether layer was removed and treated with charcoal and anhydrous magnesium sulfate in a centrifuge cone. The solids were removed by centrifugation and the supernatant solution evaporated to dryness. The residue was stored in a vacuum overnight to ensure volatilization of any residual triethylamine. The crude base was then dissolved in 25 ml. of ether and the solution saturated with dry hydrogen chloride. The solution was evaporated to dryness and the residue recrystallized three times from ethyl acetate–ether solution. The yield was 137 mg., m.p. 168–170°, and the specific activity 1.9 mc./mg. The radiochemical yield from formaldehyde-C^{14} was 40%.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Cyclic Dienes. XIX. 2,3-Dimethylenebicyclo[2.2.2]octane[1]

BY WILLIAM J. BAILEY AND WILLIAM B. LAWSON[2]

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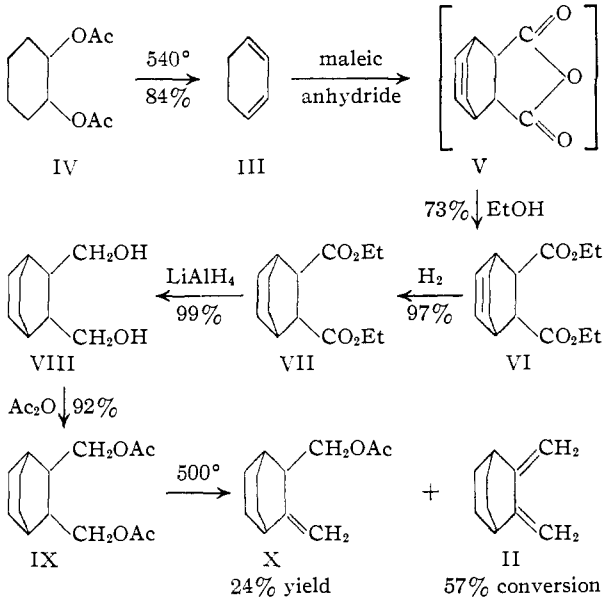
A convenient synthesis of 1,3-cyclohexadiene in an 84% yield was developed by the pyrolysis of a mixture of *cis*- and *trans*-1,2-diacetoxycyclohexane. The cyclohexadiene was then used as a starting material for a five-step synthesis of 2,3-dimethylenebicyclo[2.2.2]octane. The final step in the preparation of the latter diene was a pyrolysis of a diacetate, which produced the desired diene in a 78% yield. The structure of this diene was proved by ultraviolet and infrared absorption spectra and by conversion to two solid derivatives through Diels–Alder reactions.

In a research program designed to determine the correlation between the structure and the physical properties of all-*cis* polymers related in structure to natural rubber, a series of cyclic dienes have been prepared. In order to determine the effect of a bulky, yet compact, side group containing a bicyclic structure, 2,3-dimethylenebicyclo[2.2.1]heptane (I) was prepared.[3] However, since the diene I contained a very rigid bicyclic system that would not stabilize an endocyclic double bond in the same manner as a cyclohexane ring,[4] the polymer derived from the diene I consisted of at least 30% 1,2-addition. Since this polymer differed substantially in structure from the all-*cis* all-1,4 poly-1,2-dimethylenecyclohexane, it was difficult to determine the exact effect of the bicyclo ring system on the properties of an all-*cis* polymer. For this reason the synthesis of the more flexible and more symmetrical 2,3-dimethylenebicyclo[2.2.2]-octane (II) was undertaken. It was hoped that the fused six-membered rings would permit some stabilization of an endocyclic double bond.

The most convenient starting material for the synthesis of II appeared to be 1,3-cyclohexadiene (III). No wholly satisfactory method of synthesis has been reported for this very simple and common cyclic diene. Hine and co-workers[5] recently reviewed many of the previously reported syntheses of III and concluded that either a highly impure product was produced or the method was extremely tedious. They did conclude, however, that the most convenient preparation involved the treatment of cyclohexene dibromide with sodium hydroxide in ethylene glycol solution to give a 60% yield of 1,3-cyclohexadiene (III) (80% purity) contaminated with benzene and cyclohexene. Since the pyrolysis of esters had been so successful



for the synthesis of other cyclic dienes,[6,7] the synthesis of III by this procedure was investigated. Rice and Stallbaumer[8] previously had prepared III in a 50% yield by the pyrolysis of 1,2-diacetoxycyclohexane (IV) in a quartz tube at 750° and 6 mm. pressure. Even at this relatively high temperature, their product contained less than 5% benzene. Stork, van Tamelen, Friedman and Burgstahler[9] also pyrolyzed the distearate of 1,2-cyclohexanediol in the liquid phase to produce III, which was not isolated but was converted directly to its maleic anhydride adduct in a 42% over-all yield.

When a mixture of *cis*- and *trans*-1,2-diacetoxy-

(1) Previous paper in this series, THIS JOURNAL, **78**, 2806 (1956).
(2) Office of Naval Research Fellow, 1951–1955.
(3) W. J. Bailey and W. B. Lawson, THIS JOURNAL, **77**, 1606 (1955).
(4) W. J. Bailey and H. R. Golden, *ibid.*, **76**, 5418 (1954).
(5) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner and M. Hine, *ibid.*, **77**, 594 (1955).
(6) W. J. Bailey and H. R. Golden, *ibid.*, **75**, 4780 (1953).
(7) W. J. Bailey and J. Rosenberg, *ibid.*, **77**, 73 (1955).
(8) F. O. Rice and A. C. Stallbaumer, *ibid.*, **64**, 1527 (1942).
(9) G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, *ibid.*, **75**, 384 (1953).