Proof of Structure of the 2-Ethyl-1,3-butadiene Adducts.—The adduct Vb (1.35 g.) was degraded using the structure proof procedure described in detail for the isoprene adducts to give 30 mg. of *p*-phenylbenzoic acid (colorless needles), m.p. 223–225°. This product showed no melting point depression when mixed with an authentic sample of *p*-phenylbenzoic acid (m. p. 223–225°). However, when the product was mixed with an authentic sample of *m*-phenylbenzoic acid (m. p. 165–167°), the m. p. was 150–152°.

Six hundred milligrams of VIb was degraded in the same manner to give 15 mg. of *m*-phenylbenzoic acid (colorless plates), m. p. 164–165°. When this product was mixed with an authentic sample of *m*-phenylbenzoic acid, the m. p. of the mixture was 164–165°.

Conversion of Va to an Anhydride.—One gram of Va was heated in a test-tube by means of a Wood's metal bath at 200–210° for ten minutes. On melting, bubbles were observed but no carbon dioxide was evolved. The oil that formed resisted all attempts at crystallization. It was insoluble in 5% aqueous sodium bicarbonate but did dissolve in 50 ml. of 5% sodium hydroxide. When this alkaline solution was added to 10 ml. of concd. hydrochloric acid a colorless solid separated from solution. On recrystallization of this material from ethyl acetate–petroleum ether (high boiling) the colorless prisms obtained (m. p. 172–174°) gave no melting point depression when mixed with Va.

A similar oil was obtained when 1.0 g. of Va was heated under reflux with 10 ml. of acetic anhydride for five hours. This oil was reconverted to Va in the manner described above.

Summary

1. Phenylmaleic anhydride has been shown to form Diels–Alder type adducts with anthracene, 1,3-butadiene, 2,3-dimethyl-1,3-butadiene, cyclopentadiene, isoprene, 2-ethyl-1,3-butadiene and 2-isopropyl-1,3-butadiene.

2. It has been established that the two adducts formed by each diene, isoprene and 2-ethyl-1,3-butadiene, are structural rather than stereoisomers.

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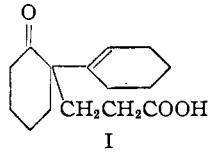
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF TEMPLE UNIVERSITY]

Aminoalkyl Esters of 2-(β-Carboxyethyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone[1]

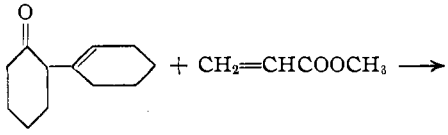
BY H. J. SCHNEIDER, T. W. RIENER AND H. A. BRUSON[2]

A large number of alkylaminoalkyl esters of aryl- and aralkylacetic and propionic acids, which have some analgesic or antispasmodic activity, are recorded in the literature. The preparation[3] of 2-(β-carboxyethyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone (I) suggested the synthesis of alkylaminoalkyl esters of this acid for pharmacological evaluation.

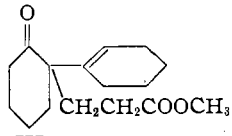


I

These esters were obtained by transesterification of 2-(β-carbomethoxyethyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone (III), which, in turn, was prepared by carbomethoxyethylation of 2-(Δ¹-cyclohexenyl)-cyclohexanone (II) with methyl acrylate. This condensation proceeded readily in the presence of a strong base; methanolic potassium hydroxide and Triton B were employed with some measure of success. However, the most satisfactory catalyst was found to be benzyltrimethylammonium methoxide. This compound was prepared according to the method of Meisenheimer[4] by the metathesis of benzyltrimethylammonium chloride and sodium methoxide in methanol.



II



III

The methyl ester, a colorless, high-boiling liquid, was hydrolyzed to the known acid (I). Small quantities of higher-boiling products were formed during the preparation of the methyl ester.

Transesterification of the methyl ester was carried out with β-dimethylaminoethanol, β-diethylaminoethanol and β-morpholinoethanol. Sodium and magnesium methoxides were suitable as catalysts for this reaction. The esters were obtained as high-boiling, viscous, light yellow liquids.

Benzyltrimethylammonium methoxide also catalyzed the condensation of (II) and methyl methacrylate to form 2-(β-carbomethoxypropyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone.

Pharmacological Activity.—The alkylaminoalkyl esters of (I) were tested as analgesics. In general, they showed an intraperitoneal toxicity in mice at 400–600 mg./kg. The morpholinoethyl ester gave a 20–26% increase of pain threshold in dogs at doses of 75 mg./kg. The dimethyl- and diethylaminoethyl esters were completely inactive at this dose level.

(1) Taken from a thesis submitted in June 1948, by H. J. Schneider to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree of Master of Arts.

(2) Address: Industrial Rayon Corp., Cleveland, Ohio.

(3) Bruson and Riener, THIS JOURNAL, **70**, 214 (1948).

(4) Meisenheimer, *Ann.*, **397**, 295 (1913).

Experimental

2-(β-Carbomethoxyethyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone (III).—The viscous sirup (23 g.), obtained by removal of excess methanol *in vacuo*, at 35–40°, from 44 g. of a 42% solution of benzyltrimethylammonium methoxide, was stirred and 150 g. of 2-(Δ¹-cyclohexenyl)-cyclohexanone[5] was added rapidly. Methyl acrylate[6] (87 g.) was added, dropwise, over a period of twenty minutes. The reaction mixture warmed rapidly, and an ice-bath was required to retain the temperature between 40–45°. After the addition of the acrylate was complete, the temperature was maintained at 40–42° for one hour. The mixture was neutralized at room temperature with 26 g. of 23% aqueous acetic acid. The oily layer was separated and distilled; b. p. 152–153° (0.8 mm.), yield 90 g., $n^{20}D$ 1.5043, d^{20}_{20} 1.079.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.72; H, 9.09; S.N., 213; M_R, 72.89. Found: C, 72.67; H, 8.85; S.N., 212; M_R, 72.46.

Hydrolysis of 50 g. of the ester with 50 g. of potassium hydroxide, dissolved in 250 cc. of water, yielded 35 g. of the acid; b. p. 175–180° (0.2 mm.); m. p. 59–60° after recrystallization from petroleum ether.

β-Dimethylaminoethyl Ester of 2-(β-Carboxyethyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone.—The methanol was distilled from a mixture of 64 g. of (III), 24 g. of β-dimethylaminoethanol and a small amount of sodium methoxide. After fractionation of the residual oil, 20 g. of the light yellow, oily ester was obtained; b. p. 168–170° (0.3 mm.), $n^{20}D$ 1.5030, d^{20}_{20} 1.054.

Anal. Calcd. for $C_{19}H_{31}O_3N$: C, 71.03; H, 9.69; N, 4.36; S.N., 176; M_R, 90.44. Found: C, 71.22; H, 9.62; N, 4.05; S.N., 175; M_R, 90.04.

β-Diethylaminoethyl Ester of (I).—A mixture of 0.5 g. of magnesium turnings and 20 cc. of anhydrous methanol was warmed on the steam-bath until the evolution of hydrogen ceased. β-Diethylaminoethanol (117 g.) was added, and the excess methanol was distilled. After the addition of 100 g. of dry xylene and 66 g. of (III), 7.3 g. of methanol was distilled from the mixture through a 12-inch, helices-packed column. After neutralization with 5 g. of 23% aqueous acetic acid, the dried oily layer was fractionated: b. p. 187–190° (0.9 mm.), yield 50 g., $n^{20}D$ 1.4989, d^{20}_{20} 1.031.

Anal. Calcd. for $C_{21}H_{35}O_3N$: C, 72.15; H, 10.03; N, 4.01; S.N., 160; M_R, 99.92. Found: C, 72.10; H, 10.14; N, 4.01; S.N., 160; M_R, 99.38.

β-Morpholinoethyl Ester of (I).—A similar procedure to that given for the diethylaminoethyl ester was employed, using 66 g. of (III) and 131 g. of β-morpholinoethanol. There was obtained 35 g. of a viscous, yellow oil, b. p. 220–225° (1 mm.). This oil was taken up in ether and repeatedly extracted with aqueous hydrochloric acid. The acid layer was neutralized with solid sodium hydrogen carbonate, and the heavy oil which separated was extracted with ether. On distillation of the ether solution, there was obtained 25 g. of the ester, b. p. 210–215° (0.3 mm.); $n^{20}D$ 1.5130, d^{20}_{20} 1.100.

Anal. Calcd. for $C_{21}H_{33}O_4N$: C, 69.42; H, 9.09; N, 3.86; M_R, 99.36; S.N., 155. Found: C, 69.55; H, 9.18; N, 3.86; M_R, 99.18; S.N., 158.

2-(β-Carbomethoxypropyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone.—Twelve grams of an 85% slurry of benzyltrimethylammonium methoxide in methanol was stirred and, after the addition of 89 g. of (II), 55 g. of methyl methacrylate[6] was added during a twenty-minute period. The temperature was maintained at 45° by cooling. The mixture was stirred at 40–45° for one hour after the addition of the methyl methacrylate, and was then neutralized with 13 g. of 23% aqueous acetic acid. The oily layer was separated and distilled; b. p. 141–143° (0.3 mm.); yield 43 g., $n^{20}D$ 1.5003, d^{20}_{20} 1.063.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.38; H, 9.36; S.N., 202; M_R, 77.50. Found: C, 73.44; H, 9.40; S.N., 205; M_R, 76.92.

Acknowledgment.—To Dr. E. L. Stanley and Mr. C. W. Nash of the Rohm and Haas Co. for all analyses, and to Dr. Harold E. Zaugg of the Abbott Laboratories, for the pharmacological tests.

Summary

1. Methyl acrylate and methyl methacrylate react with 2-(Δ¹-cyclohexenyl)-cyclohexanone to yield, respectively, 2-(β-carbomethoxy)-2-(Δ¹-cyclohexenyl)-cyclohexanone and 2-(β-carbomethoxypropyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone. Small amounts of more highly substituted compounds were obtained.

2. The β-dimethylamino-, β-diethylamino- and β-morpholinoethyl esters of 2-(β-carboxyethyl)-2-(Δ¹-cyclohexenyl)-cyclohexanone were prepared from the methyl ester by transesterification.

3. The β-morpholinoethyl ester induced mild analgesia in dogs at a dose of 75 mg./kg.

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(5) Hückel, Neunhoeffer, Gerche and Frank, *Ann.*, **477**, 119 (1930).

(6) Supplied by the Rohm and Haas Co.