Cyclic Analog of Ethacrynic Acid

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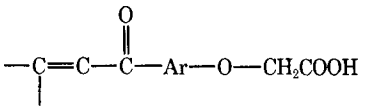
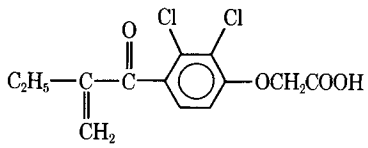
Abstract □ The α,β-unsaturated ketone (4,4-dimethyl-2-ethyl-1[4H]-naphthalenon-6-yl)oxyacetic acid (III), a cyclic analog of ethacrynic acid, has been prepared, and its diuretic activity on oral administration to rats and dogs has been evaluated. No significant activity was observed.

Keyphrases □ Ethacrynic acid cyclic analog—synthesis □ Diuretic activity—ethacrynic acid analog □ UV spectrophotometry—identity

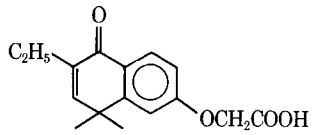
In 1962, Schultz *et al.* (1) disclosed a new class of diuretic agents possessing general structure I. Among the more potent members of this series was ethacrynic acid (II), which has received wide acceptance as a pharmaceutical agent (2). The interesting activity associated with II prompted the authors of this study to explore the preparation of cyclic congeners to assess their effectiveness as diuretic agents; in the present note they describe the preparation of III. Independent of these efforts, Topliss and Konzelman (3) reported recently the preparation and biological properties of the related compounds IV (n = 0,2).



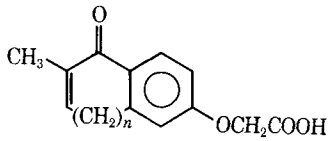
I



II



III

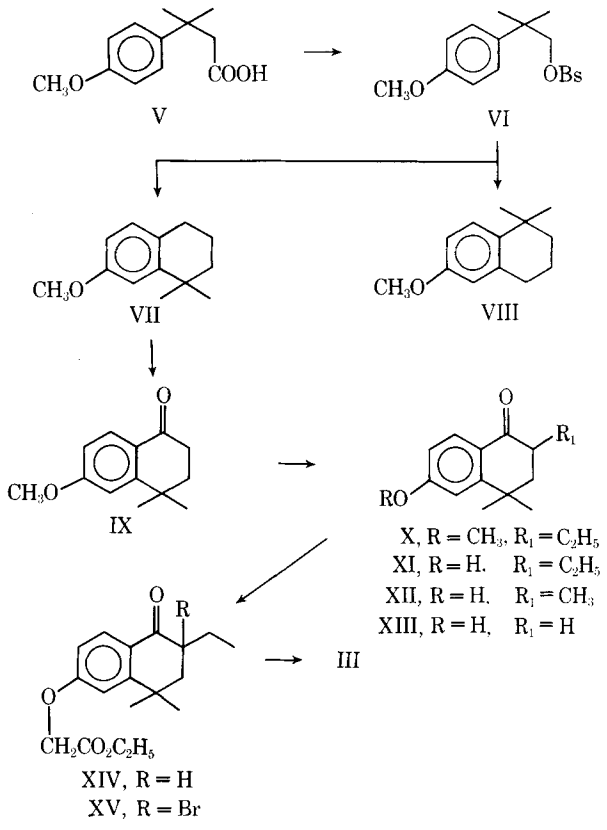


IV

The preparation of III from 4-*p*-anisyl-4-methylpentanoic acid (V) (4) is outlined in Scheme I. Lithium aluminum hydride reduction of V and treatment of the resulting alcohol with *p*-bromobenzenesulfonyl (Bs) chloride afforded the crude brosylate VI. Formolysis of VI has been reported to give the rearranged tetralin VII exclusively in 59% yield along with the formate derived from VI (5). In this study, pyrolysis of VI at 150° gave a 3:2 mixture of tetralins VII and VIII in 74% yield. This result indicates the intervention of a normal ring closure in the absence of solvent. Mild chromic acid oxidation of the tetralin mixture resulted in preferential conversion of VII to tetralone IX. Treatment of IX with methyl magnesium carbonate (6, 7), and ethylation of the resulting magnesium enolate gave the crude 2-ethyltetralone X. Phenol XI was obtained by ether cleavage of the crude alkylation product and chromatographic separation from the phenols XII, derived from methylation of IX, and XIII, derived from unalkylated IX. The genesis of XII may be a consequence of the ability of methyl magnesium carbonate to function as an alkylating agent. Reaction of XI with ethyl bromoacetate and potassium carbonate in refluxing acetone gave the ethyl aryloxyacetate XIV. Finally, bromination of XIV and treatment of the resulting XV with dilute potassium hydroxide effected saponification and dehydrohalogenation to give III.

PHARMACOLOGY

When administered orally to rats at 25 mg./kg., the aryloxyacetic acid III had no significant effect on urinary volume or chloride, sodium, and potassium-ion excretion as determined by the method of Cummings *et al.* (8). Although urine volume was slightly elevated in dogs that had been dosed orally at 5 mg./kg., electrolyte excretion was not increased (9).



X, R = CH_3, R_1 = C_2H_5
XI, R = H, R_1 = C_2H_5
XII, R = H, R_1 = CH_3
XIII, R = H, R_1 = H

XIV, R = H
XV, R = Br

Scheme I

EXPERIMENTAL

General—Melting points are uncorrected and were determined in open capillary tubes on a Mel-Temp apparatus. UV spectra were determined with a Cary recording spectrophotometer in methanol solution.

4-(*p*-Anisyl-4-methylpent-1-yl)-*p*-bromobenzenesulfonate (VI)—To a stirred suspension of lithium aluminum hydride (8.0 g.) in 250 ml. of ether was added a solution of 4-*p*-anisyl-4-methylpentanoic acid (V, 31 g.) in 250 ml. of ether over 1.5 hr. with ice-bath cooling. Following the addition the mixture was refluxed with stirring for 1.5 hr. The crude alcohol (100%) was obtained by hydrolysis with dilute sulfuric acid and solvent removal.

To a stirred solution of the alcohol (27 g.) in 240 ml. of dry pyridine at −15° was added a solution of *p*-bromobenzenesulfonyl chloride (50 g.) in 130 ml. of pyridine over 5 min. The mixture was stirred at 0° for 30 min. and poured into water. The product was extracted with ether; the extracts were washed successively with water, cold 2 *N* HCl, water, saturated $NaHCO_3$, and water. The extract was dried and evaporated to give 53 g. (95%) of crude VI, m.p. 48–55°.

4,4-Dimethyl-6-methoxy-1-tetralone (IX)—The brosylate (51 g.) was heated under argon at 150° for 110 min. The cooled product was treated with saturated $NaHCO_3$ and extracted with light petroleum ether. The solution was washed with water, dried, and evaporated to give an amber liquid which was chromatographed on an alumina column, eluting with hexane and 20:1 hexane–ether. The tetralin fraction so obtained (16.8 g.) analyzed as 60% 1,1-dimethyl-7-methoxytetralin (VII) and 40% isomer, presumably the 6-methoxyisomer VIII, on gas chromatography with a hydrocarbon oil (Apiezon L) column at 200°.

To a solution of the tetralin mixture (16.8 g.) in 85 ml. of glacial acetic acid was added a solution of chromium trioxide (20 g.) in 55 ml. of acetic acid and 10 ml. of water over 70 min. at 15-20° (ice bath). After standing at room temperature for 16 hr., the bulk of the solvent was evaporated; the resulting residue was treated with 5% H_2SO_4. Treatment with ether, filtration through diatomaceous earth (Celite), and further extraction with 1:1 ether–light petroleum ether gave an extract which was washed successively with water, saturated $NaHCO_3$, and water. Distillation of the dried concentrate afforded IX (5.51 g.) as a pale-yellow liquid, b.p. 110–114° (0.14 mm.), λ_{max} 225 mμ (ε11,300); 278 mμ (ε10,900).

Anal.—Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.52; H, 7.78.

4,4-Dimethyl-2-ethyl-6-hydroxy-1-tetralone (XI)—A solution of VIII (5.5 g.) in 60 ml. of 2.5 *M* methyl magnesium carbonate in dimethylformamide (7) was heated at 125° for 80 min. After slight cooling, ethyl iodide (42 g.) was added; the resulting mixture was refluxed for 6 hr. The reaction mixture was acidified with 4 *N* HCl and heated on the steam bath for 15 min. The reaction mixture was diluted with water and extracted with ether. The extract was washed with water, dried, and evaporated to give the crude X (6.4 g.) as a dark liquid.

The crude alkylation product (5.6 g.) was added to fused pyridine hydrochloride at 190–200° over 5 min. under argon, and the resulting mixture was stirred for 80 min. The cooled reaction mixture was treated with water and extracted with ether. The extract was washed successively with water, 2 *N* HCl, and water. Phenolic material was extracted into 0.5 *N* NaOH, and the extract was acidified with 4 *N* HCl. Ether extraction afforded a mixture of phenols which were separated by column chromatography on silica gel, eluting with hexane progressively enriched in ethyl acetate. The most mobile component was recrystallized from acetone–hexane, m.p. 128–130°, and consisted of XI (1.76 g.), λ_{max}. 227 mμ (ε11,600); 279 mμ (ε13,400).

Anal.—Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.39; H, 8.45.

The methyl derivative XII was recrystallized from acetone–hexane, m.p. 168–173° (50 mg.), λ_{max}. 227 mμ (ε11,900); 276 mμ (ε13,500).

Anal.—Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.50; H, 7.99.

Finally, elution gave XIII which was recrystallized from acetone–hexane, m.p. 143–145° (108 mg.), λ_{max}. 228 mμ (ε12,300); 279 mμ (ε14,200).

Anal.—Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.73; H, 7.52.

Intermediate fractions contained 800 mg. of an unresolved mixture of XI and XII.

Ethyl (4,4-Dimethyl-2-ethyl-1-tetralon-6-yl)oxyacetate (XIV)—A mixture containing XI (1.73 g.), potassium carbonate (1.22 g.), and ethyl bromoacetate (1.47 g.) in 20 ml. of acetone was refluxed with stirring for 3 hr. The reaction mixture was diluted with water, rendered alkaline with 2.5 *N* NaOH, and extracted with ether. The extract was washed with water, dried, and evaporated to give XIV (2.5 g.) as a pale-yellow oil.

(4,4-Dimethyl-2-ethyl-1[4H]-naphthalenon-6-yl)oxyacetic Acid (III)—To a stirred solution of XIV (2.3 g.) in 35 ml. of chloroform was added a solution of bromine (1.36 g.) in 10 ml. of chloroform over 1.5 hr. at room temperature. After 1 hr. the solution was evaporated to give the crude bromoester XV as an orange oil. This material was dissolved in 300 ml. of methanol containing potassium hydroxide (1.67 g.) and allowed to stand in the dark for 120 hr. The bulk of the methanol was evaporated and the residue was treated with water. Acidification in the cold with 4 *N* HCl and extraction with ether gave a solution of the free acid which was washed with water and dried. Evaporation and recrystallization of the residue from methanol–water gave white crystals of III (1.60 g.), m.p. 149–151°. Another recrystallization gave the analytical sample, m.p. 150–152°, λ_{max}. 238 mμ (ε12,100); 298 mμ (ε10,300).

Anal.—Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.80; H, 6.50.

REFERENCES

(1) E. M. Schultz, E. J. Cragoe, Jr., J. B. Bicking, W. A. Bolhofer, and J. M. Sprague, *J. Med. Chem.*, **5,** 660(1962).

(2) W. C. Cutting, "Handbook of Pharmacology," 3rd ed., Appleton-Century-Crofts, New York, N. Y., 1967, p. 192.

(3) J. C. Topliss and L. M. Konzelman, *J. Pharm. Sci.*, **57,** 737 (1968).

(4) S. Mukherjee, *J. Sci. Ind. Res. (India)*, **19B,** 94(1960).

(5) S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12,** 138(1956).

(6) M. Stiles and H. L. Finkbeiner, *J. Amer. Chem. Soc.*, **85,** 6161(1963).

(7) H. L. Finkbeiner and G. W. Wagner, *J. Org. Chem.*, **28,** 215(1963).

(8) J. L. Cummings, J. D. Haynes, L. M. Lipchuck, and M. A. Ronsberg, *J. Pharmacol. Exp. Ther.*, **128,** 414(1960).

(9) R. Z. Gussin, private communication.

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