6β-Bromoandrost-4-ene-3,17-dione (IV).—A solution of 105 mg. of androst-4-ene-3,17-dione (specific activity 7200 d.p.m./μmole) in 20 ml. of carbon tetrachloride was refluxed with 181 mg. of NBS for 5 hr. in the dark. After filtration of succinimide, the solvent was removed by evaporation, and the residue was chromatographed on thin layer (silica, 10% acetone in benzene). Four zones were noted on development with iodine vapor; one contained the 6β-bromo compound and another slightly more polar zone contained starting material. The product was rechromatographed three times in the same system until constant specific activity and extinction coefficient were obtained. The pure product, after recrystallization from ethyl acetate had m.p. 168–170° dec.; ultraviolet absorption, λ_{max}^{MeOH} 246 mμ (ε 11,120)[17]; specific activity 2047 d.p.m./μmole; % loss at C-6, 78% (corrected for 9% stable tritium).

Acknowledgment.—Portions of the technical work were carried out by Mr. Chi Ming Li. The authors wish to thank him for his conscientious assistance.

[17] L. Dorfman, *Chem. Rev.*, **53**, 47 (1953); L. Ruzicka, W. Bosshard, W. H. Fischer, and H. Wirg, *Helv. Chim. Acta*, **19**, 1147 (1936).

Notes

Synthesis and Structures of α-Tolyl- and α-Xylylisobutyric Acids

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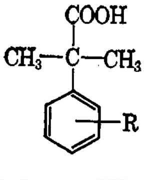
α-Arylisobutyric acids were required for a study of α,α-dimethylhomoaromatic acids. Previous workers prepared mixed α-tolylisobutyric acids by alkylation of toluene with ethyl α-bromoisobutyrate and aluminum bromide[1] or with methacrylic acid and aluminum chloride,[2] and claimed to have isolated the *ortho* and *para* isomers.[1,2] α-(*o*-Tolyl)isobutyric acid was oxidized by alkaline permanganate to an α,α-dimethylhomophthalic acid IV that readily formed an anhydride.[3] The structure of IV was further substantiated by two independent syntheses from *ortho*-substituted compounds.[3,4]



I, R = *o*-CH_3
II, R = *m*-CH_3
III, R = *p*-CH_3
IV, R = *o*-COOH
V, R = *m*-COOH
VI, R = *p*-COOH

The α-(*m*-tolyl)isobutyric acid (II), m.p. 71–73°, reported in the present work is probably the isomer previously isolated and claimed to have the *para* orientation. The large increase in the proportion of this isomer with reaction temperature is more characteristic of a *meta* isomer (34% at −10–0° and 58% at 30–40°). The infrared absorption exhibited by this acid at 12.7 μ and the 13.2-μ band observed for the *ortho* isomer are consistent with the bands reported for other *meta*- and *ortho*-disubstituted benzenes.[5]

Alkaline permanganate oxidation of II resulted in an α,α-dimethylhomophthalic acid V that gave a broad aromatic signal in the n.m.r. spectrum. Fractionation of the acids obtained from oxidation of the mixture of α-tolylisobutyric acids led to the isolation of a less soluble, higher melting α,α-dimethylhomophthalic acid VI that showed the symmetrical splitting of aromatic bands in the n.m.r. spectrum expected for the *para* isomer.

The methyl proton portion of the n.m.r. spectrum of the mixture of α-tolylisobutyric acids in benzene or carbon tetrachloride exhibits a single *gem*-dimethyl proton peak and partially resolved aromatic methyl proton bands. It was shown, using samples of the *meta* and *ortho* isomers obtained by fractional crystallization, that the *meta* isomer is resolved in carbon tetrachloride solution and the *ortho* isomer is resolved in benzene solution (Fig. 1). Estimation of the isomer distribution using these curves gave values of the order obtained by gas chromatographic analysis of the methyl esters. In the study of the solvent effects for the aromatic protons of *para*-substituted benzenes, Schaefer and Schneider[6] suggested that the changes in relative chemical shifts are due to weak hydrogen bonding. The *ortho* effect, observed for the α-tolylisobutyric acids in benzene solution, occurs for the xylenes and a series of substituted toluenes. The utility of benzene as a solvent for n.m.r. spectroscopy is complicated by the presence of "ring current" effects and solvent–solute interactions. However, a study of the methyl protons of substituted toluenes in preparation in these laboratories indicates benzene is a solvent of choice for identification or estimation of *ortho* isomers.

Four of the five possible α- (*o*- and *m*-xylyl-) isobutyric acids were isolated from the condensations of *o*- or *m*-xylene with methacrylic acid. Only one, the α-(*p*-xylyl)isobutyric acid, had been previously reported.[2] *o*-Xylene recovered from a reaction mixture did not

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[1] H. Rupe and J. Burgen, *Ber.*, **44**, 1222 (1911).

[2] J. Colonge and G. Weinstein, *Bull. soc. chim. France*, 820 (1951).

[3] S. Gabriel, *Ber.*, **20**, 1198 (1887).

[4] M. Anchel and A. H. Blatt, *J. Am. Chem. Soc.*, **63**, 1948 (1941).

[5] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 64.

[6] T. Schaefer and W. G. Schneider, *J. Chem. Phys.*, **32**, 1218 (1960).

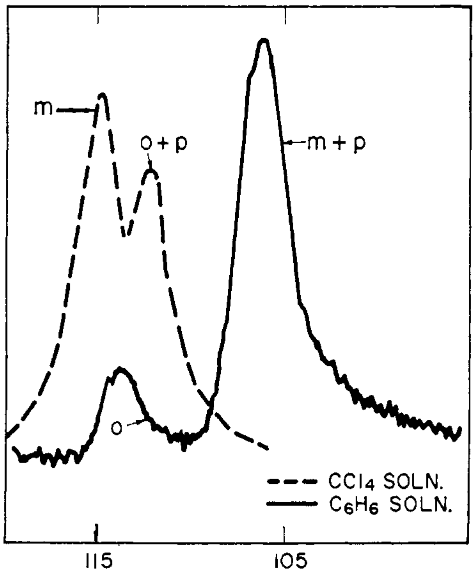


Fig. 1.—Aromatic methyl proton region of the n.m.r. spectrum of α-tolylisobutyric acids.

contain any of the other xylenes, and in each case the α-xylylisobutyric acids isolated were obtained by a condensation involving a particular xylene isomer. Figure 2 contains the aromatic methyl proton values for the xylenes and α-tolylisobutyric acids in benzene solution. The *o*-xylene methyl band is upfield with respect to the *meta* and *para* isomers, while the inverse is true for the α-tolylisobutyric acids. Inspection of the possible structures of the α-xylylisobutyric acids indicated that three of the isomers (VII, X, XII) should give two aromatic methyl proton absorptions, while the three isomers that have methyl groups in similar environments (VIII, IX, XI) should give single bands. The approximate relative positions of these bands should also be predicted by assuming that the values for the xylenes and α-tolylisobutyric acids are additive. The predicted band positions group themselves into three ranges (Fig. 2). The five α-xylylisobutyric acids give the required pattern of absorptions; the missing *meta* isomer, α-[2-(*m*-xylyl)]isobutyric acid (IX), is the most hindered. The infrared bands in the 12–13-μ region are consistent with these structural assignments[5] (Table I).

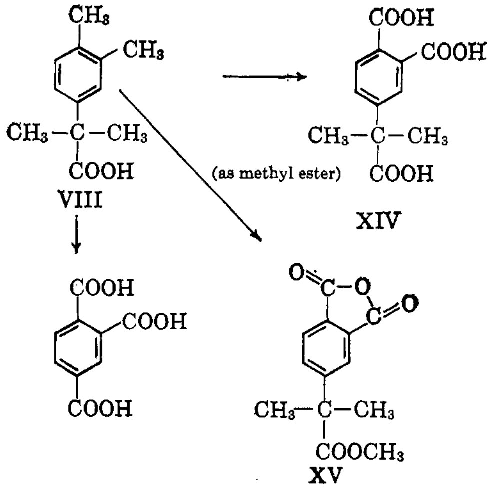
TABLE I

ABSORPTIONS IN THE 12–13-μ REGION OF THE INFRARED SPECTRA

Compound	Infrared absorptions, μ[a]
I	13.23
II	12.69
III	12.25[b]
VII	12.78
VIII	12.21
X	12.21
XI	11.79
XII	12.25

[a] See ref. 8. [b] Determined in the presence of I and II.

The α-(*o*-xylyl)isobutyric acids VII and VIII (Fig. 2) were oxidized to the 3- and 4-(2-carboxy-2-propyl)-phthalic acids (XIII and XIV), respectively, using alkaline potassium permanganate. The structure of VIII was further verified by air oxidation with cobalt and manganous bromides as catalysts in acetic acid solution. Oxidation of the free acid yielded trimellitic acid, whereas oxidation of the methyl ester under the same conditions gave 4-(2-carbomethoxy-2-propyl)-phthalic anhydride (XV). This indicates that free-radical attack on the phenylisobutyric acid structure may involve the carboxyl hydrogen. Esterification removes the vulnerable site, and ester exchange in acetic acid solution is slow enough to permit the structure to survive. The oxidation of phenylacetic acid by manganic ion is initiated by loss of the carboxyl hydrogen.[7]



Experimental[8]

α-Tolylisobutyric Acids.—To a slurry of 87.5 g. (0.66 mole) of aluminum chloride in 90 ml. of toluene, a solution of 22.6 g. (0.26 mole) of methacrylic acid in 50 ml. of toluene was added with stirring. During the 0.5-hr. addition period, the reaction was kept at room temperature and hydrogen chloride gas was introduced. The addition of hydrogen chloride was continued for an additional 0.25 hr., and then the mixture was allowed to stand for 3 hr. The organic layer, obtained by hydrolysis of the reaction mixture with ice and hydrochloric acid and addition of ether, was extracted with ammonium hydroxide solution. The basic extracts were washed with ether, acidified, and extracted with pentane. The dried pentane solution was decolorized with Norit and filtered, and the chilled concentrated filtrate provided 11.3 g. of α-(*m*-tolyl)isobutyric acid (II), m.p. 55–65°. The mother liquor was distilled yielding 22.2 g. of an oil, b.p. 105–107° (1 mm.), from which an additional 1.3 g. of II, m.p. 52–62°, was isolated by treatment with pentane. Nuclear magnetic resonance analysis indicated that the oil was solely a mixture of α-tolylisobutyric acids. The total yield of α-tolylisobutyric acids was therefore 33.5 g. (73%). In another experiment the crude acids were directly distilled, and gas chromatographic analysis of the methyl esters gave the following isomer per cents in this order of elution: *meta*, 58; *para*, 25; *ortho*, 17. This was proven by using the methyl esters of the pure acids as standards. A purified sample of the *meta* isomer II, m.p. 71–73° (the literature[1,2] reports that the melting point of the *para* isomer is 71°), was prepared by crystallization from pentane.

Repetition of the condensation at 0 to −5° gave a mixture of isomers from which the more insoluble *ortho* isomer, m.p. 99.5–100.5° (lit.[2] m.p. 102°), was isolated in 2% yield. In this case the n.m.r. spectrum of the mixture indicated that the sum of *ortho* and *para* isomers had increased; gas chromatographic

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[7] R. Van Helden and E. C. Kooyman, *Rec. trav. chim.*, **80**, 57 (1961).

[8] All boiling and melting points are uncorrected. Nuclear magnetic resonance spectra were measured at 52 Mc. with the Varian Associates DP 60 spectrophotometer. Chemical shifts are given downfield with tetramethylsilane as an internal standard. The infrared spectra were determined as mulls with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics. The gas chromatography determinations of the esters were performed using a column containing Dow Corning high-vacuum grease on acid-washed Johns-Manville Chromosorb B.

analysis of the methyl esters gave the following isomer per cents: *meta*, 34; *para*, 24; *ortho*, 43.

α-(*o*-Xylyl)isobutyric Acids (VII and VIII).—The methacrylic acid (34.0 g., 0.39 mole) in 55 ml. of *o*-xylene was added with stirring to a slurry of 135 g. (1.02 moles) of aluminum chloride in 215 ml. of *o*-xylene at −5° for 0.75 hr. After an additional 0.75 hr. at −5°, the reaction mixture was treated as described above. The crude acidic material was triturated with pentane, and the pentane-insoluble material was crystallized from ether–cyclohexane, giving 8.6 g. (11.5%) of an α-xylylisobutyric acid VII, m.p. 148.5–156.5°. A sample was crystallized from ether–cyclohexane and melted at 155.5–156.5°. Concentration of the pentane-soluble portion provided 9.0 g. (12%) of another α-xylylisobutyric acid VIII, m.p. 85–92°. An analytical sample, m.p. 91.5–93°, was prepared by crystallization from pentane. Oxidation of VIII with air in acetic acid with a cobalt and manganese bromide catalyst[9] at 200° for 1 hr. gave an acid that was mainly trimellitic acid according to its infrared spectrum and the gas chromatographic behavior of its methyl ester.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; neut. equiv., 192. Found for VII: C, 74.35; H, 8.52; neut. equiv., 192. Found for VIII: C, 74.73; H, 8.15; neut. equiv., 193.

A sample of xylene recovered from the reaction mixture was at least 99% *o*-xylene by gas chromatography. The n.m.r. spectra indicate that VII is α-[3-(*o*-xylyl)]isobutyric acid and VIII is α-[4-(*o*-xylyl)]isobutyric acid.

When the above condensation was allowed to take place at room temperature, the only crystalline acid isolated in 32% yield was VIII, the more soluble isomer. The presence of VII could not be demonstrated.

α-(*m*-Xylyl)isobutyric Acids (X and XI).—In the manner described above, 34 g. of methacrylic acid was condensed with *m*-xylene and the crude acidic material was distilled to provide 56 g. (74%), b.p. 112–120° (0.05 mm.), of a mixture of α-xylylisobutyric acids as a colorless viscous oil. Attempted fractionation using *n*-pentane as a solvent was not successful, and the combined fractions were refluxed overnight with 100 ml. of methanol and 3 ml. of concentrated sulfuric acid. After removal of most of the methanol, the residue was diluted with ether and pentane and extracted several times with sodium carbonate solution. Acidification gave a small amount of material that was crystallized three times from pentane and once from aqueous methanol to yield a single isomer X, m.p. 91–92° (mixture melting point with VIII gave a 20° depression), that is probably α-[4-(*m*-xylyl)]isobutyric acid. On distillation, the esterified portion gave a 26-g. fraction, b.p. 60–63° (0.5 mm.), that was hydrolyzed by heating and stirring with concentrated hydrochloric acid for 2 days. The resulting acidic material obtained was crystallized twice from *n*-pentane to provide large well-formed prisms, m.p. 114.5–116.5°, of α-[5-(*m*-xylyl)]isobutyric acid (XI). Analytical samples of X and XI were prepared by sublimation at 0.05 mm.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found for X: C, 75.64; H, 8.73. Found for XI: C, 74.77; H, 8.52.

α-(*p*-Xylyl)isobutyric Acid (XII).—*p*-Xylene was condensed with methacrylic acid as described above to yield α-(*p*-xylyl)-isobutyric acid (XII), m.p. 144.5–146° (lit.[2] m.p. 146.5°, mixture melting point with VII gave a 25° depression). It was purified by trituration with pentane followed by crystallization from cyclohexane and then from ether–pentane.

Preparation of the α,α-Dimethylhomophthalic Acids (IV, V, and VI). **α,α-Dimethylhomoisophthalic Acid (V).**—α-(*m*-Tolyl)-isobutyric acid (2.85 g., 0.015 mole) was oxidized in a solution of 2.6 g. of potassium hydroxide in 25 ml. of water by the addition of 5.3 g. (0.033 mole) of potassium permanganate in 50 ml. of water. The reaction mixture was maintained at steam-bath temperature during the 3-hr. addition period. After being cooled and treated with sodium bisulfite, it was acidified with sulfuric acid. The crude acid, 2.95 g., m.p. 145–160°, was crystallized from ethyl acetate, to give 2.40 g. (76%) of α,α-dimethylhomoisophthalic acid, m.p. 163.5–165°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; neut. equiv., 105. Found: C, 62.93; H, 5.66; neut. equiv., 105.

α,α-Dimethylhomoterephthalic Acid (VI).—The oxidation of 17.8 g. (0.10 mole) of the mixture of isomeric α-tolylisobutyric acids was run as described for the *meta* isomer II. The mixture of crude acids was crystallized from ethyl acetate to yield 2.73 g. (13%) of α,α-dimethylhomoterephthalic acid, m.p. 226–230°.

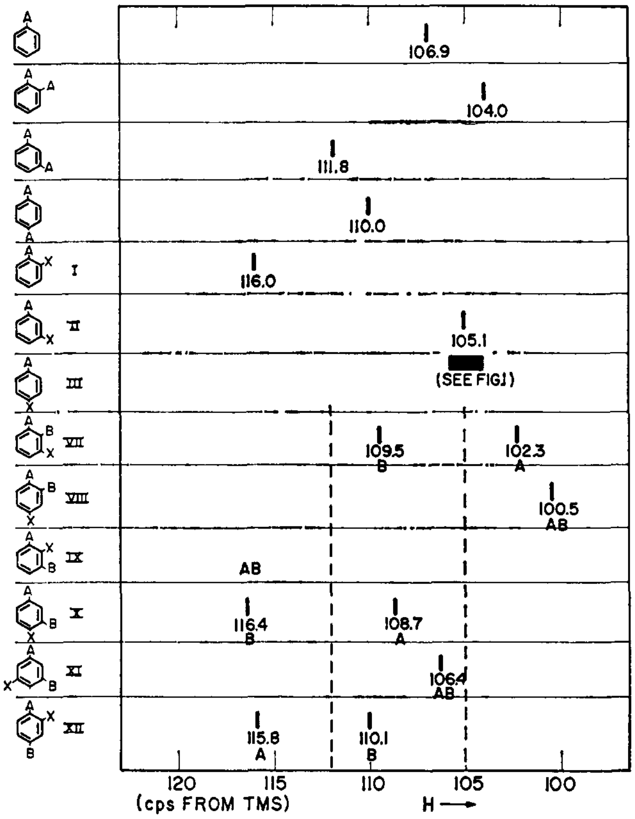

Fig. 2.—Aromatic methyl proton n.m.r. bands at 52 Mc. in benzene solution (A = B = CH_3 and X = $(CH_3)_2CCOOH$, see ref. 8). Mixture of VII, VIII, and XII produced bands at 115.8, 110.2, 107.6, and 101.4 c.p.s.; and mixture of X and XI gave bands at 114.1, 108.6, and 106.3 c.p.s.

An analytical sample, m.p. 228.5–231°, was prepared by recrystallization from ethyl acetate. The symmetrical quartet of n.m.r. bands exhibited by the aromatic hydrogens of this acid is evidence for a *para* orientation of substituents.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; neut. equiv., 104. Found: C, 63.70; H, 6.00; neut. equiv., 105.

α,α-Dimethylhomophthalic Acid (IV).—Oxidation of α-(*o*-tolyl)isobutyric acid with alkaline permanganate provided α,α-dimethylhomophthalic acid, m.p. 116–117° dec. ($-H_2O$), lit.[4] m.p. 114°, remelting at 80–82°.

3- and 4-(2-Carboxy-2-propyl)phthalic Acids (XIII and XIV).—The permanganate oxidation of 2.88 g. (0.015 mole) of α-[3-(*o*-xylyl)]isobutyric acid was run as described above, giving 3.05 g. (79%) of 3-(2-carboxy-2-propyl)phthalic acid (XIII); m.p. 202–205°, crystal transformation at 190–195°; neut. equiv. calcd. 84, found 88. Attempted purification of this acid *via* crystallization gave partial conversion to the anhydride. An analytical sample of the anhydride was prepared by sublimation at 170° and 2 mm.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.35; H, 4.49.

As described above, α-[4-(*o*-xylyl)]isobutyric acid was oxidized in 63% yield, producing 4-(2-carboxy-2-propyl)phthalic acid (XIV), m.p. 164.5–165.5°, from ethyl acetate–pentane.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.79; neut. equiv., 84. Found: C, 57.36; H, 5.18; neut. equiv., 86.

4-(2-Carbomethoxy-2-propyl)phthalic Anhydride (XV).—Methyl α-[4-(*o*-xylyl)]isobutyrate, 50.0 g. (0.243 mole), prepared by esterification of VIII with methanol and sulfuric acid, b.p. 68–72° (1 mm.), was oxidized in acetic acid solution using the method of Barker and Saffer.[9] The solvent was removed, and the acidic material remaining was distilled as the anhydride, giving 41 g. (67%) of 4-(2-carbomethoxy-2-propyl)phthalic anhydride, b.p. 158–160° (0.1 mm.). The distillate solidified, and crystallization from benzene–pentane followed by sublimation under reduced pressure provided an analytical sample; m.p. 78–79°; λ_{max}^{Nujol} 5.45 and 5.72 (anhydride C═O), and 5.89 μ (ester C═O).

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.91; H, 4.87; neut. equiv., 124. Found: C, 62.49; H, 4.42; neut. equiv., 125.

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[9] A. Saffer and R. S. Barker, U. S. Patent 2,833,816 (May 6, 1958).