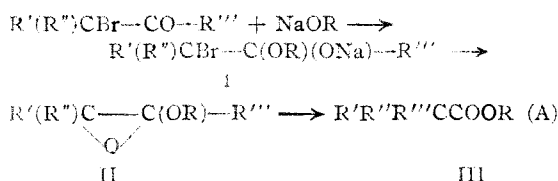


[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The New Acid Synthesis. II. The Effect of Hindrance. Methyl Tertiary-Butyl- and Methyleneethylpropylacetic Acids¹

BY J. G. ASTON, J. T. CLARKE, K. A. BURGESS AND R. B. GREENBURG

The action of sodium alcoholates in ether on α -bromo-*s*-alkyl ketones has been shown¹ to yield the ester of the tertiary acid, and it has been reasonably established that an ethylene oxide is an intermediate. The steps postulated in the production of the ester are



The ethylene oxide (II) is presumably formed from the preliminary addition product (I).

In the present paper it is shown that the series of reactions (A) is of wide generality. The reason that the initial addition product (I) is formed in preference to the product of metathesis involving the bromine atom directly is shown to be steric hindrance.

When 3-bromo-2-butanone is treated with alcohol-free sodium methylate or isopropylate, the product is identical with the one of normal metathesis, namely, the 3-alkoxy-2-butanone. This product could conceivably be produced by rearrangement of the alkoxy group or of the hydrogen on the other ring carbon atom. The first of these rearrangements is possible, but never has been found to occur when a methyl group can rearrange instead. No example of a rearrangement of the second type has been found, although one case with a hydrogen on this carbon (4,4-dimethyl-3-bromo-2-pentanone) has been studied where such a rearrangement could have been detected. Thus it seems that the above product results by normal metathesis. On the other hand, 4,4-dimethyl-3-bromo-2-pentanone on treatment with alcohol-free sodium methylate gives a 73% yield of the pure methyl ester of methyl-*t*-butylacetic acid. This shows that the presence of hydrogen on the alpha carbon is not the determining factor, and indicates that hindrance to metathesis is one of the causes of the rearrangement. This reaction product indicates that the rearrangement

discovered by Favorskii and Bozhovskii,² in which α -chlorocyclohexanone on treatment with alcoholic potassium hydroxide yields cyclopentane carboxylic acid, proceeds through the mechanism (A) which was the one advanced by Favorskii.³

While the rearrangement is favored by a hindered halogen, it is retarded by making the rearranging alkyl or aryl group larger, as would be expected. In the latter event the methoxyl group rearrangement, to give the same product as obtained by normal metathesis, is favored. Thus when 3-bromo-3-methyl-4-heptanone is treated with alcohol-free sodium methylate, a mixture of the methyl ester of methylethylpropylacetic acid and 3-methoxy-3-methyl-4-heptanone is obtained. Under similar conditions α -bromoisobutyrophenone gave only α -methoxyisobutyrophenone, as identified by oxidation.

Experimental

3-Methoxy-2-butanone.—A suspension of methanol-free sodium methylate in anhydrous ether was prepared by addition of 37.4 g. (1.17 moles) of absolute methanol to 27.0 g. (1.17 moles) of sodium wire in about 500 cc. of anhydrous ether. The mixture was stirred for three days while refluxing, at which time all the sodium had reacted. Over a period of two hours with constant stirring, 103 g. (0.681 mole) of 3-bromo-2-butanone⁴ was added to the suspension of sodium methylate in ether. The stirring was continued for twelve hours, and then water was added to dissolve the sodium bromide and excess sodium methylate. The two layers were separated, the water layer was extracted twice with ether, and the washings were added to the ether solution. After drying the ether layer, fractionation of the residual liquid gave 27.0 g. (39.1%) of a colorless oil, b. p. 87° (740 mm.); n_{D}^{20} 1.3750.

Anal. Calcd. for $C_4H_8O(OCH_3)$: C, 58.8; H, 9.89; OCH_3 , 30.4, mol. wt., 102. Found: C, 58.5; H, 10.0; OCH_3 , 30.8, 31.1; mol. wt. (cryoscopic in C_6H_6), 97.5.

Treatment with a solution of phenylhydrazine in 5% hydrochloric acid gave a derivative which, when recrystallized from ethanol, melted at 242° and did not depress the melting point of an authentic sample of the osazone of diacetyl.

(2) Favorskii and Bozhovskii, *J. Russ. Phys.-Chem. Soc.*, **46**, 1098 (1915).

(3) Favorskii had predicted this reaction on the basis of the rearrangement of α -dichloroketones to α,β unsaturated acids [Favorskii, *ibid.*, **26**, 559 (1894); *J. prakt. Chem.*, **51**, 533 (1894)].

(4) Favorskii, *ibid.*, [2] **88**, 641 (1913).

(1) The first paper of this series appeared in *THIS JOURNAL*, **62**, 2590 (1946).

4,4-Dimethyl-3-bromo-2-pentanone was prepared by the slow addition of an equimolecular portion of bromine to methyl neopentyl ketone⁵ at 0°. Carbon dioxide was passed through the solution to remove the hydrogen bromide as formed. Fractionation gave a light pink oil, b. p. 106° (88 mm.). When distilled at ordinary pressures the compound decomposed.

Anal. Calcd. for C₇H₁₃BrO: Br, 40.8. Found: Br, 39.2, 39.1.

Methyl Methyl-*t*-butylacetate from 4,4-Dimethyl-3-bromo-2-pentanone.—A suspension of methanol-free sodium methylate in anhydrous ether was prepared as above from 20.8 g. (0.652 mole) of absolute methanol and 15.0 g. (0.652 mole) of sodium wire in 500 cc. of anhydrous ether. Over a period of two hours with constant stirring, 99.0 g. (0.507 mole) of 4,4-dimethyl-3-bromo-2-pentanone was added. The stirring was continued for twelve hours and the reaction mixture worked up in the same way as that in the preparation of 3-methoxy-2-butanone. Fractionation of the dried residual liquid gave 53.0 g. (73.0%) of a colorless liquid, b. p. 95° (150 mm.); *n*²⁰_D 1.4116.

Anal. Calcd. for C₇H₁₃O(OCH₃): C, 66.6; H, 11.1; mol. wt., 144. Found: C, 66.8; H, 11.2; mol. wt. (cryoscopic in C₆H₆), 143.

Methyl-*t*-butylacetic Acid.⁶—Saponification of methyl methyl-*t*-butylacetate with 20% sodium hydroxide, followed by acidification, ether extraction and distillation, gave a white solid, b. p. 132° (55 mm.); m. p. 53.5°.

Anal. Calcd. for C₇H₁₃O₂: C, 64.6; H, 10.7. Found: C, 64.4; H, 10.5.

The Acetanilide from the Acid.—The acid chloride was prepared by treating the dry acid with thionyl chloride, and the excess thionyl chloride was removed by distillation. Treatment of a solution of the acid chloride in benzene with a solution of aniline in benzene gave a derivative which, when recrystallized from a 50–50 mixture of benzene and petroleum ether, melted at 112° and did not depress the melting point of an authentic sample⁷ of methyl-*t*-butylacetanilide.

3-Bromo-3-methyl-4-heptanone.—Two moles (320 g., 110 cc.) of liquid bromine were added with ice cooling to two moles (260 g.) of 3-methyl-4-heptanone without solvent. Fractionation of this product gave 185 g. of material (45%) boiling at 88° (22 mm.), *n*²⁰_D 1.4627–1.4630.

Anal. Calcd. for C₈H₁₅BrO: Br, 38.8. Found: Br, 38.65.

Methyl Ethylmethylpropylacetate from 3-Bromo-3-methyl-4-heptanone.—This reaction was run exactly as above using 103.5 g. (0.5 mole) 3-bromo-3-methyl-4-heptanone, 11.5 g. of sodium, 16 g. of absolute methanol and 500 cc. of anhydrous ether. Fractionation of the product under a pressure of 100 mm. resulted in a single fraction which boiled at 103–104° and had a refractive index of 1.4181–1.4182.

(5) For the preparation of this ketone in large quantities by the oxidation of diisobutylene, see Whitmore and co-workers, forthcoming publication.

(6) For a previous preparative method for this acid by oxidation of 4,5,5-trimethyl-2-hexene see Whitmore and Surmatis, forthcoming publication.

(7) Whitmore and Osborn, unpublished preparation.

Anal. Calcd. for C₉H₁₈O₂: C, 68.4; H, 11.6. Found: C, 69.0; H, 11.4.

If the product consisted solely of the corresponding ester, the yield would have been 75%. However, it seems likely that a constant boiling mixture was formed consisting of the methoxy ketone and the ester, because a small amount of a 2,4-dinitrophenylhydrazone (m. p. 139–140°) was obtained from it by boiling with 2,4-dinitrophenylhydrazine and a few drops of concentrated hydrochloric acid in 95% ethanol.

Ethylmethylpropylacetic Acid.—Five cc. of the methoxylation product and 35 cc. of constant boiling hydriodic acid were refluxed for six hours. The reaction mixture was made alkaline by adding 15% sodium hydroxide solution, and extracted with ether. The reaction mixture was then made acid with sulfuric acid, extracted with ether, the ether extract dried over calcium chloride and distilled under reduced pressure. A yield of about 50% (using the weight of the methoxylation product as a basis) of material boiling at 105° under a pressure of 20 mm. was obtained.

Anal. Calcd. for C₈H₁₆O₂: C, 66.7; H, 11.1; neut. equiv., 144.1. Found: C, 67.3; H, 10.6; neut. equiv., 146.

Ethylmethylpropylacetyl Chloride.—An equal volume of thionyl chloride was added to 2 cc. of the acid and the mixture refluxed for thirty minutes on a steam-bath. The thionyl chloride was stripped off and the residue distilled under reduced pressure. A yield of about 70% of material boiling at about 110° under a pressure of 100 mm. was obtained.

Anal. Calcd. for C₈H₁₆OCl: Cl, 21.8. Found: Cl, 19.8.

α-Methoxyisobutyrophenone from α-Bromoisobutyrophenone.—This reaction was run using 211 g. (0.93 mole) of bromoketone⁴ exactly as above, with the exception that the sodium methylate was prepared by dissolving 21.4 g. (0.93 mole) of sodium in an excess of anhydrous methyl alcohol which was then removed by evaporation and one liter of anhydrous ether added. Fractionation yielded 115.6 g. [0.65 mole (70%) of liquid b. p. 88–88.5° (14 mm.), *n*²⁰_D 1.4921].

Anal. Calcd. for C₁₁H₁₄O₂: C, 74.3; H, 7.8; MeO, 17.4. Found: C, 74.3; H, 7.6; MeO, 17.2, 16.7.

It was unsaponifiable and yielded a 2,4-dinitrophenylhydrazone on treatment with 2,4-dinitrophenylhydrazine and a few drops of concentrated hydrochloric acid in methanol (m. p. 139–140° after two recrystallizations from ligroin).

Anal. Calcd. for C₁₇H₁₈O₂N₄: C, 57.0; H, 5.07. Found: C, 57.2; H, 5.0.

The Oxidation of the Methoxylation Product from α-Bromoisobutyrophenone.—One-tenth of a mole (17.8 g.) of the methoxylation product was run into a solution of 9.6 g. (0.2 equiv.) of potassium dichromate and 10 cc. (0.36 equiv.) of concentrated sulfuric acid, the mixture kept at 75–80° for one and a half hours and finally distilled through a one-foot Vigreux column. Thus was obtained 0.035 mole (35%) of acetone as identified by its 2,4-dinitrophenylhydrazone and conversion to dibenzalacetone. From the residue, by ether extraction, was obtained 0.02 mole (20%) of crude benzoic acid as identified by a mixed melting point.

Acknowledgment.—We wish to thank Dr. F. C. Whitmore and J. D. Surmatis for supplying us with large quantities of methyl neopentyl ketone. Mr. David Jenkins kindly carried out the semimicro carbon and hydrogen determinations and Mr. A. A. Sacks performed the work on the identification of the α -methoxyisobutyrophenone.

Summary

1. The action of alcohol free sodium methylate or isopropylate on 3-bromo-2-butanone yields the product of normal metathesis.

2. The action of alcohol free sodium methylate on 4,4-dimethyl-3-bromo-2-pentanone gives a

73% yield of the pure methyl ester of methyl-*t*-butylacetic acid.

3. Under similar conditions 3-bromo-3-methyl-4-heptanone yields a mixture of methylethylpropylacetic acid and 3-methoxy-3-methyl-4-heptanone while α -bromoisobutyrophenone yields only α -methoxyisobutyrophenone.

4. It is hypothesized that when normal replacement is hindered, rearrangement occurs through an ethylene oxide intermediate. The rearranging group is the alkyl group if this is sufficiently small and the final product is the ester. Otherwise the alkoxy group rearranges to give a product identical with that of normal metathesis.

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[CONTRIBUTION FROM THE WOOD CONVERSION LABORATORY OF THE UNIVERSITY OF IDAHO]

The Constitution of Arabo-galactan. II. The Isolation of Heptamethyl- and Octamethyl-6-galactosidogalactose through Partial Hydrolysis of Methylated Arabogalactan¹

BY E. V. WHITE

The water-soluble gum of the western larch, *Larix occidentalis*, has been shown to contain *d*-galactose and *l*-arabinose as monosaccharide components in 6:1 molecular ratio^{2a,b,c,d} and was tentatively assumed to be a homogeneous polysaccharide, although more recent studies^{3a,b,c} tend to discredit this hypothesis. In the first communication⁴ of the present series it was shown that the methyl derivative of the polysaccharide, when subjected to complete hydrolysis and simultaneous glycoside formation, yielded the glycosides of 2,4-dimethyl-*d*-galactose, 2,3,4-trimethyl-*d*-galactose, 2,3,4,6-tetramethyl-*d*-galactose, and 2,3,5-trimethyl-*l*-arabinose in the approximate molecular ratio 3:1:2:1, respectively. Furthermore, the isolation of a relatively large proportion of the terminal arabo-furanose unit as the crystalline amide of the corresponding acid strongly suggested a direct linkage of the arabinose fraction to the galactose units of the polysaccharide.

(1) Presented in part before the Pacific Intersectional Division of the American Chemical Society meeting with the American Association for the Advancement of Science, Pasadena, California, June 16-21, 1941.

(2) (a) Wise and Peterson, *Ind. Eng. Chem.*, **22**, 362 (1930); (b) Wise, Hamer and Peterson, *ibid.*, **25**, 184 (1933); (c) Wise and Unkauf, *Cellulosechem.*, **14**, 20 (1933); (d) Peterson, Maugham and Wise, *ibid.*, **15**, 109 (1934).

(3) (a) Peterson, Barry, Unkauf and Wise, *THIS JOURNAL*, **62**, 2361 (1940); (b) Husemann, *J. prakt. Chem.*, **155**, 13 (1940); (c) Hirst, Jones and Campbell, *Nature*, **147**, 25 (1941).

(4) White, *THIS JOURNAL*, **63**, 2871 (1941).

The validity of this assumption might be established by the preferential hydrolysis of the furanopentose unit under mild conditions leaving a galactan residue of unchanged structure. The technique has been employed successfully in the case of xylan,⁵ and Hirst, Jones and Campbell^{3c} report its application to arabo-galactan, although the latter authors have not given the experimental details of their method. In the present experiments a successful partial hydrolysis of larch gum to arabinose and unchanged galactan has not been achieved as yet despite numerous attempts under a variety of conditions. The furanopentose unit is undoubtedly removed more rapidly than the galactopyranose residues but the preferential character of the hydrolysis has not been established. Similarly, the preferential aqueous hydrolysis of the methyl ether derivative was not successful and was complicated by precipitation of the ether in the hot aqueous acid solution unless alcohol or other diluent was used as solvent. On the other hand, hydrolysis of the methyl ether in methanol solution with anhydrous hydrochloric acid proceeded smoothly and in a regular manner. The reaction products were separable sharply into two fractions. One of these, soluble in hot petroleum ether (A), increased gradually in yield ap-

(5) Bywater, Haworth, Hirst and Peat, *J. Chem. Soc.*, 1933 (1937).