199° dec. (reported[13] m.p. 205° dec.). The melting point was not depressed on admixture with an authentic sample of the acid prepared as described below, and the infrared spectra of the two samples were identical.

Independent synthesis of pyrazinetetracarboxylic acid (VI). A hot solution of 20.6 g. (0.13 mole) of potassium permanganate in 100 ml. of water was added dropwise to a slurry of 1.8 g. (0.01 mole) of phenazine in 20 ml. of hot water containing one pellet of potassium hydroxide. The reaction and work up were carried out as described above for the oxidation of V, except that the filtrate and washings from the manganese dioxide were concentrated to only 50 ml. before acidification. The crude precipitate was washed with ethanol and recrystallized from 25 ml. of 20% hydrochloric acid to yield 0.7 g. (27%) of VI, m.p. 199–202° dec. (reported[13] m.p. 205° dec.).

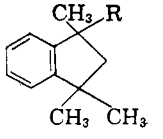
DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, N. C.

The Synthesis of Substituted Indanes by the Cyclialkylation Reaction

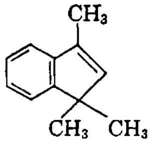
L. AMES, E. CHAITMAN, AND F. GRANT

Received August 12, 1960

The cyclialkylation reaction of Bruson and coworkers has recently provided a unique approach to the synthesis of highly substituted β-tetralones.[1] In this manner, 1,1,4,4-tetramethyltetralone has been prepared by the alkylation of benzene with 2,2,5,5-tetramethyltetrahydrofuranone. We have been interested in the synthesis of *ortho*-substituted ditertiaryalkylbenzenes from the oxidative cleavage products of compounds of this type. In this connection, it was of interest to determine whether the isomeric ketone of unknown structure also formed in the above condensation could provide an additional source of starting material for the preparation of these substituted benzenes. To this end, we have obtained evidence which, together with the data previously presented, confirms the formulation of this compound as 1,3,3-trimethyl-1-acetylindane (I).



I. R = $COCH_3$
II. R = $COOH$
III. R = $OCOCH_3$
IV. R = OH



V

$C_6H_5C(CH_3)_2CH_2COC(CH_3)_2OH$
VI

$C_6H_5C(CH_3)_2CH_2C(CH_3)(OH)COCH_3$
VII

The basic permanganate oxidation of the isomeric ketone has been reported to result in a crystalline monocarboxylic acid—$C_{13}H_{16}O_2$.[1] We have synthesized 1,3,3-trimethyl-1-indanecarboxylic acid (II) and demonstrated its identity with this oxidation product. The sequence of reactions leading to this acid are as follows. Neophylmagnesium chloride was carbonated to yield β-phenylisovaleric acid. Treatment with thionyl chloride and ring closure with aluminum chloride resulted in 3,3-dimethylindan-1-one, which added methylmagnesium iodide to give, after dehydration, 1,1,3-trimethylindene (V). Treatment of V with formic acid in sulfuric acid, following the procedure of Koch and Haaf,[2] resulted in the desired acid. The latter reaction appears to be the first application of this method to the carboxylation of an aryl-substituted double bond.

Additional support for structure I for the isomeric ketone came from the perbenzoic acid oxidation of this material. The acetate (III) was detected in the infrared spectrum of the crude oxidation mixture but was not isolated. 1,1,3-Trimethylindene (V), the dehydration product of the intermediate tertiary alcohol (IV), was isolated and identified as a product of the saponification of the oxidation mixture.

The origin of the isomeric ketone can be rationalized by a rearrangement and cyclization of the ketol (VI) which has previously been isolated and identified as a product of the cyclialkylation reaction and which is the logical precursor of the 1,1,4,4-tetramethyltetralone. Rearrangement of the type VI to VII has been described in a closely related system.[3]

EXPERIMENTAL[4]

β-Phenylisovaleric acid. The Grignard reagent prepared from 338 g. (2.0 moles) of neophyl chloride (b.p. 93°–94°/10 mm.) and 50.0 g. (2.0 moles) of magnesium turnings in 750 cc. of anhydrous ether was poured onto an excess of Dry Ice. The acid was isolated and recrystallized from 1:1 benzene-petroleum ether (b.p. 30–60°) yielding 144.3 g. (41%) of β-phenylisovaleric acid, m.p. 57°–58° (lit.,[5] m.p. 58°–58.5°).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.14; H, 7.92. Found: C, 74.84; H, 7.93.

3,3-Dimethylindan-1-one. The acid chloride derived by heating at reflux for 3 hr., 125 g. (0.70 mole) of β-phenylisovaleric acid and 100 g. (0.84 mole) of thionyl chloride, followed by removal of the excess thionyl chloride, was heated at reflux for 15 hr. with 93.3 g. (0.70 mole) of anhydrous aluminum chloride in 200 cc. of 3:1 petroleum ether (b.p. 30°–60°)-carbon disulfide. Water was added and the neutral material isolated and fractionally distilled. A 53% yield (59.0 g.) of 3,3-dimethylindanone, b.p. 86°–89°/1.7 mm., was obtained. The semicarbazone melted at 205°–206° (lit.,[6] m.p. 205°–207°).

Anal. Calcd. for $C_{12}H_{15}N_3O$: N, 19.34. Found: N, 19.58.

1,1,3-Trimethylindene. A dry ethereal solution of 48.0 g. (0.30 mole) of 3,3-dimethylindan-1-one was added dropwise with stirring to the Grignard reagent prepared from 56 g. (0.40 mole) of methyl iodide and 9.7 g. (0.40 mole) of mag-

---

[1] H. A. Bruson, F. W. Grant, and E. Bobko, *J. Am. Chem. Soc.*, **80**, 3633 (1958).

[2] H. Koch and W. Haaf, *Angew. Chem.*, **70**, 311 (1958).

[3] A. M. Khaletskii, *J. Gen. Chem.* (*U.S.S.R.*) **15**, 524 (1945), *Chem. Abstr.*, **40**, 4696 (1946).

[4] All melting and boiling points are uncorrected.

[5] A. Hoffman, *J. Am. Chem. Soc.*, **51**, 2545 (1929).

[6] K. v. Auwers, *Ber.*, **54**, 994 (1921).

nesium turnings in anhydrous ether. The tertiary alcohol formed was not isolated but dehydrated during the workup. 1,1,3-Trimethylindene (43.2 g., 98%) was recovered by distillation, b.p. 58°-62°/1.6 mm. (lit.,[7] b.p. 94°/15 mm.).

Anal. Calcd. for $C_{12}H_{14}$: C, 91.10; H, 8.90. Found: C, 90.97; H, 9.03.

1,3,3-Trimethyl-1-indanecarboxylic acid. 1,1,3-Trimethylindene (2.0 g., 0.013 mole) and 5 g. of 90% formic acid were added to 45 g. of concd. sulfuric acid at 0°-5°. After 1 hr. at 0°-5° the dark red solution was poured into water. 1,3,3-Trimethyl-1-indanecarboxylic acid (0.3 g., 12%) was isolated and recrystallized from petroleum ether to m.p. 129°-130°. This material had an infrared spectrum identical with, and did not depress the melting point of the acid, m.p. 131°-132°, obtained by the permanganate oxidation of the isomeric ketone.[1]

Peracid oxidation of the isomeric ketone. The isomeric ketone (40 g., 0.20 mole) was added to 23.2 g. (0.17 mole) of perbenzoic acid in 350 cc. of chloroform at 0°-5° and kept in the dark at this temperature for 1 week. The solution was allowed to stand for an additional month at 20° in the dark. The crude oxidation product showed a peak at 5.73 μ in its infrared spectrum consistent with the presence of ester carbonyl absorption. Saponification of 16.9 g. of the crude oxidation mixture and fractional distillation of the neutral products resulted in 2.9 g. (15%) of 1,3,3-trimethylindene, b.p. 110°-120°/18 mm., identified by comparison of its infrared spectrum with that of the synthetic sample prepared above.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, and Messrs. W. Mendelson and J. Zeger of the Johns Hopkins University for assistance in the early phases of this work.

DEPARTMENT OF CHEMISTRY
HAMILTON COLLEGE
CLINTON, N. Y.

---

(7) J. Colonge and P. Garnier, *Bull. soc. chim. France*, 436, 1948.

Isolation of the 1,4- and the 6,3-Lactones of D-Glucaric Acid[1]

R. J. BOSE, T. L. HULLAR, BERTHA A. LEWIS,
AND F. SMITH

Received July 25, 1960

Oxidation of D-glucose or starch with nitric acid yields D-glucaric acid (saccharic acid)[2] which is readily isolated as the acid potassium salt.[2,3] Removal of the potassium ions followed by evaporation afforded the monolactone of D-glucaric acid.[2] This product which was originally thought to be the 6,3-lactone[4] and which played a major role in the conversion of D-glucose into L-gulose[5] was subsequently proved[6] to be a mixture by isolating and proving the structure of the two lactones, the 1,4-lactone having m.p. 98° and $[\alpha]_D$ + 34°, and the 6,3-lactone having m.p. 149° and $[\alpha]_D$ + 45°.[7] The separation was facilitated by making use of the fact that the 1,4-lactone crystallizes as a monohydrate which is readily soluble in acetone, whereas the 6,3-lactone which crystallizes in the anhydrous form is almost insoluble in acetone.

More recently the 1,4-lactone has been shown to have anti-β-D-glucuronidase activity[8] and, as it may be a useful chemotherapeutic agent in the cure of bladder cancer,[9] there have been many requests for samples of the D-glucaro-1,4-lactone. This publication is prompted by our reinvestigation of the preparation of the 1,4-monolactone which has brought to light some simplification in procedure and an improvement in the yield. The improvement in yield has resulted from making use of the observation that when an aqueous solution of potassium hydrogen D-glucarate is boiled for thirty minutes the salt of the 1,4-lactone is generated,[10] whereas the simplification follows from the use of a cation exchange resin to remove the potassium ions from the boiled solution containing the potassium salt of D-glucaro-1,4-lactone.[11]

EXPERIMENTAL

Preparation of D-glucaro-1,4- and 6,3-lactones. Corn starch or soluble starch was oxidized to D-glucaric acid by nitric acid. Nitric acid (1 l. of concentrated acid in 2 l. of water) was added to the starch (220 g.) in a 4-l. glass beaker. A few crystals of sodium nitrite were added to catalyze the oxidation and the solution was heated on the steam bath. The beaker was removed from the heat during the vigorous evolution of brown gases which usually occurred after about 2 to 4 hr. of heating. When the gas evolution had subsided, the brownish yellow solution was heated on the steam bath for 16 to 18 hr., the solution being allowed to evaporate to about a quarter of the original volume. The solution, which was light yellow, was diluted with water (0.5 volume) and concentrated under reduced pressure (bath temp. 50-55°), water being added repeatedly to remove residual nitric acid. After most of the nitric acid was removed, the yellow solution was neutralized with solid potassium carbonate and then acidified to pH 4 with acetic acid. The potassium hydrogen D-glucarate was allowed to crystallize for 3 days at 5°, recovered by filtration, and dried in the air (yield, 130 g.). The crude salt was recrystallized from boiling water,[12] charcoal being added to effect decolorization; yield 90 g., $[\alpha]^{25}_D$ +5.2° (c 1.3, water).

A suspension of pure, recrystallized potassium hydrogen D-glucarate (129 g.) in water (525 ml.) was gently refluxed for 35 min[10]. The solution which had become yellow was

---

(1) Paper No. 4553, Scientific Journal Series, Minnesota Agricultural Experiment Station.

(2) O. Sohst and B. Tollens, *Ann.*, **245**, 1 (1888).

(3) E. Fischer, *Ber.*, **23**, 2611 (1890).

(4) K. Rehorst and H. Scholz, *Ber.*, **69**, 520 (1936).

(5) E. Fischer and O. Piloty, *Ber.*, **24**, 521 (1891).

(6) F. Smith, *J. Chem. Soc.*, 571, 633 (1944).

(7) *Cf.* M. Sutter and T. Reichstein, *Helv. Chim. Acta*, **21**, 1210 (1938).

(8) G. A. Levvy and C. A. Marsh, *Advances in Carbohydrate Chem.*, **14**, 413 (1959).

(9) E. Boyland, D. M. Wallace and D. C. Williams, *Brit. J. Cancer*, **11**, 578 (1957); E. Boyland, *Ciba Foundation Symposium* (*Carcinogenesis Mechanisms of Action*) **1958**, 218.

(10) G. A. Levvy, *Biochem. J.*, **52**, 464 (1952).

(11) *Cf.* H. Zinner and W. Fischer, *Ber.*, **89**, 1503 (1956).

(12) The heating in boiling water should be as brief as possible, otherwise the potassium hydrogen glucarate undergoes transformation.