extraction with sodium bicarbonate solution. The ether was then evaporated and the crude oxide taken up in ten times its volume of acetic acid. The acetic acid solution was added dropwise to half as much boiling 40% hydrobromic acid. The mixture was refluxed for twenty-four hours, after which the hydrocarbon was isolated as in the case of the $\beta$-methoxycarbinol method. A summary of our results is given in Table IV. In every case in which the same hydrocarbon was prepared by both methods, the two preparations were shown to be identical by mixed melting point determinations.

## Summary

Using the new method of ring closure, two hydrocarbons, 9-*n*-amyl- and 9-isopropylphenanthrene, never previously reported, have been synthesized.

The synthesis of 9-*n*-propyl- and 9-*n*-butylphenanthrene has shown that previous reports of these two hydrocarbons are erroneous.

DURHAM, N. C. RECEIVED AUGUST 10, 1940

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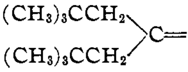
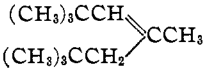
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

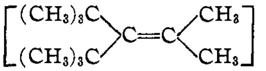
# The Isolation and Properties of 1,1-Dineopentylethylene, a Component of Triisobutylene[1]

BY PAUL D. BARTLETT, GEORGE L. FRASER AND ROBERT B. WOODWARD[2]

From the ozonolysis of triisobutylene McCubbin[3] reported the isolation of trimethylacetaldehyde, methyl neopentyl ketone, dineopentyl ketone, and an inert compound, b. p. 158–162° at 23 mm., which was assumed to be 3,3-di-*t*-butylbutanone-2 because it could be oxidized to an acid, m. p. 69–71°, apparently identical with the one to which Butlerow[4] assigned the structure of methyl-di-*t*-butylacetic acid (I). These facts were consistent with the conclusion, drawn by McCubbin, that triisobutylene was a mixture of the three isomers 1,1-dineopentylethylene (II), 1-methyl-1-neopentyl-2-*t*-butylethylene (III), and 1,1-dimethyl-2,2-di-*t*-butylethylene (IV), providing that the ozonolysis of IV could involve molecular rearrangement yielding a ketone of the same number of carbon atoms.


II


III


IV

A little later Conant and Wheland[5] showed that the chromic acid oxidation of triisobutylene yields two 12-carbon acids instead of the 11-carbon acid (I) which Butlerow believed he had. Whitmore and his co-workers[6] established the structures of these acids as dineopentylacetic acid (V), m. p. 89°, and methyl-*t*-butylneopentylacetic acid (VI), m. p. 129°, and pointed out that they must have been produced by molecular rearrangement from II and III, respectively. At the same time the evidence for the existence of IV as a component of triisobutylene was invalidated, since this rested upon Butlerow's incorrect structure I.

Such oxidative rearrangements are not known to occur except with acidic oxidizing agents. Thus it might be possible that if any of the compound IV existed in triisobutylene, it might be oxidized under vigorous conditions by alkaline permanganate to hexamethylacetone. This would not only be good structural evidence but would provide a superior way of preparing hexamethylacetone. With this in mind we treated triisobutylene with a calculated excess of hot 30% permanganate solution containing potassium hydroxide with stirring for seven hours, long after the first vigorous reaction had ceased. Although excess permanganate remained and the solution was not unduly viscous, half of the original triisobutylene appeared to remain unchanged. The oil was isolated by steam distillation, dried and distilled through a Widmer column. The entire material boiled constantly at 177.7–178°.

The unoxidized residue was shown to be one of the components of the triisobutylene, comprising about 50% of the original material. Its density, refractive index, molecular refractivity, and analysis are correct for a hydrocarbon $C_{12}H_{24}$. It is completely resistant to neutral or alkaline permanganate, but is attacked by dichromate and

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[1] Presented before the San Francisco Section of the American Chemical Society, September 12, 1940.

[2] Member of the Society of Fellows.

[3] McCubbin, THIS JOURNAL, **53**, 356 (1931).

[4] Butlerow, *Ber.*, **12**, 1482 (1879).

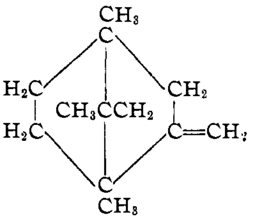
[5] Conant and Wheland, THIS JOURNAL, **55**, 2499 (1933).

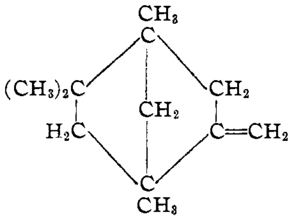
[6] Whitmore and Laughlin, *ibid.*, **56**, 1128 (1934); Whitmore and Wilson, *ibid.*, **56**, 1397 (1934).

strong acid. It reacts with bromine in carbon tetrachloride with the production of hydrogen bromide. It is hydrogenated by Raney nickel under 130 atm. pressure to a paraffin which reacts slowly with alkaline permanganate in the cold, and rapidly when warmed.

This component of triisobutylene reacts with perbenzoic acid at a normal rate, being 98% oxidized after eighty-three hours. The product, in contrast to ordinary epoxides, is not hydrated by cold dilute sulfuric acid, but is isomerized to an aldehyde. Autoxidation of this aldehyde, or direct oxidation of the epoxide by dichromate and sulfuric acid, yields an acid melting at 87–88° whose amide melts at 140–141°. These are the properties of dineopentylacetic acid (V), and accordingly our olefin can only be dineopentylethylene (II) reacting to give the corresponding epoxide and then dineopentylacetaldehyde.

This resistance of an olefin containing a terminal methylene group to oxidation by permanganate is astonishing, but its abnormal behavior is not altogether unique. A hydrocarbon believed to be (VII) or (VIII) by Farmer and Martin[7] proved resistant to the action of permanganate and, like dineopentylethylene, yielded on chromic acid oxidation an acid of the same number of carbon atoms.[8] A Stuart model of dineopentylethylene suggests a possible cause for this behavior in the complete hindrance of access of any reagent to the substituted ethylenic carbon atom. Since the first stage of alkaline permanganate oxidation is the formation of a *cis*-diol, a simultaneous attack of this reagent on both carbon atoms may be necessary to start the oxidation, and this may be prohibited by the two neopentyl groups.


VII


VIII

The fact that 1,1-dineopentylethane is attacked by permanganate is doubtless a consequence of the presence in it of a tertiary hydrogen atom. The products of this oxidation were not investigated.

The products in the aqueous mother liquor from the oxidation of triisobutylene were trimethylacetic acid, dimethylmalonic acid, and carbon dioxide. The dimethylmalonic acid, which exceeded the trimethylacetic in amount, was shown to have arisen from it by oxidation and to be itself slowly attacked, leading to no other isolable products except carbon dioxide. The attack of permanganate upon a methyl group of trimethylacetic acid makes it seem possible that hexamethylacetone might also, if formed in the oxidation of triisobutylene, undergo oxidation followed by decarboxylation to pentamethylacetone and so eventually to trimethylacetic acid. Thus the absence of hexamethylacetone among the oxidation products is not entirely satisfactory proof of the absence of 1,1-dimethyl 2,2-di-*t*-butylethylene in triisobutylene. At least the 75% yield of the acid (V) from the epoxide means that no unidentified inert hydrocarbon can constitute more than one-eighth of triisobutylene.

## Experimental

**1,1-Dineopentylethylene.**—Potassium permanganate (738 g.; 4.67 moles = 7 atoms oxygen/mole triisobutylene) and 50 g. of potassium hydroxide were dissolved in 2.5 liters of water by stirring vigorously while heating on the steam-bath. To the hot solution, with continued stirring and heating, 168 g. of triisobutylene[9] (1 mole) was added from a dropping funnel during the course of three-quarters of an hour. Considerable heat apparently was evolved in the initial stages of the oxidation, and it was advisable to have a seal for the stirrer in order to prevent considerable loss of vapor. Following the addition of the hydrocarbon, heating and stirring was continued for four hours, after which the heat was turned off, and the reaction mixture was stirred overnight. The following day heating was continued for three hours. A vigorous steam distillation then served to drive over 86 g. of a yellow oil, which after drying for a few hours was distilled through a 20-cm. Widmer column at atmospheric pressure, b. p. 177.7–178.0°. The substance was then distilled from an ordinary Claisen flask, b. p. (40 mm.) 85–86°. The product was a mobile, almost colorless oil; $n^{20.9}_{D}$ 1.4293; $d^{20}$ 0.7599; $M_R$ (found) 57.13; $M_R$ (calcd. for $C_{12}H_{24}$, $1\,|\overline{=}$) 57.17.

*Anal.*[10] Calcd. for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.50; H, 14.56.

After filtering from manganese dioxide, the spent oxidation medium was found by iodometric titration of an aliquot to contain 51 g. of potassium permanganate.

The hydrocarbon was unaffected by hot or cold permanganate solution, and could not be hydrogenated over Adams catalyst at ordinary temperature in dioxane, alcohol, or acetic acid. On the other hand, the substance smoothly absorbed a mole of hydrogen over Raney nickel on shaking for four hours at 150° and *ca.* 130 atm. The

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(7) Farmer and Martin, *J. Chem. Soc.*, 1170 (1940).

(8) Farmer and Pitkethly, *ibid.*, 290 (1938).

**(9) Prepared according to McCubbin, ref. 3.**

**(10) By Miss Ethel Holmes.**

product, b. p. 179–180°, had $n^{30}_{D}$ 1.4140, and was easily oxidized by hot alkaline permanganate.

**1,1-Dineopentylethylene Oxide.**—The method of Brooks and Brooks[11] was used to prepare a clear dry chloroform solution of perbenzoic acid. The initial volume of the oxidizing solution was 600 cc., and it contained 0.33 mole of perbenzoic acid. To this was added 46.7 g. of 1,1-dineopentylethylene (0.278 mole, *ca.* 61 cc.) and the reaction mixture was placed in the cold room at 6°. From time to time 3.00-cc. aliquots were removed and the perbenzoic acid left determined in the usual manner.[12] The final determination indicated that the compound had taken up 0.98 atom of oxygen, corresponding to one double bond per mole (Figure 1).

When the reaction was substantially complete, the chloroform solution was shaken in portions with a solution of 50 g. of anhydrous potassium carbonate and 10 g. of sodium bisulfite in 700–800 cc. water. After subsequent washing with water alone, the chloroform was distilled through a 20-cm. Widmer column, and the residual oil distilled *in vacuo* from an ordinary Claisen flask. Forty-five grams of 1,1-dineopentylethylene oxide was obtained as a clear colorless oil, b. p. (15 mm.) 85–88°, of faint characteristic oxide odor: $n^{21.5}_{D}$ 1.4330, $d^{20}$ 0.8367; $M_R$ (found) 57.31, $M_R$ (calcd.) 57.33 (using 1.89 as the value for $>O$ in ethylene oxides. This figure was obtained by averaging the empirical values based on ethylene oxide and epichlorohydrin).

*Anal.*[10] Calcd. for $C_{12}H_{24}O$: C, 78.15; H, 13.12. Found: C, 78.17; H, 12.82.

**Dineopentylacetic Acid.**—(1) By autoxidation of dineopentylacetaldehyde. Five grams of 1,1-dineopentylethylene oxide was shaken overnight with 7 cc. of 10% aqueous sulfuric acid. No development of heat or other sign of reaction often associated with the hydrolysis of oxides under these conditions was observed in the initial stages of the reaction. In the morning the oil was separated and distilled, b. p. (15 mm.) 85–90°, no high boiling residue which would be expected as a consequence of glycol formation being observed. Both before and after distillation the product responded positively to the fuchsine–sulfurous acid test. Considerable manipulation having failed to induce crystallization, the oil was allowed to stand overnight in an open vessel; in the morning a substantial portion had crystallized in very large aggregates. On further standing the whole mass became solid. This material was pressed out on the porous plate or centrifuged to remove small adherent quantities of oily material, and recrystallized from ethanol–water to constant melting point; 2.5 grams of pure dineopentylacetic acid was obtained as glistening leaflets, m. p. 87–88°. The material was completely soluble in sodium carbonate solution, and mixed with a sample of the acid obtained as in (2) had m. p. 87–88°.

*Anal.*[13] Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.91; H, 12.00.

The above experiment was repeated many times, varying the concentration of dilute acid (2–30%) and the time of shaking. In one case dioxane was added as a mutual solvent. The results were different only in that the yield of dineopentylacetic acid varied with the extent of conversion of the oxide into the aldehyde.

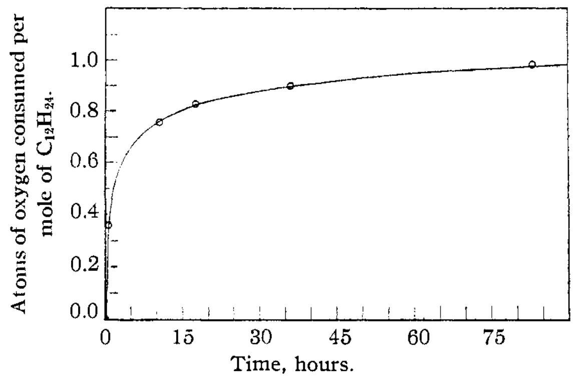

Fig. 1.—Oxidation of 1,1-dineopentylethylene by perbenzoic acid.

(2) By oxidation of 1,1-dineopentylethylene oxide with dichromate mixture: 14.7 g. of potassium dichromate (0.05 mole) was dissolved in 150–200 cc. of 15% aqueous sulfuric acid in a flask cooled in ice and equipped with a good stirrer. During three-quarters of an hour, 18.4 g. (0.10 mole) of 1,1-dineopentylethylene oxide was dropped into the well-stirred oxidizing mixture. The cooling bath was then removed and the stirring was continued overnight. In the morning the oxidation was complete, and the original oil had been replaced by a mass of glistening crystals. Owing to the fineness of the latter, it was not possible to filter without first heating on the steam-bath until the crystals had melted, and then solidified into a hard mass on cooling. The hard, somewhat green, crystalline mass so obtained weighed 15–16 g. and had m. p. 84–86°. The substance was best purified by sublimation at ordinary pressure, when it was obtained as beautiful glistening leaflets, m. p. 87–88°; mixed with the acid from (1), m. p. 87–88°.

**Dineopentylacetic Acid Amide.**—One gram of the acid from either (1) or (2) was allowed to stand overnight with 5 cc. of pure thionyl chloride, the latter was then removed in the vacuum of the water-pump, and the yellow oily residue shaken immediately for fifteen minutes (or until completely solid) with *ca.* 10 cc. of concentrated aqueous ammonia. The white granular amide was filtered, dried by boiling the benzene solution of the crude material, and crystallized from a small amount of benzene. On filtering with suction, dineopentylacetic acid amide was obtained as a mat of very fine needles, which after drying had m. p. 139–140°.[5]

**Examination of the Oxidation Products of Triisobutylene.**—The aqueous mother liquor from the oxidation of 140 g. of triisobutylene was treated with enough sodium bisulfite to reduce the remaining permanganate, filtered, acidified with sulfuric acid (yielding much carbon dioxide) and continuously extracted for one week with ether. The ether extract yielded 8.1 g. of trimethylacetic acid, b. p. 163–164°, and 24 g. of dimethylmalonic acid, m. p. 186° dec. The mixed melting point with an authentic sample

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(11) Brooks and Brooks, This Journal, **55**, 4309 (1933).

(12) "Organic Syntheses," Vol. XIII, p. 89.

(13) Analysis by Dr. Carl Tiedcke.

showed no depression, although this was of course not conclusive because of decomposition. The neutral equivalent was 66.3 and 67.2 (calculated, 66.1). The isomeric acids all melt at 112° and below.

**Preparation of Dimethylmalonic Acid from Trimethylacetic Acid.**—Pure trimethylacetic acid (20 g.), potassium permanganate (120 g.) and potassium hydroxide (10 g.) were dissolved in the minimum of water and heated seven hours on the steam-bath. The excess permanganate was destroyed with sodium bisulfite, the solution filtered, acidified, and evaporated to dryness. On acidification carbon dioxide was evolved. The solid residue was extracted with ether in a Soxhlet extractor, yielding 8.3 g. of dimethylmalonic acid. The acidified mother liquor had only a slight odor of trimethylacetic acid.

## Summary

The prolonged action of hot, concentrated alkaline permanganate upon triisobutylene leaves half of the hydrocarbon unchanged. This inert component of triisobutylene has been shown to be 1,1-dineopentylethylene (II). It has been catalytically hydrogenated, converted to an epoxide and, through this and an isomeric aldehyde, to dineopentylacetic acid (V). The attacked component of triisobutylene is converted into carbon dioxide, trimethylacetic and dimethylmalonic acids.

CAMBRIDGE, MASSACHUSETTS
RECEIVED OCTOBER 17, 1940

[CONTRIBUTION FROM THE DEPARTMENTS OF MEDICINE AND BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS COLUMBIA UNIVERSITY AND THE PRESBYTERIAN HOSPITAL]

# Phosphorylated Egg Albumin[1,2]

BY MICHAEL HEIDELBERGER, BARNARD DAVIS AND HENRY P. TREFFERS

Numerous chemical studies on natural phosphoproteins such as casein and vitellin[3] have furnished information of the greatest theoretical and practical importance but have afforded no basis for the comparison of these proteins with their unknown undegraded phosphorus-free analogs. Such correlation, however, would be of considerable interest, for the biological significance of phosphorylation is so far-reaching that the effect of the addition and removal of phosphoric acid groupings on the properties of proteins might well be considered. A beginning in this direction is described in the present paper.

Since crystalline egg albumin[4] is one of the most carefully studied proteins, it was decided to phosphorylate this substance. Use was made of the mild procedure adopted by Rimington[5] for the introduction of phosphorus into caseinogen, dephosphorylated (and degraded) caseinogen, and denatured serum globulin, a method based on earlier studies on lactalbumin and "blood globulin" by Neuberg and Pollak.[6]

The properties of the phosphorylated egg albumin (PEa) varied through a wide range depending upon the relative proportions of Ea and $POCl_3$ used. Products with nitrogen–phosphorus ratios of less than 30:1 were precipitable by acid below *p*H 4.5, but preparations with higher N:P ratios still showed definite differences from Ea. Physical, chemical, and immunological properties of the more representative preparations were studied and comparisons were made with Ea and certain of its derivatives.

**Preparation of Phosphorylated Egg Albumin (PEa).**—Crystalline egg albumin (Ea) prepared by a previously described method[7] was recrystallized three times. A typical lot contained 0.06% of phosphorus. 2.15 grams of Ea in 100 ml. of water was chilled in an ice–salt-bath at −2 to −3° and a solution of 5 g. of freshly distilled $POCl_3$ in 25 ml. of carbon tetrachloride was dropped in with mechanical stirring, during four hours. The solution, at 0–3°, was maintained at an alkalinity just pink to phenolphthalein by dropwise addition of 3 *N* sodium hydroxide. It was found necessary to add indicator from time to time, as it reacted with the $POCl_3$. When no more alkali was used up the pink color was discharged with a few drops of *N* hydrochloric acid and the mixture was centrifuged. The carbon tetrachloride layer, which had partly gelled, was washed with several small portions of water and discarded. The aqueous solution was acidified in the cold preferably with *N* hydrochloric acid to maximum precipitation after which the PEa was easily centrifuged off, leav-

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[1] The work reported in this communication was carried out under the Harkness Research Fund of the Presbyterian Hospital. This study was commenced by Barnard Davis and was to have been submitted by him to the Faculty of Pure Science, Columbia University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Unfortunately the career of this engaging and promising young chemist was terminated by his tragic death.

[2] This paper was summarized in part before the New York Academy of Sciences at the Protein Symposium, February 2 and 3, 1940, and in part at the American Chemical Society Meeting, Detroit, Michigan, on September 12, 1940.

[3] References to the literature on the phosphorus linkage are cited by P. A. Levene and D. W. Hill, *J. Biol. Chem.*, **101**, 711 (1933); F. Lipmann, *Biochem. Z.*, **262**, 3 (1933); and G. Schmidt, *Z. physiol. Chem.*, **223**, 86 (1934).

[4] Subsequently referred to as Ea.

[5] C. Rimington, *Biochem. J.*, **21**, 272 (1927).

[6] C. Neuberg and H. Pollak, *Biochem. Z.*, **26**, 529 (1910).

[7] M. Heidelberger, "An Advanced Laboratory Manual of Organic Chemistry," Chemical Catalog Co., New York, N. Y., 1923.