perature in an atmosphere of carbon dioxide, but no violet color of diphenyldiazomethane was observed.

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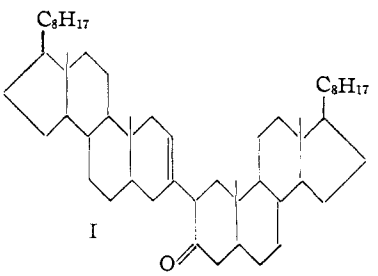
A New Steroid Coupling Product from Cholesterol

BY ELIAS J. COREY AND RICHARD L. YOUNG

RECEIVED OCTOBER 28, 1954

The catalytic hydrogenation of cholestanone over platinum in di-*n*-butyl ether containing a small amount of concentrated aqueous hydrobromic acid affords epicholestanol as the major product together with a small amount of cholestanol.[2,3] We have found, however, that if the hydrogenation is carried out in anhydrous medium using an acetic acid solution of hydrogen bromide instead of a concentrated aqueous solution a new substance, $C_{54}H_{90}O$, is formed in *ca.* 40% yield. Furthermore, the same substance can be obtained in the absence of hydrogen and platinum simply by heating cholestanone in dibutyl ether–acetic acid–hydrogen bromide solution. The new compound is an unsaturated, non-conjugated ketone as is indicated by the infrared spectrum (carbonyl absorption at 1710 cm.$^{-1}$), formation of a yellow 2,4-dinitrophenylhydrazone, yellow coloration with tetranitromethane and lack of high-intensity absorption in the ultraviolet. Only one structure (I) seems to accommodate these facts and to be consistent with the conditions of the transformation. The attachment of the cholestene moiety to C_2 follows from the preferred direction



I

of enolization of cholestanone and the position of the double bond follows from the greater stability of Δ^2- over Δ^3-cholestene. The more stable α-orientation of the cholestene substituent seems probable because the compound is not isomerized even by long treatment with strong acid.

Although the coupling product reacts rapidly with bromine in carbon tetrachloride to form an unstable, bromine-containing material (presumably a dibromide), all attempts to reduce either the double bond or the carbonyl group catalytically were unsuccessful.

Experimental

Aldol Coupling of Cholestanone.—A solution of 5 g. of cholestanone in 125 ml. of di-*n*-butyl ether containing 15 ml. of 3.3% hydrogen bromide in acetic acid was heated to 60° for four hours. The catalyst was removed by filtration and the filtrate was washed with 10% aqueous sodium hydroxide, then with water, and evaporated under reduced pressure. Recrystallization of the residual solid from methylene chloride–acetone afforded 2.28 g. of crude product, m.p. *ca.* 175°. Further recrystallization furnished 2.0 g. of pure material as a colorless, granular solid, m.p. 209–211°, $[\alpha]_D$ +40.9° (*c* 2.3, chloroform).

Anal. Calcd. for $C_{54}H_{90}O$: C, 85.63; H, 12.24; mol. wt., 757.26. Found: C, 85.51; H, 12.27; mol. wt., 706 (ebullioscopic, benzene).

The same product was obtained when the reaction mixture was shaken with hydrogen and pre-reduced platinum catalyst; identified by m.p., mixture m.p. and infrared spectra.

The 2,4-dinitrophenylhydrazone was prepared in the usual way and recrystallized from methylene chloride–acetone, m.p. 150° dec. The same dinitrophenylhydrazone was made from samples of I formed by condensation in the presence or absence of hydrogen–platinum.

Anal. Calcd. for $C_{60}H_{94}O_4N_4$: C, 76.87; H, 10.32; N, 5.97. Found: C, 77.14; H, 10.46; N, 6.05.

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2,5-Di-*t*-butyl-4-methoxyphenol and 2,6-Di-*t*-butyl-4-methoxyphenol

BY CLINTON D. COOK, RICHARD G. INSKEEP, ARTHUR S. ROSENBERG AND EARL C. CURTIS, JR.

RECEIVED JULY 21, 1954

During a study[1] of the thermal decomposition of bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide[2] a product believed to be 2,6-di-*t*-butylbenzoquinone was isolated. Bickel and Kooyman[3] have reported this compound from the reaction of 2,4,6-tri-*t*-butylphenol with oxygen initiated by 2,2′-azoisobutylnitrile. However, they cite no structural evidence. To prove the identity of our product, it was reduced to the corresponding hydroquinone and alkylated with methyl sulfate to give 2,6-di-*t*-butyl-4-methoxyphenol. This product has been reported by Sears and Kitchen[4] as a result of the alkylation of 4-methoxyphenol with isobutylene by the method of Stillson, Sawyer and Hunt.[5] In our hands the products prepared by these two methods were not identical.[6] Further investigation showed that the major product formed on isobutylene alkylation—under conditions closely approximating those cited by Stillson, *et al.*, for the preparation of 2,4,6-tri-*t*-butylphenol—is 2,5-di-*t*-butyl-4-methoxyphenol. Our evidence is as follows: The infrared spectrum of the product formed from the di-*t*-butylhydroquinone shows a marked absorption for the hydroxyl group at 3659 cm.$^{-1}$ but only slight indications of hydrogen bonding in the region from 3300 to 3500 cm.$^{-1}$ (see Fig. 1, A). This product was insoluble in Claisen solution. These facts are consistent with a 2,6-orientation of the *t*-butyl groups. (For comparison with a com-

(1) From the B.S. thesis of R. L. Young.

(2) G. Vavon and B. Jakubowicz, *Bull. soc. chim. France*, [4] **53**, 583 (1933).

(3) L. Ruzicka, H. Brungger, E. Eichenberger and J. Meyers, *Helv. Chim. Acta*, **17**, 1407 (1934).

(1) C. D. Cook and R. C. Woodworth, unpublished work.

(2) C. D. Cook and R. C. Woodworth, THIS JOURNAL, **75**, 6242 (1953).

(3) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 3211 (1953).

(4) W. C. Sears and L. J. Kitchen, THIS JOURNAL, **71**, 4110 (1949).

(5) G. H. Stillson, D. W. Sawyer and C. K. Hunt, *ibid.*, **67**, 303 (1945).

(6) In a personal communication, Dr. Kitchen reports that this reaction is unusually sensitive to conditions and that, under his conditions, the 2,6-isomer predominates. He plans to report this work in a forthcoming publication.

pound of established structure, see the curve for 2,4,6-tri-*t*-butylphenol, Fig. 1, B.)

The infrared spectrum of the compound prepared by isobutylene alkylation shows the hydroxyl group at 3610 cm.$^{-1}$ and also shows a much higher degree of hydrogen bonding in the region from 3300 to 3500 cm.$^{-1}$ (Fig. 1, C) than the compound assigned the 2,6-structure (Fig. 1, A). This compound was very soluble in Claisen solution and slightly soluble in aqueous sodium hydroxide. Alkylation with methyl sulfate gave 2,5-di-*t*-butyl-4-methoxyanisole, identical with a specimen prepared by similar alkylation of 2,5-di-*t*-butylhydroquinone.

That alkylation of 4-methoxyphenol with isobutylene may yield the 2,5-di-*t*-butyl derivative as the major product is not surprising and, indeed, has already been noted.[7] Whilst the hydroxyl group generally has a greater directive influence than the methoxyl, the difference is not great (see, for example, the Hammett σ-values cited by Jaffé[8]). A *t*-butyl group in the 2-position will supplement the 4-methoxyl group in activating positi ns 3 and 5 and since the *t*-butyl group is a fairly strong *para* director (Hammett σ-value of -0.197[5]) it is not unreasonable that the combined effect of the two groups should frequently outweigh the hydroxyl group. Substitution in the 3-position can be ruled out on steric grounds.[9]

Acknowledgment.—The authors are grateful to the Research Corporation for grants to Clinton D. Cook and Richard G. Inskeep.

Experimental

Alkylation of 4-Methoxyphenol with Isobutylene.—This alkylation was carried out in an apparatus previously described for the preparation of 2,4,6-tri-*t*-butylphenol. One mole (124 g.) of *p*-methoxyphenol, 5 ml. of concentrated sulfuric acid and 45 ml. of benzene were placed in the apparatus and the mixture warmed to 50°. Isobutylene was passed through the apparatus until a weight gain of 131 g. (2.34 moles) was achieved. The temperature was maintained at 50–60° throughout the run (below 50° the rate of reaction was rather slow). The reaction mixture was diluted with 370 ml. of benzene and washed three times with 100-ml. portions of water. The benzene was evaporated and the product recrystallized from ligroin (b.p. 90–120°); yield 132 g. (56%), m.p. (uncor.) 101.5–103°, reported 101–102.6°.[6] *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.46; H, 10.50. The ultraviolet spectrum was typical of a phenol,[10] showing (in ethanol) a minimum at 255 mμ and a maximum at 290 mμ (ϵ_{max} 3.9×10^3).

Alkylation of 2,5-Di-*t*-butyl-4-methoxyphenol with Dimethyl Sulfate.—Four grams (0.017 mole) of the above phenol was dissolved in 100 ml. of 50% (volume) aqueous acetone and 5 g. of sodium hydroxide added. After warming to reflux temperature, a total of 6 ml. of dimethyl sulfate was added over a period of one hour. Evaporation of the acetone gave 4.1 g. (97%) of white crystals which were insoluble in Claisen solution. After recrystallization from ligroin (b.p. 90–120°) the product melted at 103–105° (uncor.). *Anal.* Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.70; H, 10.26. The infrared spectrum of this compound showed no hydroxyl absorption in the region 3300–3700 cm.$^{-1}$. The ultraviolet adsorption was very similar to the parent phenol showing a minimum at 253 mμ and a maximum at 288 mμ (ϵ_{max} 3.9×10^3).

Alkylation of 2,5-Di-*t*-butylhydroquinone with Dimethyl Sulfate.—Ten grams (0.045 mole) of 2,5-di-*t*-butylhydroquinone (Eastman Kodak Co. 5681) was dissolved in 100 ml. of 50% (by volume) aqueous acetone and 10 g. of potassium hydroxide added. After warming to reflux 7.5 ml. of dimethyl sulfate was added over a period of two hours. The acetone was evaporated and the reaction mixture extracted with 200 ml. of petroleum ether (Eastman Kodak Co. 950). Upon reduction of the volume to 25 ml., 3 g. (0.012 mole) of product was deposited. After recrystallization from methanol the material melted at 103–105°. A mixture melting point with the product prepared from 2,5-di-*t*-butyl-4-methoxyphenol showed no depression and the ultraviolet spectra were identical.

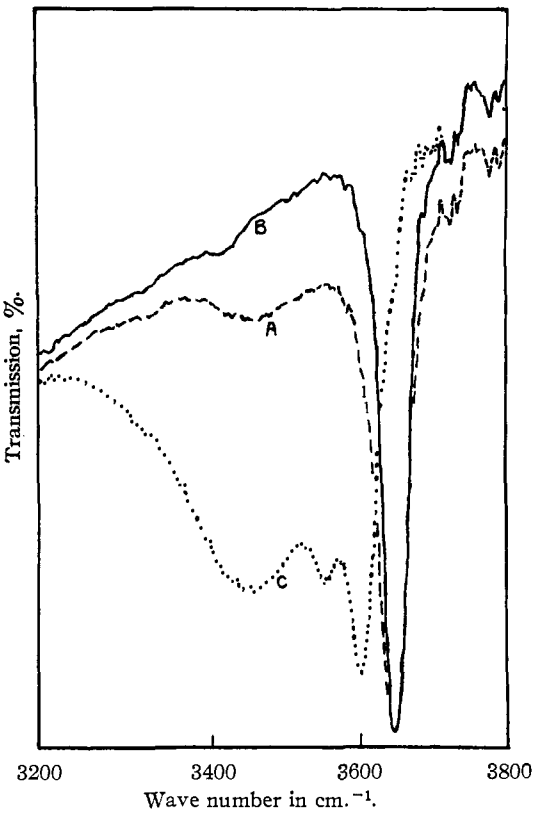

Fig. 1.—A, 2,6-di-*t*-butyl-4-methoxyphenol; B, 2,4,6-tri-*t*-butylphenol; C, 2,5-di-*t*-butyl-4-methoxyphenol; 2 *M* carbon disulfide solutions.

Preparation of the Hydroquinone.—Five to thirty grams of bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide[2] was maintained at 210° for 30 minutes. At the end of this time the evolution of isobutylene, which was very vigorous at the start, was very slight. The orange reaction mixture, dissolved in petroleum ether, was reduced with zinc dust and acetic acid to a nearly colorless solution and the hydroquinone extracted with 5% sodium hydroxide solution containing a trace of sodium hydrosulfite. Acidification with hydrochloric acid gave the crude hydroquinone in an average yield of 95% based on one mole of quinone per mole of peroxide. Recrystallization from petroleum ether gave white crystals melting at 115–116°.

Alkylation of 2,6-Di-*t*-butylhydroquinone with Dimethyl Sulfate.—Six ml. of dimethyl sulfate was added slowly to a cold solution of 5.55 g. of 2,6-di-*t*-butylhydroquinone in 100 ml. of 4% aqueous sodium hydroxide. After vigorous shaking for one-half hour, the product (5.5 g.) was filtered and recrystallized twice from ligroin (b.p. 90–120°), m.p. 105–106°, reported 103.5–104.5°.[4,11] *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.46; H, 9.95. The ultraviolet spectrum was similar to those of other hindered phenols showing a minimum at 251 mμ and a maximum at 290 mμ (ϵ_{max} 3.0×10^3).

Spectra.—The ultraviolet spectra were taken with a Beck-

(7) R. H. Rosenwald, U. S. Patent 2,470,902 (1949); *C. A.*, **43**, 6235 (1949).

(8) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(9) H. C. Brown and K. L. Nelson, THIS JOURNAL, **75**, 24 (1953).

(10) See, for example, N. D. Coggeshall and E. M. Lang, *ibid.*, **70**, 3283 (1948).

(11) A mixture melting point with a sample very kindly provided by Dr. Kitchen showed no depression.

man model DU quartz spectrophotometer at concentrations of approximately 3×10^{-4} *M* in ethanol. The infrared spectra were run with a Perkin–Elmer model 112 in the region 3200–3700 cm.$^{-1}$ using a lithium fluoride prism. Each compound was run at two different concentrations (0.5 and 2.0 *M*) in carbon disulfide.

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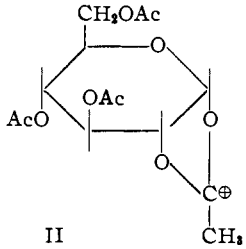
A Study of the Reaction of β-D-Glucose Pentaacetate with Phosphorus Pentachloride

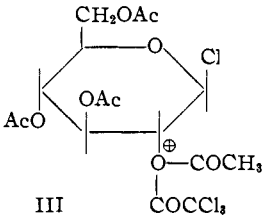
BY WILLIAM G. DAUBEN AND C. WHEATON VAUGHAN

RECEIVED JULY 6, 1954

The reaction of β-D-glucose pentaacetate with phosphorus pentachloride to yield β-2-trichloroacetyl-3,4,6-triacetylglucosyl chloride (I) has received attention in recent years with regard to the mechanistic pathways involved in the reaction sequence. Marcy and Scattergood,[1] as well as Lemieux,[2] have postulated that the reaction proceeds through the positive ion of type II which, in turn, is chlorinated.



II



III

On the other hand, Abramovitch[3] has suggested that trichlorination is due solely to the -I effect of the C_1-chlorine. An entirely different suggestion has been made by Brigl[4] who viewed the reaction as proceeding *via* an exchange reaction between the C_2-acetyl group and the trichloroacetyl chloride formed from the original C_1-acetyl group. In view of the recent demonstration of an intramolecular exchange reaction with acid chlorides[5] it was believed of interest to investigate the possibility of an intermolecular exchange, proceeding through an ion of type III, in this reaction of glucose pentaacetate.

C^{14}-Labeled pentaacetate was prepared by allowing carboxyl-labeled acetyl chloride to react with 2,3,4,6-tetraacetyl-D-glucose in pyridine solution. The highly purified β-pentaacetate, after isotopic dilution, was allowed to react with phosphorus pentachloride and the two reaction products, acetyl chloride and I, were isolated and purified. The radioactivity was found to reside in the acetyl chloride fraction, the glucose derivative being entirely inactive. Such results clearly rule out any exchange reaction but they are entirely in accord with the other mechanisms.

It was of further interest to investigate whether acetyl chloride did trichlorinate under the conditions of the reaction. To obtain some information pertaining to this reaction, the volatile phosphorus residues of the reaction were diluted with non-labeled trichloroacetyl chloride which, in turn, was recovered by distillation. The chloride was found to possess a small amount of radioactivity, indicating that some trichlorination of acetyl chloride indeed had occurred. Unfortunately, the counting error introduced by the low activity of the highly diluted trichloroacetyl chloride makes inexact any estimate of the degree of the chlorination reaction. However, it appears that a value of 6 ± 3% is reasonable.

Acknowledgment.—The authors are indebted to Dr. E. Hardegger of the Organisch-chemisches Laboratorium der Eidg. Technischen Hochschule, Zurich, for kindly supplying the tetraacetylglucose employed in this study.

Experimental[6]

1-Acetyl-labeled β-D-Glucose Pentaacetate.—A mixture of carboxyl-labeled sodium acetate (0.707 g., 8.6 mmoles, 50 μc.) and benzoyl chloride (2.42 g., 17 mmoles) was heated and the acetyl chloride allowed to distil. The product (0.5 ml.) was added, with stirring, to a solution of 2.99 g. (8.6 mmoles) of β-D-2,3,4,6-tetraacetylglucose (m.p. 130–131°) in 3.4 ml. of anhydrous pyridine at 0°. Upon standing for 20 hours, the solution was poured, with stirring, into 15 ml. of water and allowed to stand one hour. Filtration, followed by recrystallization from 95% ethanol, yielded 1.15 g. of pure β-D-glucose pentaacetate, m.p. 132.5–133°. A mixed melting point of the product with an authentic sample showed no depression. The active product was diluted with 22 g. of inactive material and recrystallized from ethanol. The specific activity was 14.1 cts./min./mg. $BaCO_3$ (corrected, 225 cts./min./mg. $BaCO_3$).[7]

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.69. Found: C, 49.16; H, 5.88.

β-D-2-Trichloroacetyl-3,4,6-triacetylglucosyl Chloride (I).—Labeled β-D-glucose pentaacetate (23.0 g., 59 mmoles) was well ground with phosphorus pentachloride (61.5 g., 0.3 mole) in a flask which subsequently was fitted with a reflux condenser. The mixture was heated on a steam-bath for 2.5 hours during which time all the solids had turned to a viscous sirup. The placement of a cold trap (cooled by Dry Ice) after the reflux condenser was essential to condense the evolved acetyl chloride. The crude acid chloride then was distilled through a small column packed with glass helices: b.p. 51.5°, specific activity 112 cts./min./mg. $BaCO_3$ (corrected, 224). The anilide prepared from the acetyl chloride melts from 114–115° (lit. 114°).

After completion of the heating period, the volatile compounds of phosphorus were removed from the reaction mixture by distillation at 1 mm. pressure and the distillate was collected in a cold trap. The residue after this operation was dissolved in ether and allowed to stand at 0° overnight.

The crystalline material from the ether solution was filtered and the solid ground under 10 ml. of absolute methanol and then filtered immediately. A second wash with 5 ml. of methanol was performed and the product dried at room temperature at reduced pressure, m.p. 139–141° (lit.[4] 142°), yield 3.0 g., specific activity 0.0 cts./min./mg. $BaCO_3$.

Anal. Calcd. for $C_{14}H_{16}O_9Cl$: C, 35.77; H, 3.44; Cl, 30.26. Found: C, 35.64; H, 3.64; Cl, 30.08.

Isotopic Dilution of Trichloroacetyl Chloride.—Trichloroacetyl chloride (24.0 g., 0.132 mole) was added to the

(1) W. Marcy and A. Scattergood, Abstracts of the 115th Meeting of the A.C.S., San Francisco, Calif., 1949, p. 46-L.

(2) R. U. Lemieux, *Can. J. Chem.*, **29**, 1079 (1951); **31**, 1040 (1953).

(3) R. A. Abramovitch, *J. Chem. Soc.*, 2996 (1951).

(4) P. Brigl, *Z. physiol. Chem.*, **116**, 1 (1921).

(5) For leading references concerning intramolecular exchange of this type, see J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953).

(6) Analyses and combustion of the C^{14}-labeled materials were performed by the Microanalytical Laboratory of the Department of Chemistry and Chemical Engineering, University of California, Berkeley. All melting points are corrected. All boiling points are uncorrected.

(7) The corrected specific activity is obtained by multiplying the original specific activity by the number of carbon atoms in the molecule. This value then corresponds to the specific activity of the singly labeled carbon atom.