[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Steric Effect of Methylene Groups. I

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As was pointed out in an earlier publication,[1] a distortion of the Mills–Nixon[2] type in the hydrocarbon hydrindene (I) should result in a diminution in the steric influence of the methylene groups adjacent to the benzenoid ring. It follows that the steric effect of a five-membered ring should be smaller than that of a corresponding six-membered ring (i. e., as in tetralin (II)).

By employing the haloform reaction with appropriately substituted ketones, we have observed some marked differences in the steric effects of methylene groups in five- and six-membered rings.

The mechanism of the haloform reaction is now well understood and can be described by the following equation.[3]
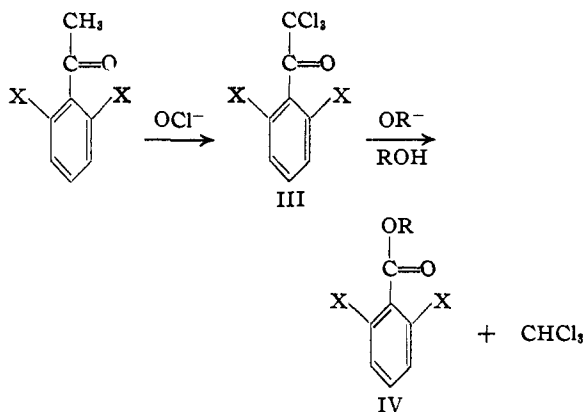
(R = H or alkyl) The compound ROH must, of course, be water or some alcohol (such as methanol), which is not oxidized by hypochlorite under the conditions of the experiment.

If the ortho substituent "X" is sufficiently small, the haloform reaction proceeds rapidly to give chloroform and an acid (IV) or its ester.[4] When, however, group "X" is large enough (even methyl), the last step in the haloform reaction is sterically inhibited and the trichloro ketone (III) is isolated as the reaction product.
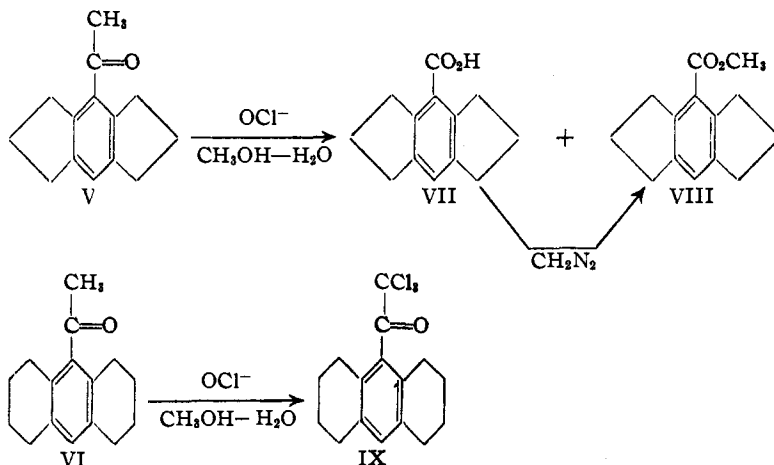
We have now shown that 4-acetylhydrindacene (V) and 9-acetyloctahydroanthracene (VI) react differently toward alkaline hypochlorite. The

former ketone in aqueous methanol gives a mixture of acid (VII) and methyl ester (VIII) whereas the latter ketone under the same conditions gives a trichloro ketone (IX) which is relatively stable toward alkali.[1]

Since, electronically, the trimethylene and tetramethylene groups are quite analogous, we are forced to conclude that the steric effect of the five-membered ring is smaller than that of the six-membered ring. This evidence supports the contention of Mills and Nixon that a distortion of the ortho valence bonds in hydrindene does exist.

The synthetic steps employed during this study are outlined below.
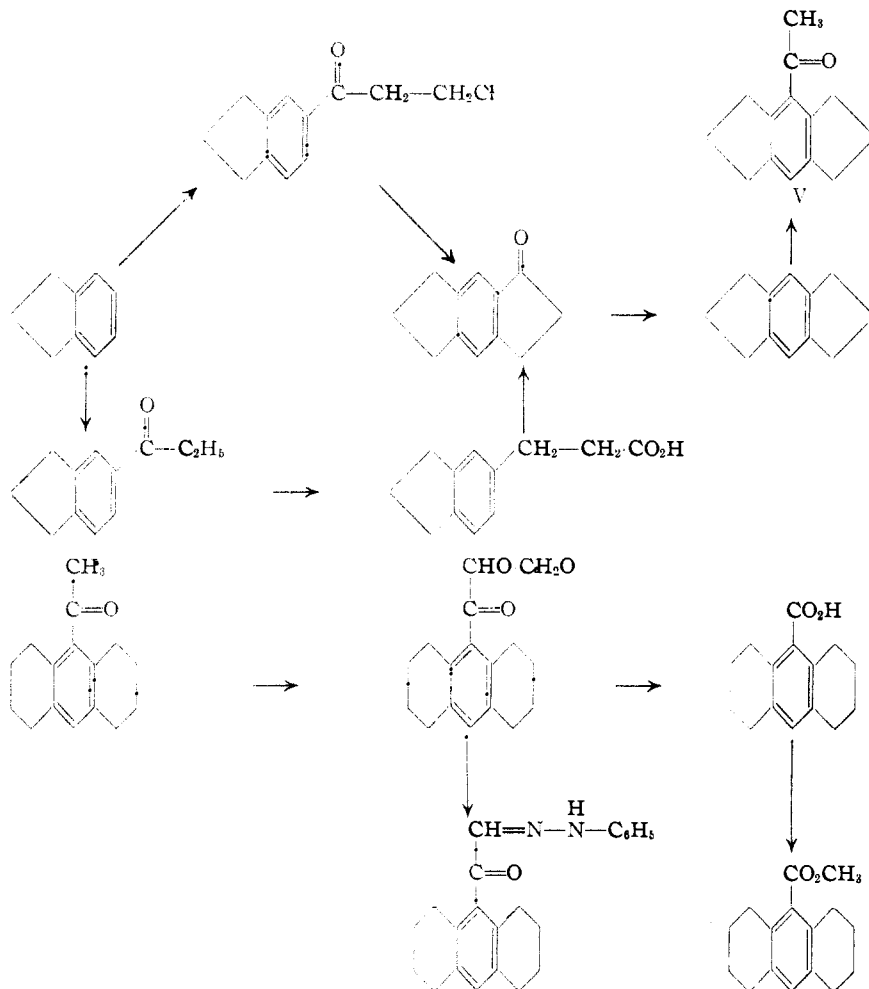
Although no absolute proof (synthetic or degradative) for the structure (V) has been obtained, the assigned formula 4-acetylhydrindacene is supported by the high yield of ketone in the Friedel–Crafts reaction and the reluctance of s-hydrindacene to isomerize in the presence of aluminum chloride at low temperatures.

This study of the relative steric effects of methylene groups in five- and six-membered rings will continue when conditions permit.

Experimental[5]

β-5-Hydrindenylpropionic Acid.—A mixture of 5-propionylhydrindene[1] (172.2 g.), morpholine (90 g.) and sulfur (33 g.) was heated for twenty-one hours at 130°. The cooled product was poured onto ice and after three hours a solid formed. This was triturated with alcohol and separated by filtration. Saponification of the precipitate with potassium hydroxide (60 g.) dissolved in water (600 cc.) gave an alkaline solution which after being extracted with ether and treated with norite was filtered. Acidification gave a tan precipitate which was further

(1) Arnold and Barnes, THIS JOURNAL, 66, 960 (1944).
(2) Mills and Nixon, J. Chem. Soc., 2510 (1930).
(3) Fuson, Chem. Rev., 15, 291 (1934).
(4) Arnold, Buckles and Stoltenberg, THIS JOURNAL, 66, 208 (1944).

O
‖
C—CH₂—CH₂Cl

O

O

CH₃
|
C=O

V

O
‖
C—C₂H₅

CH₂—CH₂·CO₂H

CH₃
|
C=O

CH₃
|
C=O

CHO CH₂O
|
C=O

CO₂H

CO₂H

H
|
CH=N—N—C₆H₅
|
C=O

CO₂CH₃

s-Hydrindacen-1-one.—
This compound was obtained by the cyclization of either 5-β-chloropropionylhydrindene or β-5-hydrindenylpropionic acid. The former procedure is to be preferred.

5-β-Chloropropionylhydrindene (45.6 g.) was added in small portions to concentrated sulfuric acid (180 cc.). During the addition the mixture was shaken and cooled frequently. After four hours on the steam-bath with occasional shaking the product was poured onto ice and extracted with benzene and water. Evaporation of the benzene solution gave a residue from which 19.0 g. of ketone was obtained by distillation in a sausage flask at reduced pressure (2–3 mm.). After one crystallization from petroleum ether (60–68°), the product melted at 69–75°. Sublimation and recrystallization gave pure s-hydrindacen-1-one; m. p. 80–81°.

The crude ketone (m. p. 69–75°, 19.0 g.) gave 8.9 g. of pure s-hydrindacene (m. p. 52.5–53.5°) when reduced according to the directions of Arnold and Barnes.[1]

4-Acetylhydrindacene.—
Hydrindacene (5.0 g.) was added to a well-stirred, cooled (ice–salt bath) mixture of aluminum chloride (20 g.) and tetrachloroethane (100 cc.). To this solution, acetic anhydride (6.6 g.) was added dropwise in the course of one hour. After two hours the reaction mixture was poured onto ice and hydrochloric acid, and worked up in the usual way; yield 4.4 g., b. p. 145–147° (4 mm.); m. p. 64–64.5° when crystallized from methanol.

Anal. Calcd. for C₁₄H₁₆O: C, 83.96; H, 8.05. Found: C, 83.79; H, 8.54.

Hydrindacene (2.0 g.), dissolved in tetrachloroethane (40 g.), was treated at 0° with aluminum chloride (8 g.) and allowed to stand for four hours. After decomposition with ice and hydrochloric acid there was obtained 0.79 g. of material (b. p. 1.10° (10 mm.)) from which 0.25 g. of pure hydrindacene could be recovered by crystallization. The main product of the reaction was polymeric. It is apparent that hydrindacene did not undergo an isomerization to 1,2,3,4-dicyclopentenobenzene during the course of the Friedel–Crafts reaction.

Haloform Reaction.—An aqueous solution of potassium hypochlorite prepared from bleaching powder (15 g. H.T.H.) was shaken with 4-acetylhydrindacene (0.9 g.) in methanol (80 cc.). A white precipitate formed and was separated by filtration; weight 0.5 g.; m. p. 64.5–65°. This neutral product contained no halogen. When a portion was mixed with the starting ketone (m. p. 64–64.5°), the sample melted at 40–52°. That this substance is a methyl ester was established by its synthesis from 4-hydrindacenecarboxylic acid and diazomethane.

Anal. Calcd. for C₁₄H₁₆O₂: C, 77.75; H, 7.46. Found: C, 77.89; H, 7.90.

The filtrate, formed after separating the methyl ester, was acidified and the resulting acid (0.2 g.) was separated by filtration. This compound was recrystallized from

purified by dissolving it in sodium bicarbonate, filtering, and then neutralizing the filtrate with hydrochloric acid. This sample of acid weighed 63.5 g. Distillation in a sausage flask at 3 mm. pressure gave 37.9 g. of product. This when recrystallized from acetic acid (50%) melted at 82–83.5°.[1]

Evaporation of the alcoholic extract of the crude thiomorpholide as obtained above gave a solid from which 5-hydrindenecarboxylic acid was isolated in small yield. The amide melted at 141–142°. v. Braun, *et al.*,[6] report 137–138°.

5-β-Chloropropionylhydrindene.[7]—A solution containing hydrindene (11.8 g.) and β-chloropropionyl chloride (12.7 g.) was added in the course of thirty minutes to a well-stirred solution of aluminum chloride (30 g.) in nitromethane (100 cc.) at room temperature. After four and one-half hours the mixture was decomposed with ice and hydrochloric acid and diluted with water to 1500 cc. After standing for one and one-half days, the tarry solid could be removed by filtration. This solid was dissolved in benzene and the resulting solution washed with dilute hydrochloric acid. Low temperature evaporation of the benzene gave a brown crystalline residue from which 15.5 g. of the expected product could be removed by using petroleum ether (30–60°) and a Soxhlet extractor; m. p. 68–69°.

Anal. Calcd. for C₁₂H₁₃OCl: C, 69.06; H, 6.28. Found: C, 69.25; H, 6.61.

(6) v. Braun, Kirschbaum and Schuhmann, *Ber.*, **53**, 1159 (1920).

(7) *Cf.* Mayer and Müller, *ibid.*, **60**, 2278 (1927).

aqueous ethanol; it sintered at 212° and melted at 229.5–231°.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98; neut. equiv., 202.6. Found: C, 77.31; H, 6.70; neut. equiv., 206.2.

Octahydroanthracene-9-glyoxal Hydrate.—9-Acetyl-octahydroanthracene (15 g.) was added to a stirred solution containing freshly sublimed selenium dioxide (7.3 g.), water (1.2 cc.) and dioxane (100 cc.) at 50–55°. The mixture was refluxed for four hours. Removal of the precipitated selenium, dilution with water, and cooling gave 14.1 g. of the glyoxal hydrate; m. p. 100–105° (dec.). This material although it crystallized well gave variable analytical results lying between those of the anhydrous and hydrated glyoxal. The monophenylhydrazone melted at 201.5–202.5°.

Anal. Calcd. for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28. Found: C, 79.54; H, 7.51.

Octahydroanthracene-9-carboxylic Acid.—To a solution of the glyoxal (4.0 g.) in ethanol (60 cc.) was added hydrogen peroxide (20 cc., 30%). Sodium hydroxide (10%) was added dropwise until vigorous reaction no longer occurred with each additional drop. The solution was warmed at 80° for thirty minutes, diluted with water, treated with

norite, filtered, cooled, and made acidic with hydrochloric acid. The crude acid was purified by recrystallization from aqueous ethanol; wt. 2.2 g. It sintered at 186° and melted at 216.5–219°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.17; H, 8.26.

The methyl ester, prepared by treating a solution of the acid in ether with diazomethane, melted at 74.5–75°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.87; H, 8.45.

Summary

1. 4-Acetylhydrindacene in the haloform reaction behaves as if it were an unhindered ketone, whereas 9-acetyloctahydroanthracene reacts like a hindered ketone.

2. This difference in the steric influence of the methylene groups in five- and six-membered rings supports the proposal by Mills and Nixon[2] that the orthomethylene groups in hydrindene are distorted toward one another.

Methyl 6-Iodo-6-desoxy-α-D-glucopyranoside

BY MORRIS ZIEF AND ROBERT C. HOCKETT

The methods most frequently employed to hydrolyze the acetates of sugars and sugar derivatives make use of mild alkaline agents.[1] Such agents are quite suitable for saponification of the esters of glycosides because of the extreme stability of the glycosidic link to bases. Acids, while suitable for catalysis of ester hydrolysis, are also able to attack the glycosidic link and are therefore much less selective.

However, when one acetoxyl group of an acetylated glycoside has been replaced by a halogen, the problem of selective hydrolysis of the ester linkages becomes a delicate one. The tendency of alkaline agents to attack the halogen as well as the acetyls and of acids to hydrolyze both esters and glycosides, requires dependence upon differences in the relative rates of the various reactions for selectivity.

Fischer, Helferich and Ostmann[2] obtained methyl 6-bromo-6-desoxy-β-D-glucopyranoside in an 88% yield from the corresponding triacetate by the action of a saturated solution of ammonia in methanol for five hours at room temperature. Oldham[3] obtained methyl 6-iodo-6-desoxy-β-D-

glucopyranoside in a "bad yield" from the triacetate by the action of a 5% methanol solution of dimethylamine.

When Helferich and Brederick[4] subjected methyl 2,3,4-triacetyl-6-chloro-6-desoxy-α-D-glucopyranoside to the action of 10% aqueous hydrochloric acid at steam-bath temperature for three hours, both the acetyl groups and methyl were removed and the product was 6-chloro-6-desoxy-D-glucose in an unspecified yield.

We were therefore rather surprised to discover that methyl 2,3,4-triacetyl-6-iodo-6-desoxy-α-D-glucopyranoside can be deacetylated without rupture of the glucosidic linkage by heating under reflux for two hours at steam-bath temperature with a mixture of two parts of 95% alcohol and five parts of 5% aqueous hydrochloric acid.

Our thanks are due to Hoffmann–LaRoche, Inc., for a fellowship under which the present investigation was carried out.

Experimental

Methyl 2,3,4-Triacetyl-6-tosyl-α-D-glucopyranoside.—The sirupy compound was prepared exactly as described by Compton[5] from a 10-g. sample of methyl α-D-glucopyranoside.

Methyl 2,3,4-Triacetyl-6-iodo-6-desoxy-α-D-glucopyranoside.—In the conversion of the tosyl to the iodo derivative the conventional sealed tube reaction with sodium iodide in acetone was eliminated. The entire sample of sirupy tosyl compound was dissolved in 250 cc. of methyl isobutyl ketone, which boils at 119°. A quantity of 22 g.

(1) Ammonia in methanol: Fischer and Bergmann, *Ber.*, **50**, 1047 (1917). Liquid ammonia: Fischer and Strauss, *ibid.*, **45**, 2467 (1917). Alcoholic dimethylamine: Irvine, Oldham and Skinner, THIS JOURNAL, **51**, 1279 (1929). Barium methylate: Weltzien and Singer, *Ann.*, **443**, 104 (1925). Sodium methylate: Fischer and Bergmann, *Ber.*, **52**, 830 (1919); Zemplén, *ibid.*, **59**, 1258 (1926); Zemplén and Kunz, *ibid.*, **56**, 1705 (1923); Zemplén and Pacsu, *ibid.*, **62**, 1613 (1929).

(2) Fischer, Helferich and Ostmann, *Ber.*, **53**, 876 (1920).

(3) Oldham, *J. Chem. Soc.*, **127**, 2844 (1925).

(4) Helferich and Brederick, *Ber.*, **60**, 1995 (1927).

(5) Compton, THIS JOURNAL, **60**, 397 (1938).