Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.77; H, 6.98.

Oxidation of the Enol IX.—The enol (1 g.) was added to a mixture of sulfuric acid (4 cc.) and nitric acid (12 cc.) at room temperature. Heat was evolved and brown oxides of nitrogen were given off; the solid dissolved completely within twenty seconds. The solution was warmed (60–70°) for one hour and then poured into water (50 cc.). The yellow solid was removed, washed with water and dried in vacuum over potassium hydroxide. It weighed 0.48 g. and melted at 88–94°. The material was extracted several times with warm petroleum ether (b. p. 60–68°); the combined extracts were evaporated and the residue was crystallized, first from petroleum ether and then from aqueous ethanol (50%). The material then weighed 97 mg. (16%) and melted at 109–111°, alone or when mixed with an authentic sample of nitrotrimethylquinone. The acetate X (1 g.) subjected to the above procedure, gave 72 mg. (13%) of nitrotrimethylquinone.

Action of Sodiomalonic Ester upon the Acetate X.—A solution of X (1.06 g., 0.003 mole) in dioxane (50 cc.) was slowly (ten minutes) added dropwise to a cooled solution of sodio malonic ester in dioxane (from sodium, 0.21 g., dimethyl malonate 1.33 g., and dioxane, 20 cc.). The solution was stirred for six hours at room temperature and allowed to stand thereafter for fifteen hours. There was no apparent reaction; when the mixture was poured into water (200 cc.) and hydrochloric acid (10 cc.), the precipitate (0.9 g.) consisted of unchanged X, which, after crystallization from ethanol, melted at 193–194°, alone or when mixed with authentic X. The experiment was repeated, except that the solution was refluxed for two hours and then allowed to stand at room temperature for eighteen hours before pouring it into water (500 cc.) and hydrochloric acid (10 cc.). The orange brown product weighed 0.96 g. and melted at 160–210°. It was extracted twice with petroleum ether (100 cc., b. p. 60–68°); this removed 0.19 g. of material (X) which melted at 192–194° after crystallization from methanol. The residue was extracted exhaustively (10 times) with petroleum ether, leaving a red material (0.11 g.) which, after crystallization from methanol, melted at 253–255° (dec.) alone or when mixed with IX.

Action of Sodiomalonic Ester upon the Methyl Ether XII.—A solution of the methyl ether XII in dioxane (100 cc.) was added to a solution of sodiomalonic ester (from sodium, 0.46 g., methyl malonate, 2.9 g., and dioxane, 20 cc.). The mixture was stirred for three hours; there was no apparent reaction. The mixture was then refluxed and stirred for three hours; the color became red within a few minutes, and a dark red solid separated. The solid was removed, washed with dioxane, triturated with acetone (50 cc.) and then suspended in acetone. Hydrochloric acid (1 cc.) and then water (100 cc.) were added; the tan amorphous material was removed in vacuum over potassium hydroxide. It weighed 1.25 g., and melted at 147–195°. The filtrate from this material was acidified with hydrochloric acid (15 cc.) and diluted with water (1.5 l.). The yellow, amorphous solid was removed; it weighed 2.4 g. and melted at 110–145°. Neither solid could be resolved into any pure materials by crystallization from any of the common solvents or mixtures of solvents, nor was any resolution into pure materials achieved by chromatographic adsorption on alumina. Essentially, the same results were obtained when cyanoacetic ester was substituted for malonic ester; from 2.16 g. of XII, the only pure material obtained was a small amount of unchanged XII.

Summary

1. A new and efficient synthesis for bis-(2,4,5-trimethylquinonyl)-methane (I) has been devised, and the transformations of this substance have been studied.

2. The bis-quinone has been converted, by action of pyridine, into a stable isomer IX, and evidence has been accumulated to show that this isomer is a stable pentad-enol of an alkylated quinone, the first of its class to be prepared.

3. The diquinone I, as well as two derivatives of the isomeric enol, all failed to add sodio malonic ester.

4. The structure of the high melting by-product obtained from chloromethylation of trimethylhydroquinone diacetate has been established as 2,2'-dihydroxy-5,5'-diacetoxyhexamethyldiphenylmethane, II.

MINNEAPOLIS 14, MINNESOTA

RECEIVED FEBRUARY 4, 1950

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

The Rearrangement of α,α,α'-Tribromoketones

BY R. B. WAGNER AND JAMES A. MOORE

In the course of studies of steroidal bromoketones, these compounds have been found to be generally very susceptible to rearrangements when subjected to basic reagents. The α-bromo-*s*-alkyl ketones when treated with mild base undergo a rearrangement to esters of tertiary acids, *e. g.*, 17-bromopregnane-3(β)-ol-20-one to methyl 3(β)-hydroxy-17-methyl-*etio*-cholanate. This reaction is analogous to the Favorski rearrangement in which α-chlorocyclohexanones are converted by alkali into cyclopentanecarboxylic acids[1,2,3] (Eqn. 1). The rearrangement of α,α'-dibromoketones under similar conditions gives esters of α,β-unsaturated acids, *e. g.*, 17,21-dibromopregnane-3(β)-ol-20-one to methyl 17-pregnene-3(β)-ol-21-oate; a reaction first discovered by Favorski and recently extended to simple aliphatic and alicyclic α,α'-dibromoketones (Eqn. 2).[4,5,6] The rearrangement of a steroidal α,β-dibromoketone, namely, 16,17-dibromopregnene-3(β)-ol-20-one, gave this same pregnenoic ester. On the other hand, extension of this rearrangement to simpler alicylic and aliphatic α,β-dibromoketones showed that β,γ-unsaturated

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[1] Favorski and Boshowski, *J. Russ. Phys.-Chem. Soc.*, **46**, 1097 (1914); *Chem. Zentr.*, **85**, I, 984 (1915).

[2] Aston and Greenburg, THIS JOURNAL, **62**, 2590 (1940).

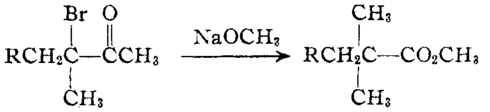
[3] Marker and Wagner, *ibid.*, **216**, 1273 (1942).

[4] Marker, Crooks and Wagner, *ibid.*, **64**, 213, 817 (1942).

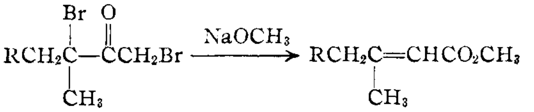
[5] Favorski, *J. prakt. Chem.*, [2], **88**, 658 (1913).

[6] Wagner and Moore, THIS JOURNAL, **72**, 974 (1950).

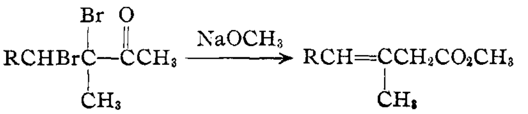
esters were obtained (and if unstable, underwent a migration of the double bond)[7,8] (Eqn. 3).



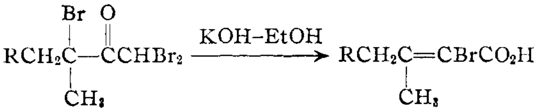
$$\mathrm{RCH_2\overset{Br}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{NaOCH_3} RCH_2\overset{CH_3}{\underset{CH_3}{C}}-CO_2CH_3} \tag{1}$$



$$\mathrm{RCH_2\overset{Br}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}CH_2Br \xrightarrow{NaOCH_3} RCH_2\underset{CH_3}{C}{=}CHCO_2CH_3} \tag{2}$$



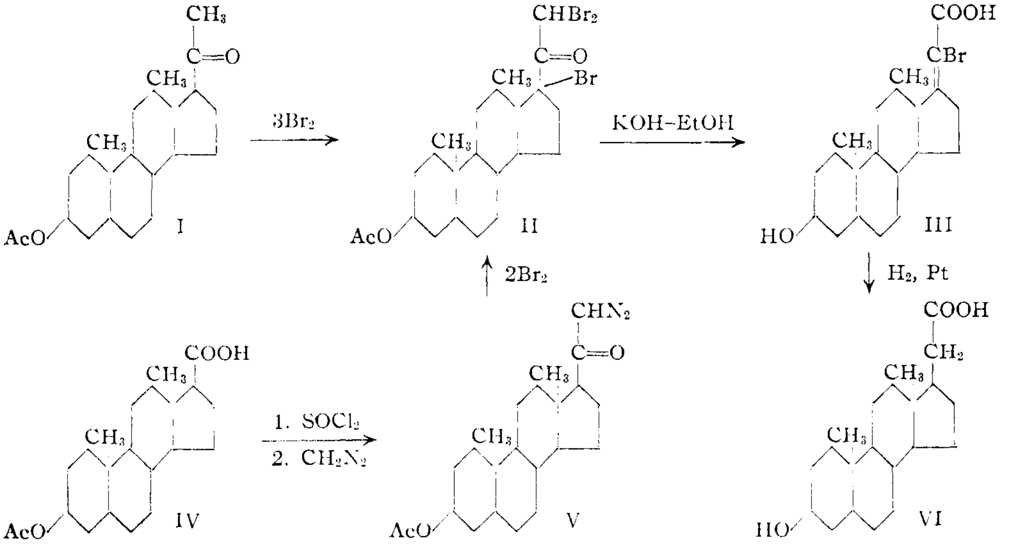
$$\mathrm{RCHBr\overset{Br}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{NaOCH_3} RCH{=}\underset{CH_3}{C}CH_2CO_2CH_3} \tag{3}$$



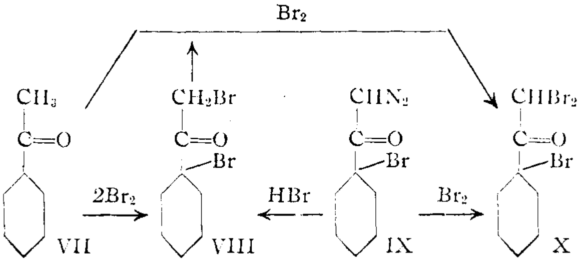
$$\mathrm{RCH_2\overset{Br}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}CHBr_2 \xrightarrow{KOH-EtOH} RCH_2\underset{CH_3}{C}{=}CBrCO_2H} \tag{4}$$

We have now prepared a steroidal tribromoketone, 17,21,21-tribromopregnane-3(β)-ol-20-one acetate (II), and subjected it to rearrangement conditions, namely, heating with alcoholic potassium hydroxide. The product was an α-bromo-α,β-unsaturated acid, 20-bromo-17-pregnene-3(β)-ol-21-oic acid (III), obtained in 57% yield.

Following our previous practice, this rearrangement (Eqn. 4) has been extended and further studied with simpler compounds as model substances, namely, the tribromo derivatives of methyl isopropyl ketone and methyl cyclohexyl ketone. These compounds underwent the same reaction, giving the α-bromo-α,β-unsaturated acid, although in considerably lower yield (10–30%).



The tribromoketones were most readily prepared from either the parent ketone or the α,α'-dibromoketone by direct bromination. The position of the bromine atoms has been ascertained by preparing two of the compounds by alternate and unequivocal routes. The direct dibromination of methyl cyclohexyl ketone (VII) has been reported,[6] and the structure of the resulting 1-(bromoacetyl)-1-bromocyclohexane (VIII) was confirmed by its synthesis from diazomethyl α-bromocyclohexyl ketone (IX). The tribromoketone (X) resulting from the reaction of this diazoketone (IX) with bromine is identical with the tribromoketone obtained by direct bromination of VII or VIII. Similarly, the 21-diazoketone (V) from 3(β)-acetoxy-*etio*-cholanic acid (IV) on treatment with two moles of bromine gave the same tribromoketone (II) as before.



The unsaturated bromo acid (III) obtained from this rearrangement is unchanged by further treatment with potassium hydroxide, indicating the stability of the bromine atom. This behavior is to be expected since both the α-bromocarboxyl and the vinyl bromide systems are unreactive under basic conditions. The bromine atom in the steroidal acid (III) is not easily removed by zinc in acetic acid treatment; however with hydrogen in acetic acid (PtO_2), the reduction is readily accomplished to give pregnan-3(β)-ol-21-oic acid (VI), previously described.[4]

The double bond in the steroidal acid is unusually resistant to oxidation, being recovered unchanged from attempted permanganate and

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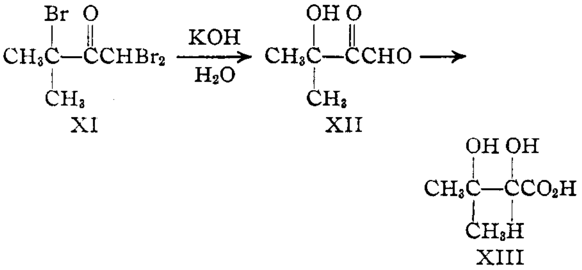
(7) Marker, Wagner and Wittbecker, This Journal, **64**, 2093 (1942).

(8) Wagner, *ibid.*, **71**, 3214 (1949).

chromic acid oxidations. The bromocyclohexylideneacetic acid was successfully oxidized with hot neutral permanganate, however, to yield cyclohexanone.

Although no other products were isolated in these rearrangements, it seems quite likely that a second reaction, namely, metathesis in the form of hydrolysis, might occur to a varying extent. Favorski[6] has reported the reaction of 1,1,3-tribromo-3-methyl-2-butanone (XI) with aqueous caustic to yield β,β-dimethylglyceric acid (XIII), and this product was considered to be the result of a hydrolysis followed by an internal oxidation–reduction or proton shift of the intermediate ketoaldehyde (XII). This postulation receives considerable support from the recent work of Neville,[9] who has demonstrated by the use of isotopic carbon that the conversion of α,α-dibromoacetophenone to mandelic acid is not accompanied by carbon-skeleton rearrangement. It should be pointed out that no attempt was made in the present work to isolate such metathesis products.



$$CH_3\overset{Br}{\underset{CH_3}{C}}-\overset{O}{C}CHBr_2 \xrightarrow[H_2O]{KOH} CH_3\overset{OH}{\underset{CH_3}{C}}-\overset{O}{C}CHO \longrightarrow CH_3\overset{OH}{\underset{CH_3}{C}}-\overset{OH}{\underset{H}{C}}CO_2H$$

XI XII XIII

While no definitive evidence is available as yet, it appears that the formation of the unsaturated bromo acid from a tribromoketone (Eqn. 4) involves a process which is formally analogous to that which occurs in the transformation of an α,α'-dibromoketone to an α,β-unsaturated acid (Eqn. 2). This latter reaction has been definitely found to involve carbon-skeleton rearrangement.[6]

We thank Parke, Davis and Co. for their assistance.

Experimental[10]

17,21,21-Tribromopregnan-3(β)-ol-20-one Acetate (II).—This compound was prepared by three different procedures which are described below. The most reliable criterion of the relative merits of these procedures was found to be the yield and purity of the acid which was obtained by treatment of the resulting tribromoketone with potassium hydroxide. When procedures (a) and (b) were used, it was necessary to recrystallize the crude tribromoketone before treatment with alkali in order to realize even a moderately successful conversion to the bromo acid. Since the tribromoketone is quite sensitive to warming in solvents, some material was lost during this process, and the over-all yield of the desired bromo acid was always lower than that obtained when procedure (c) was employed for the preparation of the tribromoketone. In the latter case, the crude tribromoketone could be utilized directly in the rearrangement reaction to give significantly higher over-all yields of the acid.

(a) **From Pregnan-3(β)-ol-20-one Acetate (I).**—To a solution of 5 g. of pregnanolone acetate in 200 cc. of acetic acid was added 42 cc. of 1 *M* bromine in acetic acid solution. The first two equivalents of bromine were rapidly decolorized at room temperature; the solution was warmed to 60° during the addition of the third equivalent of bromine. After standing at this temperature for thirty minutes, the solution was cooled and poured into one liter of ice-water. The tan precipitate was filtered, washed free of acid and dried. This material was recrystallized from 80 cc. of acetone to yield 4.8 g. of white needles, m. p. 191–193° (dec.), $[\alpha]^{25}D$ $-3.4 \pm 0.2°$ (c = 3.56 in chloroform). A mixed m. p. of this material with 17,21-dibromopregnan-3(β)-ol-20-one acetate, m. p. 190–191°, showed no depression.

Anal. Calcd. for $C_{23}H_{33}O_3Br_3$: Br, 40.1. Found: Br (Stepanoff), 40.3.

(b) **From 17,21-Dibromopregnan-3(β)-ol-20-one Acetate.**—To a solution of 4.5 g. of dibromopregnanolone acetate[4] in 160 cc. of acetic acid was added 3 drops of concentrated hydrobromic acid, and then 8.70 ml. of 1 *M* bromine in acetic acid solution was added in *ca.* 0.3-cc. portions. The temperature of the solution was maintained at 70°; each portion of the bromine solution was decolorized in two minutes. After cooling, the reaction mixture was poured into water, and the precipitated tribromoketone was filtered, washed free of acid, dried and recrystallized from acetone to yield 3.2 g. of white needles, m. p. 193–196° (dec.). Further recrystallization lowered the melting point to 185–190° (dec.).

(c) **From Dibromopregnanolone Acetate in the Presence of Sodium Acetate.**—It was thought that some of the difficulties encountered in the above procedures may have resulted from the action of hydrogen bromide; accordingly, bromination in the presence of sodium acetate was investigated. To a solution of 5 g. of the dibromopregnanolone acetate and 5 g. of fused sodium acetate in 400 cc. of acetic acid was added 9.7 ml. of 1 *M* bromine in acetic acid solution. All of the bromine was added at once, and the solution was allowed to stand at 30° for ten hours. The bromine color was not perceptibly lighter after this time, so the solution was warmed to 70°, and after one hour the color was pale yellow. After cooling, the solution was poured into water. The white precipitate was washed free of acid and treated directly under rearrangement conditions.

17,21,21-Tribromopregnan-3(β)-ol-20-one Acetate (II) from 21-Diazo-pregnan-3(β)-ol-20-one Acetate (V).—A solution of the 21-diazoketone was prepared from 660 mg. of 3(β)-acetoxy-*etio*-cholanic acid by the procedure of Reichstein and Fuchs,[11] *via* the acid chloride. The amorphous yellow ketone was dissolved in 10 cc. of redistilled chloroform, and to this solution was added 18.2 cc. of 0.1 *M* bromine in chloroform solution. The bromine was decolorized immediately, and nitrogen evolution was rapid. The chloroform was removed *in vacuum*, and the residual 21,21-dibromopregnane-3(β)-ol-20-one acetate was dissolved in 20 cc. of acetic acid. The yellow solution was treated with 1.8 cc. of 1 *M* bromine in acetic acid and warmed for ten minutes at 50°. At the end of this time, the solution gave a negative potassium iodide–starch test. The solution was then poured into water, and the oily precipitate was extracted with ether. The ethereal solution was washed with dilute potassium hydroxide solution and water, dried, and evaporated. The concentrated solution deposited two small crops of white crystals upon cooling, yield, 215 mg., m. p. 182–183° (dec.).

For characterization, this material was converted to the rearrangement product, 20-bromo-17-pregnene-3(β)-ol-21-oic acid, in the manner described below. The acid, which crystallized from ether, was recrystallized from methanol to give fine white needles, m. p. and mixed m. p. with an authentic sample of the bromo acid, 261–262° (dec.).

20-Bromo-17-pregnene-3(β)-ol-21-oic Acid (III).—This compound was prepared several times, and different sol-

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[9] Neville, THIS JOURNAL, **70**, 3499 (1948).

[10] All melting points are uncorrected. All rotations were observed in a 1-dm. tube of 2-cc. capacity.

[11] Reichstein and Fuchs, *Helv. Chim. Acta*, **23**, 658 (1940).

vents were employed for the rearrangements; methanol, ethanol, propanol and dioxane–water were used, and the same product was obtained in all cases. The most satisfactory conditions which were found are described.

To a solution of 3.0 g. of 17,21,21-tribromopregnan-3-(β)-ol-20-one acetate in 600 cc. of boiling ethanol was added 12 g. of potassium hydroxide in 40 cc. of aqueous ethanol. The solution was refluxed for two hours, and the alcohol was then removed *in vacuum* until solid material separated. The residue was diluted with water and extracted with several portions of ether to remove neutral products. The aqueous layer, containing the sparingly soluble potassium salt of the acid, was treated with an excess of dilute sulfuric acid, and the organic acid was then extracted with ether. The ethereal solution was washed with water, dried with sodium sulfate and concentrated. When the volume was reduced to 100 cc., crystals began to appear. After further concentrating the solution, the crystals were filtered and dried, m. p. 264–265° (dec.), yield 1270 mg. The material was recrystallized from methanol to give glistening prisms, m. p. 271–273° (dec.), $[\alpha]^{25}\text{D}$ +41 ± 1° (c = 1.608 in dioxane).

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.4; H, 7.6; Br, 19.4. Found: C, 62.0; H, 7.7; Br, 19.1.

In a larger experiment, the tribromoketone which was obtained from 5 g. of dibromoketone was treated in the manner described, and a yield of 2.25 g. of bromoacid was obtained, representing a yield of 57% of the theoretical.

Methyl Ester of 20-Bromo-17-pregnene-3(β)-ol-21-oic Acid.—To a solution of 400 mg. of the bromopregnenoic acid in 15 cc. of dioxane and 15 cc. of ether was added an excess of an ethereal solution of diazomethane. After standing at 25° for thirty minutes, the mixture was treated with acetic acid to destroy the excess diazomethane, and the solvents were removed *in vacuum.* The residue was dissolved in ether, and the solution was washed with dilute potassium hydroxide and water. The ethereal solution was dried and evaporated to yield long fine needles, m. p. 143–146°, yield 380 mg. The ester was recrystallized from methanol, m. p. 152–153°, $[\alpha]^{25}\text{D}$ +37 ± 1° (c = 2.40 in chloroform).

Anal. Calcd. for $C_{22}H_{33}O_3Br$: C, 62.1; H, 7.8; Br, 18.8. Found: C, 61.9; H, 7.8; Br, 18.4.

This compound furnished an acetate by the pyridine–acetic anhydride method which crystallized from ether as large needles, m. p. 180–182°.

Anal. Calcd. for $C_{24}H_{35}O_4Br$: C, 61.7; H, 7.6. Found: C, 61.1; H, 7.5.

Reduction of 20-Bromo-17-pregnene-3(β)-ol-21-oic Acid.—A solution of 500 mg. of the bromo acid in 150 cc. of acetic acid was shaken with 500 mg. of Adams catalyst in an atmosphere of hydrogen for two hours at 3 atm. pressure.

The contents of the bottle were filtered and the solvent was removed *in vacuum.* The crystalline residue was recrystallized twice from methanol to yield white crystals, m. p. and mixed m. p. with pregnan-3(β)-ol-21-oic acid (VI), 217–220°.

For further comparison, a sample of this material was converted to the methyl ester with diazomethane. The product crystallized as plates, m. p. and mixed m. p. with methyl pregnan-3(β)-ol-21-oate, 138–140°.

1-(Dibromoacetyl)-1-bromocyclohexane (X): (a) By Direct Bromination.—Methyl cyclohexyl ketone (VII), 31.5 g. (0.25 mole), was treated dropwise with stirring with 120 g. (0.75 mole) of bromine. The first two moles of bromine reacted readily at 0°; the reaction mixture was warmed to 60° for the introduction of the third bromine atom. After all of the bromine had reacted, the material was cooled, and the entire mass crystallized. The tribromoketone was dissolved in ether and the solution washed with water to remove the hydrogen bromide. This solution was then dried and concentrated to a volume of 150 ml. Two crops of large white crystals were obtained, m. p. 72.5–74°, yield 72 g. (80%).

Anal. Calcd. for $C_8H_{11}OBr_3$: Br, 66.1. Found: Br (Stepanoff), 66.5.

This material was extremely resistant to further bromination; in one preparation, an excess of bromine was used, and the mixture was refluxed for some time. The tribromoketone was obtained in excellent yield.

(b) From Diazomethyl α-Bromocyclohexyl Ketone (IX).—A solution of 1 g. of the bromodiazoketone[6] in 5 cc. of carbon tetrachloride was treated with bromine–carbon-tetrachloride solution. The reaction was quite vigorous, refluxing the solvent. When the evolution of nitrogen had ceased, the solvent was removed, and the crystalline residue was recrystallized from ether–pentane, m. p. and mixed m. p. 73–74°.

α-Bromocyclohexylideneacetic Acid.—To a solution of 4 g. of the tribromomethyl cyclohexyl ketone (X) in 300 cc. of 95% ethanol was added 8 g. of potassium hydroxide. After refluxing for twenty minutes, the mixture was concentrated *in vacuum,* and the residue was dissolved in ether and water. The aqueous solution was extracted with ether to remove neutral products, and then it was acidified with dilute sulfuric acid. The solid acid which precipitated was recrystallized from aqueous methanol, m. p. 118–119.5°. A second crop of acid was obtained from the combined mother liquors after four days standing; the total yield was 800 mg. (33%).

Anal. Calcd. for $C_8H_{11}O_2Br$: C, 43.9; H, 5.1. Found: C, 43.9; H, 5.0.

Oxidation of α-Bromocyclohexylideneacetic Acid.—To a stirred suspension of 400 mg. of the bromo acid in 50 ml. of hot water was added an aqueous solution of 660 mg. of magnesium permanganate. The mixture was then steam-distilled, and a small portion of the distillate was treated with 2,4-dinitrophenylhydrazine. After two crystallizations from alcohol, the derivative was obtained as golden plates, m. p. and mixed m. p. with the 2,4-dinitrophenylhydrazone of cyclohexanone, 159–160°.

α-Bromo-β,β-dimethylacrylic Acid.—The tribromo ketone used in this reaction, 1,1,3-tribromo-2-butanone, was obtained as a by-product in the dibromination of methyl isopropyl ketone and had m. p. 52°, which agrees with the value reported by Favorskii.[5]

For the rearrangement, 8 g. of the tribromo ketone in 40 cc. of 60% ethanol was refluxed for thirty-five minutes with 12 g. of potassium hydroxide. After removing the solvent *in vacuum,* the residue was processed in the usual manner to yield 420 mg. of a crystalline acid. The material was recrystallized from hot water to yield white needles, m. p. 88.5–90°.[12]

Anal. Calcd. for $C_5H_7O_2Br$: neut. equiv., 179. Found: neut. equiv., 180.

Summary

1. A steroidal tribromoketone, 17,21,21-tribromopregnan-3(β)-ol-20-one acetate, has been prepared and found to undergo rearrangement under basic conditions to yield an α-bromo-α,β-unsaturated acid, namely, 20-bromo-17-pregnene-3(β)-ol-21-oic acid (III).

2. The reaction has been extended to simpler compounds and found to be general.

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Received December 21, 1949

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[12] Doeuvre, *Bull. soc. chim.*, [4] **39**, 1599 (1926), reports for α-bromo-β,β-dimethylacrylic acid m. p. 88–89°.