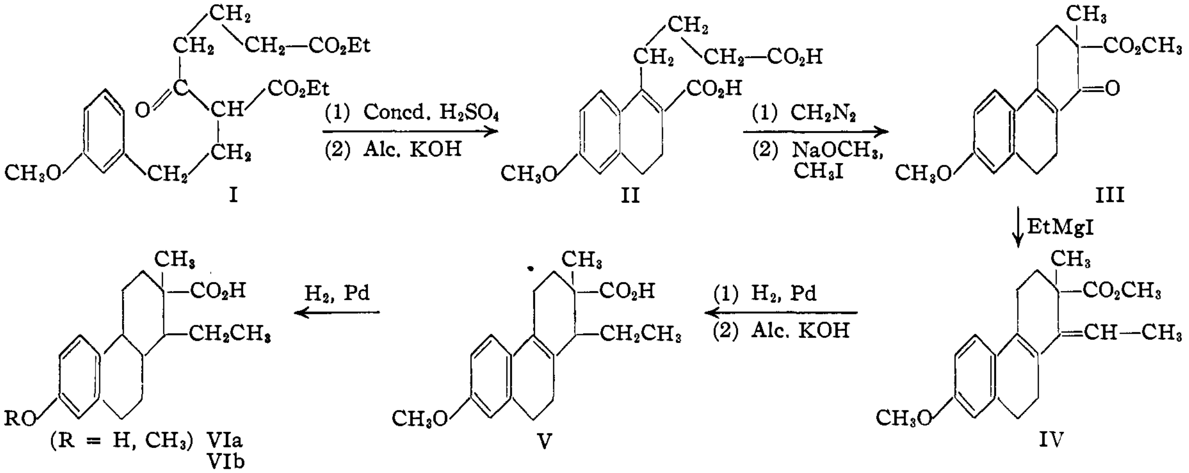
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Synthetic Sterols. III.[1] Isomers of 1-Ethyl-2-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic Acid

BY JAMES H. HUNTER AND JOHN A. HOGG

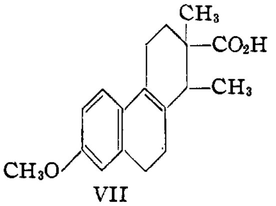
The complete hydrogenation and subsequent demethylation of methyl 1-ethylidene-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate (IV) to a mixture of isomers of structure VI[2] (R' = H) was reported previously from this laboratory.[3] Compound IV was prepared by the action of ethylmagnesium iodide on the ketone III. Since that time we have endeavored to evaluate partially the applicability of the isomer technique described in the previous paper of this series[1] by the stepwise hydrogenation of IV, although this method of synthesis does not utilize completely the variations of that technique.

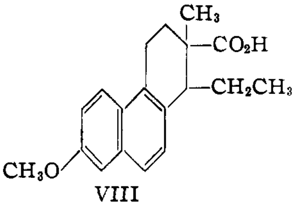
CHART I

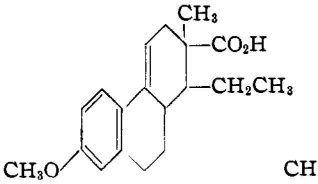


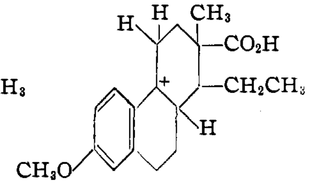
Recently Anner and Miescher[4] have prepared five of the eight isomeric forms of VI (R = CH_3) by the reaction of an ethylmagnesium halide with methyl-1-keto-2-methyl-7-methoxy-1,2,3,4,9,10,-11,12-octahydrophenanthrene-2-carboxylate (prepared from the ketone III[5] by catalytic reduction) and hydrogenation of the resultant double bond. These authors have also eliminated the double bonds in IV in a stepwise manner. The final hydrogenation, which was more sluggish, gave small amounts of two of the forms of VI (m. p. 187–188° and 213–215°), hence this was apparently not as satisfactory for them as the above mentioned procedure.

We have noted the same marked change in the reaction rate of IV with hydrogen in the presence of palladium on Norite after one mole of hydrogen had been absorbed. The reaction was terminated when one mole of hydrogen was absorbed, and the resulting material was hydrolyzed by heating under reflux for several hours in alcoholic potassium hydroxide. The potassium salt which remained after removal of the alcohol was partially insoluble in water. This insoluble salt yielded the acid V. The position of the double bond in this acid is most probably in the 11,12-position, as is indicated by the comparison of its ultraviolet absorption curve (see Fig. 1) with that of 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (VII, max. 272 mμ) reported in an earlier paper.[1,6] None of the geometric isomer of V was obtained from the alkali-soluble portion of the crude hydrogenation product.


VII


VIII


IX


X

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[1] For previous paper of this series see Hogg, THIS JOURNAL, **71**, 1918 (1949).

[2] Compound VI (R = H), or doisynolic acid, was characterized as the degradation product resulting from the action of potassium hydroxide with estradiol. Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944).

[3] Hunter and Hogg, THIS JOURNAL, **68**, 1676 (1946).

[4] Anner and Miescher, *Helv. Chim. Acta*, **30**, 1422 (1947).

[5] Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 977 (1942).

[6] Hogg, *ibid.*, **70**, 161 (1948).

The acid V was resistant to hydrogenation in the presence of palladium when treated in salt form in an aqueous-alcoholic sodium hydroxide solution. By applying the procedure used in the second paper of this series[1] to V, namely, by hydrogenating the double bond in alcoholic solution in the presence of palladium on Norite and isolating the resulting isomers of VI by virtue of the difference in their solubility in aqueous alkali, two forms of VI (R = CH_3) were obtained in good combined yield. The more insoluble salt yielded an acid melting at 188–190°, while the alkali-soluble acid melted at 133–134°. When diethylamine was added to an alcohol solution of V with the same catalyst, the hydrogenation reaction yielded a larger proportion of the acid (VIa) melting at 188–190°, while none of the acid (VIb) melting at 133–134° was obtained. However, under these conditions a very small amount of an acid melting at 228° was obtained. The ultraviolet absorption curve (max. 235, 266, 276, 320, and 335) shows that this acid contains the naphthalene nucleus; this is likely the estrogenic acid of Heer, Billeter and Miescher[7] (VIII) which is reported to melt at the same temperature.

The compounds VIa and VIb showed identical maxima in their ultraviolet absorption curves (280 mμ), which is in good agreement with that of 6-methoxytetralin (max. 280 mμ).

When V (m. p. 174–175°) was treated with dry hydrogen chloride in benzene solution, the resulting crude product was found to melt at 130–140°. By a process utilizing the differential solubility of the alkali salts combined with a process of fractional crystallization, a small amount of a new acid isomeric with V was obtained (m. p. 144–146°). The ultraviolet absorption maxima of this isomeric acid are 273 and 225 mμ, while V shows a maximum at 272 mμ and the approach to a maximum below 220 mμ (see Fig. 1). No effect was observed when V was treated with dry hydrogen chloride in ether. It is suggested that the double bond in V has migrated to a new position, possibly 4–12, since the absorption data indicate conjugation with the benzene ring. It is conceivable that such a rearrangement can occur by the addition of hydrogen ion to the double bond of V at the 11-position resulting in a carbonium ion at the 12-position as shown in X. In the reverse reaction hydrogen ion may be abstracted from either the 4- or 11-position to give the rearranged acid (IX) or the starting acid (V), respectively. The amount of IX isolated was too small for complete characterization. It is believed that reversion to the original form (V) occurs during the isolation process. A considerable quantity of V was recovered, but none of the geometric isomer of V.

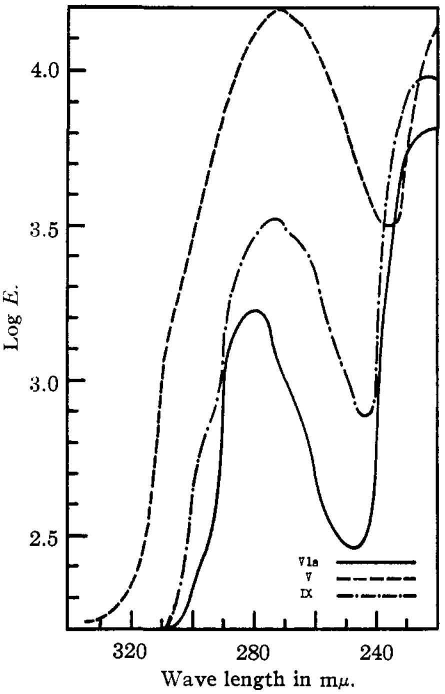

Fig. 1.

The ketone III[5] was prepared by a modified procedure. *m*-Methoxyphenylacetic acid[8] was esterified in absolute ethyl alcohol saturated with dry hydrogen chloride, and the resulting ester reduced to *m*-methoxyphenylethyl alcohol by means of sodium in ethanol in an over-all yield of 40–50%. By a superior method,[9] the acid was reduced directly to the alcohol in 90% yield with lithium aluminum hydride. The alcohol was then converted to *m*-methoxyphenylethyl bromide with phosphorus tribromide.[5]

Diethyl β-ketopimelate was prepared according to the general method of Riegel and Lilienfield[10] (γ-carbethoxybutyryl chloride[5] was condensed with magnesium malonic ester, and the resulting acyl derivative of ethyl malonate was decarbethoxylated by heating with naphthalenesulfonic acid monohydrate.). *m*-Methoxyphenylethyl bromide was condensed with the β-ketopimelate in the presence of potassium tertiary butoxide. The condensation product (I) was cyclized by means of concentrated sulfuric acid to give II in 84% yield. The latter dibasic acid was then converted to III by the method of Bachmann, Kushner and Stevenson.[5]

The acids VIa (R = CH_3) and VIb (R = CH_3) showed estrogenic activity in white rats when assayed[11] by the Kahnt–Doisy method in doses of 0.73 and 10.6 γ, respectively. Acid V was active at 0.36 γ.

Experimental[12]

Ethyl *m*-Methoxyphenylacetate.—*m*-Methoxyphenylacetic acid (166 g., 1 mole) in one liter of commercial ab-

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[7] Heer, Billeter and Miescher, *Helv. Chim. Acta*, **28**, 1343 (1945).

[8] Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

[9] Nystrom and Brown, *ibid.*, **69**, 2548 (1947).

[10] Riegel and Lilienfield, *ibid.*, **67**, 1273 (1945).

[11] The estrogenic assays were carried out by Stanley C. Lyster of the Department of Pharmacology, The Upjohn Company.

[12] All melting points are uncorrected.

solute ethanol was treated with dry hydrogen chloride gas until 98 g. had been absorbed. The mixture was heated under reflux for three hours and allowed to stand overnight. The solvent was removed under diminished pressure, and the residue treated with water. The ester was extracted with ether. The ether layer was washed with water, 10% sodium carbonate solution, and again with water. After drying with magnesium sulfate, the ether was removed, and the residue distilled. There was obtained 167 g. (86%) of ethyl *m*-methoxyphenylacetate boiling at 141–143° (12 mm.).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.07; H, 7.30.

m-**Methoxyphenylethyl Alcohol. (A) By Reduction of Ethyl *m*-Methoxyphenylacetate with Sodium in Alcohol.**—One mole of the ester (194.22 g.) in 1200 cc. of absolute ethyl alcohol was heated to vigorous boiling under reflux, and 173 g. (7.5 moles) of sodium added as rapidly as possible. After the addition of all of the sodium one liter of commercial ethyl alcohol was added in portions. The mixture was heated under reflux vigorously for two hours. The alcohol was removed by steam distillation. The residue was diluted with water and extracted three times with ether. The organic layer was washed with water and dried over magnesium sulfate. On distillation there was obtained 81.50 g. (53.5%) of *m*-methoxyphenylethyl alcohol (b.p. 141–143° at 12 mm.).

(B) By Reduction of *m*-Methoxyphenylacetic Acid with Lithium Aluminum Hydride.—A solution of 332 g. (2 moles) of *m*-methoxyphenylacetic acid in two liters of dry ether was added dropwise to a suspension of 95 g. (1.87 moles) of lithium aluminum hydride in two liters of dry ether. Stirring was continued for fifteen minutes after the addition of the acid. Excess water was added cautiously, followed by 2500 cc. of 10% sulfuric acid. The ether layer was separated and washed with dilute sodium carbonate and then with water. After drying over anhydrous magnesium sulfate and removal of the solvent, 275 g. (90%) of *m*-methoxyphenylethyl alcohol was distilled at 145° (13 mm.).

Diethyl β-Ketopimelate.—Diethyl malonate (240 g., 1.5 moles) in 120 cc. of absolute ethyl alcohol was added from a dropping funnel to 37.5 g. of magnesium in 40 cc. of absolute ethyl alcohol containing 1.5 cc. of carbon tetrachloride. Ether (450 cc.) was then added, and the mixture heated under reflux for six hours. The ether was removed, benzene added, and this in turn was removed under reduced pressure.

The magnesium malonate thus prepared was caused to react with 285 g. of γ-carbethoxybutyryl chloride[5] essentially in the manner employed by Riegel and Lilienfield.[10]

The yield of diethyl β-ketopimelate of boiling point 120–121° at 0.15 mm. was 30%.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.35; H, 7.88. Found: C, 57.23; H, 7.92.

Diethyl α-(*m*-Methoxyphenylethyl)-β-ketopimelate (I).—In an atmosphere of nitrogen, 152 g. (0.662 mole) of diethyl β-ketopimelate was added to a stirred solution of 25.8 g. (0.662 mole) of potassium in 500 cc. of anhydrous tertiary butanol. Then 154 g. (0.715 mole) of *m*-methoxyphenylethyl bromide was added rapidly, and the mixture heated under reflux for twelve hours. After filtration from potassium bromide the solvent was removed under reduced pressure. The residue was taken up in ether, washed three times with water, dried over anhydrous magnesium sulfate, and distilled. The product (I) distilled at 215–220° (0.6 mm. pressure) and weighed 130 g. (45%).

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.88. Found: C, 66.47; H, 7.92.

γ-(6-Methoxy-2-carboxy-3,4-dihydro-1-naphthyl)-butyric Acid (II).—The substituted β-ketopimelate (I) (75 g., 0.205 mole) was cooled to −20° in an ethanol–Dry Ice-bath and, in very small portions at first, 200 cc. of cold concentrated sulfuric acid was added. The temperature was never allowed to rise above 5°. The thick viscous mixture was stirred with a heavy glass rod. The final portions of sulfuric acid were added more rapidly. After the complete addition of sulfuric acid and thorough mixing of the ingredients, the flask was allowed to warm to near room temperature (about 20°). The total time of the reaction is one-half to three-fourths hours.

This deep red solution was then poured into a large excess of cracked ice. The heavy gum was isolated by ether extraction, and hydrolyzed by heating under reflux for two and one-half hours in 350 cc. of ethyl alcohol containing 50 g. of potassium hydroxide and 50 cc. of water. The alcohol was removed under reduced pressure, and the residue diluted with water. After one extraction with ether, the aqueous alkaline solution was acidified with concentrated hydrochloric acid. The crude acid thus obtained weighed 49 g. (82%) and melted at 175–182°. One recrystallization from ethanol raised the melting point to 184–186°.

Methyl 1-Ethylidene-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate (IV).—Slightly more than one equivalent of ethylmagnesium iodide was added rapidly to a stirred solution of 5 g. (0.0617 mole) of III in 150 cc. of dry ether under an atmosphere of nitrogen. A yellow precipitate formed at once. The mixture was stirred for ten minutes after addition of the ethylmagnesium iodide, and an equal volume of water was added, followed by an excess of concentrated hydrochloric acid. Evaporation of the organic layer yielded a solid. This crude solid was triturated with methanol and filtered quickly to yield 4.0 g. (77%) of a product (IV) melting at 138–140°. Recrystallization from ethyl alcohol raised the melting point to 144–145°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.80; H, 7.80. Found: C, 76.35; H, 8.20.

1-Ethyl-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic Acid (V).—The theoretical amount (0.0134 mole) of hydrogen for one equivalent of IV was absorbed rapidly in the presence of palladium on Norite when 4.2 g. (0.0134 mole) of IV, dissolved in 95% ethyl alcohol, was hydrogenated at 30 lb. pressure. The residue, after removal of the catalyst and solvent, was hydrolyzed in 150 cc. of 90% ethyl alcohol containing 12 g. of potassium hydroxide by heating under reflux for twenty hours. The solvent was evaporated, and the residue diluted with water to 50 cc. The insoluble potassium salt which appeared was filtered, dissolved in hot 50% ethanol, and acidified with concentrated hydrochloric acid. There was formed 1.6 g. of V melting at 173–174° (after one recrystallization from ethyl alcohol). The second possible isomer was not isolated.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 76.00; H, 8.00. Found: C, 75.60; H, 7.92.

1-Ethyl-2-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic Acid (VI). (A) By the Hydrogenation of V in Neutral Medium.—One gram (0.00318 mole) of V was dissolved in 75 cc. of methanol and hydrogenated in the presence of palladium on Norite at 30 lb. pressure. The calculated amount of hydrogen was absorbed in two hours. The product was a white gum which yielded an insoluble sodium salt when triturated with 100 cc. of a 1% sodium hydroxide solution. After filtration and drying the salt weighed 0.64 g.

Regeneration of the acid by acidifying a hot 50% ethanolic solution of the salt with concentrated hydrochloric acid yielded a crystalline material which melted at 188–189° (VIa) after crystallization from ethyl alcohol and weighed 0.5 g.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.6; H, 8.67. Found: C, 75.78; H, 8.76.

The alkaline mother liquor from above after acidification yielded 0.4 g. of material which melted over a long range (63–100°). After two recrystallizations from dilute methanol there was obtained 150 mg. of fine silky needles melting at 134–135.5 (VIb).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.6; H, 8.67. Found: C, 75.04; H, 8.44.

(B) **By Hydrogenation in Alkaline Medium.**—When V was dissolved in aqueous-ethanolic sodium carbonate no absorption of hydrogen was observed. Palladium on Norite was the catalyst.

(C) **By Hydrogenation of V in the Presence of Diethylamine.**—One-half gram of V was treated exactly as in (A) except for the presence of a few drops of diethylamine. The isolation of the products was also carried out in the same manner. The isomer of VI melting at 188–189° was obtained in larger proportion (0.35 g.), while the lower melting isomer, if present at all, was not isolated.

Isomerization of V.—One-half gram of V (m. p. 174–175°) was dissolved in 40 cc. of dry benzene, and a stream of dry hydrogen chloride gas was passed through the solution for one hour. The stoppered flask was then allowed to stand for two days at room temperature before removing the solvent on the steam-bath. The gummy residue solidified after a few minutes (m. p. 115–140°). There seemed to be a negligible difference in the solubility of the sodium salts, hence little purification could be brought about in this way. The regenerated acids were recrystallized from ethanol and ethanol–water combinations. About 350 mg. of the starting acid (V) was recovered in this way. Finally, a small amount of a new acid (tentatively designated as IX) melting at 144–145° was obtained. The amount was too small for satisfactory characterization.

Summary

Two crystalline racemates of 1-ethyl-2-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic acid (VIa, VIb) have been prepared from ethyl 1-keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate.[1] These compounds, as well as the intermediate hexahydro acid (V), exhibited strong estrogenic activity in white rats.

KALAMAZOO, MICHIGAN RECEIVED AUGUST 27, 1948

[COMMUNICATION NO. 1180 FROM THE KODAK RESEARCH LABORATORIES]

Heats of Polymerization. IV. Copolymerization[1]

BY L. K. J. TONG AND W. O. KENYON

Introduction

This paper deals with heats of polymerization of a special type of copolymeric system in which the original monomeric units are, for the most part, arranged in the copolymer chain in an alternate sequence. Though this structural limitation definitely simplifies interpretation of the observed heats of polymerization, it is impossible to define and interpret exactly the energy changes, as will be shown. Without such structural limitation, the interpretation would be much more difficult because of the unknown sequence of units along the polymer chain.[1a]

Thus, in general, if a given unsaturate is not capable of homopolymerizing, or does so only very sluggishly under given conditions of temperature and catalyst concentration, but will form copolymers[2] at a fairly rapid rate when a second unsaturate is present, the probability of two units of the first component adding consecutively is very small. If the two monomer units are found to disappear from various monomer compositions at substantially equal molar rates, it is highly probable that the adjacent combined units are different. In terms of copolymerization kinetics as described by Mayo and Lewis[3] this can be interpreted that the reaction of each monomer with radicals that are different is much faster than the reaction of the same monomer with radicals that are similar. The reactions described in this article belong to this category, as subsequent evidence will show. The kinetics of allyl acetate and maleic anhydride copolymerization, also an example of this type of reaction, have been studied and discussed by Bartlett and Nozaki.[4]

Experimental

Vinyl acetate (VA) was purified from a commercial product by fractional distillation through a five-foot column under atmospheric pressure, b. p. 72.2–72.3°.

Maleic anhydride (MA) was Eastman Kodak Co. white label grade product again distilled under reduced pressure and kept in a desiccator over phosphorus pentoxide.

Diethyl maleate (DEM) was Eastman white label grade product again fractionally distilled through a two-foot column under reduced pressure, b. p. 102.5–102.7° (11 mm.) $n^{20}\mathrm{D}$ 1.4408. Part of this material was further purified by crystallizing four times in brine and ice mixtures. Each time the unfrozen portion, which amounted to about half the total, was discarded; final product $n^{20}\mathrm{D}$ 1.4402, m. p. −8.8°.

Diethyl fumarate (DEF) was Eastman white label grade again distilled through a two-foot column under reduced pressure, b. p. 95.1° (10 mm.), $n^{20}\mathrm{D}$ 1.4408. A portion was further purified by crystallizing four times in an ice-bath with about half of the material discarded each time, m. p. 0.6°.

Benzoyl peroxide used as catalyst was Eastman white label grade.

Isopropenyl acetate was purified by washing with saturated sodium chloride solution, with dilute sodium chloride and sodium bisulfate solution, then again with sodium chloride solution. It was dried over magnesium sulfate and fractionated through a ten-inch column, b. p. 97.5°.

The apparatus has been described previously.[5]

The procedures are those described before, with the following modifications: Air was not removed from the reaction system except for one case mentioned later. The earlier practice of flushing the air space with nitrogen will change the composition of the monomer mixtures owing to their differences in vapor pressures. When both compo-

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[1] Presented before the High Polymer Forum at the Chicago, Illinois meeting of the American Chemical Society, 1948.

[1a] Since the original submission of this paper, the kinetics of some of the reactions concerned here have been published by Lewis and Mayo, THIS JOURNAL, **70**, 1533 (1948).

[2] The term "heteropolymers" is sometimes applied when one or more of the monomers will not homopolymerize. This term has unfortunate implications as to the physical homogeneity of the product, so we prefer the term "copolymer."

[3] Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944).

[4] Bartlett and Nozaki, *ibid.*, **68**, 1495 (1946).

[5] Tong and Kenyon, *ibid.*, **67**, 1278 (1945); **68**, 1355 (1946); **69**, 1402 (1947); **69**, 2245 (1947).