quickly cooling the solution. It was collected on a filter, washed with water and dried: N-benzoyl-L-homoserine[17]; m. p. 139–141°.

The N-benzoyl-L-homoserine obtained was dissolved in 20 ml. of hot water containing two drops of concd. hydrochloric acid, the solution was boiled for two minutes and cooled. Beautifully formed needles of L-α-benzamidobutyrolactone crystallized and were collected; m. p. 139°, $[\alpha]^{20}D$ −21.5° (1.25% in 95% EtOH).[18]

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.82. Found: N, 6.80.

D-α-Benzamidobutyrolactone.—Prepared from D-α-aminobutyrolactone hydrobromide in the same manner as described for the L compound; N-benzoyl-D-homoserine, m. p. 139–141°; D-α-benzamidobutyrolactone m. p. 139–140°, $[\alpha]^{23}D$ +22.5° (1% in 95% EtOH).[18a]

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.82. Found: N, 6.93.

DL-Homoserine.—To a solution of 1.0 g. of DL-α-aminobutyrolactone hydrobromide in 5 ml. of water was added 0.7 g. of silver oxide and the suspension was shaken at room temperature for five minutes. The silver bromide was removed at the centrifuge, the clear supernatant solution was treated with hydrogen sulfide, again centrifuged, and the clear colorless solution was evaporated to dryness on a steam-bath. The residue was dissolved in 2 ml. of water, filtered, and the filtrate was diluted with 10 ml. of warm absolute ethanol and allowed to stand overnight in a refrigerator. The crystalline product was collected on a filter, washed with 95% ethanol and dried; yield 0.30 g., (46% yield); m. p. 186–187° dec.

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 11.98.

(17) Kitagawa and Monobe, refs. 3, 4, reported the following physical properties for homoserine and its derivatives as obtained by the degradation of canavanine: (1) homoserine, m. p., 201–202° dec.; $[\alpha]^{14}D$ −8.20, (2) N-benzoylhomoserine, m. p., 140–144°, (3) α-benzamidobuytrolactone, m. p. 139°, $[\alpha]^{17}D$ −27.99° (in EtOH).

(18) $[\alpha]^{20}D$ −27.0° (1% w/v in 95% EtOH).

(18a) $[\alpha]^{23}D$ +28.0° (1% w./v. in 95% EtOH).

L-Homoserine.—Prepared from 1.0 g. of L-α-aminobutyrolactone hydrobromide as described above for the DL compound; yield, 0.28 g. (43% yield); m. p. 203° dec., $[\alpha]^{23}D$ −8.0° (1% in water).

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 11.98.

D-Homoserine.—Prepared from 1.0 g. of D-α-aminobutyrolactone hydrobromide as described above; yield 0.30 g. (46% yield); m. p. 203° dec., $[\alpha]^{23}D$ +8.0° (1% in water).

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 12.00.

3,6-bis-(β-Hydroxyethyl)-2,5-diketopiperazine.—Prepared from 3.34 g. of DL-α-aminobutyrolactone hydrobromide according to the directions of Livak, *et al.*[10]; yield, 1.10 g. (60% yield); m. p. 189–191° dec.

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 14.22.

L-3,6-bis-(β-Hydroxyethyl)-2,5-diketopiperazine.—The above reaction was repeated using 3.34 g. of L-α-aminobutyrolactone hydrobromide; yield, 1.25 g. (67% yield); m. p. 190.5–191° dec.; $[\alpha]^{27}D$ −30.0° (1% in water).

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 13.79.

Acknowledgment.—The author wishes to thank Marie S. Hanson for performing the nitrogen analyses reported in this paper.

Summary

D- and L-homoserine have been prepared by the acid hydrolysis of the corresponding O-phenylhomoserines. The properties of L-homoserine were shown to agree with those reported for the optically active α-amino-γ-hydroxybutyric acid obtained by the degradation of canavanine.

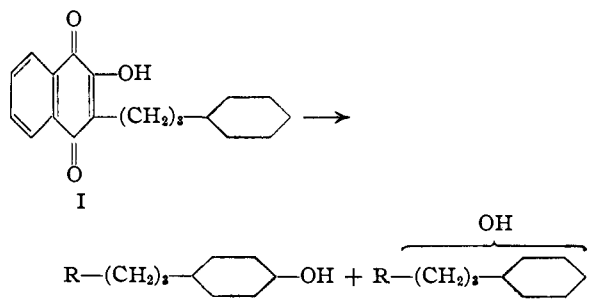
SALT LAKE CITY, UTAH RECEIVED OCTOBER 18, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Synthesis of 2-Hydroxy-3-[3′-*cis*-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone

BY WILLIAM G. DAUBEN AND RAYLENE E. ADAMS

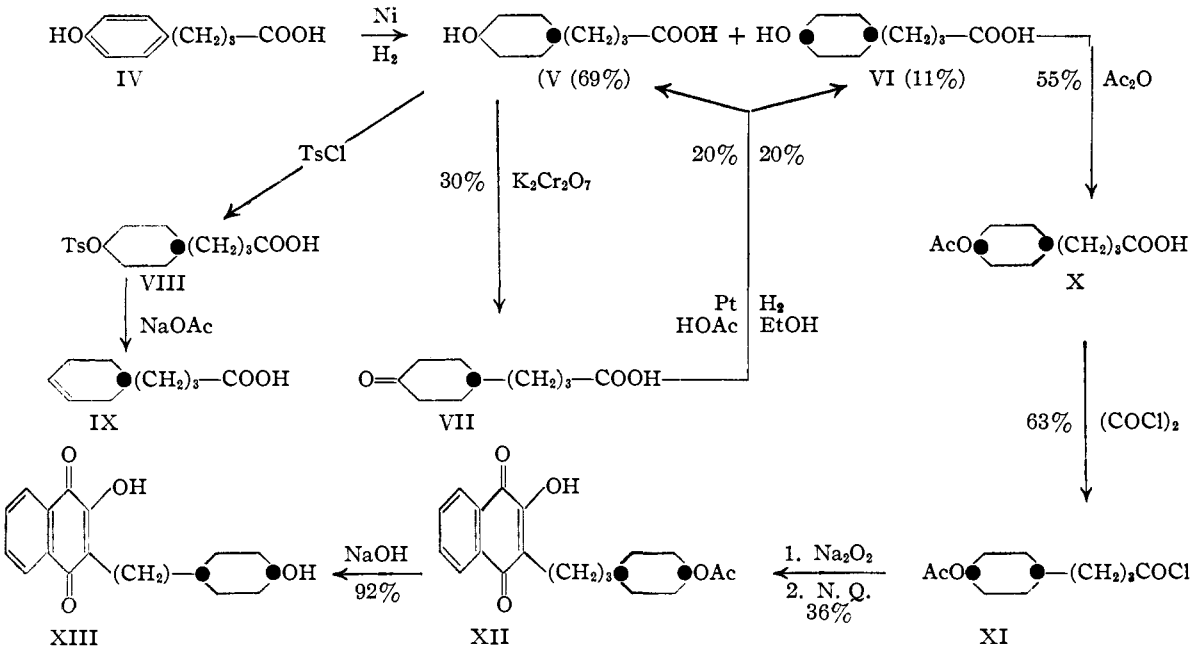
It has recently been reported by Fieser[1] that various [2-hydroxy-3-alkyl-1,4-naphthoquinones when administered to humans undergo degradation. It was found that when the alkyl group was 3-cyclohexylpropyl (I), two hydroxylated quinones (II and III) could be isolated. Compound II, which melts at 155°, was shown to be 2-hydroxy-3-[3′-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone by synthesis from γ-(*p*-hydroxycyclohexyl)-butyric acid (V). This series of compounds can be assumed to be of the *trans* configuration since the starting acid (V) was obtained by the hydrogenation of γ-(*p*-hydroxyphenyl)-butyric acid (IV) in basic solution over Raney nickel catalyst.[2] Compound III was shown to be optically inactive, to contain a secondary hydroxyl group, and to melt at 112°. In view of these facts it was thought that this degradation product might be the *cis*-isomer of compound II and the synthesis of this isomer is reported in this paper.



R = 2-Hydroxy-1,4-naphthoquinone-3-yl

(1) Fieser and co-workers, THIS JOURNAL, in preparation.

(2) (a) Macbeth and Mills, *J. Chem. Soc.*, 709 (1945); (b) Skita, *Ber.*, **53**, 1792 (1920), and later papers.



It was found that fractionation of the hydrogenation product of γ-(*p*-hydroxyphenyl)-butyric acid (IV) gave, in addition to the *trans* acid (V), 11% of the *cis* isomer (VI). However, since a large amount of the *trans* compound was formed in the hydrogenation, a study was made of the possible methods for conversion of it to the *cis* isomer.

It is well-known that alcohols can be inverted by the process of tosylation and subsequent displacement with acetate ion.[3] For example, Kenyon and co-workers have inverted *trans*-4-methoxycyclohexanol in a yield of 30% by this method. However, the major reaction product was 4-methyl-1-cyclohexene. When the *trans* acid (V) was tosylated in pyridine solution and then treated with an alcoholic solution of sodium acetate only the unsaturated acid (IX) was obtained.

Another mode of preparation of *cis–trans*-isomers in the cyclohexanol series is the hydrogenation of the corresponding ketone.[2a] MacBeth and Mills have found that when *trans*-3-methylcyclohexanol was oxidized to 3-methyl-1-cyclohexanone and the ketone hydrogenated at room temperature over Adams catalyst in acetic acid solution the *cis*-3-methylcyclohexanol was obtained in 69% yield.

Various methods were tried in order to prepare γ-(*p*-cyclohexanone)-butyric acid (VII). Numerous Oppenauer oxidations were conducted on the methyl ester of the *trans* acid using either acetone or cyclohexanone as the hydrogen acceptor. No ketone or ketone derivative could be isolated. A dark red oil was always obtained and it is believed that an aldol-type condensation may have occurred under the conditions of the reaction. The catalyst, aluminum *t*-butoxide, was checked for its activity by oxidizing cyclohexanol. High yields of cyclohexanone were always obtained.

Various chemical methods are described in the literature for the oxidation of analogous secondary alcohols to ketones. However, with the *trans*-acid (V) very low yields were obtained by almost all the methods. It was found that the keto-acid (VII) could be prepared in a yield of 30–45% by means of potassium dichromate, acetic acid, sulfuric acid, and water at room temperature.

The hydrogenation of the keto-acid (VII) was attempted with various catalysts and solvents, but the amount of *cis* isomer isolated was invariably low (0–20%). A mixture containing small amounts of the *cis* and *trans*-hydroxycyclohexylbutyric acids, a large amount of the cyclohexylbutyric acid, and often a little unreacted ketone was usually received. The best results were obtained when platinum oxide was used as the catalyst and ethanol containing one drop of acetic acid or hydrochloric acid as the solvent. The various unsuccessful methods were platinum oxide in water or absolute ethanol, platinum black in ethanol and Raney nickel in ethanol or water. No reduction occurred when barium sulfate containing ten per cent. palladium was used as the catalyst and ethanol or acetic acid as the solvent.

The results of these experiments are quite similar to those obtained recently by Hardegger, Heusser and Blank.[4] These workers have reported that the hydrogenation of α-hydroxy-β-(*p*-cyclohexanone)-butanolide in aqueous acetic acid over Adams catalyst gave mainly the hydrogenolysis product. The small amount of the desired hydroxyl compound obtained was a mixture of the

(3) Gough, Hunter and Kenyon, *J. Chem. Soc.*, 2052 (1926).

(4) Hardegger, Heusser and Blank, *Helv. Chim. Acta*, **29**, 477 (1946).

cis and *trans* isomers. Gauthier[5] also has reported that 4-propylcyclohexanone is hydrogenated in acetic acid in the presence of hydrochloric acid and platinum catalyst to a mixture of *cis* and *trans* isomers.

The *cis* isomer of the naphthoquinone (XIII) was prepared following the usual methods.[1] The *cis*-γ-(*p*-acetoxycyclohexyl)-butyric acid (X) was obtained in a yield of 55% by treating the *cis*-hydroxy acid (VI) with acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid. This acid was then converted to the acid chloride with oxalyl chloride in 63% yield. The acid chloride was allowed to react with sodium peroxide following the general procedure of Fieser and Oxford[6] to give the peroxide which in turn was decomposed in an acetic acid solution of 2-hydroxy-1,4-naphthoquinone. The 2 - hydroxy - 3 - [3′ - *cis* - (4 - acetoxycyclohexyl)-propyl]-1,4-naphthoquinone (XII) was isolated in 36% yield and then deactylated to give *cis*-hydroxy compound (XIII). This latter compound melts at 136–137°. Hence the compound III isolated in the metabolism studies is not the *cis* isomer of compound II. L. F. Fieser has reported in a private communication that the *cis* compound, XIII, is completely inactive when assayed by the antirespiration method previously described by him.[1] The isolated degradation products, II and III, however, show definite activity.

Acknowledgment.—The authors wish to express their appreciation to Professor L. F. Fieser for his interest in this work, and to the Abbott Laboratories for their financial aid.

Experimental[7]

β-(*p*-Anisoyl)-propionic Acid.—The acid was prepared from anisole and succinic anhydride according to the procedure of Rosemund and Shapiro[8] using nitrobenzene as the solvent. The yield was 75–85%. When nitroethane was employed as the solvent the yield was slightly less but this method was more convenient since anhydrous aluminum chloride is soluble in this solvent and could be added in the form of a solution.

γ-(*p*-Methoxyphenyl)-butyric Acid.—The reduced acid was prepared from the above keto-acid either by the Martin modification[9] of the Clemmensen reduction or by the Huang-Minlon[10] modification of the Wolff–Kishner reaction. This latter method was more convenient and the product was obtained in 75% yield.

γ-(*p*-Hydroxyphenyl)-butyric Acid.—The methoxy-acid was demethylated by heating under reflux with 48% hydrobromic acid. The crude acid was recrystallized from benzene and the pure acid melts at 107–108°.

γ-(*p*-Hydroxycyclohexyl)-butyric Acid (V and VI).—This acid was prepared following the procedure described by Fieser and co-workers.[1] From 45 g. (0.25 mole) of γ-(*p*-hydroxyphenyl)-butyric acid, 40 g. (86%) of crude product, which sinters from 80° and melts by 114°, was obtained. This material was added to 300 cc. of ether and the mixture heated under reflux for fifteen minutes. The solid which did not dissolve was filtered and it melts from 118–122°. After recrystallization from aqueous acetic acid, the pure acid melts from 123–124°, yield 32 g. (68.9%). This compound is presumably the *trans* isomer.

The above ethereal extract was concentrated and then petroleum ether was added until turbidity. On cooling, white crystals (6.1 g.) which sinter at 80° and melt from 84–89° were obtained. This solid was fractionally crystallized from a mixture of ether and petroleum ether. The first small fraction was impure *trans* isomer. The second fraction contained 5.0 g. (10.7%) of the pure *cis* acid, m. p. 83–84°. *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.77; H, 9.95.

***cis*-γ-(*p*-Acetoxycyclohexyl)-butyric Acid (X).**—*cis*-γ-(*p*-Hydroxycyclohexyl)-butyric acid (1.0 g., 0.006 mole) was mixed with 6 cc. of acetic anhydride and three drops of concentrated sulfuric acid, allowed to stand at room temperature for eighteen hours, and then poured into 250 cc. of water. The aqueous mixture was extracted with three 25-cc. portions of ether. The water layer then was concentrated, saturated with sodium chloride, and extracted again with ether.

The combined ethereal extracts were washed, dried, and the solvent evaporated. The residual liquid was distilled in a sublimation-type still at a block temperature of 125° and a pressure of 2 mm. The yield was 0.55 g. (44.7%).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.40; H, 8.57.

***cis*-γ-(*p*-Acetoxycyclohexyl)-butyryl Chloride (XI).**—A mixture of 7.2 g. (0.032 mole) of the *cis*-acetoxy acid and 12.2 g. (8.2 cc., 0.01 mole) of oxalyl chloride was warmed at 70° for a period of four hours. The excess oxalyl chloride was then removed and the product distilled, b. p. 139–141° (1 mm.), yield 4.9 g. (63%).

Di-[*cis*-γ-(*p*-acetoxycyclohexyl)-butyryl] Peroxide.—The peroxide was prepared following the procedure of Fieser and Oxford[6] using 4.9 g. (0.02 mole) of acid chloride. A yield of 88% was indicated by titration of an aliquot.[11]

2-Hydroxy-3-[3′-*cis*-(4-acetoxycyclohexyl)-propyl]-1,4-naphthoquinone (XII).—The alkylation was conducted in the flash-off manner[1] using 1.50 g. (0.086 mole) of 2-hydroxy-1,4-naphthoquinone, the peroxide prepared above and 35 cc. of acetic acid. After the evolution of carbon dioxide had ceased, the mixture was refluxed for one hour and the acetic acid removed under reduced pressure. The residual sirup was dissolved in ether and the ethereal solution extracted with dilute, freshly-prepared, aqueous sodium bicarbonate until only a faint pink color was discernible in the aqueous layer. After removal of the ether, the residue was crystallized from aqueous methanol. After several recrystallizations, the yellow solid sinters slightly from 79–99° and melts from 99–100°. When a sample was immersed in a bath at 94°, it melted completely. The yield of the dimorphic compound was 1.1 g. (35.7%) and no single form of dimorph could be isolated.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.46; H, 6.58.

2-Hydroxy-3-[3′-*cis*-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone (XIII).—A solution of 0.43 g. (0.0012 mole) of the acetyl compound, 0.1 g. (0.018 mole) of potassium hydroxide and 30 cc. of water was refluxed for one hour. The solution was acidified and a small volume of ethanol was added to effect solution. The product crystallized slowly from this mixture. The yellow solid was best recrystallized by long standing in a large volume of ethanol highly diluted with water containing a trace of acetic acid. The yield was 0.35 g. (92.2%), m. p. 136–137°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.71; H, 7.10.

(5) Gauthier, *Ann. chim.*, **20**, 581 (1945).

(6) Fieser and Oxford, THIS JOURNAL, **64**, 2061 (1942).

(7) Microanalyses by Mr. C. W. Koch. All melting points are uncorrected.

(8) Rosemund and Shapiro, *Arch. Pharm.*, **272**, 313 (1934).

(9) Martin, THIS JOURNAL, **58**, 1438 (1936).

(10) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(11) Kokatnur and Jelling, *ibid.*, **63**, 1432 (1941).

γ-(*p*-Cyclohexanone)-butyric Acid (VII).—A mixture of 3.5 g. of γ-(*p*-hydroxycyclohexyl)-butyric acid (0.019 mole), 10 cc. of acetic acid and 40 cc. of water was placed in a flask equipped with a mechanical stirrer, a dropping funnel and a thermometer which was immersed in the liquid and warmed to 60°. After the acid had dissolved, the solution was cooled to 35° and kept at that temperature for the rest of the reaction.

An oxidizing mixture of 1.9 g. (0.0065 mole) of potassium dichromate, 6 cc. of concentrated sulfuric acid and 14 cc. of water was added over a period of fifteen minutes to the stirred solution. The reaction mixture was stirred for an additional thirty minutes and then it was allowed to stand until all of the oxidizing agent had been consumed. This usually required eight to ten hours. The mixture was then diluted with 200 cc. of water, saturated with sodium chloride and was extracted with ether. Upon evaporation of the ether, a yellow sirup remained which on cooling and scratching crystallized. The product was recrystallized from a mixture of ether and ligroin, yield 1.05 g. (30%), m. p. 81–82°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 64.91; H, 8.74.

The semicarbazone melts at 183–184°.

Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94. Found: C, 54.99; H, 7.82.

Summary

1. 2-Hydroxy-3-[3′-*cis*-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone has been prepared and has been shown to be different from the low melting metabolite of 2-hydroxy-3-(3′-cyclohexyl-propyl)-1,4-naphthoquinone isolated by Fieser and associates.

2. The hydrogenation of γ-(*p*-cyclohexanone)-butyric acid has been studied.

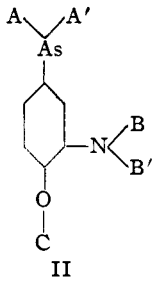
BERKELEY 4, CALIFORNIA RECEIVED DECEMBER 10, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

3-Amino-4-hydroxybenzenearsonous Acid. II. Derivatives

BY C. K. BANKS, JOHN CONTROULIS, D. F. WALKER, E. W. TILLITSON,[1] L. A. SWEET AND O. M. GRUHZIT

The amine salts and arsenite hemiesters of 3-amino-4-hydroxybenzenearsonous acid (I, oxophenarsine) were described in the first paper of this series.[2] All of these compounds, as well as the dihalo derivatives, equilibrate readily in solution to a common ion, postulated to be 3-ammonium-4-hydroxybenzenearsonite. Since this nucleus has been unique in therapeutic agents for the treatment of spirochetal diseases, further variations of the general structure II have been made.

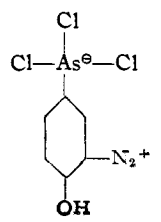


II

Previously reported compounds of this type include the aforementioned salts, hemiesters and acid adducts,[2] mercaptan derivatives in which A and A′ were mercaptoacetic acid, mercaptoacetamide and cysteine,[3] the acetyl derivative (B = $COCH_3$)[4] and compounds in which C was replaced by hydroxyalkyl[5–7] and alkyl groups.[8] Since variations in C appeared to be explored adequately, the principal variants studied were those of A and B. Since 3-amino-4-β-hydroxyethoxybenzenearsonous acid (III)[5] has been found to have practically the same *in vivo* spirochetal activity as I, the β-hydroxyethyl group was selected as the C variant for the study of multiple substitution.

The mercaptol derivatives of I were extended to include mercaptoacetone, octyl mercaptoacetate, thiomalic acid and unsubstituted sulfides. Hydrogen sulfide reacted with I to yield compounds having —$As(SH)_2$, —As(SH)(OH) and —AsS structures, depending on the conditions employed. The mercaptoacetic acid, octyl mercaptoacetate and mercaptoacetamide derivatives of III were also formed. The octyl mercaptoacetates were of interest in that they are soluble in oils.

The amine group was modified by substituting B and B′ with the acid succinamide, benzal, formaldehyde bisulfite and glucose bisulfite groups. Attempts to prepare the analogous formaldehyde sulfoxylate resulted in neoarsphenamine types. Similar amine derivatives were prepared in which A and A′ were replaced by thiols and where C was the hydroxyethyl group. The formaldehyde sul-



IV

(1) Present address, Department of Chemical Engineering, Wayne University, Detroit, Michigan.
(2) Banks, *et al.*, THIS JOURNAL, **69**, 5 (1947).
(3) Barber, *J. Chem. Soc.*, 1020 (1929).
(4) Newbery and Phillips, *ibid.*, 2375 (1928).
(5) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934).
(6) Bare and Hamilton, *ibid.*, **59**, 2444 (1937).
(7) Holcomb and Hamilton, *ibid.*, **61**, 1236 (1939).
(8) Doak, Steinman and Eagle, *ibid.*, **65**, 99 (1941).