5,7-Dichloroheptyl Thiolacetate (IV).—Thiolacetic acid (15.6 g., 0.21 mole) was cooled in an ice-bath and neutralized to the phenolphthalein end-point with a 2.5 *N* solution of potassium ethoxide in ethanol (approximately 81 ml. required). The resulting suspension was added in portions to a solution of 51 g. (0.21 mole) of 7-bromo-1,3-dichloroheptane in 80 ml. of ethanol. During the addition (2.5 hours) the reaction mixture was stirred and maintained under reflux in an atmosphere of nitrogen. Stirring and heating were continued for an additional 4 hours. The reaction mixture was cooled, filtered, and the filtrate was poured into 750 ml. of water. The product was extracted with two 150-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The oily residue was distilled through a 6-in. Vigreux column to yield 38.5 g. (77%) of product; b.p. 116–120° (0.55 mm.); $n^{25}D$ 1.5032; $\lambda_{max}^{95\% \text{ ethanol}}$ 232 mμ (ε 4640).

Anal. Calcd. for $C_9H_{16}Cl_2OS$: C, 44.45; H, 6.63; Cl, 29.16; S, 13.19. Found: C, 44.73; H, 6.64; Cl, 29.38; S, 13.55.

5,7-Dichloroheptanesulfonamide (V).—A suspension of 5 g. (0.02 mole) of 5,7-dichloroheptyl thiolacetate in 100 ml. of water was stirred vigorously and maintained below 3° during the introduction of chlorine. When the reaction mixture became yellowish green in color, indicating an excess of chlorine, it was extracted with ether. The ether extract was washed successively with cold 5% sodium bisulfite solution, 5% sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was stirred and heated at 60° for 1 hour with 40 ml. of concentrated ammonium hydroxide. The product was extracted into ether and the ether extract was dried and then evaporated *in vacuo*. The solid residue was crystallized from dilute ethanol to yield 3.13 g. (63%) of 5,7-dichloroheptanesulfonamide, m.p. 72–73°. A sample was recrystallized for analysis, m.p. 74–75°.

Anal. Calcd. for $C_7H_{15}Cl_2NO_2S$: C, 33.85; H, 6.09; Cl, 28.57; N, 5.64. Found: C, 34.22; H, 6.29: Cl, 28.72; N, 5.59.

5,7-Di-(benzylthio)-heptanesulfonamide (VI).—To 2.97 g. (0.012 mole) of 5,7-dichloroheptanesulfonamide was added 3.23 g. (0.026 mole) of benzyl mercaptan and 20 ml. of a 1.3 *N* solution of sodium ethoxide in absolute ethanol. The mixture was stirred and heated under reflux in an atmosphere of nitrogen for 14 hours. The reaction mixture was cooled, poured into 150 ml. of water, and the mixture was extracted with ether. The aqueous layer was acidified and the product extracted into ether. The ether extract was dried over anhydrous sodium sulfate and then the solvent was removed *in vacuo*. The oily residue was crystallized from benzene–Skellysolve B[12] to yield 3.51 g. (69%) of product. A sample was recrystallized for analysis, m.p. 67.5–68°.

Anal. Calcd. for $C_{21}H_{29}NO_2S_3$: C, 59.50; H, 6.90; N, 3.31; S, 22.71. Found: C, 59.41; H, 7.08; N, 3.33; S, 22.80.

DL-1,2-Dithiolane-3-butanesulfonamide (VII).—5,7-Di-(benzylthio)-heptanesulfonamide (3.0 g., 0.0069 mole) was reduced with sodium in liquid ammonia in a manner described previously.[5] After removal of the ammonia 50 ml. of water was added to the residue and the mixture was extracted with 30 ml. of ether. The aqueous layer was adjusted to *p*H 11.5 and 0.2 ml. of 1% ferric chloride solution was added. A rapid stream of oxygen was bubbled through the solution from a sintered glass tube until the reddish color changed to pale yellow (approximately 15 minutes). The solution was acidified and the mixture was extracted with three 15-ml. portions of chloroform. Yellow chloroform extracts and an insoluble, gray polymeric material were obtained. The polymeric material was warmed on a steam-bath with 20 ml. of 0.5 *N* sodium hydroxide until it dissolved (approximately 10 minutes). The resulting bright yellow solution[13] was acidified and the yellow oil extracted with two 15-ml. portions of chloroform. These chloroform extracts were combined with those obtained as described above and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the bright yellow residue was extracted with 20 ml. of warm benzene. When the benzene solution was cooled, 768 mg. (45%) of yellow crystals separated, m.p. 65–67°. To the filtrate was added 8 ml. of Skellysolve B. When this solution was cooled, 160 mg. (9%) of yellow crystals was obtained, m.p. 65–67°. A sample was recrystallized for analysis; m.p. 68–69°; $\lambda_{max}^{95\% \text{ ethanol}}$ 332 mμ (ε 157), λ_{min} 280 mμ.

Anal. Calcd. for $C_7H_{15}NO_2S_3$: C, 34.80; H, 6.26; N, 5.80; S, 39.85. Found: C, 35.11; H, 6.24; N, 6.04; S, 39.89.

Acknowledgments.—We are indebted to Dr. C. G. Skinner and Staff of the Biochemical Institute and to the Clark Microanalytical Laboratory, Urbana, Illinois, for the elemental analyses.

(12) A *n*-hexane fraction, b.p. 60–68°, obtained from the Skelly Oil Co., Kansas City, Missouri.

(13) It has been observed that sticky, colorless polymers are produced as by-products in the oxidation of DL-6,8-dithioloctanoic acid to the cyclic disulfide, DL-α-lipoic acid (ref. 5), and also when the cyclic disulfide is heated. These polymeric materials are converted to DL-α-lipoic acid in high yield when they are treated with dilute alkali (R. C. Thomas and L. J. Reed, THIS JOURNAL, **78**, 6148 (1956)).

AUSTIN 12, TEXAS

[CONTRIBUTION FROM THE CLAYTON FOUNDATION FOR RESEARCH, THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of DL-1,2-Dithiolane-3-caproic Acid and DL-1,2-Dithiolane-3-butyric Acid, Homologs of α-Lipoic Acid

BY RICHARD C. THOMAS AND LESTER J. REED

RECEIVED JUNE 29, 1956

DL-1,2-Dithiolane-3-caproic acid and DL-1,2-dithiolane-3-butyric acid have been synthesized. These homologs exhibited slight α-lipoic acid activity in the acetate-replacing factor assay.

It has been reported[1] that homologs of biotin are potent inhibitors of the utilization of this vitamin. Accordingly, the length of the valeric acid side chain in α-lipoic acid (1,2-dithiolane-3-valeric acid) was varied in an attempt to obtain metabolic antagonists of this biocatalyst. This paper describes a synthesis of DL-1,2-dithiolane-3-caproic acid (VIII) and DL-1,2-dithiolane-3-butyric acid (XII). These homologs exhibited, respectively, approximately 0.1 and 0.01% of the biological activity of DL-α-lipoic acid in the acetate-replacing factor assay.[2]

Ethyl 6,8-dichloroöctanoate (I)[3] was reduced to 6,8-dichloroöctanol (II) with lithium aluminum

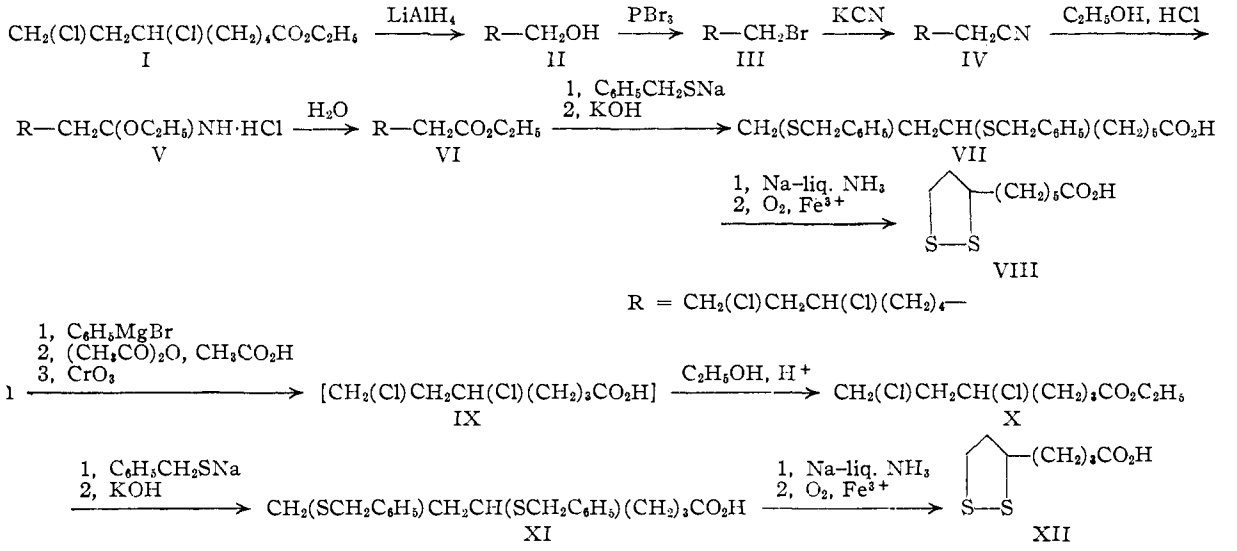
(1) M. W. Goldberg, L. H. Sternbach, S. Kaiser, S. D. Heineman, J. Scheiner and S. H. Rubin, *Arch. Biochem.*, **14**, 480 (1947).

(2) B. M. Guirard, E. E. Snell and R. J. Williams, *ibid.*, **9**, 361 (1946); L. J. Reed, B. G. DeBusk, P. M. Johnston and M. E. Getzendaner, *J. Biol. Chem.*, **192**, 851 (1951).

(3) L. J. Reed and C-I. Niu, THIS JOURNAL, **77**, 416 (1955).

hydride. Treatment of compound II with phosphorus tribromide gave 8-bromo-1,3-dichloroöctane (III). The latter compound was converted to 7,9-dichlorononanenitrile (IV) by treatment with potassium cyanide in boiling ethanol. The dichloronitrile IV was converted to ethyl 7,9-dichlorononanimidate hydrochloride (V) by the action of hydrogen chloride in absolute ethanol.[4] Hydrolysis of compound V produced ethyl 7,9-dichlorononanoate (VI). The dichloro ester VI was allowed to react with sodium benzylmercaptide in boiling ethanol,[3] followed by hydrolysis, to give 7,9-di-(benzylthio)-nonanoic acid (VII). The latter compound was reduced with sodium in liquid ammonia, and the dimercapto acid produced was oxidized to DL-1,2-dithiolane-3-caproic acid (VIII).

DL-1,2-Dithiolane-3-butyric acid (XII) was prepared from ethyl 5,7-dichloroheptanoate (X) in a similar manner (X → XI → XII). The dichloro ester X was obtained by subjecting ethyl 6,8-dichloroöctanoate (I) to a Barbier–Wieland degradation[5] to produce 5,7-dichloroheptanoic acid (IX), followed by esterification.



I II III IV

V VI VII

VIII

IX X

XI XII

The two cyclic disulfides VIII and XII were yellow crystalline solids which exhibited the characteristic ultraviolet absorption spectrum of the 1,2-dithiolane moiety, with an absorption maximum at 332 mμ.[3,6]

Experimental[7]

6,8-Dichloroöctanol (II).—To a stirred suspension of 7.2 g. (0.19 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether at room temperature was added dropwise (1 hour) a solution of 58 g. (0.24 mole) of ethyl 6,8-dichloroöctanoate[3] in 120 ml. of anhydrous ether. The reaction mixture was stirred an additional hour at room temperature and then water was added dropwise to decompose the excess lithium aluminum hydride. The mixture was stirred with 175 ml. of 10% sulfuric acid and then the ether layer was separated and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the oily residue was distilled through a 6-in. Vigreux column. A small forerun was collected, followed by the main fraction, 46.2 g. (96%), b.p. 106–108° (0.6 mm.), $n^{25}D$ 1.4782.

Anal. Calcd. for $C_8H_{16}Cl_2O$: C, 48.25; H, 8.10; Cl 35.62. Found: C, 48.46; H, 8.16; Cl, 35.18.

8-Bromo-1,3-dichloroöctane (III).—A solution of 83 g. (0.32 mole) of 6,8-dichloroöctanol in 85 ml. of reagent-grade carbon tetrachloride was maintained below 0° while 45 g. (0.17 mole) of phosphorus tribromide was added dropwise with stirring. Stirring was continued for 3 hours at 0° and the reaction mixture was allowed to stand at room temperature for 18 hours. The reaction mixture was worked up in a manner described previously[3] to yield 73 g. (67%) of product, b.p. 95–97° (0.2 mm.), $n^{25}D$ 1.4976.

Anal. Calcd. for $C_8H_{15}BrCl_2$: C, 36.67; H, 5.77. Found: C, 37.01; H, 5.95.

7,9-Dichlorononanenitrile (IV).—To a solution of 21 g. (0.32 mole) of potassium cyanide in 30 ml. of water was added 105 ml. of 95% ethanol. This mixture was maintained under gentle reflux while 66.7 g. (0.26 mole) of 8-bromo-1,3-dichloroöctane was added dropwise (30 minutes). The reaction mixture was heated under reflux for an additional 1.5 hours, then cooled and poured into 150 ml. of water. The product was extracted into 150 ml. of chloroform and the organic layer was washed with 60 ml. of a half-saturated solution of calcium chloride and then with 60 ml. of water. The chloroform extract was dried over calcium chloride and the solvent was removed *in vacuo*. The oily residue was distilled through a 6-in. Vigreux column to yield 38.2 g. (72%) of product, b.p. 119–125° (0.4 mm.). A sample was redistilled for analysis, b.p. 119° (0.3 mm.), $n^{25}D$ 1.4749.

Anal. Calcd. for $C_9H_{15}Cl_2N$: C, 51.94; H, 7.27; Cl, 34.08; N, 6.74. Found: C, 51.64; H, 6.85; Cl, 33.76; N, 6.93.

Ethyl 7,9-Dichlorononanimidate Hydrochloride (V).—A mixture of 32.2 g. (0.154 mole) of 7,9-dichlorononanenitrile[8] and 7.1 g. (0.154 mole) of absolute ethanol was cooled in an ice-salt bath while anhydrous hydrogen chloride was passed in. When 5.6 g. (0.154 mole) of hydrogen chloride had been absorbed, the flask was stoppered and allowed to stand in a deep freeze for 7 days. The crystalline mass was ground to a powder, washed thoroughly with anhydrous ether and dried in a vacuum desiccator. The yield of product was 40 g. (89%), m.p. 72–73°.

Anal. Calcd. for $C_{11}H_{22}Cl_3NO$: C, 45.45; H, 7.61; N, 4.82; neut. equiv., 291. Found: C, 45.06; H, 7.46; N, 5.05; neut. equiv., 281.

Ethyl 7,9-Dichlorononanoate (VI).—A mixture of 39.6 g. (0.14 mole) of ethyl 7,9-dichlorononanimidate hydrochloride and 100 ml. of water was shaken periodically for 2 hours at room temperature and then for 1 hour at 60°. The reac-

(4) A. Pinner, *Ber.*, **16**, 352 (1883).

(5) P. Barbier and R. Locquin, *Compt. rend.*, **156**, 1443 (1913); H. Wieland, O. Schlichting and R. Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926).

(6) J. A. Barltrop, P. M. Hayes and M. Calvin, THIS JOURNAL, **76**, 4348 (1954).

(7) Boiling points and melting points are uncorrected.

(8) Redistilled, b.p. 116–119° (0.3 mm.).

tion mixture was extracted with three 50-ml. portions of ether and the combined ether extracts were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the product distilled through a 6-in. Vigreux column. A small forerun was collected, followed by the main fraction, 30.2 g. (87%), b.p. 119° (0.5 mm.), $n^{25}D$ 1.4622.

Anal. Calcd. for $C_{11}H_{20}Cl_2O_2$: C, 51.77; H, 7.90; Cl, 27.79. Found: C, 51.49; H, 8.07; Cl, 28.14.

7,9-Di-(benzylthio)-nonanoic Acid (VII).—Ethyl 7,9-dichlorononanoate (29.6 g., 0.12 mole) was heated under reflux for 14 hours with an ethanol solution (175 ml.) of sodium benzylmercaptide prepared from 5.9 g. (0.26 mole) of sodium and 31.8 g. (0.26 mole) of benzyl mercaptan, and the product isolated in a manner described previously.[3] The crude product was crystallized from 600 ml. of benzene–Skellysolve B[9] (1:5); yield 29.7 g. (64%), m.p. 42.5–43.5°. A sample was recrystallized for analysis, m.p. 43–43.5°.

Anal. Calcd. for $C_{23}H_{30}O_2S_2$: C, 68.61; H, 7.51; S, 15.93. Found: C, 68.73; H, 7.31; S, 15.59.

DL-1,2-Dithiolane-3-caproic Acid (VIII).—7,9-Di-(benzylthio)-nonanoic acid (15.0 g., 0.037 mole) was reduced with sodium in liquid ammonia in a manner described previously.[3] The crude dimercapto acid was oxidized[3] with oxygen in the presence of ferric ion and the product was crystallized[10] from Skellysolve B, to yield 4.08 g. (50%) of low melting (*ca.* 27°) yellow crystals. A sample was recrystallized from Skellysolve B for analysis; m.p. 31–33°; $\lambda_{max}^{95\%\ ethanol}$ 332 mμ (ε 152), λ_{min} 280 mμ.

Anal. Calcd. for $C_9H_{16}O_2S_2$: C, 49.05; H, 7.32; S, 29.10. Found: C, 49.16; H, 7.55; S, 29.36.

Ethyl 5,7-Dichloroheptanoate (X).—A solution of 44.2 g. (0.195 mole) of ethyl 6,8-dichlorooctanoate in 100 ml. of anhydrous ether was added dropwise with stirring (30 minutes) to an ether solution (200 ml.) of phenylmagnesium bromide prepared from 72 g. (0.46 mole) of bromobenzene and 10.3 g. (0.44 mole) of magnesium. The mixture was heated under reflux for 3 hours and then decomposed with a solution of 25 g. of ammonium chloride in 75 ml. of water. The ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was dehydrated by heating under reflux for 4 hours with 300 ml. of acetic acid and 140 ml. of acetic anhydride. The solvents were removed *in vacuo* to yield 53.7 g. of an oily residue which did not distil at a bath temperature of 220° (0.2 mm.). It was dissolved in 110 ml. of isooctane and 450 ml. of acetic acid. This solution was maintained at 65° while a solution of 62.5 g. of chromic oxide in 45 ml. of water and 330 ml. of acetic acid was added during a period of 1.5 hours. The reaction mixture was poured into 2 l. of water and extracted with ether. The ether extract was washed with water, evaporated *in vacuo* and the residue extracted with 1 *N* sodium hydroxide. The insoluble material was removed by extraction with ether and the aqueous layer was acidified and the product extracted into ether. The ether extract was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 22.3 g. of crude 5,7-dichloroheptanoic acid. This material was esterified by heating under reflux with 30 ml. of absolute ethanol, 80 ml. of benzene and 3 ml. of sulfuric acid in an apparatus equipped with a Dean–Stark trap. The ester, yield 16.12 g. (39%), boiled at 102° (0.5 mm.), $n^{25}D$ 1.4618. A sample was redistilled for analysis, b.p. 92° (0.2 mm.), $n^{25}D$ 1.4612.

Anal. Calcd. for $C_9H_{16}Cl_2O_2$: C, 47.60; H, 7.10; Cl, 31.23. Found: C, 47.85; H, 7.08; Cl, 30.68.

5,7-Di-(benzylthio)-heptanoic Acid (XI).—Ethyl 5,7-dichloroheptanoate (14.3 g., 0.063 mole) was treated with sodium benzylmercaptide and the product isolated as described previously.[3] It was obtained as a light tan oil, 19.7 g. (84%).

Anal. Calcd. for $C_{21}H_{26}O_2S_2$: C, 67.32; H, 6.99; S, 17.12. Found: C, 67.72; H, 7.22; S, 17.73.

DL-1,2-Dithiolane-3-butyric Acid (XII).—5,7-Di-(benzylthio)-heptanoic acid (19.1 g., 0.051 mole) was reduced with sodium in liquid ammonia as described previously.[3] The crude dimercapto acid was oxidized[3] with oxygen in the presence of ferric ion and the product was crystallized[10] from Skellysolve B to yield 5.22 g. (56%) of yellow crystals, m.p. 38–39°. A sample was recrystallized from Skellysolve B for analysis: m.p. 40–41°; $\lambda_{max}^{95\%\ ethanol}$ 332 mμ (ε 148), λ_{min} 280 mμ.

Anal. Calcd. for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29; S, 33.35. Found: C, 43.77; H, 6.55; S, 33.41.

Acknowledgments.—We are indebted to Dr. C. G. Skinner and staff of the Biochemical Institute and to the Clark Microanalytical Laboratory, Urbana, Illinois, for the elemental analyses.

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(9) A *n*-hexane fraction, b.p. 60–68°, obtained from the Skelly Oil Co., Kansas City, Missouri.

(10) The cyclic disulfides VIII and XII polymerized to a significant extent when extracted with hot Skellysolve B. The sticky polymeric materials were insoluble in Skellysolve B and benzene, and could be converted in high yield to the cyclic disulfides by treatment with dilute alkali (R. C. Thomas and L. J. Reed, THIS JOURNAL, **78**, 6150 (1956).

[CONTRIBUTION FROM THE COLLIP MEDICAL RESEARCH LABORATORY AND FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Steroids and Related Products. VI.[1] The Synthesis of 11-Dehydro-17α-methylprogesterone, a Highly Active Gestogen[2]

BY CH. R. ENGEL, K. F. JENNINGS[3] AND G. JUST[4,5]

RECEIVED JULY 13, 1956

The synthesis of a new progesterone analog of high biological activity, 11-dehydro-17α-methylprogesterone, from 3α,12α-diacetoxy-20-oxopregnane is described. The 17α-methyl group was introduced by subjecting the 17-bromide of the starting material to a Faworsky rearrangement and the Δ^{11}-double bond by dehydrotosylation of 12α-tosylates, most effectively performed by the action of slightly alkaline activated aluminum oxide. In the course of this work, ultraviolet spectra of steroid tosylates were studied.

Both 11-dehydroprogesterone (I)[6a–c] and 17α-methylprogesterone (II)[7a–c] exceed the natural

(1) Paper V of this series: Ch. R. Engel, THIS JOURNAL, **78**, 4727 (1956).

(2) The main results of this communication were described in a paper presented before the Division of Medicinal Chemistry at the 126th National Meeting of the American Chemical Society in Dallas, Texas, April, 1956.

(3) In part from the M.Sc. thesis of K. F. Jennings, presented to the Faculty of Graduate Studies of the University of Western Ontario, September, 1953.

(4) In part from the Ph.D. thesis submitted by G. Just to the Faculty of Graduate Studies of the University of Western Ontario, May, 1956.

(5) Holder of an Ontario Research Council Special Fellowship 1953–1954 and of a Canadian National Research Council Studentship 1954–1955.

(6) (a) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 715 (1943); (b) J. von Euw and T. Reichstein, *ibid.*, **29**, 654 (1946); (c) Ch. Meystre, E. Tschopp and A. Wettstein, *ibid.*, **31**, 1463 (1948).

(7) (a) Pl. A. Plattner, H. Heusser and P. Th. Herzig, *ibid.*, **32**, 270 (1949); (b) H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner, *ibid.*, **33**, 2229 (1950); (c) Hs. H. Günthard, E. Beriger, Ch. R. Engel and H. Heusser, *ibid.*, **35**, 2437 (1952).