Synthesis of Some γ-Substituted α-Amino γ-Lactones

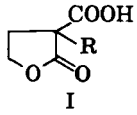
By METRO FEDORCHUK† and FRED T. SEMENIUK

γ-Substituted α-amino γ-lactones were synthesized as potential antibacterial agents. A series of new γ-substituted α-aceto and α-oximino γ-lactones is reported.

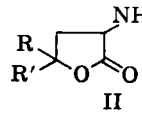
THE OCCURRENCE of the lactone ring in many physiologically active compounds has been reported throughout the literature. Of interest here are the γ- and δ-lactones with antibacterial activity.

The mechanisms by which these antibacterials exert their activity differ from one series to the next. Nevertheless, the presence of the lactone structure cannot be ignored. Patulin (1), crepin (2), the active principles of *Spiraea aruncus* (2), and *Arctium minus* (3), for example, lose their antibacterial activity after their lactone moieties are broken. Similarly the macrolide, etamycin (4), is inactivated on hydrolysis of the lactone ring. Geiger and Conn (5) theorized that, since both penicillic acid and patulin are inactivated by an excess of thiol, their antibacterial activities are probably due to the addition of the —SH groups of bacterial enzyme systems or the —SH groups of essential metabolites with the double bond of the α-unsaturated lactones. They were able to show that α,β-unsaturated ketones closely resembled patulin and penicillic acid, both in their reactivity toward thiols and in their bacteriostatic and fungistatic properties. Cavallito and Haskell (6) pointed out that these reactions appear to proceed by addition of the thiol group to the double bond, followed (in the case of the β-angelicalactone and cysteine or homocysteine) by reaction of the lactone with the amino group and loss of water. Cavallito, *et al.* (7), indicated that a series of lactone aliphatic acids of type I showed a close parallelism in the ability to inhibit growth and in their power to lower surface tension. Asano, *et al.* (8), suggested that the lactones of the γ-hydroxy fatty acids prepared by them inhibited the growth of avian tubercle bacilli through antagonism of the many fatty acids that make up the cell wall.

Since the simple lactone structure appears to confer possible antibacterial activity, the authors have chosen for their study a series of γ-substituted α-amino γ-lactones of type II. These are cyclized γ-hydroxy amino acids. It has been previously found (9) that the exchange of hydrogen atoms for hydroxyl groups in some amino acids converts them into antimetabolites. Many antibiotics (10, 11) derived from bacteria and fungi are amino acid derivatives, peptides, or polypeptides. These naturally occurring antibiotics frequently contain amino acids not found in ordinary proteins. Hence, the authors have modified the simple γ-lactone structure to α-amino acid analogs by varying R and R′ in II, providing a series of new γ-lactones as possible antibacterial agents.



I



II

Based upon analogy to published results of previous researches, a plausible route for the synthesis of a series of α-amino γ-lactones would have been through the interaction of the epoxide and diethyl acetamidomalonate as illustrated in Fig. 1. In such a manner Sudo, *et al.* (12), prepared α-acetamido-γ-butyrolactone in a 100% yield. Beasley, *et al.* (13), reacted diethyl acetamidomalonate with 1,2-epoxy-3-*o*-toloxypropane, hydrolyzed the resultant α-acetamido γ-lactone, and obtained the α-amino-δ-*o*-toloxy-γ-valerolactone hydrochloride in a 15.2% yield. Sudo, *et al.* (12), used ethanolic sodium ethoxide as a condensing medium, while Beasley, *et al.* (13), used methanolic sodium methoxide as a medium. Dakin (14) was unsuccessful in using ethanolic sodium ethoxide in condensing isobutylene oxide with diethyl acetamidomalonate, but by the use of dry sodium methoxide (with or without dioxane as a solvent) he obtained the desired product in a 50% yield.

In the initial part of this program the authors attempted to condense styrene oxide with diethyl acetamidomalonate in an ethanolic sodium ethoxide medium at room temperature, and at reflux temperature. In both cases attempts failed to isolate the α-acetamido-γ-phenyl-γ-butyrolactone, or the corresponding hydrochloride. When the reaction was carried out at room temperature, 44.2% of the styrene oxide was recovered as the β-ethoxy-α-phenylethyl alcohol resulting from the reaction of sodium ethoxide with styrene oxide; 31.5% of the diethyl acetamidomalonate was also recovered. When the reaction mixture was refluxed, the yield of β-ethoxy-α-phenylethyl alcohol was 56% and only 6% of the diethyl acetamidomalonate was recovered. In the latter case an additional 32.5% of the diethyl acetamidomalonate was recovered as glycine hydrochloride when the residue, assumed to contain the α-acetamido-γ-phenyl-γ-butyrolactone, was hydrolyzed with concentrated hydrochloric acid. Dakin (14) and Beasley, *et al.* (13), also found

Received September 21, 1962, from University of North Carolina, School of Pharmacy, Chapel Hill.
Accepted for publication December 17, 1962.
Abstracted from a portion of a thesis submitted by Metro Fedorchuk to the Graduate School of the University of North Carolina in partial fulfillment of Doctor of Philosophy degree requirements.
† Present address: Wallace and Tiernan, Inc., 25 Main Street, Belleville 9, N. J.

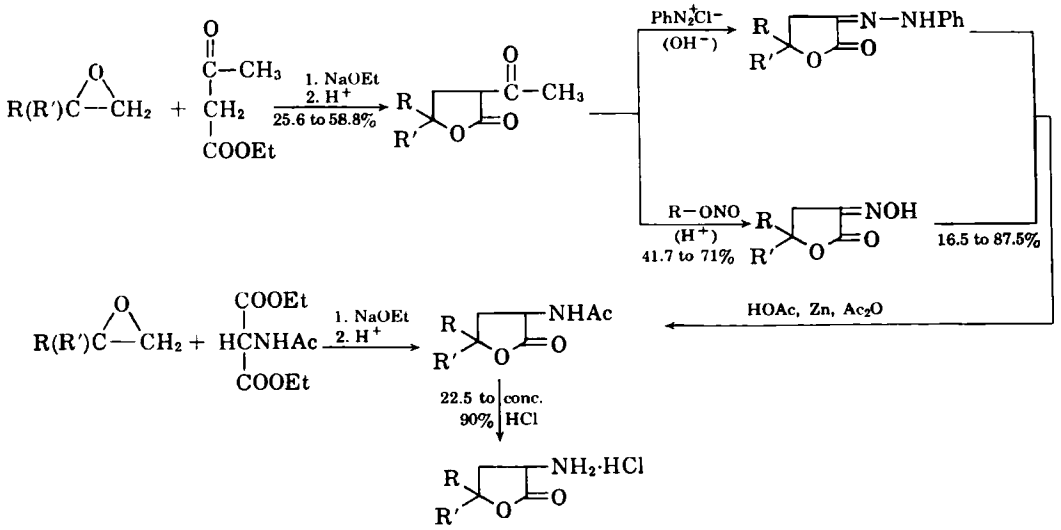


Fig. 1.—Pathways for γ-substituted α-amino γ-lactone syntheses.

that glycine hydrochloride (from hydrolysis of the unreacted diethyl acetamidomalonate) contaminated their final products, presenting some difficulty in purification.

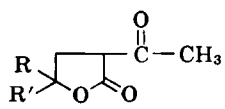
The condensation of propylene oxide with diethyl acetamidomalonate in an ethanolic sodium ethoxide medium at room temperature yielded 3.3% of α-amino-γ-valerolactone hydrochloride on hydrolysis of the corresponding amide—36.6% of the diethyl acetamidomalonate was recovered.

In view of the apparent difficulty to reproduce satisfactorily the published success of others in condensing an epoxide with diethyl acetamidomalonate in an ethanolic sodium ethoxide medium and of the difficulty of separating the unreacted diethyl acetamidomalonate from any product formed, another route for the synthesis of γ-substituted α-amino γ-lactones was sought.

A feasible method for the preparation of these γ-lactones was found in the interaction of the epoxide and ethyl acetoacetate as illustrated in Fig. 1. Four of the α-oximino γ-lactones were not isolated. These were the γ-ethyl-, γ-butyl-γ-ethyl-, and γ-phenyl-substituted α-oximino-γ-butyrolactones, and α-oximino-δ-hydroxy-γ-valerolactone. Attempts to crystallize these oximes from the reaction mixtures failed. Since oximes are known to decompose violently when subjected to elevated temperatures no attempt was made to isolate them by distillation. Consequently the reaction mixtures containing these oximes were subjected to reductive acetylations and the α-acetamido γ-lactones were isolated in all cases except the α-acetamido-δ-hydroxy-γ-valerolactone. In the latter case, the reaction mixture was treated with concentrated hydrochloric acid and the corresponding α-amino-δ-hydroxy-γ-valerolactone hydrochloride isolated.

The yields at the various steps are indicated in Fig. 1 for all cases where the compounds were isolated. α-Acetamido-δ,δ-diethoxy-γ-valerolactone

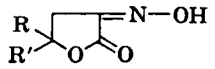
TABLE I.—α-ACETO γ-LACTONES



R	R′	Boiling Range, °C./mm. Hg	Refr. Index/Temp., °C.	Yield, %	Analyses[a] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
CH_3—	H—[b]	84–86/2.0	1.4525/25	58.8	...	...	...	...
CH_3CH_2—	H—	98–103/0.3	1.4548/26.5	34.7	61.52	61.35	7.75	7.98
$CH_3(CH_2)_4$—	H—	114–118/40	1.4551/28	42.3	66.62	64.94	9.15	8.92
$CH_3(CH_2)_5$—	H—	125–130/1.0	1.4535/28.5	55.5	67.89	67.76	9.50	9.55
$CH_3(CH_2)_7$—	H—	143–150/1.0	1.4570/28	36.4	69.96	69.94	10.07	10.25
C_6H_5—	H—[b]	138–145/2.0	1.5395/25	46.0	...	...	...	...
p-CH_3O—C_6H_4—CH_2—	H—	175–180/0.2	1.5345/22.5	44	...	...	...	...
C_6H_5—O—CH_2—	H—[c]	185–190/1.0	1.5310/27	47.5	...	...	...	...
CH_3—$(CH_2)_3$—	CH_3CH_2—	120–130/2.5	1.4635/24	25.6	...	...	...	...
HO—CH_2—	H—	155–160/0.33	1.4805/26.8	47.5	53.16	53.16	6.37	6.45
$(C_2H_5O)_2CH$—	H—	122–125/0.15	1.4525/25	58.3	...	...	...	...

[a] Analyses by Weiler and Strauss, Oxford, England. [b] Previously reported (15). [c] Previously reported (16).

TABLE II.—α-OXIMINO γ-LACTONES



R	R′	M.p., °C.	Purification Solvent	Yield, %	Analyses[a] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
CH_3—	H—	106–107	Benzene	71.0	46.53	46.59	5.47	5.55	10.85	10.85
$CH_3(CH_2)_4$—	H—	102–103	Pet. ether (b.p. 60–90°)	59.0	58.35	58.79	8.16	8.08	7.56	8.09
$CH_3(CH_2)_5$—	H—	104–106	Pet. ether (b.p. 60–90°)	63.0	60.26	60.23	8.60	8.17	7.03	7.27
$CH_3(CH_2)_7$—	H—	103–104	Pet. ether (b.p. 60–90°)	67.5	63.40	63.50	9.31	9.18	6.16	6.13
p-CH_3O—C_6H_4—CH_2—	H—	138–140	Benzene	71.0	61.27	61.55	5.57	5.09	...	...
$C_6H_5OCH_2$—	H—	129–131	Benzene-ethanol	45.5	59.72	60.09	5.01	4.87	...	...
$(C_2H_5O)_2CH$—	H—	100–102	Benzene-Pet. ether (b.p. 60–90°)	41.7	49.76	49.86	6.96	7.18	6.45	6.51

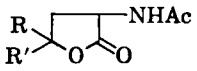
[a] Analyses by Weiler and Strauss, Oxford, England.

was obtained in a 16.5% yield by the reductive acetylation of the corresponding oxime. The other six α-acetamido γ-lactones similarly prepared were obtained in 73 to 87.5% yields.

The reductive acetylation of α-keto γ-lactone phenylhydrazones was also studied as a possible method for the preparation of α-amino γ-lactones. In this study phenylhydrazones of α-keto-γ-valerolactone and α-keto-γ-phenyl-γ-butyrolactone were prepared by the Japp-Klingemann reaction from α-aceto-γ-valerolactone and α-aceto-γ-phenyl-γ-butyrolactone, respectively. The phenylhydrazones were obtained in yields comparable to the yields of oximes obtained from nitrosation reactions. However, upon reductive acetylation of these phenylhydrazones, the yields of the resulting α-acetamido γ-lactones were lower than those obtained when the corresponding oximes were similarly reduced. The most significant disadvantage of this method was the difficulty in separating the acetanilide, formed as a by-product, from the reaction mixture and the product.

α-Amino-γ-phenyl-γ-butyrolactone hydrochloride, α-acetamido-γ-valerolactone, α-amino-γ-valerolactone hydrochloride, and α-amino-γ-pentyl-γ-butyrolactone hydrochloride were screened for biological

TABLE III.—α-ACETAMIDO γ-LACTONES



R	R′	M.p., °C. (b.p., °C/mm. Hg)	Yield, %	Analyses[a] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
CH_3—	H—	(140–155/20) n^{27} = 1.4820	74.5	53.49	53.65	7.05	7.09	8.91	8.65
CH_3CH_2—	H—	(150–155/0.33) $n_D^{26.5}$ = 1.4782	79.0	56.13	56.63	7.65	7.95	8.18	7.88
$CH_3(CH_2)_4$—	H—	(175–181/1.0) n_D^{27} = 1.4743	81.5	...	...	...	...	6.57	6.96
$CH_3(CH_2)_5$—	H—	67–68.5 from benzene-pet. ether	80.0	63.41	63.70	9.31	9.32	...	...
$CH_3(CH_2)_7$—	H—	59–61 from benzene-pet. ether	80.5	65.86	66.25	9.87	10.04	5.49	4.91
C_6H_5—	H—	159–161 from benzene	10.0	65.75	66.19	5.98	5.86	6.39	6.25
p-CH_3O—C_6H_4—CH_2—	H—	125–127 from benzene-pet. ether	73.0	63.86	64.45	6.51	6.82	...	...
C_6H_5—O—CH_2—	H—	121–123 from benzene-ethanol	87.5	62.64	62.98	6.07	6.58	...	...
$CH_3(CH_2)_7$—	CH_3CH_2—	(167–177/0.5)	58.5	...	...	...	...	...	...
$(C_2H_5O)_2CH$—	H—	108–110 from benzene-pet. ether	16.7	53.86	54.37	7.81	8.08	...	...

[a] Analyses by Weiler and Strauss, Oxford, England.

TABLE IV.—α-AMINO γ-LACTONE HYDROCHLORIDES

R	R′	M.p., °C. (Purification Solvent)	Yield, %	Analyses[a] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Cl, % Calcd.	Cl, % Found
CH_3—	H—[b]	200–201 (ethanol)	47.0	...	...	...	7.12	...	7.95	...	...
CH_3CH_2—	H—	203–205 (ethanol)	74.5	43.51	43.53	7.30	8.71	8.46	6.92	17.07	17.22
$CH_3(CH_2)_4$—	H—	131–132 (ethanol-ether)	85.5	52.04	52.52	8.73	8.78	6.74	5.94	...	...
$CH_3(CH_2)_5$—	H—	135–136 (ethanol)	72.0	54.17	54.14	9.09	9.85	6.32	...	...	...
$CH_3(CH_2)_7$—	H—	125–127 (ethanol)	35.0	57.69	58.00	9.68	5.77	5.56	6.45	16.59	16.60
C_6H_5—	H—	223–224 dec. (ethanol-water-ether)	58.0	56.19	56.51	5.66					
p-CH_3O—C_6H_4—CH_2—	H—	201–203 dec. (ethanol)	22.5	55.92	56.59	6.26	6.44	5.44	6.37	...	...
C_6H_5—O—CH_2—	H—	222 dec. (ethanol)	90.0	54.21	53.96	5.79	5.45	5.75	5.40	...	...
CH_3CH_2—	CH_3CH_2—	140–143 (ethanol-ether)	20.5	54.17	51.97	9.09	9.53	6.32	6.33	...	...
HO—CH_2—	H—	213 dec. (ethanol)	19.0	35.83	36.24	6.02	5.89	8.36	8.32	...	...

[a] Analyses by Weiler and Strauss, Oxford, England. [b] Previously reported (17).

activity.[1] The two latter compounds showed some antibacterial activity.

EXPERIMENTAL

The chemical procedures used for the preparation of the various intermediates and products are illustrated by examples which follow.

Epoxides.—1,2-Epoxyoctane, 1,2-epoxydecane, 1,2-epoxy-2-ethylhexane, and 1,2-epoxy-3-*p*-methoxyphenylpropane were prepared according to the method described in "Organic Synthesis" (18) for preparing styrene oxide from styrene. Glycidaldehyde diethyl acetal was prepared according to the method described for preparing acrolein diethyl acetal from acrolein (19).[2]

α-Aceto γ-Lactones (see Table I).—The procedure is essentially that used by Adams and VanderWerf (15) for preparing α-aceto-γ-valerolactone, modified with features used by Van Zyl and Van Tamelen (20) for preparing α-carbethoxy-γ-butyrolactones.

To a cooled solution of 23.0 Gm. (1.0 mole) of sodium in 400 ml. of absolute ethanol (prepared in a three-necked flask equipped with a sealed mechanical stirrer and a reflux condenser fitted with a drying tube), 130.2 Gm. (1.0 mole) of ethyl acetoacetate was added rapidly. The mixture was again cooled in an ice bath and 58.1 Gm. (1.0 mole) of propylene oxide was added dropwise with stirring over a period of 30 minutes. While being stirred, the mixture was kept in the ice bath for several hours and then allowed to come to room temperature. Stirring at room temperature was continued overnight. After cooling the resulting yellow-orange solution in an ice bath to 10°, 60.0 Gm. (1.0 mole) of glacial acetic acid was added; a slurry of sodium acetate formed immediately. The ethanol was removed under reduced pressure, the temperature never being permitted to rise above 50°. Sufficient ice water was added to dissolve the sodium acetate and to separate the resulting oily layer. The aqueous layer was extracted with several portions of ether and the combined crude lactone and extracts were dried overnight over anhydrous magnesium sulfate. The ether was removed and the residue was distilled from a modified Claisen flask equipped with a 15-cm. Vigreux column. Yield was 83.5 Gm. (58.8%) of a colorless oil, b.p.$_2$ = 84–86°, n_D^{25} = 1.4525; reported (15) b.p.$_2$ = 88–90°, n_D^{25} = 1.4489.

α-Oximino γ-Lactones (see Table II).—All of the oximes were prepared by the procedure described for α-oximino-γ-valerolactone: a stream of dry hydrogen chloride gas was introduced for 30 seconds into 60 ml. of cold (0 to −5°) absolute methanol in a three-necked flask, fitted with a mechanical stirrer and thermometer, protected with a drying tube, and surrounded by a freezing mixture. To the methanolic hydrogen chloride solution was added 14.2 Gm. (0.1 mole) of α-aceto-γ-valerolactone. To the cold (0 to −5°) mixture 9.4 Gm. of *n*-propyl nitrite was added dropwise, with stirring, at such a

[1] The authors thank Mead Johnson and Co. for having gratuitously screened these compounds for biological activity.

[2] A sample of glycidaldehyde was provided by the Shell Development Co. 1,2-Butylene oxide was provided by The Dow Chemical Co., glycidol by Roberts Chemicals, Inc.

rate that the temperature did not rise above 0°. On addition of the *n*-propyl nitrite the reaction mixture immediately turned blue. The mixture was maintained at 0° for several hours and was then placed in a refrigerator (5°) overnight. At this point the reaction mixture had assumed a pale yellow color. The methanol and excess *n*-propyl nitrite were removed under reduced pressure with the aid of moderate heat from a water bath. The resulting yellow oil crystallized into a solid mass. This was recrystallized from benzene to give 9.1 Gm. (71.0%) of α-oximino-γ-valerolactone. A sample for analysis, three times recrystallized from benzene, melted at 106–107°.

α-Acetamido γ-Lactones (see Table III).—The procedure used by Fillman and Albertson (21) for the preparation of α-acetamido-γ-butyrolactone was followed as described for α-acetamido-γ-valerolactone. To a solution of 12.9 Gm. (0.1 mole) of α-oximino-γ-valerolactone in 250 ml. of glacial acetic acid and 100 ml. of acetic anhydride 30 Gm. of zinc dust was added portionwise while stirring. The zinc was added at such a rate as to maintain the temperature of the reaction mixture of 50°. After addition of the zinc the temperature was maintained at 50° by applying heat. At the end of 9 hours the warm reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the product distilled at 140–155° at 2 mm. of Hg to give 11.7 Gm. (74.5%) of a clear, slightly yellow, viscid oil, $n_D^{27} = 1.4820$.

α-Amino γ-Lactone Hydrochlorides (see Table IV).—All of the hydrochlorides were prepared by the procedure described for α-amino-γ-valerolactone hydrochloride. A mixture of 5.88 Gm. (0.0375 mole) of α-acetamido-γ-valerolactone and 40 ml. of concentrated hydrochloric acid was refluxed for 5.5 hours. The reaction mixture was then evaporated to dryness under reduced pressure. The crystalline residue was digested with 7 ml. of absolute ethanol, cooled, and the crystals removed by filtration to yield 2.68 Gm. (47%) of the product, m.p. 194–198°. After three recrystallizations from absolute ethanol, the hydrochloride melted at 200–201°; reported (17) m.p. 198–200°.

REFERENCES

(1) Krebs, H. A., *Biochem. J.*, **38**, XXIX(1944).
(2) Florey, H. W., Chain, E., Heatley, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. P., and Florey, M. E., "Antibiotics," Vol. I, Oxford University Press, London, 1949, pp. 600–602.
(3) Cavallito, C. J., Bailey, J. H., and Kirchner, F. K., *J. Am. Chem. Soc.*, **67**, 948(1945).
(4) Sheehan, J. C., Zachau, H. G., and Lawson, W. B., "The Chemistry of Etamycin," Ciba Foundation Symposium, edited by Wolstenholme, G. E., and O'Connor, C. M., Little, Brown, and Co., Boston, Mass., 1958, p. 151.
(5) Geiger, W. B., and Conn, J. E., *J. Am. Chem. Soc.*, **67**, 112(1945).
(6) Cavallito, C. J., and Haskell, T. H., *ibid.*, **67**, 1991 (1945).
(7) Cavallito, C. J., Fruehauf, D. M., and Bailey, J. H., *ibid.*, **70**, 3724(1948).
(8) Asano, M., Takahaski, K., Murakami, T., Tsutsumi, Y., Miura, Y., and Toyoizumi, Y., *Yakugaku Zasshi*, **70**, 202 (1950).
(9) Woolley, D. W., "A Study of Antimetabolites," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 222.
(10) Newton, G. G. F., and Abraham, E. P., *J. Pharm. Pharmacol.*, **10**, 401(1958).
(11) Chain, E. B., *Ann. Rev. Biochem.*, **27**, 167(1958).
(12) Sudo, R., Akiyama, Y., Kato, T., and Ohta, M., *Nippon Kagaku Zasshi*, **74**, 1009(1953).
(13) Beasley, Y. M., Petrow, V., Stephenson, O., and Thomas, A. J., *J. Pharm. Pharmacol.*, **9**, 10(1957).
(14) Dakin, H. D., *J. Biol. Chem.*, **154**, 549(1949).
(15) Adams, R. M., and VanderWerf, C. A., *J. Am. Chem. Soc.*, **72**, 4368(1950).
(16) Van Zyl, G., Zuidema, G. D., Zack, J. F., and Kromann, P. B., *ibid.*, **75**, 5002(1953).
(17) Fischer, E., and Leuchs, H., *Ber.*, **35**, 3787(1902).
(18) Hibbert, H., and Burt, P., "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 494.
(19) Fischer, H. O. L., and Baer, E., *Helv. Chim. Acta*, **18**, 514(1935).
(20) Van Zyl, G., and Van Tamelen, E. E., *J. Am. Chem. Soc.*, **72**, 1357(1950).
(21) Fillman, J., and Albertson, N., *ibid.*, **70**, 171(1948).