[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ISRAEL INSTITUTE OF TECHNOLOGY]

The Reaction of β-Hydroxyalkylcarbamates with Carbonyl Compounds[1]

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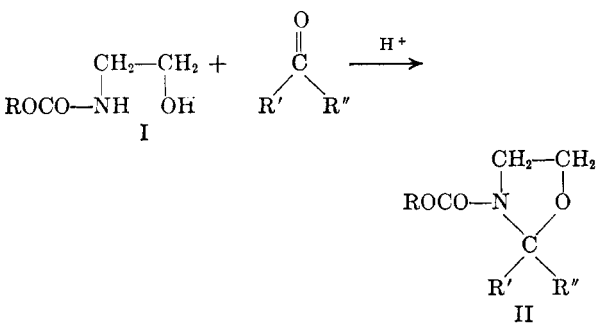
β-Hydroxyalkylcarbamates (*e.g.*, I) have been found to react, in the presence of an acid catalyst, with various carbonyl compounds to give *N*-carbalkoxyoxazolidines (*e.g.*, II). The influence of substituents on the rate of the reaction shows that steric effects are of paramount importance while the electronic effects appear to have minor influence.

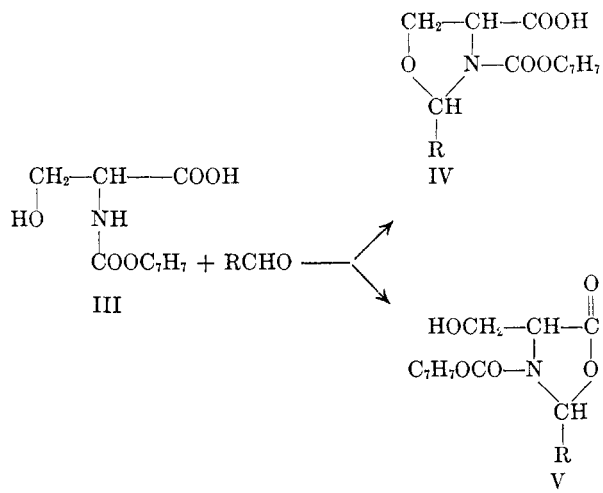
In continuation of our studies on the reactions of substituted carbamates containing an additional hydroxyl or carboxyl function with electrophilic reagents,[3] the investigation of the reaction of β-hydroxyalkylcarbamates with carbonyl compounds was undertaken. Refluxing benzene solutions of β-hydroxyethylcarbamates (I) with various aldehydes and ketones, in the presence of a sulfonic acid catalyst, affords *N*-carbalkoxyoxazolidines(II) in good yields (Table I):

The rate of the reaction was followed qualitatively by measuring the water formed in the reaction by azeotropic distillation. The influence of substitution in the carbonyl component shows that steric factors are very important. The order of reactivity is: aliphatic aldehydes > aromatic aldehydes > aliphatic ketones > aromatic ketones. *p*-Methoxy- and *p*-nitrobenzaldehyde were found to react at approximately the same rate, while a nitro group in the *ortho*-position strongly retards the reaction (Table I).



In order to obtain further information as to the steric effects on oxazolidine ring formation, the behavior of *cis*- and *trans*-β-carbalkoxyaminocyclohexanols was examined. The *cis*-isomers reacts smoothly with aldehydes and ketones to give good yields of the corresponding oxazolidines (Table II). In contradistinction, the *trans*-isomers react extremely slowly with ketones and no oxazolidines were isolated in these cases. Most of the starting material was recovered after refluxing these isomers with acetone or cyclopentanone for twenty hours. The reaction of the *trans*-isomers with aldehydes is much slower as compared with the corresponding *cis*-compounds. Only in the case of *n*-butyraldehyde was an analytical pure oxazolidine obtained.

The condensation of carbobenzoxyserine (III) with aldehydes may lead to two different products: an acidic oxazolidine derivative (IV) or a neutral oxazolidone derivative (V):



Condensation of carbobenzoxy-*d,l*-serine with paraformaldehyde yields two oily products; one acidic, the other neutral. The acidic one, which is obtained in 60% yield, was converted to a crystalline benzylamide. The neutral product, which was obtained in 10% yield, shows two carbonyl absorptions at 1700 cm.$^{-1}$ and 1800 cm.$^{-1}$ in the infrared. These bands are characteristic of *N*-carbobenzoxy-5-oxazolidones.[3] The reaction of carbobenzoxy-*d,l*-serine with isobutyraldehyde and benzaldehyde, respectively, affords crystalline oxazolidine derivatives in 70% yield. The neutral products in each case were obtained in less than 5% yield.

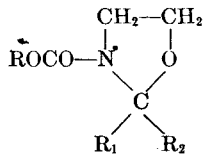
The *N*-carbalkoxyoxazolidine structure assigned to the reaction products described above is based on their analytical data and on their infrared spectra. The infrared spectra of the products lack the alcoholic OH absorption at 3650 cm.$^{-1}$ and the strong carbamate NH absorptions at 3440 and 1510–1520 cm.$^{-1}$ present in the starting materials.

(1) Presented at the 23rd meeting of the Israel Chemical Society, Haifa April, 1958.

(2) From a thesis submitted for the M.Sc. degree by M. Rona, Israel Institute of Technology, Haifa, 1959.

(3) D. Ben-Ishai, *J. Am. Chem. Soc.*, **78**, 4962 (1956); 5736 (1957).

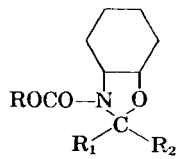
TABLE I



No.	R_1	R_2	Time of Reaction, Hr.	Yield, %	B.P., Mm.	n_D^{15}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
						R = C_2H_5							
1	H	H	0.5	83	58 (0.2)	1.4500	$C_6H_{11}O_3N$	49.63	49.22	7.63	7.68	9.65	9.22
2	H	CH_3	1.5	73	57 (0.15)	1.4405	$C_7H_{13}O_3N$	52.81	52.96	8.23	8.37	8.79	8.76
3	H	C_3H_7	1.3	71	68 (0.2)	1.4472	$C_9H_{17}O_3N$	57.73	57.41	9.15	9.11	7.48	7.39
4	H	$(CH_3)_2CH$	2.3	82	60 (0.1)	1.4471	$C_9H_{17}O_3N$	57.73	57.40	9.15	9.37	7.48	7.47
5	H	$C_6H_5CH_2CH_2$	1.0	80	132 (0.3)	1.5138	$C_{14}H_{19}O_3N$	67.44	67.84	7.86	7.73	5.62	5.48
6	H	$C_6H_5CH{=}CH$	4.0	62	148 (0.2)	1.5490	$C_{14}H_{17}O_3N$	67.99	68.00	6.93	6.91	5.66	5.69
7	CH_3	CH_3	6.5	60	58 (0.3)	1.4410	$C_8H_{15}O_3N$	55.49	54.73	8.73	8.78	8.09	8.40
8	CH_3	C_2H_5	4.0	46	74 (0.2)	1.4452	$C_9H_{17}O_3N$	57.73	58.26	9.15	9.02	7.48	7.03
9	CH_3	$(CH_3)_2CHCH_2$	20.0	30	76 (0.1)	1.4471	$C_{11}H_{21}O_3N$	61.36	61.05	9.83	10.06	6.51	7.11
10		$(CH_2)_5$	3.5	80	106 (0.8)	1.4471	$C_{11}H_{19}O_3N$	61.94	61.74	8.98	8.89	6.57	6.57
11		$(CH_2)_4$	5.5	65	76 (0.2)	1.4725	$C_{10}H_{17}O_3N$	60.28	60.22	8.60	8.64	7.03	6.98
12	H	C_6H_5	2.5	74	117 (0.2)	1.5162	$C_{12}H_{15}O_3N$	65.14	64.65	6.83	7.39	6.33	6.39
13	H	p-$O_2NC_6H_4$	2.0	70	168 (0.2)	1.5433	$C_{12}H_{14}O_5N_2$	54.13	54.32	5.30	5.17	10.52	10.48
14	H	p-$CH_3OC_6H_4$	2.5	80	140 (0.1)	1.5210	$C_{13}H_{17}O_4N$	62.14	61.41	6.82	6.52	5.57	5.77
15	H	o-$O_2NC_6H_4$	11.5	71	156 (0.1)[a]	—	$C_{12}H_{14}O_5N_2$	54.13	54.09	5.30	4.81	10.52	10.41
16	H	o-$CH_3OC_6H_4$	3.0	73	140 (0.2)	1.5300	$C_{13}H_{17}O_4N$	62.14	61.42	6.82	6.90	5.57	5.58
17	CH_3	C_6H_5	20.0	30	116 (0.2)	1.5120	$C_{13}H_{17}O_3N$	66.36	66.35	7.28	7.69	5.95	5.84
						R = $C_6H_5CH_2$							
18	H	H	0.5	70	125 (0.15)	1.5281	$C_{11}H_{13}O_3N$	63.75	63.95	6.32	6.30	6.75	7.01
19	H	$(CH_3)_2CH$	2.0	82	124 (0.2)	1.5120	$C_{14}H_{17}O_3N$	67.44	67.39	7.60	7.77	5.62	5.67
20	CH_3	CH_3	4.5	77	114 (0.2)	1.5142	$C_{13}H_{17}O_3N$	66.36	66.61	7.28	7.39	5.95	6.03
21		$(CH_2)_5$	3.3	73	148 (0.15)	1.5318	$C_{16}H_{21}O_3N$	69.79	69.52	7.63	7.78	5.09	5.07
22	H	C_6H_5	3.0	82	174 (0.2)[b]	—	$C_{17}H_{17}O_3N$	72.06	71.59	6.09	6.01	4.54	5.14

[a] M.p. 23°. [b] M.p. 60°.

TABLE II



No.	R_1	R_2	Time of Reaction, Hr.	Yield, %	B.P., Mm.	$n_D^{1.5}$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
						R = C_2H_5							
1	H	H	0.3	80	82 (0.1)	1.4748	$C_{10}H_{17}O_3N$	60.28	60.14	8.60	8.45	7.03	7.21
2	H	CH_3	1.0	85	78 (0.1)	1.4698	$C_{11}H_{19}O_3N$	61.94	61.51	8.98	8.46	6.57	6.56
3	H	$(CH_3)_2CH$	1.5	83	96 (0.1)	1.4705	$C_{13}H_{23}O_3N$	64.70	63.95	9.61	9.22	5.80	5.96
4	CH_3	CH_3	4.5	73	89 (0.1)[a]	—	$C_{12}H_{21}O_3N$	63.41	63.68	9.31	9.11	6.16	6.04
5	CH_3	C_2H_5	3.5	45	98 (0.2)	1.4720	$C_{13}H_{23}O_3N$	64.70	64.50	9.61	9.19	5.80	5.78
6		$(CH_2)_5$	3.0	70	114 (0.1)	1.4922	$C_{15}H_{25}O_3N$	67.38	67.32	9.43	9.42	5.24	5.20
7		$(CH_2)_4$	4.0	50	112 (0.1)	1.4879	$C_{14}H_{23}O_3N$	66.37	65.80	9.15	9.02	5.53	5.53
8	H	C_6H_5	3.5	81	157 (0.3)	1.5285	$C_{16}H_{21}O_3N$	69.79	69.39	7.69	7.60	5.09	5.12
						R = $C_6H_5CH_2$							
9	H	H	0.3	80	159 (0.4)	1.5321	$C_{15}H_{19}O_3N$	68.94	68.82	7.33	7.40	5.36	5.52
10	H	CH_3	1.5	75	152 (0.4)	1.5200	$C_{16}H_{21}O_3N$	69.79	69.57	7.69	7.08	5.08	5.00
11	H	$(CH_3)_2CH$	2.5	90	148 (0.4)	1.5250	$C_{18}H_{25}O_3N$	71.25	71.09	8.31	8.57	4.62	4.36
12	CH_3	CH_3	5.5	70	138 (0.1)	1.5205	$C_{17}H_{23}O_3N$	70.56	69.86	8.01	7.89	4.84	4.92
13	CH_3	C_2H_5	4.5	40	150 (0.2)	1.5210	$C_{18}H_{25}O_3N$	71.25	71.62	8.31	8.15	4.62	4.45
14		$(CH_2)_5$	2.5	82	178 (0.2)[b]	—	$C_{20}H_{27}O_3N$	72.52	72.55	8.26	8.09	4.25	4.50
15		$(CH_2)_4$	4.0	80	168 (0.5)	1.5335	$C_{19}H_{25}O_3N$	72.35	72.11	7.99	7.84	4.44	4.26
16	H	C_6H_5	4.5	79	—[c]	—	$C_{21}H_{23}O_3N$	74.72	74.72	6.87	6.71	4.75	4.50

[a] M.p. 51°. [b] M.p. 69°. [c] M.p. 99°.

The carbamate carbonyl absorption is shifted from 1715 cm.$^{-1}$ in the starting materials to 1680–1700 cm.$^{-1}$ in the products; such a shift is characteristic in the conversion of secondary carbamate to a tertiary one.[4] The oxazolidines show strong absorptions in the C—H bending, C—N and C—O stretching regions. Of particular interest is a strong band at 1410–1430 cm.$^{-1}$ which is present in all of the carbalkoxyoxazolidines prepared. This band is either absent or very weak in the starting materials. The sharp strong bands at 1100–1200 cm.$^{-1}$ which were used to characterize the N—C—O system of oxazolidines[5] could not be used to characterize the *N*-carbalkoxyoxazolidines as the starting materials (β-hydroxyalkylcarbamates) show, in the same region, absorptions which are due to the carbamate group.

The *N*-carbalkoxyoxazolidines resemble oxalanes, ketals, and acetals, in their chemical properties. They are cleaved by dilute acids at room temperature within twenty-four hours into the corresponding starting materials (hydroxyalkylcarbamate and the carbonyl component) and are stable to alkali under the same experimental conditions. This behavior would explain the positive 2,4-dinitrophenylhydrazine test given by all carbalkoxyoxazolidine tested and their negative response to semicarbazide. Carbalkoxyoxazolidines derived from benzaldehyde gave a positive semicarbazone test, probably since the *O*-benzyl bond which is present in the oxazoline ring is cleaved even under the mild conditions of the reaction (*p*H 6).

EXPERIMENTAL

Preparation of β-hydroxyethylcarbamates. N-(β-Hydroxyethyl) ethylcarbamate[6] was prepared from ethanolamine and ethyl chloroformate by the Schotten-Baumann procedure. The aqueous solution was acidified and the water soluble product continuously extracted with chloroform for 24 hr. The chloroform was removed by distillation and the residual oil distilled under reduced pressure. The yield was 79%, b.p. 112–114° (0.6 mm.). *N*-(β-Hydroxy)benzyl carbamate was prepared from ethanolamine and benzyl chloroformate by the method of Rose.[7]

d,l-cis-2-Carbethoxyaminocyclohexanol. This compound was prepared from *d,l-cis*-2-aminocyclohexanol and ethyl chloroformate by the Schotten-Baumann procedure. The product melted at 61° after recrystallization from ethyl acetate-hexane; yield 72%.

Anal. Calcd. for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.96; H, 9.09; N, 7.30.

d,l-trans-2-Carbethoxyaminocyclohexanol. This compound was prepared from *d,l-trans*-2-aminocyclohexanol and ethyl chloroformate by the Schotten-Baumann procedure. The product melted at 72° after recrystallization from ethyl acetate-hexane; yield 75%.

Anal. Calcd. for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.00; H, 8.97; N, 7.50.

The carbobenzoxyaminocyclohexanols were prepared from the corresponding aminocyclohexanol and benzyl chloroformate.[8]

Reaction of β-hydroxyalkylcarbamates with aldehydes and ketones. General procedure. A solution of the carbamate (0.1 mole), carbonyl compound (0.11 mole), and *p*-toluenesulfonic acid (300 mg.) in benzene (200 ml.) was refluxed, and the water distilled and collected in a water separator as it was formed. The time of the reaction is recorded in Tables I and II. The benzene solution was washed with aqueous bicarbonate (5%), with water, and then dried over sodium sulfate. The *N*-carbalkoxyoxazolidine obtained, after removal of the benzene *in vacuo*, was distilled twice under reduced pressure.

In the case of the corresponding carbobenzoxy derivatives and the carbalkoxyaminocyclohexanols 0.05*M* quantities were used in the condensation reaction.

N-Carbobenzoxy-2-isopropyloxazolidine-4-carboxylic acid. A mixture of carbobenzoxy-*d,l*-serine (0.025 mole), isobutyraldehyde (0.03 mole), and *p*-toluenesulfonic acid (250 mg.) in benzene (100 ml.) was refluxed for 3 hr., the water being distilled and collected in a water separator as it was formed. The benzene solution was extracted with 10% aqueous sodium bicarbonate (50 ml.) and with water (50 ml.). The combined bicarbonate and water solution was acidified with acetic acid and extracted with ethyl acetate. The oxazolidine derivative obtained, after the removal of the ethyl acetate *in vacuo*, was crystallized from benzene-methylcyclohexane and melted at 97°. The yield was 5.2 g. (70%).

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.29; H, 6.30; N, 4.89.

The benzene solution was washed with water, dried over sodium sulfate and evaporated to dryness. The oily residue showed two carbonyl absorptions at 1800 cm.$^{-1}$ and 1720 cm.$^{-1}$ in the infrared characteristic, of *N*-carbobenzoxy-5-oxazolidones[3].

N-Carbobenzoxy-2-phenyloxazolidine-4-carboxylic acid. A mixture of carbobenzoxy-*d,l*-serine (0.025 mole), benzaldehyde (0.03 mole) and *p*-toluenesulfonic acid (250 mg.) in benzene (100 ml.) was refluxed for 3.5 hr., as described above. The product, which crystallized from the reaction mixture, melted at 135° after recrystallization from ethanol. The yield was 6.13 g. (75%).

Anal. Calcd. for. $C_{18}H_{17}O_5N$: C, 66.05; H, 5.24; N, 4.28. Found: C, 65.87; H, 5.08; N, 4.30.

N-Carbobenzoxyoxazolidine-4-carboxylic acid. A mixture of carbobenzoxy-*d,l*-serine (0.025 mole), paraformaldehyde (1 g.), and *p*-toluenesulfonic acid (250 mg.) in benzene (100 ml.) was refluxed for 0.5 hr., as described above for the isopropyl derivative. The oily acidic product obtained after removal of the ethyl acetate (3.81 g.) was converted to a crystalline benzylamide on treatment with benzylamine and dicyclohexylcarbodiimide in tetrahydrofuran.[8] The benzylamide melted at 91–92° after crystallization from benzene-methylcyclohexane; yield 55%.

Anal. Calcd. for $C_{19}H_{20}O_4N_2$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.18; H, 6.40; N, 8.65.

The neutral oily residue (600 mg.) obtained after evaporation of the benzene solution showed two carbonyl absorptions at 1810 cm.$^{-1}$ and 1720 cm.$^{-1}$ in the infrared characteristic of *N*-carbobenzoxy-5-oxazolidones.[3]

Acid hydrolysis of N-carbobenzoxy-2,2-dimethyloxazolidine. The oxazolidine (1 g.) was dissolved in 50 ml. of 2.5*N* aqueous-ethanolic (1:1) hydrochloric acid and the solution allowed to stand at room temperature for 24 hr. The solution was diluted with water (50 ml.) and extracted with ethyl

(4) S. Pinchas and D. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 4099 (1957).

(5) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952).

(6) A. P. M. Franchimont and L. Lublin, *Rec. trav. chim.*, **21**, 45 (1902).

(7) W. G. Rose, *J. Am. Chem. Soc.*, **69**, 1384 (1947).

(8) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

acetate. The ethyl acetate solution was dried over sodium sulfate and evaporated *in vacuo* to dryness. The residue was identified as *N*-(β-hydroxyethyl)benzylcarbamate (mixed melting point and infrared); yield 82%. Similar results were obtained with compounds 19,21,22 (Table I) and compounds 3,4,11 (Table II).

The qualitative 2,4-dinitrophenylhydrazine and the semicarbazide tests were performed by the standard procedure.[9] The infrared spectra were determined in chloroform solutions on a Perkin-Elmer Model 21 Spectrophotometer.

HAIFA, ISRAEL

(9) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 4th ed., Wiley, New York, 1956.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Reactions of α,α-Dialkyl-α-mercaptoacetamides with Carbonyl Compounds

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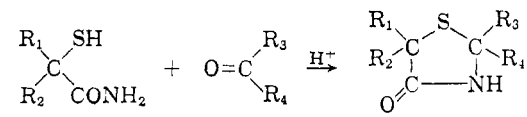
The condensation of α,α-dialkyl-α-mercaptoacetamides with aliphatic aldehydes gave a series of high-melting dimeric 4-thiazolidinones all having a characteristic infrared absorption in the region of 2.94 μ. In cases where the substituents at position 5, or 2, were different, two isomeric dimers were isolated which were then *N*-methylated to the same product. The same mercapto amides condensed with aromatic aldehydes or ketones to give monomeric 4-thiazolidinones having a characteristic infrared absorption in the region of 3.14 μ. Alkaline hydrolysis of both 5,5-diphenyl-2-imino-4-thiazolidinone and 5,5-diphenyl-2,4-thiazolidinedione yielded α,α-diphenylacetamide and gave none of the expected α,α-diphenyl-α-mercaptoacetamide. In general, the carbamyldiphenylmethylsulfur bond and the carboxydiphenylmethylsulfur bond were cleaved by bases with the loss of elemental sulfur.

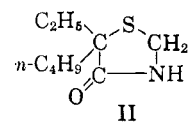
This study was prompted in part by the recent availability of α,α-dialkyl-α-mercaptoacetamides.[2] The objective of the present work was their use in the synthesis of derivatives of 4-thiazolidinones.

Previous investigators have explored a variety of condensation reactions of carbonyl compounds with β-mercaptoamines to form thiazolidines.[3,4] Although a few examples of reactions of thioglycollamide with carbonyl compounds have been reported, the literature contains no reference to the use of α,α-dialkyl-α-mercaptoacetamides. The reactions of thioglycollamide with benzaldehyde[5] and with *n*-heptaldehyde[6] gave the corresponding 2-substituted 4-thiazolidinones. Evidence given for the structure of 2-phenyl-4-thiazolidinone was the lack of reaction with sodium nitroprusside reagent and with cold sodium plumbite, and the fact that the infrared spectrum indicated the absence of the SH group and the presence of the NH group.[5]

In the present work we have found that the α,α-dialkyl-α-mercaptoacetamides react readily with a variety of carbonyl reagents in the presence of mineral acids, under both hydrous and anhydrous conditions, to give the corresponding di-, tri-, and tetrasubstituted 4-thiazolidinones. In cases where an aliphatic aldehyde was employed as the carbonyl



reagent, high melting 4-thiazolidinones were obtained. For example, the reaction of α-ethyl-α-mercapto-*n*-caproamide with formalin gave a mixture of isomers (IIa) and (IIb), both of which had an analysis corresponding to II. Structure



II

II indicates the presence of only one asymmetric carbon atom; thus, only one racemate should be expected. Inasmuch as two isomeric compounds, IIa and IIb, were actually isolated, the possibility of bimolecular compounds was investigated. Molecular weight determinations indicated dimeric values for each of the isomers. Bimolecular compounds composed of two units of II would have the two necessary asymmetric centers.

Numerous examples of hydrogen-bonded dimers of cyclic amides have been reported, both in solution[7-9] and in the crystalline state.[10,11] The occur-

(1) Abstracted from the Ph.D. thesis of John C. James, University of Delaware, 1960.

(2) G. S. Skinner, J. S. Elmslie, and J. D. Gabbert, *J. Am. Chem. Soc.*, **81**, 3756 (1959).

(3) S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, **59**, 200 (1937).

(4) "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 921, 957.

(5) W. Davies, T. H. Ramsey, and E. R. Stove, *J. Chem. Soc.*, 2633 (1949).

(6) J. R. Schenck and R. K. Clarke, Jr., *Arch. Biochem. Biophys.*, **40**, 270 (1952).

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(10) D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2202 (1956).

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