bons form fine microcrystals which produce an easily stirred slurry.

Several authors state that materials which show marked triboluminescence contain small amounts of impurities which serve as activators.[7] The role of impurities in the present case is not known. Samples ranging from 85–98 mole % purity exhibited the phenomenon; material of higher purity was not available. *cis*-4-Octene prepared either by quantitative inversion of the *trans* isomer[8] or by catalytic hydrogenation of 4-octyne exhibits the phenomenon equally well, and apparently neither of the most probable impurities, *trans*-4-octene and *n*-octane, respectively, in the *cis*-4-octene exhibits the phenomenon by itself. Thus, either *cis*-4-octene plus an impurity, or *cis*-4-octene alone is responsible for the triboluminescence.

The fact that *cis*-4-octene exhibits the phenomenon and that *trans*-4-octene does not, serves to emphasize the differences in crystallizing habits of *cis–trans* pairs.

(7) Dake and DeMent, "Fluorescent Light," Chemical Publishing Company, Inc., Brooklyn, N. Y., 1941.

(8) Presented in part at the 115th meeting of the American Chemical Society before the Organic Division and soon to be published in THIS JOURNAL.

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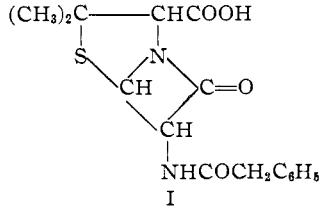
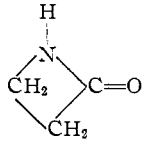
The Reactivity of Benzylpenicillin and Model β-Lactams toward Alkali

BY ANN D. HOLLEY AND ROBERT W. HOLLEY

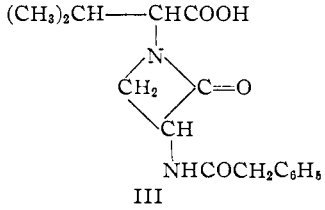
The chemical reactivity of the penicillins has been the subject of considerable discussion.[1,2] One difficulty with the thiazolidine-β-lactam structure (I for benzylpenicillin) has been that the reactivity of the penicillins toward alkali is much greater than that of the model β-lactams which have been studied.



I



II



III

The synthesis of 2-azetidinone (β-propiolactam) (II)[3] has provided a model to which hydrolysis rate studies may be referred. Accordingly, an investigation of the rates of alkaline hydrolysis of benzylpenicillin and desthiobenzylpenicillin (III) was undertaken, with the hope that the additional data would be of value in the comparison of the reactivities of benzylpenicillin and model β-lactams.

Hydrolyses were carried out in 85% ethanol using equimolar concentrations of compound and sodium hydroxide, as in previous studies of β-lactams.[3] As the alkaline hydrolysis of amides is known to be a bimolecular reaction,[4] apparent second order rate constants were calculated. The data are summarized in the table.

TABLE I

ALKALINE HYDROLYSES

Compound	Initial concn., moles/l.	T, °C.	Time, min.	Amount reacted, %		$k \times 10^2$, liter moles^{-1} min.$^{-1}$
Benzyl-penicillin	0.10	0	7	20		36
			15	38		41
			25	48		37
					Av.	38
II		0	See ref. 3		Av.	0.12
		50 ± 1	See ref. 3		Av.	13
III	.45	50 ± 1	30	35		4.0
			60	52		4.0
					Av.	4.0
V	.49	0	3300	20		0.016
			6100	31		.015
			10000	43		.015
					Av.	0.015
VI	.39	50 ± 5	2340	24		0.035
			3120	32		.039
			3900	40		.044
					Av.	0.04
VII		50 ± 1	See ref. 3		Av.	1.0

Desthiobenzylpenicillin (III) was found to be somewhat less reactive than 2-azetidinone (II) toward alkali. Therefore, the combination of the effects of the carboxyalkyl group and the phenylacetamido group present in desthiobenzylpenicillin does not result in increased reactivity of the β-lactam ring for this reaction.[5] Presumably this would also be true in a compound having the thiazolidine-β-lactam structure (I).

Benzylpenicillin is much more reactive than 2-

(1) Clarke, Johnson and Robinson, Editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949; especially (a) Woodward, pp. 443–449, (b) Robinson, pp. 449–454, and (c) Ballard, Melstrom and Smith, Chapter XXVI.

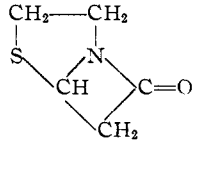
(2) Chain, *Endeavour*, **7**, 152 (1948).

(3) Holley and Holley, THIS JOURNAL, **71**, 2124, 2129 (1949).

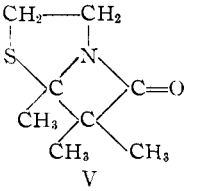
(4) (a) Crocker and Lowe, *J. Chem. Soc.*, **91**, 952 (1907); (b) Calvet, *Compt. rend.*, **192**, 1569 (1931); (c) Reitz, *Z. physik. Chem.*, **A183**, 371 (1939).

(5) It seems likely that the presence of the carboxyl group (carboxylate group in alkali) decreases the rate of alkaline hydrolysis. In a summary of relative rates of alkaline ester hydrolysis in water at 25°, Hammett ("Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 212) gives the ratio of rates of hydrolysis of CH_3COOCH_3 and $^-OOCCH_2COOCH_3$ as 1:0.19. In the present study, the carboxylate group might be expected to influence the hydrolysis rate by increasing the basicity of the lactam nitrogen, thus retarding the reaction, as well as by simply repelling the attacking hydroxyl ion (approach of one anion to another). It also seems likely that the α-phenylacetamido group would increase the rate of alkaline hydrolysis.[10] Whatever the magnitudes of the effects of these two substituents, the combination does not result in an increased rate of alkaline hydrolysis.

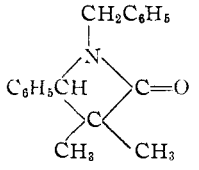
azetidinone. If formula I is correct for benzylpenicillin, its alkaline hydrolysis must be greatly facilitated by the sulfur bonded to the β-lactam ring and/or fusion of the β-lactam ring with a five-membered ring.[1a] These two structural features would be incorporated in the unknown β-lactam (IV) of 2-thiazolidineacetic acid, and, if formula I is correct for benzylpenicillin, IV should be very reactive toward alkali. The simplest thiazolidine-β-lactam known is the β-lactam (V) of 2-methyl-2-thiazolidine-α-isobutyric acid.[1c] It may be inferred from published data,[1c] however, that V and other substituted thiazolidine-β-lactams are not very reactive toward alkali. To resolve this apparent inconsistency, the rate of alkaline hydrolysis of V was studied and an attempt was made to estimate the effect of the methyl groups. To this end, the rate of hydrolysis of 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (VI)[6] was studied and compared with that of 1-benzyl-4-phenyl-2-azetidinone (VII).[3]



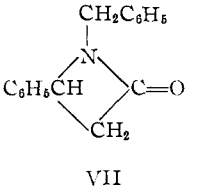
IV



V



VI



VII

From the data in the table it can be seen that compound V is somewhat less reactive than 2-azetidinone (II). From the comparison of the reactivity of VI and VII and from consideration of the retarding influence of a β-methyl group on the hydrolysis of amides,[7] it may be inferred that the unknown β-lactam (IV) of 2-thiazolidineacetic acid would be more reactive than 2-azetidinone toward alkali and that its reactivity toward alkali would approach that of benzylpenicillin. This is consistent with the view that the alkaline hydrolysis of benzylpenicillin is greatly facilitated by the sulfur bonded to the β-lactam ring and/or fusion of the β-lactam ring with a five-membered ring.

Experimental

To a weighed sample of the compound was added the calculated volume of standardized sodium hydroxide solution in 85% ethanol. Reactions were run in glass-stoppered Pyrex test-tubes. Reactants were heated or cooled to the proper temperature before mixing. Reactions which were run for a short period of time were quenched by cooling or by dilution with 85% ethanol. The amount reacted was determined by titration with standard hydrochloric acid (in 85% ethanol) using phenolphthalein as indicator.[8] Initial concentrations were not determined by titration in the experiments with benzylpenicillin and desthiobenzylpenicillin because of a limited supply of benzylpenicillin.

Benzylpenicillin.—Crystalline commercial sodium benzylpenicillin was recrystallized by solution in water followed by the addition of acetone. After the hydrolysis period, an equivalent of standard aqueous hydrochloric acid was added to quench the reaction. The amount reacted was determined by titration with standard aqueous sodium hydroxide. The alkaline hydrolysis of benzylpenicillin yields benzylpenicilloic acid.[9]

Desthiobenzylpenicillin (III) was prepared at room temperature, by the desulfurization of benzylpenicillin in water using Raney nickel according to the procedure described for deuteriumolysis at room temperature.[10] The yield of recrystallized desthiobenzylpenicillin was 26–46%. In hydrolysis studies two moles of sodium hydroxide per mole were used to allow for neutralization of the carboxyl group. Alkaline hydrolysis of desthiobenzylpenicillin yields desthiobenzylpenicilloic acid.[10]

β-Lactam of 2-Methyl-2-thiazolidine-α-isobutyric Acid (V).[10]—In attempted hydrolysis rate studies at 50°, when less than 15% (by titration) of the β-lactam had reacted sodium carbonate precipitated, presumably from decarboxylation of the amino acid. (Benzylpenicilloic acid also decarboxylates readily, though it is relatively stable in alkaline solution.[9]) At 0°, only a minute amount of crystalline sodium carbonate was present when 30% of the β-lactam had reacted. 2-Methyl-2-thiazolidine-α-isobutyric acid has not been isolated. Methanolysis, catalyzed by alkali, of the β-lactam gives the methyl ester of 2-methyl-2-thiazolidine-α-isobutyric acid.[10]

(6) Staudinger, Klever and Kober, *Ann.*, **374**, 1 (1910).

(7) Casou and Wolfhagen, *J. Org. Chem.*, **14**, 155 (1949).

(8) Foreman, *Biochem. J.*, **14**, 451 (1920).

(9) Ref. 1, Mozingo and Folkers, Chapter XVIII.

(10) Ref. 1, Kaczka and Folkers, Chapter IX.

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RECEIVED OCTOBER 28, 1949

Isomerization Accompanying Alkylation. V.[1] Reaction of 4-Methylcyclohexene with Benzene in the Presence of Hydrogen Fluoride

BY V. N. IPATIEFF, E. E. MEISINGER AND HERMAN PINES

In previous papers of this series it was noticed that shifting of a double bond often accompanies the reaction of olefinic hydrocarbons with benzene.[2,3] Heretofore this observation was limited to open-chain olefins. In connection with the study of terpenic hydrocarbons it was deemed of importance to show that a similar shift occurs in the case of alkylcycloölefins. For that reason isomeric methylcyclohexenes, including pure 4-methylcyclohexene, were treated with benzene in the presence of hydrogen fluoride at 0–5°. It was found in each case the same product was obtained, which is most likely 1-methyl-1-phenylcyclohexane. The structure of this compound was indicated by means of dehydrogenation, which consisted in passing it over a chromia-

(1) For paper IV of this series see H. Pines, A. Edeleanu and V. N. Ipatieff, THIS JOURNAL, **67**, 2193 (1945).

(2) V. N. Ipatieff, H. Pines and L. Schmerling, *ibid.*, **60**, 353 (1938).

(3) V. N. Ipatieff, H. Pines and L. Schmerling, *J. Org. Chem.*, **5**, 253 (1940).