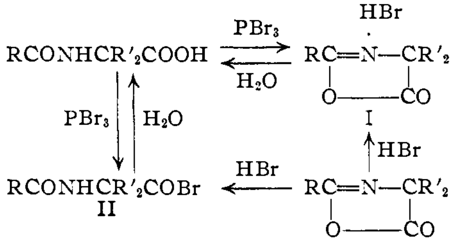
[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

Spectroscopic Evidence Concerning the Structure of 2-Phenyl-4,4-dimethyl-5(4)-oxazolone Hydrobromide

BY CURTIS W. SMITH AND ROBERT S. RASMUSSEN

The reactions of phosphorus tribromide, phosphorus trichloride, or thionyl chloride with α-acylamino acids give products which have been considered as oxazolone hydrohalides (I) or as α-acylamino acid halides (II). Treatment of an oxazolone with hydrogen chloride or hydrogen bromide gives similar products.



Fischer,[1] Mohr,[2] and Neher, Wettstein and Miescher[3] assigned the α-acylamino acid halide structure (II) to products of this type.

Evidence presented in two chapters[4,5] of the Monograph on Penicillin might be interpreted to favor the oxazolone hydrohalide structure. However, it was pointed out by Cornforth[5] that it was not possible to distinguish between the two structures, I and II, with the evidence at present available. He further suggested that the two structures may be in equilibrium.

In an attempt to gain further knowledge as to the structure of these reaction products the infrared absorption of the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide has been obtained in these laboratories.

α-Benzamidoisobutyric acid in dry chloroform was treated with an equimolar quantity of phosphorus tribromide and the infrared absorption of the solution was examined shortly thereafter. This same procedure was carried out using as the solvent, dioxane, which had been freshly distilled over sodium. The spectra of the two solutions (see Table I, spectra 2 and 3) were consistent with each other and showed a broad general absorption around the 4 μ (2500 cm.$^{-1}$) region, a rather sharp band near 5.28 μ (1894 cm.$^{-1}$) and a strong, sharp band near 6.10 μ (1639 cm.$^{-1}$), with only a trace of absorption in the 5.78 μ (1730 cm.$^{-1}$) region. The lack of a 6.6 μ (1515 cm.$^{-1}$) band was evident in the chloroform solution but was especially striking in the dioxane solution.

In an experiment in which more concentrated solutions were used, phosphorus tribromide was added in equimolar quantity to a solution of α-benzamidoisobutyric acid in dry dioxane. The precipitate which separated was collected on a funnel and washed twice quickly with small quantities of dioxane with minimum exposure to air. A five per cent. solution of this material in chloroform was prepared immediately and its infrared absorption spectrum obtained within an hour. The spectrum (Table I, spectrum 4) still showed the strong bands at 5.28 μ (1894 cm.$^{-1}$) and 6.10 μ (1639 cm.$^{-1}$) observed in the preceding experiments but now showed in addition a band of about equal intensity at 5.75 μ (1739 cm.$^{-1}$) attributable to the expected hydrolysis product, α-benzamidoisobutyric acid (Table I, spectrum 1).

Spectral Interpretations

On the basis of these infrared absorption spectra the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide has been assigned the formula 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide (II) instead of α-benzamidoisobutyryl bromide (I) for the following reasons:

(1) An extensive study of the infrared absorption of monosubstituted amides[6] has shown that this grouping almost without exception gives rise to two bands at about 6.0 and 6.6 μ (1667 and 1515 cm.$^{-1}$). With α-benzamidoisobutyric acid the bands due to the amide linkage are at 6.01 and 6.56 μ (1664 and 1524 cm.$^{-1}$). Two bands near these same positions would be expected from the amide grouping in the α-benzamidoisobutyryl bromide structure. The absence of the band in the 6.6 μ (1515 cm.$^{-1}$) region from the spectra under consideration furnishes strong evidence against the α-benzamidoisobutyryl bromide formula.

(2) The infrared absorption spectra of acetyl chloride, acetyl bromide and α-toluyl chloride[7] show strong bands respectively as follows: 5.52, 5.52 and 5.54 μ (1812, 1812 and 1805 cm.$^{-1}$). The acid bromide grouping of α-benzamidoisobutyryl bromide might be expected to give rise to a band in this region (5.5–5.65 μ) (1818–1770 cm.$^{-1}$). The absence of such a band in the

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(1) Fischer, *Ber.*, **38**, 612 (1905).

(2) Mohr, *Ber.*, **42**, 252 (1909); *J. prakt. Chem.*, [2] **81**, 49, 322, 473 (1910).

(3) Neher, Wettstein and Miescher, *Helv. Chim. Acta*, **29**, 1815 (1946).

(4) Hunter, Hinman and Carter, "Methyl Benzylpseudopenicillinate" in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(5) Cornforth, "Oxazoles and Oxazolones," *ibid.*

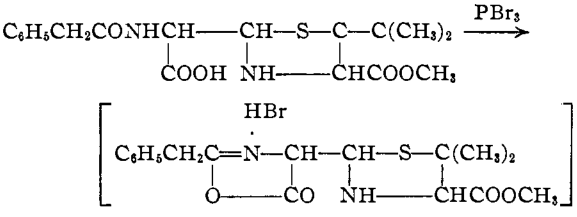
(6) Thompson, Brattain, Randall and Rasmussen, "Infrared Spectroscopic Studies on the Structure of Penicillin" in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(7) O. S. R. D., Penicillin Program, Randall and Fowler, R2, Chart VII (U. S. Office of Publication Board, PB L80195).

spectra observed for the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide is evidence against the acid bromide structure. The band near 5.30 μ (1887 cm.$^{-1}$) observed with this reaction product is definitely outside the range found in known acid halides.

(3) Triamylamine hydrochloride and an N-alkyldialkylketimine hydrochloride[8] showed a broad general absorption in the 4 μ (2500 cm.$^{-1}$) region attributable to the $^+$NH grouping. The 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide (I) would be expected to show this absorption. α-Benzamidoisobutyryl bromide (II) would not be expected to show this absorption. Thus the presence of the 4μ (2500 cm.$^{-1}$) band in the spectra observed might be considered evidence favoring the oxazolone hydrobromide formula. However, absorption due to dissolved hydrogen bromide[9] would appear at the 4 μ (2500 cm.$^{-1}$) position and have a similar appearance. Since some hydrogen bromide could have been present in each case where a 4 μ band appeared, evidence for an $^+$NH group is not without question.

During a study of the reaction of β-methyl benzylpenicilloate with phosphorus tribromide, collaborators from the University of Michigan and the Upjohn Company[4] determined the infrared absorption of a solution of the penicilloate and phosphorus tribromide in carefully dried dioxane immediately after combination and then again at short intervals. The oxazolone hydrobromide shown in the accompanying equation was considered as a more or less transitory (V) intermediate in the reaction.



$$C_6H_5CH_2CONH\underset{\displaystyle COOH}{CH}—\underset{\displaystyle NH—}{CH}—S—\underset{\displaystyle CHCOOCH_3}{C}—C(CH_3)_2 \xrightarrow{PBr_3}$$

$$\left[\overset{\displaystyle HBr}{\cdot}\; C_6H_5CH_2C{=}N—\underset{\displaystyle O——CO}{CH}—\underset{\displaystyle NH——}{CH}—S—\underset{\displaystyle CHCOOCH_3}{C}(CH_3)_2\right]$$

V

In the spectrum obtained immediately after combination, and to a decreasing degree in later spectra, bands at 5.60 and 5.98 μ (1786 and 1672 cm.$^{-1}$) not present in the β-methyl benzylpenicilloate or phosphorus tribromide were noted. Since these bands were at 5.60 μ (1786 cm.$^{-1}$) and 5.98 μ (1672 cm.$^{-1}$) instead of at 5.28 μ (1899 cm.$^{-1}$) and 6.10 μ (1639 cm.$^{-1}$) as observed with the 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide, it is difficult to see how the bands at 5.60 and 5.98 μ (1768 and 1672 cm.$^{-1}$) could be assigned to an oxazolone hydrobromide and, consequently, the infrared evidence may be considered as contraindicating the formation of a transitory oxazolone hydrobromide.

Experimental

2-Phenyl-4,4-dimethyl-5(4)-oxazolone Hydrobromide. —A. In Chloroform.—A solution of 0.30 g. of α-benzamidoisobutyric acid,[10] m. p. 201.4–202.4°, in 15 ml. of chloroform was treated with 0.40 g. of phosphorus tribromide. After the solution had stood for thirty minutes its infrared absorption was determined (Table I (2)).

B. In Dioxane.—To 0.4 g. of α-benzamidoisobutyric acid in 35 ml. of dioxane was added 1.30 g. of phosphorus tribromide. The solution was allowed to stand for ten minutes before determining its infrared absorption (Table I (3)).

C. Isolated.—To a solution of 1.03 g. of α-benzamidoisobutyric acid in 25 ml. of dioxane, freshly distilled over sodium, was added 0.37 ml. of phosphorus tribromide. After the solution had stood for about three minutes, crystals began separating. The solution was allowed to stand at room temperature for ten minutes and was then cooled in an ice-bath. The precipitate was collected on a filter and washed twice with dry dioxane with a minimum of contact with air. The infrared absorption of a solution (5%) of this material in chloroform was obtained without delay (Table I (4)). Most of the crystalline material was dried over phosphorus pentoxide at 56° (0.05 mm.) for two and one-half hours. Another sample was placed immediately on a melting block under a cover glass and melted at 153–158° with decomposition.

The bromide content of the dried product was determined shortly by Volhard titration.

Anal. Calcd. for $C_{11}H_{12}NO_2Br$: Br, 29.58. Found: Br, 29.0, 28.8.

Two factors may be responsible for the low bromine content: (1) loss of hydrogen bromide; (2) absorption of water.

TABLE I

INFRARED ABSORPTION SPECTRA

1. α-Benzamidoisobutyric acid, 0.15 mm. < 1% soln. in $CHCl_3$.
2. Same + PBr_3 (equimolar), 0.15 mm. 2% soln. in $CHCl_3$.
3. Same + PBr_3 (equimolar), 0.15 mm. 2% soln. in dioxane.
4. Ppt. from dioxane soln. of α-benzamidoisobutyric acid + PBr_3 redissolved in $CHCl_3$, 0.15 mm. 5% soln.

(Wave lengths in μ; intensity (figures in parentheses) in units of 10% absorption; S = solvent interference; concentrations of solutions are on a wt./vol. basis.)

1	2	3	4
5.78(1)	3.2–3.4 S	3.2–3.7 S	3.2–3.4 S
6.01(1)	~4(7)	5.38(4)	4(6)
~6.56(1)	5.28(3)	~5.68(3)	5.27(4)
No other bands observed because of diluteness of solution	6.10(6)	6.07(8)	5.75(8)
	6.24(1)		
	6.31(1)	6.25(2)	6.10(10)
	6.86(2)		6.22(2)
	7.24(3)	6.32(1)	6.31(1)
	7.37(2)		
	7.44(2)	>6.7 S	6.58(6)
	7.56(1)		
	7.67(1)		7.20(1)
	8.1–8.4 S		
	8.97(5)		7.33(5)
	9.26(3)		
	9.93(7)		7.43(2)
	10.39(4)		
	11.74(4)		Discontinued
	>12 S		

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(8) O. S. R. D., Penicillin Program, Shell Development Co., Sh 7, Figure 44 (U. S. Office of Publication Board, PB L80258).

(9) Plyler and Williams, *Phys. Rev.*, **49**, 215 (1936).

(10) Mohr and Geis, *Ber.*, **41**, 798 (1908).

Summary

On the basis of its infrared absorption spectrum the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide has been assigned the structure, 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide rather than α-benzamidoisobutyryl bromide. This is the first reported instance of an infrared absorption spectrum of a compound of this type.

Since the infrared absorption observed in the reaction of β-methyl benzylpenicilloate with phosphorus tribromide is at distinct variance with that of the above oxazolone hydrobromide, it would appear that this later reaction does not involve an oxazolone hydrobromide.

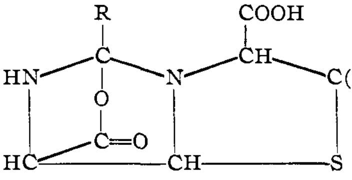
Emeryville, California Received August 23, 1948

[Contribution from the Shell Development Company]

Assignment of Amide Structures to the Supposed 2,3-Dihydro-2-benzimidazolols and their Acylation Products[1]

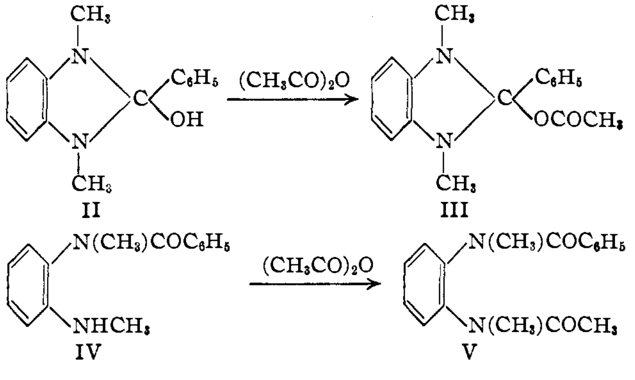
By Curtis W. Smith, Robert S. Rasmussen and Seaver A. Ballard

One of the structures proposed for penicillin which had received much consideration before acceptance of the fused thiazolidine-β-lactam formula is shown as formula I.



I

As a part of the general program of examining the infrared absorption spectra of model compounds as nearly like the most plausible structures for penicillin as possible, the infrared absorption was obtained of a compound previously presumed from chemical evidence to be 1,3-dimethyl-2-phenyl-2,3-dihydro-2-benzimidazolol acetate[2] (III). However, when the infrared absorption spectrum of this compound was obtained in these laboratories, it was indicated that instead of the ester grouping shown in formula III there existed amide linkages which would be more consistent with the isomeric formula V, namely, N-acetyl-N′-benzoyl-N,N′-dimethyl-*o*-phenylenediamine. The compound previously thought to have structure III and now indicated as having structure V had been first prepared in the laboratories of Eli Lilly and Company,[2] by acetylation of a compound thought to be 1,3-dimethyl-2-phenyl-2,3-dihydro-2-benzimidazolol (II). The infrared absorption of this parent compound II or IV gave strong indication of the presence of an amide group and was thus in agreement with structure IV and contrary to structure II.



II III IV V

The first example of a compound thought to be of type II was prepared by Niementowski[3] in 1887. Subsequently Fischer and Romer[4] gave a serious and lengthy consideration to the structures of these compounds. The literature now contains a large number of compounds assigned the benzimidazolol structure.

The following discussion is divided into four sections. First is a critique of the literature designed to show the fallacy of some of the steps which led the earlier workers to favor the benzimidazolol formula (II) instead of the amide formula (IV). Second is the presentation of evidence definitely establishing for the first time the diamide structure of a compound N-acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XV), similar to V. Thus the benzimidazolol ester formula (III) has been eliminated as a possibility for this type of compound. Third is the presentation of new evidence strongly favoring the amide structure (IV) rather than the benzimidazolol structure (II) for a compound, N-acetyl-N,N′-dimethyl-4-methyl-1,2-phenylenediamine (XIII). Fourth is a short section on the stability of benzimidazolium hydroxides.

I. Critique of the Literature on the Structure of 2-Benzimidazolols

The arguments for the benzimidazolol, structure

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[1] The work discussed in this paper was carried out at Shell Development Company, during a study of the structure of penicillin, under contract with the Office of Scientific Research and Development (O. S. R. D.). *Cf. Science*, **105**, 653 (1947).

[2] O. S. R. D., Penicillin Program, Eli Lilly and Company, L6, 6; **11**, 14 (U. S. Office of Publication Board, PB/L80033 and 80037).

[3] Niementowski, *Ber.*, **20**, 1886 (1887).

[4] Fischer and Romer, *J. prakt. Chem.*, [2] **73**, 419 (1906).