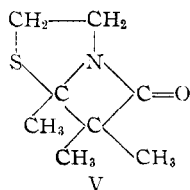
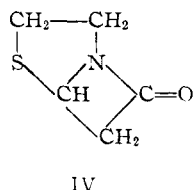
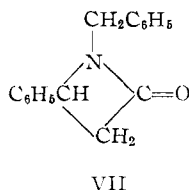
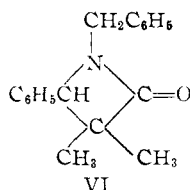


azetidinone. If formula I is correct for benzylpenicillin, its alkaline hydrolysis must be greatly facilitated by the sulfur bonded to the  $\beta$ -lactam ring and/or fusion of the  $\beta$ -lactam ring with a five-membered ring.<sup>1a</sup> These two structural features would be incorporated in the unknown  $\beta$ -lactam (IV) of 2-thiazolidineacetic acid, and, if formula I is correct for benzylpenicillin, IV should be very reactive toward alkali. The simplest thiazolidine- $\beta$ -lactam known is the  $\beta$ -lactam (V) of 2-methyl-2-thiazolidine- $\alpha$ -isobutyric acid.<sup>1c</sup> It may be inferred from pub-



lished data,<sup>1c</sup> however, that V and other substituted thiazolidine- $\beta$ -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)<sup>6</sup> was studied and compared with that of 1-benzyl-4-phenyl-2-azetidinone (VII).<sup>3</sup>



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  $\beta$ -methyl group on the hydrolysis of amides,<sup>7</sup> it may be inferred that the unknown  $\beta$ -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  $\beta$ -lactam ring and/or fusion of the  $\beta$ -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.

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

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

The amount reacted was determined by titration with standard hydrochloric acid (in 85% ethanol) using phenolphthalein as indicator.<sup>8</sup> 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.<sup>9</sup>

**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.<sup>10</sup> 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.<sup>10</sup>

**$\beta$ -Lactam of 2-Methyl-2-thiazolidine- $\alpha$ -isobutyric Acid (V).**<sup>1c</sup>—In attempted hydrolysis rate studies at 50°, when less than 15% (by titration) of the  $\beta$ -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.<sup>9</sup>) At 0°, only a minute amount of crystalline sodium carbonate was present when 30% of the  $\beta$ -lactam had reacted. 2-Methyl-2-thiazolidine- $\alpha$ -isobutyric acid has not been isolated. Methanolysis, catalyzed by alkali, of the  $\beta$ -lactam gives the methyl ester of 2-methyl-2-thiazolidine- $\alpha$ -isobutyric acid.<sup>1c</sup>

(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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### Isomerization Accompanying Alkylation. V.<sup>1</sup> 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.<sup>2,3</sup> 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 alkylcycloolefins. 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).

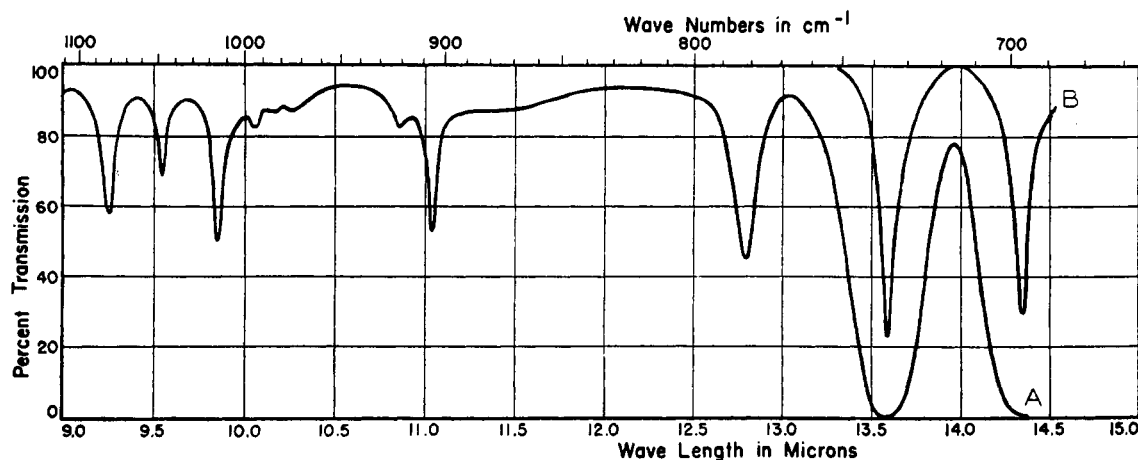


Fig. 1.—Biphenyl, in carbon disulfide, cell length, 0.1 mm.: A, 10% by weight, B, 2.5% by weight.

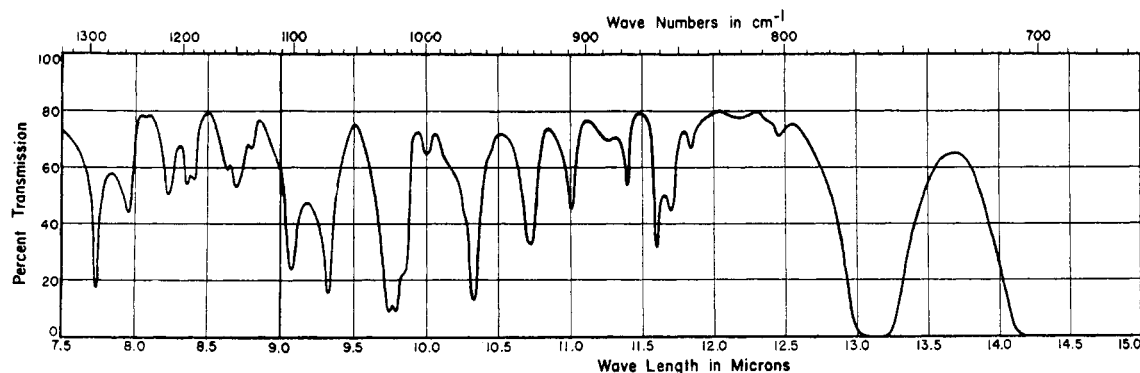
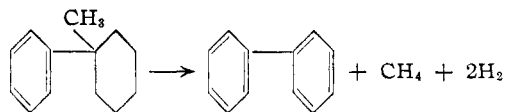


Fig. 2.—1-Methyl-1-phenylcyclohexane, cell length, 0.1 mm.

alumina<sup>4</sup> catalyst at 435°. The liquid product obtained from the dehydrogenation consisted of biphenyl and of the unreacted material; a small amount of toluene and benzene was also formed. The gaseous product was composed of methane and hydrogen. The main reaction seems to proceed as shown



This type of demethanation always occurs when one of the carbon atoms on the hexahydroaromatic ring is completely substituted.<sup>5,6</sup>

In the case of chromia-alumina catalyst the biphenyl was separated and its melting and mixed melting point with a known sample of biphenyl were taken.

The liquid product from the cycloalkylation reaction was identified and its composition was

(4) R. C. Archibald and B. S. Greensfelder, *Ind. Eng. Chem.*, **37**, 356 (1945).

(5) V. N. Ipatieff, H. Pines and R. C. Olberg, *THIS JOURNAL*, **68**, 1709 (1946).

(6) V. N. Ipatieff, H. Appell and H. Pines, unpublished results, have shown that chromia-alumina catalyst does not cause the removal of a methyl group from a cyclohexyl ring when it is not attached to a carbon atom which is completely substituted.

determined by means of infrared analysis<sup>7</sup> as described by Webb and Gallaway.<sup>8</sup> The infrared spectra of the biphenyl and the compound corresponding to 1-methyl-1-phenylcyclohexane are given in Fig. 1.

#### Experimental Part

4-Methylcyclohexene was prepared by dehydration of 4-methylcyclohexanol by passing it over activated alumina at 350°. The infrared spectra of the methylcyclohexene formed was identical with that of 4-methylcyclohexene reported by the API Project 44.<sup>9</sup>

Isomeric methylcyclohexenes were prepared by a similar method from 2- and 3-methylcyclohexanol.

The cycloalkylation was carried out by the method described previously.<sup>1</sup> In a typical experiment 3 moles of benzene, 1.5 moles of 4-methylcyclohexene and 100 g. of hydrogen fluoride were used. The yield of the compound corresponding to 1-methyl-1-phenylcyclohexane formed amounted to 75%. The product distilled at 118° (12 mm.),  $n_D^{20}$  1.5277,  $d_4^{20}$  0.9478,  $M_{RD}$  calcd. 56.6, obsd. 56.3.

Anal. Calcd. for  $\text{C}_{13}\text{H}_{18}$ : C, 89.65; H, 10.35. Found: C, 89.53; H, 10.43.

**Acetylation.**—One gram of the 1-methyl-1-phenylcyclohexane was added to a cold mixture of 0.5 g. of acetyl chlo-

(7) The authors are indebted to Dr. W. S. Gallaway for the infrared analysis.

(8) G. M. Webb and W. S. Gallaway, *Pet. Processes*, **2**, 356 (1947).

(9) Private communication of Dr. F. D. Rossini to Dr. W. S. Gallaway indicated that the spectrum labeled "3-methylcyclohexene" should be called "4-methylcyclohexene."

ride, 0.8 g. of aluminum chloride and 5 ml. of carbon disulfide; the product was hydrolyzed, washed and dried. The 2,4-dinitrophenylhydrazone of the ketone melted at 181°.

*Anal.* Calcd. for  $C_{21}H_{23}N_4O_4$ : C, 63.79; H, 5.83; N, 14.17. Found: C, 63.31; H, 6.00; N, 13.83.

The product remaining from the distillation solidified, it consisted of dicycloalkylated benzene, amounting to 22% based on methylcyclohexene reacted. On recrystallization from alcohol it melted at 70–71°. The probable structure of this compound was *p*-di-(1-methylcyclohexyl)-benzene.

*Anal.* Calcd. for  $C_{20}H_{30}$ : C, 88.89; H, 11.11. Found: C, 88.36; H, 11.06.

**Dehydrogenation.**—Eight grams of the compound corresponding to 1-methyl-1-phenylcyclohexane was dehydrogenated by passing it over 20 ml. of chromia-on-alumina,<sup>4</sup> promoted with cerium and potassium, catalyst at 435° and an hourly liquid space velocity of 0.10. The product began to solidify at the outlet when half the material had been passed; recovery, 7.0 g.

The solid material was recrystallized from Skellysolve "A"; melting point and mixed melting point with a known sample of biphenyl, 69–70°.

The gaseous product was composed of 30% methane and 70% hydrogen.

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### *pK* Values of Methyl Red Indicator in Alcohol-Water Mixtures<sup>1</sup>

By W. D. LARSON AND W. J. TOMSICEK

Data on the ionization constant of *o*-methyl red in mixtures of methanol and water cannot be found in the literature. In order to interpret polarographic data on methyl red it became desirable to have this information. It was obtained by a spectrophotometric method which had been used by Reimers<sup>2</sup> for determining the *pK* for this indicator in ethanol-water mixtures.

A Coleman model 11 spectrophotometer was used for the absorption measurements. No temperature control was used. All measurements were made between 27 and 30°. A sample of *o*-methyl red was prepared according to directions given in "Organic Syntheses,"<sup>3</sup> and purified by a recrystallization from toluene.<sup>4</sup> Its melting point was 182–184° (cor.). For comparison, the measurements of Reimers<sup>2</sup> in ethanol-water mixtures were repeated. Ethanol was commercially available absolute alcohol (U.S.I.); methanol was a synthetic product, dried by the method of Lund and Bjerrum.<sup>5</sup> Standard solutions of the dye were prepared in the dry solvents, with adequate protection from moisture. The working solutions were prepared from these standard solutions by diluting with weighed

(1) This work was supported by a grant from the Research Corporation, which we gratefully acknowledge. The experimental work reported was done by Mr. George N. Sausen.

(2) Reimers, *Z. anorg. allgem. Chem.*, **228**, 33 (1936).

(3) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1932, p. 366.

(4) Livingston and Pariser, *THIS JOURNAL*, **70**, 1510 (1948).

(5) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

amounts of water and either pure ethanol or pure methanol to give a solvent of the desired composition. The dye was approximately  $2 \times 10^{-5}$  molar in each case.

The composition of the solvent is given in volume per cent. so as to be comparable to Reimers<sup>2</sup> results, and so that the *pK* values for benzoic acid in ethanol-water mixtures given by Michaelis<sup>6</sup> could be used. Nevertheless, the solvent mixtures were prepared by weight, and the weight per cent. is given in each case. The *pH* of the methanol-water solutions containing benzoate buffers was measured with a Beckman type G glass electrode. Measured *pH* values in ethanol-water mixtures agreed with those of Michaelis<sup>6</sup> to within 0.02 *pH*. An aqueous buffer 0.01 molar in sodium benzoate and in benzoic acid had a measured *pH* of 4.21, in satisfactory agreement with the *pK* for benzoic acid given by Harned and Owen.<sup>7</sup> The dye was converted to the yellow form by addition of sufficient sodium hydroxide or potassium hydroxide to give a *pH* of 11.6, calculated on the assumption that these bases are completely ionized and have unit activity coefficients in all the solvent

TABLE I

*pK* VALUES OF *o*-METHYL RED IN ETHANOL-WATER MIXTURES

| Vol. % ethanol | Wt. % ethanol | <i>pK</i> (Reimers) | <i>pK</i> (this study) |
|----------------|---------------|---------------------|------------------------|
| 10             | 8.02          | ..                  | 5.38                   |
| 30             | 25.13         | 5.75                | 5.90                   |
| 50             | 43.92         | 6.26                | 6.35                   |
| 70             | 64.65         | 6.75                | 6.80                   |
| 90             | 87.59         | ..                  | 7.46                   |

TABLE II

*pK* VALUES OF *o*-METHYL RED IN METHANOL-WATER MIXTURES

| Vol. % methanol | Wt. % methanol | <i>pK</i> |
|-----------------|----------------|-----------|
| 10              | 8.04           | 5.37      |
| 30              | 25.17          | 5.54      |
| 50              | 43.96          | 5.83      |
| 70              | 64.65          | 6.12      |
| 90              | 87.63          | 6.66      |

TABLE III

*pH* OF 0.01 MOLAR BENZOIC ACID + 0.01 MOLAR SODIUM BENZOATE SOLUTION IN WATER, AND IN MIXTURES OF METHANOL OR ETHANOL AND WATER

| Vol. % alcohol | <i>pH</i> methanol | <i>pH</i> ethanol |
|----------------|--------------------|-------------------|
| 0              | 4.21               | 4.21              |
| 10             | 4.30               | 4.31 <sup>a</sup> |
| 30             | 4.72               | 4.83 <sup>a</sup> |
| 50             | 5.38               | 5.62 <sup>a</sup> |
| 70             | 5.88               | 6.30 <sup>a</sup> |
| 90             | 6.48               | 7.03 <sup>a</sup> |

<sup>a</sup> Data of Michaelis and Mizutani, ref. 6.

(6) Michaelis and Mizutani, *Biochem. Z.*, **147**, 7 (1924).

(7) Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1943, p. 210.