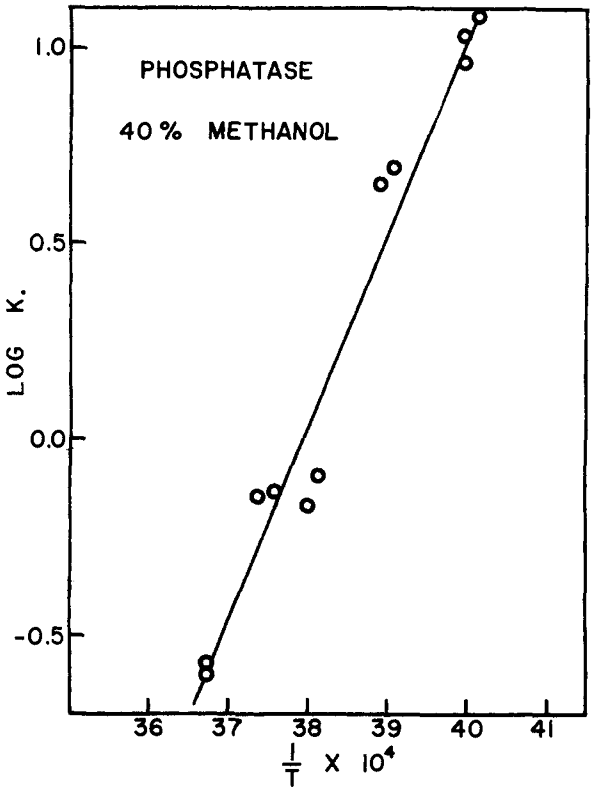

Fig. 4.—Dependence of $K$, the equilibrium constant for inactivation, on temperature.

TABLE I

FREE ENERGIES, HEATS AND ENTROPIES FOR THE EQUILIBRIUM BETWEEN ACTIVE AND INACTIVE ENZYME ($T$ = 263°K.) AND FOR REVERSIBLE DENATURATION OF SOME PROTEINS

| Enzyme and solvent | $\Delta F°$, kcal. | $\Delta H°$, kcal. | $\Delta S°$, e.u. |
|---|---|---|---|
| Peroxidase<br>40% methanol | 0.770 | −18.9 | − 75 |
| Peroxidase<br>60% glycerol | .294 | −16.8 | − 65 |
| Peroxidase<br>5 $M$ sodium acetate | .452 | −21.8 | − 85 |
| Phosphatase<br>40% methanol | − .050 | −22.3 | − 85 |
| Phosphatase<br>60% glycerol | .440 | −17.8 | − 68 |
| Phosphatase<br>23% sodium chloride | .764 | −25.6 | −100 |
| Trypsin[9] (50.0°) | −1.27 | 67.0 | 213.1 |
| Chymotrypsinogen[10] (47.2°) | −1.44 | 99.6 | 316 |
| Soy bean trypsin inhibitor[11] (50.0°) | −0.95 | 57.3 | 180 |

bonded compared to unbonded structures, presumably 4–7 kcal. per mole of hydrogen bond,[8] one finds an entropy change of 12–22 e.u. per mole of hydrogen bond broken in the proteins and (−16)–(−28) e.u. per mole of hydrogen bond formed in the enzyme inactivation.

[8] A. E. Stern, *Adv. Enzymol.*, **9**, 25 (1949).

[9] A. E. Mirsky and M. L. Anson, *J. Gen. Physiol.*, **17**, 393 (1934).

[10] M. A. Eisenberg and G. W. Schwert, *ibid.*, **34**, 583 (1951).

[11] M. Kunitz, *ibid.*, **32**, 241 (1948).

DAVIS, CALIFORNIA

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# NOTES

## The Preparation of Alkyl ψ-Oxatriazoles[1]

BY J. H. BOYER AND F. C. CANTER

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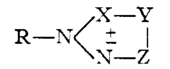
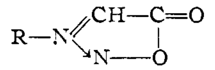
A class of heterocyclic compounds (I) which has contributed a certain amount of interest in connection with structural requirements is probably best known by the special case, the sydnones. The proposed *meso*-ionic representation (Ia)[2] and the more recently suggested use of a coördinate covalent bond between the two ring nitrogen atoms in sydnones (Ib)[3] have indicated the complex nature of this ring system.

An additional member of this class of heterocycles

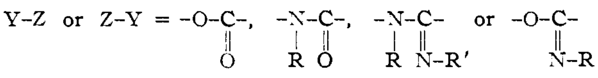


Ia



Ib

X = >CH, >CR or >N



$$Y\text{-}Z \text{ or } Z\text{-}Y = \text{-O-}\underset{\substack{\|\\ O}}{C}\text{-},\quad \text{-}\underset{\substack{|\\ R}}{N}\text{-}\underset{\substack{\|\\ O}}{C}\text{-},\quad \text{-}\underset{\substack{|\\ R}}{N}\text{-}\underset{\substack{\|\\ N\text{-}R'}}{C}\text{-} \text{ or } \text{-O-}\underset{\substack{\|\\ N\text{-}R}}{C}\text{-}$$

in which X = –N– and Y–Z = $\text{-O—}\overset{\substack{O\\ \|}}{C}\text{-}$ has been known since 1933.[4] Certain aryl ψ-oxatriazoles (III)[5] were prepared by treating nitroform with an appropriate diazonium salt.[4,6] Alkyl ψ-oxatriazoles now have been obtained from the action of

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[1] This research was supported by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-331.

[2] W. Baker, W. D. Ollis, V. D. Poole, J. A. Barltrop, R. A. W. Hill and L. E. Sutton, *Nature*, **160**, 366 (1947).

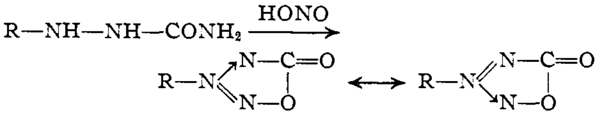
[3] J. C. Earl, *Chem. and Ind.*, 746 (1953).

[4] G. Ponzio, *Gazz. chim. ital.*, **63**, 471 (1933).

[5] The use of the prefix, ψ, to indicate the hybrid nature of the corresponding sydnones (ψ-oxadiazoles) was suggested by W. Baker, W. D. Ollis and V. D. Poole, *J. Chem. Soc.*, 307 (1949).

[6] A. Quilico, *Gazz. chim. ital.*, **63**, 912 (1932).

nitrous acid upon the corresponding semicarbazide, a reaction which parallels the preparation of sydnones from N-substituted glycines. Apparently the preparation of aryl ψ-oxatriazoles by this method is not applicable since N-nitrosoarylsemicarbazides readily undergo the loss of nitroxyl with the formation of an azocarboxamide.[7] The representation used here for the ψ-oxatriazoles has extended the use of a ring coördinate-covalent bond between nitrogen atoms as suggested by Earl.[3]



III

In agreement with similar observations on sydnones, the ψ-oxatriazoles gave no indication of the presence of either the nitroso or the isocyanate groups.

### Experimental[8]

**Preparation of Semicarbazones.**—To a solution of 0.10 mole of a substituted cyclohexanone in 60 ml. of methanol was added just enough water to produce cloudiness. To this solution was added 18.0 g. of sodium acetate and 12.0 g. (0.108 mole) of semicarbazide hydrochloride. After vigorous shaking, the reaction mixture was placed in a 75° water-bath and allowed to come to room temperature. The solid was filtered off, washed with cold methanol, and dried overnight in a vacuum oven at 60°. Quantitative yields of 2-methylcyclohexanone semicarbazone, m.p. 185–187° and menthone semicarbazone, m.p. 189–191° were obtained.

**Reduction of Semicarbazones.**—The procedure of Poth and Bailey[9] for the reduction of menthone semicarbazone was followed. A solution of 100 ml. of water, 50 ml. of methanol, 0.2 g. of gum arabic and 5 ml. of 10% chloroplatinic acid solution was shaken under a hydrogen pressure of about 35 lb. per sq. in. until a black colloid developed. To this catalyst was added 0.132 mole of semicarbazone and 11 ml. (0.13 mole) of concentrated hydrochloric acid. The reaction mixture was shaken under a hydrogen pressure of about 30 to 40 lb. per sq. in. until hydrogen uptake had ceased (about 1.5 hours for 2-methylcyclohexanone semicarbazone, 6.5 hours for menthone semicarbazone). The reaction mixture was diluted to about twice its volume with acetone to break the platinum colloid. After the platinum had been filtered off, the filtrate was evaporated to about 100 ml. Addition of 10% sodium hydroxide solution until the solution was basic caused precipitation of a solid which was removed by filtration. Menthyl semicarbazide, m.p. 181–183° was obtained in 64% yield and 2-methylcyclohexyl semicarbazide, m.p. 162–165°, in 86% yield.

**Preparation of Alkyl ψ-Oxatriazoles.**—A solution or slurry of 0.030 mole of the semicarbazide in 10 ml. of water and 10 ml. of concentrated hydrochloric acid was cooled to 0° in an ice-bath. With stirring, 50 ml. of 10% sodium nitrite solution was added dropwise at such a rate that the temperature of the reaction did not rise above 5°. After all of the sodium nitrite had been added, there was a light yellow solid present (probably an intermediate nitroso compound). The ice-bath was replaced by a 50° water-bath and the material was stirred vigorously at this temperature for 30 minutes.

From the reaction on 2-methylcyclohexyl semicarbazide, there was a suspension of yellow oil droplets in the reaction mixture. The reaction mixture was poured into a separatory funnel and the bottom layer was separated. The aqueous layer was extracted with three 20-ml. portions of ether, the extracts being added to the organic layer. The combined organic solution was washed with dilute ammonium hydroxide and then washed with water. After the solution had been dried over magnesium sulfate, the ether was distilled at reduced pressure and gave 3.1 g. (57% yield) of ψ 5-keto-3-(2-methylcyclohexyl)-3,5-dihydro-1,2,3,4-oxatriazole, b.p. 103–106° (0.08 mm.), $n^{32}\text{D}$ 1.4950, $d^{24.5}_4$ 1.1626.

*Anal.* Calcd. for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.93. Found: C, 52.53; H, 7.25; N, 22.65; $M_D$, 55.05.

From the reaction on menthyl semicarbazide a slightly yellow solid was filtered off and recrystallized from ethanol and water. After being dried for 3 hours in a vacuum oven at 60° there was 4.3 g. (64% yield) of ψ 5-keto-3-menthyl-3,5-dihydro-1,2,3,4-oxatriazole, m.p. 97–98°. Recrystallization from 95% ethanol gave material with constant m.p. at 94.8–95.3°. A portion of this material was submitted for analysis.

*Anal.* Calcd. for $C_{11}H_{19}N_3O_2$: C, 58.63; H, 8.50; N, 18.65. Found: C, 58.77; H, 8.37; N, 18.50.

Strong absorption by both of the alkyl ψ-oxatriazoles at 1790$^{-1}$ cm. was indicative of the carbonyl group and was in close agreement with the carbonyl absorption of γ-lactones (1800–1760 cm.$^{-1}$)[10] and of sydnones (1752–1756 cm.$^{-1}$).[11] Lack of strong absorption by the ψ-oxatriazoles at 1400 cm.$^{-1}$ was indicative of the absence of the nitroso group and was in agreement with the failure of these compounds to give a positive test with the Liebermann nitroso reaction.

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(7) O. Widman, *Ber.*, **28**, 1925 (1895).

(8) Melting points are corrected. Elementary analyses by Microtech Laboratory, Skokie, Ill. Infrared analyses by Mr. J. E. Baudean, Perkin-Elmer Corp., New Orleans, La.

(9) E. J. Poth and J. R. Bailey, THIS JOURNAL, **45**, 3001 (1923).

(10) F. A. Miller, "Applications of Infrared-red and Ultraviolet Spectra to Organic Chemistry," in H. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, 1953, p. 146.

(11) J. C. Earl, R. J. W. LeFevre, A. G. Pulford and A. Walsh, *J. Chem. Soc.*, 2207 (1951).

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## The Action of Acetic Anhydride on 4-Methylpyridine-N-oxide[1]

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RECEIVED SEPTEMBER 7, 1954

The recent reports by Boekelheide and Linn[2] and by Bullitt and Maynard[3] on the rearrangements of alkylpyridine-N-oxides prompt us to communicate the results of similar experiments in this field which were completed before we were aware of the work of these authors. Our observations confirm the previous findings in part and, in addition, provide a basis for a mechanistic proposal.

Aromatic N-oxides, when heated with acetic anhydride or benzoic anhydride, rearrange to the corresponding 2-acyloxy heterocycles.[2,4–6] However, when an alkyl group is in the 2- or 4-position, rearrangement gives the corresponding 2- or 4-acyloxyalkyl derivative.[2,3] For example, pyridine-N-oxide gives 2-acetoxypyridine[4] and 3-methylpyridine-N-oxide gives 3-methyl-2-acetoxypyridine,[2] but 2-methylpyridine-N-oxide gives 2-pyridinemethanol acetate.[2,3]

We have investigated the action of acetic anhydride on 4-methylpyridine-N-oxide, previously reported[2,3] to give 4-pyridinemethanol acetate. Our procedure for working up the reaction mixture

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(1) This investigation was supported in part by a research grant, G-3149-CR, from the National Institutes of Health, Public Health Service.

(2) V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954).

(3) O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

(4) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).

(5) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(6) F. Montanari and L. Pentimalli, *Gazz. chim. ital.*, **83**, 273 (1953).