tain the temperature at 50–55°. Stirring was continued for 2.75 hr., and the catalyst was neutralized by addition of a solution of 10 ml. of potassium acetate in 10 ml. of water. The organic phase was separated and distilled to give 66 g. of recovered isobutyraldehyde, b.p. 62–64° at atmospheric pressure. The distillation was then continued under vacuum to give 66 g. of the isobutyraldehyde trimer, 2,4,6-triisopropyl-s-trioxane (b.p. 88° at 12 mm., m.p. 61°); 271 g. (59%) of 2,4-diisopropylhexahydropyrano[2,3-d]-*m*-dioxin, b.p. 128° (12 mm.), $n_D^{20}$ 1.4562; and 72.5 g. of residue.

The infrared spectrum showed strong bands at 8.6 and 9.1 $\mu$, which are the positions of C—O—C absorption in s-trioxane and tetrahydropyran, respectively. No other functional group, such as C=O or C=C, was indicated to be present.

*Anal.* Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.62; H, 10.73.

*2,4-Dipropylhexahydropyrano[2,3-d]-m-dioxin.* Under conditions similar to those described above, butyraldehyde (2 mol.) and dihydropyran (2 mol.) gave, after a small forerun, 269 g. (59%) of 2,4-dipropylhexahydropyrano[2,3-d]-*m*-dioxin, b.p. 115–121° (4–5 mm.), $n_D^{20}$ 1.4578. The infrared spectrum was similar to that of the product from isobutyraldehyde.

*Anal.* Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.54; H, 10.54.

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## Rate of Reduction of Some Steroid Ketones with Sodium Borohydride

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In connection with a previous investigation on the rate of reduction of steroid ketones in the A and B rings,[1] some other ketones in the C and D rings and in the chain inserted on C-17 were studied.

Although the experimental data (Table I) gave results as normally expected, they showed the reason for the selectivity found sometimes when polycarbonyl compounds are treated with sodium borohydride.[2]

The more interesting facts are that a C-11 ketone is reduced 1000 times slower than a 3-ketone, and that the introduction of a bromine atom in the $\alpha$-position of a carbonyl increases the rate of reduction by a factor of ten. It is known[3] that sodium borohydride reduction of $\alpha$-halo ketones proceeds normally to give bromohydrins and the rate increase is very probably due to the interaction between the carbonyl and halogen dipoles that is released when the keto group is reduced.

TABLE I

RATE OF REDUCTION WITH SODIUM BOROHYDRIDE[a]

| | $k \times 10^4$ | Ratio[b] |
|---|---|---|
| Cholestan-3-one | 397[c] | 100 |
| 2-Bromo-cholestan 3-one | 5000[d] | 1260 |
| 11-Keto-tigogenin | 0.5[d] | 0.126 |
| Hecogenin (12 keto) | 42 | 10.6 |
| Estrone methyl ether | 28 | 7.05 |
| Estrone | 30 | 7.55 |
| Cyclopentanone | 34[c] | 8.55 |
| $\Delta^5$-Androsten-3$\beta$-ol-17-one | 23.5 | 5.94 |
| $\Delta^5$-Pregnen-3$\beta$-ol-20-one | 5.8 | 1.45 |
| 16-$\beta$-Methyl-$\Delta^5$-isopregnen-3$\beta$-ol-20-one | 4.5 | 1.13 |

[a] In 2-propanol at 25. Rate constants in liter mol.$^{-1}$ sec.$^{-1}$ [b] Ratio of rate constants to cholestan-3-one = 100.0. [c] From ref. (1). [d] Approximate result.

When a 3,11 diketone or a 3,20,11 triketone is reduced with one or two equivalents of sodium borohydride, the 11 keto group remains unaltered. The explanation can be seen in the kinetic values, since in the reduction of a 3,11 diketone only 0.1% of the 11-ketone would be reduced. The reason for the lack of reactivity of the C-11 position is steric in nature and it has been discussed elsewhere.[4]

The kinetic results also explain the high selectivity in the reduction of 3,17 and 3,20 diketones.[5]

The relative rates of reduction of the 3,17 and 20 keto group are 100, 5, and 1. Therefore, a minimum percentage of the 17 and 20 alcohols is obtained allowing an easy purification of the reduced product.

The 12 ketone is more reactive than the 17,11 or 20 ketones but nevertheless is reduced 12 times slower that the 3-ketone. The relative rates of reduction for steroidal keto groups can be summarized as follows: 3 keto, 100; 2-bromo 3 keto, 1000; 12 keto, 8.4; 17 keto, 5.2; 20 keto, 1.08; 11-ketone, 0.1.

Taking these results together with the data already reported[1] it is possible to establish the following order of reactivity on sodium borohydride reduction for most of the ketones in the steroid molecule: $\Delta^5$ —3 keto > $\Delta^{8(14)}$ —3 keto > 3 keto A/B *cis* > 3 keto A/B *trans* > 6 keto > 7 keto > $\Delta^4$ —3 keto > 12 keto > 17 keto > 20 keto > 11 keto.

The C-2 ketone is expected to be as reactive as the C-3, the C-16 as reactive as the 3-17, and the C-1 and C-4 as reactive as the C-6 ketone.

### EXPERIMENTAL

The ketones used were samples carefully purified and whose melting point agreed with the ones reported in the

(1) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).

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(3) C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 1657 (1958).

(4) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Co., New York, 1949, p. 408.

(5) A. H. Soloway, A. S. Deutsch, and T. F. Gallagher, *J. Am. Chem. Soc.*, **75**, 2356 (1953).

literature. Since all of the ketones are known their preparations can be found elsewhere.

*Kinetics.* The kinetic method was the same used previously.[1] In all cases the rate constants were calculated from a second order rate plot.

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## Studies in Purine Chemistry. V. 7-Methyladenine-3-*N*-oxide[1]

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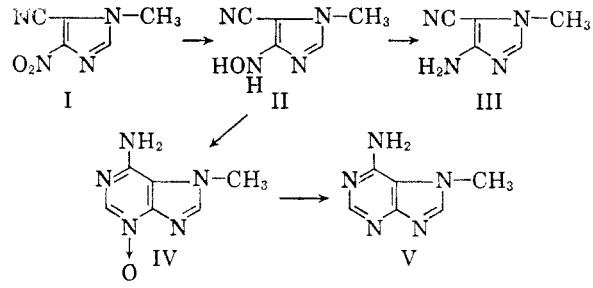
Of the four possible structural types of purine-mono-*N*-oxides, representatives of only the 1- and 7-oxides have been reported.[2] The present paper describes the synthesis and properties of 7-methyladenine-3-N-oxide.

Although reduction of 1-methyl-4-nitro-5-cyanoimidazole (I) with Raney nickel is known to yield 1-methyl-4-amino-5-cyanoimidazole (III),[3] we have found that yields in the reduction are variable and dependent upon the quality of the Raney nickel employed. In an attempt to improve on this conversion by the use of other catalysts, reduction of I was carried out with platinum oxide. Absorption of hydrogen either in ethanol or in ethanolic hydrogen chloride solution was complete within 8 minutes, but the reduction product proved to be 1-methyl-4-hydroxylamino-5-cyanoimidazole (II). Complete reduction to III had occurred only to a negligible (2.5%) extent. The structure of II was readily confirmed by further reduction with hydrogen in the presence of Raney nickel to 1-methyl-4-amino-5-cyanoimidazole (III).

Attempted cyclization of II by heating with formamide led only to extensive decomposition, but smooth cyclization to 7-methyladenine-3-*N*-oxide (IV) was effected by refluxing II in ethanol solution with formamidine acetate. 7-Methyladenine-3-*N*-oxide (IV) was similar in properties to previously described purine-1-*N*-oxides[2] in the following respects: (a) it was extremely hygroscopic and readily formed a stable monohydrate (b) it was appreciably more soluble in water than the parent purine, and (c) its ultraviolet absorption spectrum in dilute sodium hydroxide solution showed two absorption maxima, the more intense peak being at the shorter wave length. Compound IV also exhibited two absorption maxima in 0.1 *N* hydrochloric acid solution, in contrast to adenine-1-*N*-oxide, which has been reported to have only one maximum in this solvent.[4]

The structure of 7-methyladenine-3-*N*-oxide follows not only from its method of preparation and its physical properties, but also from its facile reduction with hydrogen and Raney nickel to 7-methyladenine. It is of interest to note that similar conditions, which have been successfully employed for the reduction of adenine-1-*N*-oxide to adenine,[5] were without effect on hypoxanthine-1-*N*-oxide.[2] Apparently the N—O bond in hypoxanthine-1-*N*-oxide (which is a cyclic hydroxamic acid) is appreciably stronger than the N—O bond of the adenine-*N*-oxides.




### EXPERIMENTAL[6]

*1-Methyl-4-hydroxylamino-5-cyanoimidazole (II).* A solution of 10 g. of 1-methyl-4-nitro-5-cyanoimidazole in 200 ml. of ethanol containing 1 g. of platinum oxide was hydrogenated at room temperature and 3 atmospheres pressure until hydrogen absorption ceased (about 8 minutes). The reduction mixture was heated to boiling, filtered from the catalyst, and the filtrate chilled to give 6.0 g. (66%) of 1-methyl-4-hydroxylamino-5-cyanoimidazole as pale yellow needles which were recrystallized from ethanol; m.p. 178° (dec.).

*Anal.* Calcd. for $C_5H_6N_4O$: C, 43.5; H, 4.4; N, 40.6. Found: C, 43.8; H, 4.2; N, 40.4.

Evaporation of the filtrate yielded 0.2 g. (2.5%) of 1-methyl-4-amino-5-cyanoimidazole, identical with an authentic sample.[3]

*Reduction of 1-Methyl-4-hydroxylamino-5-cyanoimidazole to 1-Methyl-4-amino-5-cyanoimidazole (III).* A solution of 2.0 g. of 1-methyl-4-hydroxylamino-5-cyanoimidazole in 30 ml. of ethanol was hydrogenated in the presence of 2 g. of Raney nickel catalyst (wet with ethanol) at room temperature and at 3 atmospheres pressure for 12 hr. The reduction mixture was filtered from the catalyst, the filtrate concentrated under reduced pressure and the residue recrystallized from benzene to give 0.65 g. (37%) of light yellow crystals, m.p. 178–179, identical in all respects with an authentic sample of 1-methyl-4-amino-5-cyanoimidazole.[3]

*7-Methyladenine-3-N-oxide (IV).* A solution of 5 g. of 1-methyl-4-hydroxylamino-5-cyanoimidazole and 6.5 g. of

(1) This investigation was supported by a research grant (C-2551-PET) to Princeton University from the National Cancer Institute of the National Institutes of Health.

(2) For a summary of and appropriate references to previous work in this field, see the accompanying paper: E. C. Taylor, C. C. Cheng, and O. Vogl, *J. Org. Chem.*, 24, 2019 (1959).

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(4) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, 80, 2759 (1958).

(5) M. A. Stevens, D. J. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 80, 2755 (1958).

(6) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J. All melting points are uncorrected.