This compound is then subjected to hydrolysis by the action of either sulfuric or hydrochloric acid when the corresponding salts of uracil-5 methylamine IV are obtained in excellent yields.

A complete discussion of the experimental technique of this interesting synthesis will be presented in a future publication from this Laboratory.

## Experimental Part

**Uracil-5-methylamine Sulfate,** $(C_5H_7O_2N_3)_2 \cdot H_2SO_4$.—This salt is very soluble in cold water and insoluble in alcohol. It separates from alcohol–water mixtures in the form of colorless, glistening plates, m. p. 245–246° with decomposition. Aqueous solutions of this salt are acid to litmus and are apparently very stable.

*Anal.* Calcd. for $(C_5H_7O_2N_3)_2 \cdot H_2SO_4 \cdot H_2O$: $H_2O$, 4.50; N, 21.11. Found: $H_2O$, 3.60; N, 21.18.

**Uracil-5-methylamine Hydrochloride,** $C_5H_7O_2N_3 \cdot HCl$.—This salt is more soluble in water than the sulfate. Alcohol–water solutions slowly deposit colorless elongated, glistening plates, m. p. 242–243° with decomposition.

*Anal.* Calcd. for $C_5H_7O_2N_3 \cdot HCl \cdot 0.5H_2O$: $H_2O$, 4.88; N, 23.66 (anhyd.). Found: $H_2O$, 4.82; N, 23.86 (anhyd.).

Both salts are decomposed by the action of alkali and the free amine separates from hot aqueous solutions as a fine amorphous powder melting at about 295–300° with decomposition. Aqueous solutions of the amine are strongly basic to litmus. The study of this interesting base is now in progress.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

# Ergotocin

BY M. S. KHARASCH AND R. R. LEGAULT

**Empirical Formula.**—In a recent note[1] we announced the isolation of ergotocin (the active component responsible for the oral effectiveness of some ergot extracts), and recorded some of its chemical and physical properties. It now appears desirable to present more detailed data on the chemistry of this substance.

The empirical formula which best accords with our analyses of the free base (ergotocin), the picrate, the oxalate and the maleate, is $C_{21}H_{27}N_3O_3$ (calculated for $C_{21}H_{27}N_3O_3$: C, 68.30; H, 7.32; N, 11.38. Found: C, 68.41; H, 7.35; N, 11.43. $C_{25}H_{31}N_3O_7$ (maleate salt): C, 61.86; H, 6.39; N, 8.66. Found: C, 61.84; H, 6.48; N, 8.73. $C_{23}H_{29}N_3O_7$ (oxalate salt): C, 60.13; H, 6.32; N, 9.15. Found: C, 60.41; H, 6.25; N, 9.19). Due caution, however, forbids summary dismissal from consideration of the alternative compositions, $C_{21}H_{25}N_3O_3$ and $C_{21}H_{29}N_3O_3$; a critical evaluation of the evidence will be undertaken in a future paper. In either case, it is obvious that the ergotocin molecule is much simpler than those of ergotamine, ergotoxine, sensibamine or ergoclavine.

**Chemical Properties**—Ergotocin gives the characteristic blue color with *p*-dimethylaminobenzaldehyde (Ehrlich's reagent). It differs from the other alkaloids, however, in that the blue color has a reddish tinge. On a weight basis ergotocin produces more color than pure commercial samples of either ergotamine or ergotoxine; on a mole basis, however, the color is somewhat weaker (10–20%). Ergotocin gives a blue color with the Folin–Denis phenol reagent.

The *p*H value of a 0.012 *M* solution of ergotocin in 50% alcohol is 7.5. The neutralization equivalent (in 30% alcohol) is 374, in excellent agreement with a calculated molecular weight of 369. Treatment of a solution of ergotocin in quinoline with a dibutyl ether solution of methylmagnesium bromide according to the Zerewitinoff method indicates the presence of three active hydrogens. (Calcd. change in volume for three active hydrogens, 1.18 cc.; found, 1.12 cc.) This fact may account for the observation that ergotocin apparently combines with alkali metal ions to form salts. We have also noticed that upon chloroform extraction of ergotocin from aqueous solution made alkaline with either sodium carbonate or bicarbonate and evaporation of the solvent, the product, even when crystallized twice from benzene or chloroform, still contained about one per cent. of ash upon ignition. In spite of this fact the substance begins to darken at 155° and melts with decomposition at 158–160°.[2] The ash is unquestionably sodium carbonate for it is alkaline to litmus and liberates carbon dioxide with acids.

(1) Kharasch and Legault, THIS JOURNAL, **57**, 956 (1935).

(2) The isolation of a substance from ergot melting at 152 or 155–158° with decomposition is not in itself a criterion that a new substance has been obtained, for a melting point of 162° has been recorded for ergotoxine (presumably impure). It is the chemical reactions, analyses and the effect on human mothers that differentiate ergotocin from ergotoxine, but not necessarily the melting point.

To avoid the difficulty in purification thus introduced, we ordinarily extract our material from a buffered solution at *p*H 6.8–7.0. In this connection, it is pertinent to note that neither ether, trichloroethylene nor benzene will extract ergotocin from a water solution.

Ergotocin differs strikingly from the other ergot alkaloids in that it does not eliminate ammonia upon heating with potassium hydroxide. Alkaline hydrolysis of ergotocin, however, yields, *inter alia*, a substance which is acid in character, gives the test with Ehrlich's reagent and forms a water insoluble sulfate. Presumably, this substance is lysergic acid. (Calcd. for $C_{16}H_{16}N_2O_3$: N, 10.45. Found: N, 10.43.)

There is another material which we have isolated from the alkaline hydrolysate in the form of a salt, the structure of which we have not ascertained as yet. If our empirical formula is correct, the other fragment or fragments cannot contain more than five carbon atoms. In consideration of the total hydrogen content it would appear that the residue is either a reduced ring compound or an amino acid, or simple saturated fragments. The work on the identification of this "fragment" is actively under way.

**Salts of Ergotocin.**—Ergotocin differs markedly from the other ergot alkaloids in that it forms easily crystallizable "onium" salts of the type $B^{++}X^{=}$ with aliphatic dibasic acids. Ergotocin salts of monobasic acids are not very well defined and are much harder to isolate. In our experience best results are obtained with aliphatic dicarboxylic acids with primary ionization constants ($K$) between $10^{-2}$ and $10^{-4}$. Of the acids whose ergotocin salts we have isolated, oxalic, maleic, malonic, tartaric and malic seem to be the most useful. On the other hand, succinic acid ($K = 6.6 \times 10^{-5}$) is not satisfactory.

**The Absorption Spectra.**—The absorption spectra of ergotocin, ergotoxine, ergotamine and ergotocin maleate are strikingly similar. Thus, they all have maxima at about 2250 Å. and 3150 Å. and minima at 2700 Å. The molecular absorption coefficients of all these substances are approximately the same. On the other hand, ergine, while possessing the same characteristic bands, differs from ergotocin and the alkaloids, in that it has a much lower molecular absorption coefficient. The complete data will be given in a future paper.

In conclusion, we would like to call attention to the fact that the oxytoxic activity of ergotocin does not reside wholly in the lysergic acid part of the molecule. We have found that doses of ergine (amide of lysergic acid) as large as 4 mg. are inactive when administered orally to human mothers, as compared with the powerful activity of 0.3 mg. doses of ergotocin. It is possible that the pharmacodynamic activity of ergotocin may reside in the still unidentified fragments of the molecule to which we have already called attention, although the activity may be a function of the entire molecule. This question is now being studied. Our program includes also the attempt to synthesize molecules of the same empirical formula as the unidentified fragments.

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