THE ERGOT ALKALOIDS

I. THE OXIDATION OF ERGOTININE

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Some time ago we became interested in the problem of the structure of the ergot alkaloids. Experiments on the oxidative degradation of ergotinine were already in progress when Barger's monograph[1] came to our attention, in which certain observations of Soltys[2] were discussed. The latter have since been separately published. In this work benzoic acid was obtained on oxidation of each of the alkaloids with permanganate. When nitric acid was used as the oxidizing agent, *p*-nitrobenzoic acid was the only substance recovered.

In our own experiments we have also used nitric acid and regularly obtained *p*-nitrobenzoic acid in addition to small amounts of benzoic acid. Since, however, we have constantly isolated from the reaction mixture a third crystalline substance of more complicated character, we wish to present a preliminary report of these experiments. After oxidation of the alkaloid as later described, benzoic acid, *p*-nitrobenzoic acid, and other substances were removed by ether extraction. The remaining aqueous solution yielded a sparingly soluble, ether-insoluble, substance in a naturally poor yield (6 per cent). The first suspicion that the substance is a nitro derivative was removed by the negative outcome of reduction experiments. It was then found to have retained the methylimino group of the parent ergotinine, the only one of the original 5 nitrogen atoms which remained. The analytical figures indicated a formula $C_{14}H_9O_8N$. Repeated titrations of a number of preparations were in excellent agreement for a substance containing three carboxyl groups. The remaining 2 oxygen atoms have

[1] Barger, G., Ergot and ergotism, London (1931).

[2] Soltys, A., *Ber. chem. Ges.*, **65**, 553 (1932).

not yet been accounted for. No evidence of the presence of a lactone group could be obtained on boiling with alkali. A methyl indole or perhaps a methyl hydroquinoline nucleus appears to be indicated in this substance. Whether a third, perhaps furane, ring is present cannot be considered until further data are available.

Attempts to prepare a methyl ester with diazomethane resulted only in a non-crystalline reaction product. When the tribasic acid was heated with methyl alcoholic hydrochloric acid, only one carboxyl group was esterified with the formation of a *monomethyl ester*. The acid is readily oxidized by permanganate. Owing to the difficulty of procuring sufficient material, a report of this reaction will be left to a later communication.

Further work on the oxidative degradation of the ergot alkaloids is in progress.

EXPERIMENTAL

In the oxidation of ergotinine with nitric acid a number of experiments was made in which the procedure was modified somewhat in each case according to the objective. The following experiments are reported as they were actually performed.

2 gm. of ergotinine were treated with 50 cc. of HNO_3 (1.4 sp. gr.). A vigorous reaction occurred. The mixture was then heated on the water bath for 18 hours. On dilution a definite odor of isobutyric acid was in evidence. The mixture was distilled over into dilute alkali but the amount of volatile material which was collected was too small in amount for study.

The orange-red acid solution which remained was evaporated on the bath to about 50 cc. On standing, clusters of pale yellow platelets separated. These were collected on a Jena funnel with nitric acid and then washed with water. The yield was 70 mg. After recrystallization from dilute acetone lustrous leaflets of *p*-nitrobenzoic acid separated, which melted at 235–236°, and showed no depression when mixed with *p*-nitrobenzoic acid.

3.815 mg. substance: 1.030 mg. H_2O, 7.052 mg. CO_2
3.870 " " : 0.292 cc. N (758.7 mm., 24°)

$C_7H_5O_4N$.	Calculated.	C 50.28,	H 3.02, N 8.39
	Found.	" 50.41,	" 3.02, " 8.66

The mother liquor of the above crude *p*-nitrobenzoic acid was concentrated practically to dryness and left a considerable resinous

residue. This was treated with water and after standing additional crystalline material mixed with a brown-red resin deposited. After collection with water all that could be recovered from this material was an additional small quantity of impure *p*-nitrobenzoic acid.

The mother liquor from this second crude fraction was diluted somewhat and then extracted in a continuous extractor for 24 hours with ether. The aqueous layer which remained on concentration gave a small amount of the crystalline acid which softened above 280° after preliminary darkening. This substance was obtained in larger yield in later experiments as follows:

5 gm. of ergotinine were treated with a mixture of 120 cc. of HNO_3 (1.4) and 675 cc. of water and slowly distilled in an all-glass apparatus. The alkaloid rapidly became superficially colored a dark greenish brown and remained at first mostly as an undissolved resin. Shortly, a copious CO_2 formation could be readily detected with barium hydroxide. As the concentration of acid increased, the mixture became gradually a deep brown-red and small amounts of volatile material which crystallized in the receiver were carried over. The odor of this suggested somewhat *p*-nitrotoluene but the amount which could be collected was too small for identification. On reaching a stronger concentration of acid, the alkaloid had mostly dissolved and red fumes began to appear. At this point 400 cc. of water were again added and the distillation was resumed. On reaching the point of strong acid the dilution and concentration were repeated. These operations were repeated several times more. By this time the appearance of volatile solid material had practically ceased. Finally, the mixture was boiled down to the point of strong nitric acid when the odor of benzoic acid became evident in the distillate. At this point the operation was interrupted. The combined distillates were treated as given further on.

The deep brown-red acid solution was then concentrated *in vacuo* in an all-glass apparatus to remove the excess of nitric acid. The residue was dissolved in about 75 cc. of hot water. On standing, a small amount of red tar deposited. The supernatant liquor was decanted and concentrated to smaller volume. A crop of somewhat sulfur-yellow crystalline aggregates slowly deposited. After collection, this was recrystallized by solution in 100 cc. of boiling

water. On standing, faintly yellow aggregates of minute prisms slowly separated. The yield was 0.14 gm. The substance sintered above 280° after preliminary darkening. The mother liquor of this last recrystallization gave on concentration a second crop which was collected with water. It was found to be contaminated with considerable ether-soluble material and was therefore digested with ether and collected with this solvent. The yield was 50 mg. of this second crop which also softened above 280°. The ether washings on concentration gave 40 mg. of crystalline material which melted at 234° and proved to be *p*-nitrobenzoic acid.

The fact that the above high melting substance is practically insoluble in ether was then made use of in later experiments. 5 gm. of ergotinine were oxidized as previously. After final removal of the excess of nitric acid by concentration under diminished pressure the residue was dissolved in about 250 cc. of water. The brown-red mixture which contained suspended resin was placed in an extractor and continuously extracted with ether for 2 days, by which time no more color passed into the ether layer. The aqueous layer which was still brown-red and contained some suspended resin, was filtered and concentrated to small volume. Successive crops of crude crystalline acid were obtained, all of which softened at about 280–285°. The yield was 0.3 gm.

This was dissolved in 300 cc. of boiling water and cleared with norit. The filtrate was a faint straw-yellow. On concentration to about half and addition of dilute HCl the acid separated as almost colorless needles. It does not possess a characteristic melting point. On rapid heating it darkened above 265° and sintered together at about 290°, but did not melt even up to 350°. The substance is less soluble in dilute acid than in water. It is very sparingly soluble in the usual organic solvents. Its solution in dilute alkali, which is a pale yellow, exhibits a slight fluorescence. The substance gives only a faint pine splinter test.

14.322 mg. of substance were suspended in a few cc. of water and titrated against phenolphthalein with 0.1 N NaOH. Calculated for 3 equivalents, 1.346 cc.; found, 1.345 cc.

4.458 mg. substance: 1.085 mg. H_2O, 8.626 mg. CO_2
5.287 " " : 0.201 cc. N (759.2 mm., 25°)
4.760 " " : 3.275 mg. AgI

$C_{14}H_9O_8N$. Calculated. C 52.65, H 2.84, N 4.39, NCH_3 9.10
Found. " 52.77, " 2.72, " 4.36, " 8.51

The attempt to prepare a crystalline neutral methyl ester from the acid with diazomethane was unsuccessful. Only resinous material resulted. A monomethyl ester was prepared as follows: The acid was heated in a sealed tube for 18 hours with 50 parts of absolute methyl alcohol which contained 4 per cent of HCl. The crystalline powder was collected with methyl alcohol in which it is sparingly soluble. On heating, it behaves like the parent acid with no distinct melting point. It darkened above 260° and sintered at about 285° but did not melt below 350°.

4.050 mg. substance: 1.150 mg. H_2O, 7.970 mg. CO_2
3.700 " " : 2.555 " AgI
$C_{15}H_{11}O_8N$. Calculated. C 54.04, H 3.33, OCH_3 9.31
Found. " 53.67, " 3.18, " 9.13

The combined distillates obtained during the nitric acid oxidations were repeatedly extracted with ether. The latter was washed once with a little water and then extracted with dilute sodium hydroxide solution. The alkaline solution was acidified with sulfuric acid and as there was a pronounced odor of isobutyric acid the attempt was made to distil this into dilute alkali. The amount which distilled over, however, proved to be inadequate for definite identification. During this distillation a small amount of crystalline material was also carried over, which was obviously benzoic acid. This substance was also recovered from the acid solution which remained after the distillation of the volatile material. On cooling, a relatively very small amount crystallized. After recrystallization from ligroin it melted at 120–121°.

4.493 mg. substance: 1.998 mg. H_2O, 11.340 mg. CO_2
$C_7H_6O_2$. Calculated. C 68.82, H 4.96
Found. " 68.83, " 4.98

The ether solution which retained neutral material after the above extraction with alkali gave on concentration a small partly crystalline residue. The amount was too small for identification.