

THE ERGOT ALKALOIDS

II. THE DEGRADATION OF ERGOTININE WITH ALKALI. LYSERGIC ACID

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About 2 years ago Smith and Timmis¹ recorded the important observation of the formation of a basic degradation product, ergine, by the action of methyl alcoholic alkali on the ergot alkaloids, ergotinine and ergotoxine. From the analysis of ergine and a number of its salts, they derived for it the formula $C_{17}H_{21}ON_3$. In the course of a systematic investigation of the effect of various hydrolytic procedures on ergotinine while confirming the formation of ergine by the procedure employed by Smith and Timmis, we have observed the formation in better yield of a new degradation product when aqueous alkali is used.

In preliminary experiments it was found that crystalline ergotinine could be refluxed as a suspension in 6 per cent aqueous potassium hydroxide without appreciable alteration. This apparent resistance proved to be due to its insolubility. If ergotinine is first rapidly dissolved in methyl alcoholic potassium hydroxide and the solvent is immediately removed at low temperature and pressure, a resinous residue remains. When this residue is heated with aqueous alkali, as described later, it gradually dissolves with the liberation of ammonia due to cleavage of the amide group of ergotinine. Naturally, no ergotinine could be recovered from this reaction mixture. Furthermore, none of the base, ergine, could be detected on direct extraction of the alkaline hydrolysate. However, a new substance was obtained in good yield on gentle acidification, which possessed both acid and basic properties and which we have named *lysergic acid*. This acid is optically active ($[\alpha]_D^{20} = +40^\circ$ in pyridine) and crystallizes in beautiful leaflets.

¹ Smith, S., and Timmis, G. M., *J. Chem. Soc.*, 763 (1932).

The analytical data obtained with the acid indicate a formula $C_{16}H_{16}O_2N_2$. This is supported by the analysis of its *methyl ester* which was obtained with diazomethane. The acid has no methoxyl group but still possesses the original N-methyl group of ergotinine. Titration showed the presence of one carboxyl group. It still gives the characteristic blue Keller reaction of the original alkaloid.

The comparative accessibility of this degradation product in workable yield from ergotinine makes it an important object for further study. An attempt to determine its structure is therefore in progress.

The natural thought occurred that the failure to recover ergine from the above reaction mixture might have been due to the fact that although it could have been formed during the reaction in aqueous alkali it might have been further degraded to lysergic acid. In order to determine this point we have replaced ergotinine in the above procedure by ergine. Although a crystalline acid was obtained in small yield it appeared on analysis to be definitely different from lysergic acid. With the amount available it was possible to give it but preliminary study. A report of this work will be left to a later occasion.

When the above crude mother liquor from lysergic acid was continuously extracted with ether it was found that other acid material was formed in the reaction. From the ether extract, which smelled faintly of isobutyric acid, a crystalline ammonium salt was obtained which on analysis gave figures which approximated those of the salt of isobutyryl formic acid. This was definitely confirmed by its decomposition into isobutyric acid and by the formation of the phenylhydrazone of isobutyryl formic acid.

Isobutyryl formamide was first obtained by Barger and Ewins by the destructive distillation of ergotinine. This experiment we have also repeated. The formation of isobutyryl formic acid itself, however, by what appears to be a hydrolytic cleavage under the influence of alkali may be significant. It is still premature, however, to attempt to interpret its mode of linkage in the molecule. Although probable, it is not as yet certain that the amide group present in ergotinine itself is the same as that which emerges as isobutyryl formamide on destructive distillation.

* Barger, G., and Ewins, A. J., *J. Chem. Soc.*, 113, 235 (1918).

EXPERIMENTAL

1 gm. of ergotinine was dissolved in 20 cc. of N-methyl alcoholic potassium hydroxide and the methyl alcohol was removed at once by distillation at low pressure. The residue was treated with 20 cc. of an 8 per cent aqueous solution of potassium hydroxide and the mixture was heated on the steam bath for 1 hour. A stream of nitrogen was passed through the flask during the heating and basic volatile material from the reaction mixture was collected by passing the gas through a solution of dilute hydrochloric acid.

After the reaction was completed, the hydrochloric acid solution following evaporation gave a residue of 75 mg. which proved to be ammonium chloride. The theoretical weight for 1 mole of NH_4Cl is 58 mg.

The alkaline solution was made acid to Congo red with sulfuric acid. At this point a considerable amount of partly crystalline material precipitated. The acid suspension as such was placed in an extractor and exhaustively extracted with ether. This ether extract was worked up as given below for isobutyryl formic acid. The aqueous suspension which remained was then filtered. The dark colored solid was treated successively with two 20 cc. portions of ammoniacal ethyl alcohol which left a residue which was inorganic. The filtrate on evaporation to dryness under reduced pressure gave a residue which was digested a short time with 5 cc. of methyl alcohol to remove colored impurities. After cooling, the undissolved crystals were collected. 0.26 gm. of a slightly colored crystalline solid was obtained which melted with decomposition at 235° .

Lysergic acid (although rather sparingly soluble) can be recrystallized best from water. It crystallizes as very thin hexagonal leaflets which melt with decomposition at 238° . The melting point varies somewhat with the rate of heating. Repeated recrystallization failed to raise the melting point. It separates with approximately 1 mole of water of crystallization. This water is held very tenaciously and can be removed completely only on drying at 140° and 2 mm.

$[\alpha]_D^{25} = +40^\circ$ ($c = 0.500$ in pyridine)

$\text{C}_{16}\text{H}_{16}\text{O}_2\text{N}_2 \cdot \text{H}_2\text{O}$. Calculated, H_2O 6.29; found, 6.12

$\text{C}_{16}\text{H}_{16}\text{O}_2\text{N}_2$. Calculated. C 71.69, H 6.00, N 10.45, CH_2 5.60

Found. " 71.84, " 6.03, " 10.87, " 4.92

" " 71.69, " 5.93, " 10.50

Lysergic acid gives the characteristic blue Keller test of the ergot alkaloids. In dilute sulfuric acid solution it gives with benzaldehyde and sulfuric acid a violet-blue ring which rises through the solution. With diazobenzenesulfonic acid a brown amber color is given in carbonate solution. With alkaline nitroprusside a yellow is first formed which gradually changes to a yellow-green.

Lysergic acid behaves both as an acid and a base. It is soluble in sodium hydroxide, ammonium hydroxide, sodium carbonate, and hydrochloric acid. It is but slightly soluble in dilute sulfuric acid. It is sparingly soluble in the usual neutral organic solvents but is quite soluble in pyridine.

On titration with alkali against phenolphthalein, the acid does not give a sharp end-point. However, the results indicated a neutralization equivalent of approximately 300 when the air-dried substance was used. Material dried at 140° was not suitable for titration because of appreciable discoloration which interfered with the detection of the end-point. 12.735 mg. of substance were dissolved in 10 cc. of hot water and the solution was titrated against phenolphthalein with 0.1 N sodium hydroxide. Calculated for 1 equivalent, 0.489 cc.; found, 0.415 cc.

Lysergic Methyl Ester.—Lysergic acid suspended in dry acetone slowly dissolved after the addition of diazomethane. The ester crystallized from benzene in thin leaflets which melted at 168°. It is soluble in ether, acetone, alcohol, and hydrochloric acid. It is insoluble in ammonium hydroxide and petroleum ether.

$C_{17}H_{19}O_2N_2$.	Calculated.	C 72.34,	H 6.41,	N 9.92,	OCH ₃ , 11.00
	Found.	" 72.40,	" 6.19,	" 9.66,	" 11.95
	"	" 72.16,	" 6.35,	"	" 11.98

The ethereal extract of the original acidified alkaline reaction mixture was dried with sodium sulfate and concentrated under reduced pressure. About 0.2 gm. of an oil remained which smelled distinctly of isobutyric acid. It was completely soluble in water but not in petroleic ether.

A solution of the oil in 1 cc. of absolute alcohol was saturated with dry ammonia. On careful addition of ether crystals separated. After chilling the colorless material was collected. 50 mg. were obtained. It melted at 175° with considerable sublima-

tion before melting. A solution of the salt in 80 per cent sulfuric acid, although odorless at first, developed a distinct odor of isobutyric acid on warming. The salt was analyzed as such without attempting recrystallization.

$C_6H_{11}O_3N$.	Calculated.	C 45.1,	H 8.28
	Found.	" 46.50,	" 8.99

These analytical figures thus only approximated those required by the ammonium salt of isobutyryl formic acid and because of the limited amount of the material available the phenylhydrazone was prepared for characterization as follows: The ammonium salt was dissolved in 0.5 cc. of water and an equivalent of phenylhydrazine dissolved in 0.5 cc. of acetic acid was added. After a few minutes heating on the steam bath the solution was carefully diluted. The phenylhydrazone crystallized on chilling. On recrystallization from dilute alcohol it formed long needles which melted at 152°. This is higher than the figures given by Tschtschenke (128°)³ and Tschelinzeff and Schmidt (143°).⁴ Our substance was readily soluble in dilute ammonia and was reprecipitated in crystalline form on reacidification.

$C_{11}H_{14}O_2N_2$.	Calculated.	C 64.08,	H 6.84,	N 13.59
	Found.	" 64.50,	" 6.86,	" 13.47
	"	" 64.32,	" 6.67,	" 13.72

³ Tschtschenke, D., *Bull. Soc. chim.*, series 4, **37**, 623 (1925).

⁴ Tschelinzeff, W., and Schmidt, W., *Ber. chem. Ges.*, **62**, 2210 (1929).