

III.—*Cannabinol. Part I.*

By THOMAS BARLOW WOOD, M.A.; W. T. NEWTON SPIVEY, M.A.;
THOMAS HILL EASTERFIELD, M.A., Ph.D.

IN a paper communicated to the Society in 1896 (Trans., 1896, 69, 539) the authors, under the name of "cannabinol," described a physiologically active substance which they had isolated from "charas," the exuded resin of Indian hemp. From the constancy of composition of a number of preparations of this substance obtained from different samples of "charas," it was believed to be a definite chemical compound of the formula $C_{18}H_{24}O_2$; this conclusion seemed to be justified by the determination of the molecular weight, and by the examination of several derivatives. Since then, the authors have further examined cannabinol, and have found that it is a mixture of at least two compounds having similar physical characters. One of these, of the formula $C_{21}H_{26}O_2$, has been isolated, and it is proposed to retain the name cannabinol for this compound.

During the progress of this investigation, a note on oxycannabin by Messrs. Dunstan and Henry appeared in the Proceedings of the Society (Proc., 1898, p. 44), in which the formulæ $C_{10}H_{10}NO_4$ and $C_{18}H_{23}OAc$ were assigned to oxycannabin and acetylcannabinol respectively. From the description of these substances, there can be no doubt that they are identical with those we have obtained, but the results of our analyses correspond with the formulæ $C_{11}H_{11}NO_4$ for oxycannabin and $C_{21}H_{25}O_2 \cdot C_2H_5O$ for acetylcannabinol. These formulæ are confirmed by molecular weight determinations, and by analyses of many derivatives. Dunstan and Henry (*loc. cit.*) state that, on oxidising cannabinol with nitric acid, normal butyric acid is formed; we can confirm this statement, with the addition that larger quantities of normal valeric and caproic acids are produced at the same time.

As the present paper deals mainly with the substances produced by the breaking down of the cannabinol molecule, the authors have only described such of its reactions as suffice to show that it is a true chemical compound. An account of the reactions of cannabinol, together with a more complete examination of several of the compounds described below, will shortly be brought before the Society.

When crude cannabinol (the red oil obtained by fractionating alcoholic charas extract under diminished pressure) is treated with nitric acid under certain conditions, it yields a yellow, crystalline substance, the analysis of which corresponds with the formula $C_{13}H_{15}N_2O_5$ (Proc., 1898, p. 66), but determinations of the molecular weight show that a higher formula is required. As it has acidic

properties, salts were prepared and analysed, and their composition proves that the formula is $C_{21}H_{23}N_3O_8$, which agrees with the molecular weight determinations. It is readily reduced by boiling with hydriodic acid and phosphorus, yielding the hydriodide of a base; the latter has not as yet been isolated, owing to the readiness with which it oxidises. As the formula $C_{21}H_{23}N_3O_8$ represents the trinitro-derivative of a compound, $C_{21}H_{26}O_2$, the presence of the latter in crude cannabinol is probable, and this is definitely proved by the isolation of the acetyl derivative, $C_{21}H_{25}O_2 \cdot C_2H_3O$, from a crude cannabinol.

After the separation of the crystalline acetyl derivative from the products obtained by the acetylation of crude cannabinol, an oily residue was left amounting to more than three-quarters of the acetylation product, and from it by treatment with acetic anhydride, no other crystalline acetyl derivative could be obtained; it appears to contain the acetyl derivatives of one or more substances with a lower percentage of carbon than $C_{21}H_{26}O_2$.

"Crude cannabinol" is, therefore, a mixture of cannabinol, $C_{21}H_{26}O_2$, with one or more compounds probably of lower molecular weight.

The fact that cannabinol forms an acetyl derivative proves that it contains a hydroxylic group, and the failure of all attempts to obtain an ethereal salt from the trinitro-compound referred to above, makes it probable that the acidity of the latter is not due to the presence of a carboxyl group, but to the influence of the nitro-groups on the hydroxyl group.

On oxidising the trinitro-derivative by boiling it for several hours with fuming nitric acid, and pouring the product into water, a yellow, flocculent precipitate was deposited; this was filtered off, and the acid filtrate steam distilled; the distillate was found to contain normal butyric, valeric, and caproic acids. The normal butyric acid was identified by its calcium salt, the normal valeric and caproic acids by their anilides. By direct oxidation of crude cannabinol with nitric acid, the same fatty acids were obtained, and caproic acid was also obtained when potassium permanganate or chromic acid mixture was employed.

The yellow, flocculent precipitate, on crystallisation, gave a mixture of oily acids containing nitrogen, and a pale yellow, crystalline compound, the oxycannabin of Bolas and Francis (*Chem. News*, 1871, **24**, 77); to this they gave the formula $C_{20}H_{20}N_2O_7$, but the results of their analyses agree equally well with the authors' formula $C_{11}H_{11}NO_4$. Dunstan and Henry, in their note (*Proc., loc. cit.*), state that oxycannabin "does not dissolve in aqueous alkalis unless warmed with them in a closed tube. By acidifying the resulting solution, an acid is precipitated which is at present under investigation. Oxycannabin would, therefore, appear to be a lactone." The present authors find,

22 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

however, that oxycannabin dissolves in aqueous caustic soda if boiled with it for a few minutes, and that unaltered oxycannabin is precipitated on acidification. They have proved it to be a lactone by the preparation and analysis of salts of the corresponding oxy-acid, but this oxy-acid has not been isolated, since it is at once re-converted into the lactone when set free from its salts. In fact, its tendency to undergo this change is so great that, on treating the silver salt with ethylic iodide, the lactone is obtained instead of the ethylic salt.

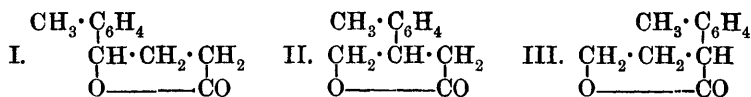
On oxidation with dilute nitric acid at 185° , oxycannabin yields a sparingly soluble nitro-lactonic acid of the formula $C_{10}H_8NO_4 \cdot COOH$ together with a very soluble tribasic acid, $C_9H_5NO_8$.

On reduction, oxycannabin yields a compound, $C_{11}H_{13}NO_2$, which corresponds to the reduction of a nitro-group in oxycannabin to an amido-group. On this evidence, the authors propose for oxycannabin the name nitrocannabinolactone, and for the reduction product the name amidocannabinolactone.

The amido-lactone is readily diazotised, and an attempt was made to prepare cannabinolactone directly from it by Friedländer's method, but it was found more convenient to prepare iodocannabinolactone, $C_{11}H_{11}IO_2$, by adding potassium iodide to the diazotised solution, and to reduce this with sodium amalgam in alkaline solution. The oily cannabinolactone, $C_{11}H_{12}O_2$, thus obtained, was converted into colourless crystalline, cannabinolactonic acid, $C_{11}H_{10}O_4$, by boiling it with an alkaline solution of potassium permanganate; this action corresponds to the oxidation of a methyl group to a carboxyl group. On reduction with hydriodic acid and phosphorus, the lactonic acid yields a dibasic acid of the formula $C_{11}H_{12}O_4$, thus affording confirmation of its lactonic nature.

From the fact that a methyl group, both in cannabinolactone and in its nitro-derivative, is oxidised to a carboxyl group, and from the behaviour of nitrocannabinolactone on reduction, and subsequent diazotisation, the presence of a benzene nucleus in cannabinolactone is probable. In order to confirm this, and, further, to ascertain the structure of the lactone ring, the lactonic acid was fused with caustic potash; in this way, isophthalic acid was obtained, and identified by conversion into its methylic salt. However, when cannabinolactone was fused with potash, metatoluic acid was formed, together with isophthalic acid. The formation of these two acids definitely proves the presence in cannabinolactone of a benzene nucleus, with two side chains in the meta-position relatively to each other, one of these chains being a methyl group. The second side chain must evidently contain the lactone ring, and on the assumption that it is a γ -lactone, which from its great stability is probable, there appear to

be only three possible formulæ, namely, those of the three metatolylbutyrolactones,



Syntheses of these three lactones are at present in progress, with a view to deciding which of them is identical with cannabino-lactone.

The following table shows the relationships of the compounds described in this paper.

Cannabinol, $\text{C}_{21}\text{H}_{26}\text{O}_2$.

Acetylcannabinol, $\text{C}_{21}\text{H}_{25}\text{O}_2 \cdot \text{COCH}_3$.

Trinitrocannabinol, $\text{C}_{21}\text{H}_{23}(\text{NO}_2)_3 \cdot \text{O}_2$.

Cannabino-lactone, (1) $\text{CH}_3 \cdot \text{C}_6\text{H}_4 \langle \text{C}_3\text{H}_5 \rangle \text{CO}$ (3).

Nitrocannabino-lactone (oxycannabin), (1) $\text{CH}_3 \rangle \text{C}_6\text{H}_3 \langle \text{C}_3\text{H}_5 \rangle \text{CO}$
 NO_2

Amidocannabino-lactone, (1) $\text{CH}_3 \rangle \text{C}_6\text{H}_3 \langle \text{C}_3\text{H}_5 \rangle \text{CO}$ (3).
 NH_2

Iodocannabino-lactone, (1) $\text{CH}_3 \rangle \text{C}_6\text{H}_3 \langle \text{C}_3\text{H}_5 \rangle \text{CO}$ (3).
 I

Cannabino-lactonic acid, (1) $\text{COOH} \cdot \text{C}_6\text{H}_4 \langle \text{C}_3\text{H}_5 \rangle \text{CO}$ (3).

Nitrocannabino-lactonic acid, (1) $\text{COOH} \rangle \text{C}_6\text{H}_3 \langle \text{C}_3\text{H}_5 \rangle \text{CO}$ (3).
 NO_2

Carboxyphenylbutyric acid, $\text{COOH} \cdot \text{C}_6\text{H}_4 \cdot \text{C}_3\text{H}_6 \cdot \text{COOH}$ (3).

EXPERIMENTAL.

Trinitrocannabinol, $\text{C}_{21}\text{H}_{23}(\text{NO}_2)_3\text{O}_2$.—This compound is produced on adding fuming nitric acid (5 c.c.), drop by drop, to a well cooled solution of crude cannabinol (8 grams), dissolved in glacial acetic acid (18 c.c.), the temperature being kept down by immersing the flask in ice cold water. After standing for several days, the crystals are collected; the yield is 20 per cent. (1.6 grams) of the crude cannabinol used. The compound is easily soluble in benzene, phenol, alcohol, and ether; it is also readily soluble in hot, but only sparingly in cold, glacial acetic acid, which is the most convenient solvent for its recrystallisation. It crystallises in bright yellow plates, which, when quickly heated, melt at 160° (uncorr.) with some decomposition.

Four preparations were analysed

A and B, purified through the ammonium salt. C. Five times recrystallised from glacial acetic acid. D. Sample C, once recrystallised from alcohol.

24 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

- A. $\begin{cases} 0.1417 \text{ gave } 0.2935 \text{ CO}_2 \text{ and } 0.0678 \text{ H}_2\text{O}. \\ 0.1235 \text{ ,, } 10 \text{ c.c. moist nitrogen at } 18^\circ \text{ and } 760 \text{ mm.} \end{cases}$
 B. $0.1676 \text{ ,, } 0.3480 \text{ CO}_2 \text{ and } 0.0835 \text{ H}_2\text{O}.$
 C. $\begin{cases} 0.1860 \text{ ,, } 0.3855 \text{ CO}_2 \text{ ,, } 0.0913 \text{ H}_2\text{O}. \\ 0.1440 \text{ ,, } 11.5 \text{ c.c. moist nitrogen at } 21^\circ \text{ and } 756 \text{ mm.} \end{cases}$
 D. $0.1527 \text{ ,, } 0.3180 \text{ CO}_2 \text{ and } 0.0750 \text{ H}_2\text{O}.$

Calculated for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_8$.	A.	B.	C.	D.
C = 56.6 per cent.	56.5	56.6	56.5	56.8
H = 5.2 ,,	5.3	5.5	5.4	5.5
N = 9.4 ,,	9.3	—	9.0	—

The molecular weight was determined by the freezing point method in benzene and in phenol.

In *benzene* (i) 0.5220 gram, dissolved in 20 grams of benzene, lowered the freezing point by 0.312° .

(ii) 0.9513 gram, dissolved in 20 grams benzene, lowered the freezing point by 0.570° .

In *phenol* (iii) 0.4733 gram, dissolved in 20 grams phenol, lowered the freezing point by 0.410° .

(iv) 1.0023 grams, dissolved in 20 grams phenol, lowered the freezing point by 0.900° .

Calculated for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_8$.	(i).	(ii).	(iii).	(iv).
Molecular weight = 445.....	409	409	427	412

Salts.—The compound has acidic properties, forming salts of potassium, sodium, ammonium, and silver, all of which are bright yellow, crystalline compounds sparingly soluble in water, easily in alcohol. They are best crystallised by diluting their hot alcoholic solutions with water. The potassium and sodium salts are explosive, the silver salt is not.

Sodium Salt.—The most soluble of all the salts examined, the saturated solution at 15° containing 1 part of salt in 120 parts of solution. It is prepared by dissolving the acid in excess of alcoholic soda solution and diluting with water. Two samples were analysed.

0.2130, at 160° , lost $0.0290 \text{ H}_2\text{O}$ and gave $0.0255 \text{ Na}_2\text{SO}_4$. $\text{Na} = 3.9$;
 $\text{H}_2\text{O} = 13.6$.

0.1545 gave $0.0205 \text{ Na}_2\text{SO}_4$. $\text{Na} = 4.3$.

$\text{NaC}_{21}\text{H}_{22}\text{N}_3\text{O}_8 + 4\text{H}_2\text{O}$ requires $\text{Na} = 4.3$; $\text{H}_2\text{O} = 13.4$ per cent.

Potassium salt, prepared in the same way as the sodium salt, requires for solution 2000 parts of water at 15° , and 500 at 100° .

0.1210 lost no weight at 150° , and gave $0.0220 \text{ K}_2\text{SO}_4$. $\text{K} = 8.2$.

0.1300 gave $0.230 \text{ K}_2\text{SO}_4$; $\text{K} = 7.9$.

$\text{KC}_{21}\text{H}_{22}\text{N}_3\text{O}_8$ requires $\text{K} = 8.1$ per cent.

Ammonium salt may be prepared by dissolving the acid in boiling ammonia solution, when the salt crystallises out on cooling, or by dissolving the acid in excess of alcoholic ammonia and diluting with water. It requires for solution 1600 parts of water at 15°, and 200 at 100°.

0.1170 gave 0.2330 CO₂ and 0.0605 H₂O. C = 54.3; H = 5.7.

0.1312 „ 13.3 c.c. moist nitrogen at 18° and 758 mm. N = 11.7.

0.4190 „ on distillation with soda, NH₃ = 9.7 c.c. N/10 HCl. NH₃ = 3.9.

0.1320 „ 0.2640 CO₂ and 0.0690 H₂O. C = 54.5; H = 5.8.

0.1595 „ 17.0 c.c. moist nitrogen at 19° and 750 mm. N = 12.1.

NH₄·C₂₁H₂₂N₃O₈ requires C = 54.5; H = 5.6; N = 12.1; NH₃ = 3.7 per cent.

Silver salt, prepared either by adding silver nitrate solution to the solution of the sodium salt, or by boiling the alcoholic solution of the acid with excess of silver carbonate. A. Was prepared from the sodium salt and recrystallised from alcohol. B. From the acid and silver carbonate. C is B recrystallised.

A. { 0.1900 gave 0.3180 CO₂, 0.0715 H₂O, and 0.0362 Ag. C = 45.6;
H = 4.2; Ag = 19.1.

0.1829 gave 11.2 c.c. moist nitrogen at 16° and 766 mm. N = 7.2.

B. 0.1580 „ 0.2673 CO₂, 0.0586 H₂O and 0.0295 Ag. C = 46.1;
H = 4.1; Ag = 18.8.

C. { 0.1850 gave 0.3090 CO₂, 0.0675 H₂O „ 0.0357 Ag. C = 45.5;
H = 4.1; Ag = 19.3.

0.2600 gave 16.2 c.c. moist nitrogen at 18° and 758 mm. N = 7.2.

AgC₂₁H₂₃N₃O₈ requires C = 45.6; H = 4.0; N = 7.6; Ag = 19.4 per cent.

Reduction of Trinitrocannabinol.—Trinitrocannabinol is reduced by boiling with hydriodic acid and phosphorus in acetic acid solution; 3.7 grams of trinitrocannabinol were dissolved in 50 c.c. of glacial acetic acid, and boiled for 1½ hours with 25 c.c. of hydriodic acid sp. gr. 1.6, and 4 grams of yellow phosphorus; the almost colourless solution was then filtered from the excess of phosphorus, and distilled down to one-third its volume. The pale yellow crystals of hydriodide which were deposited on cooling were collected, washed with acetic acid, and dried in a vacuum over solid potash.

Attempts to isolate the base failed, as when set free from the hydriodide it is at once oxidised, with formation of coloured products.

The hydriodide was analysed, and gave the following numbers, C = 41.2; H = 5.2; I = 41.3; N = 5.0 per cent.

The authors do not feel justified in making any statement as to the constitution of the product of reduction until they have isolated the base and made a further examination.

Acetylcannabinol, C₂₁H₂₅O₂·CO·CH₃.—Crude cannabinol is readily

26 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

acetylated by boiling it with acetic anhydride or with acetic chloride. After distilling off the excess of acetic anhydride and rectifying the residue under diminished pressure, an oil, lighter in colour and more mobile than the original crude cannabinol, is obtained; this sometimes, on standing, but, better, by dissolving it in alcohol and cooling the solution to 0° , deposits a white, crystalline substance, which can be purified by crystallisation from alcohol, light petroleum, or acetic acid; it melts at 75° , and is evidently identical with the 'acetylcannabinol, $C_{18}H_{23}OAc$,' mentioned by Dunstan and Henry (*loc. cit.*).

Analysis indicated as the simplest formula $C_{15}H_{18}O_2$ (Proc., 1898, 66), but determination of the molecular weight and the results of saponification show that the higher formula, $C_{23}H_{28}O_3$, must be adopted (Proc., 1898, 153).

The following samples were analysed. A. Recrystallised from alcohol. B. Four times recrystallised from alcohol. C. Recrystallised from light petroleum and then from acetic acid.

A.	{	0.1537	gave	0.4420	CO ₂	and	0.1101	H ₂ O.	C = 78.4 ; H = 7.9.
		0.1118	"	0.3208	CO ₂	"	0.0820	H ₂ O.	C = 78.3 ; H = 8.1.
B.	{	0.1250	"	0.3595	CO ₂	"	0.0914	H ₂ O.	C = 78.4 ; H = 8.1.
		0.1290	"	0.3692	CO ₂	"	0.0928	H ₂ O.	C = 78.1 ; H = 8.0.
C.		0.1860	"	0.5315	CO ₂	"	0.1330	H ₂ O.	C = 77.9 ; H = 8.0.

$C_{15}H_{18}O_2$ requires C = 78.3 ; H = 7.8 per cent.

$C_{21}H_{25}O_2 \cdot CO \cdot CH_3$ requires C = 78.4 ; H₂O = 8.0 per cent.

$C_{18}H_{23}OAc$ (Dunstan and Henry) requires C = 80.5 ; H = 8.7 per cent.

The molecular weight was determined by the freezing point method, in glacial acetic acid and in benzene.

In glacial acetic acid.—(i) 0.2043 gram, dissolved in 20 grams of glacial acetic acid, caused a depression of 0.123° .

(ii) 0.5052 gram, dissolved in 20 grams of glacial acetic acid, caused a depression of 0.310° .

*In benzene.**—(iii) 0.1877 gram, dissolved in 17.04 grams of benzene, caused a depression of 0.140° .

(iv) 0.3032 gram, dissolved in 17.04 grams of benzene, caused a depression of 0.240° .

	Calculated for	Calculated for	Found.			
	$C_{15}H_{18}O_2$	$C_{21}H_{25}O_2 \cdot CO \cdot CH_3$	(i).	(ii).	(iii).	(iv).
Mol. wt. = 230		352	324	318	385	365.

The percentage of acetyl was determined by saponifying the compound, either by boiling with alcoholic potash, or by heating with it in a sealed tube at 130° . Water was added to the product,

* For the molecular weight determination in benzene solution, we are indebted to the kindness of Mr. H. Jackson, B.A., Downing College.

9.0 " " " 52.4 c.c. "

Calculated for $C_{15}H_{18}O_2$.	Calculated for $C_{21}H_{25}O_2 \cdot CO \cdot CH_3$.	Found.
Acetyl = 18.7 per cent.	12.2	11.9, 12.5.

The residues left in the distilling flasks in the above acetyl determinations were extracted with ether. The ethereal solution was dried over calcium chloride, the ether distilled off, and the residue distilled under diminished pressure, when practically the whole passed over at 285° under 80 mm. pressure; the distillate was an almost colourless oil, which, on cooling, set to a transparent resin. A second preparation was made, and both were analysed.

$$0.1715 \text{ } ^9, \text{ } 0.5100 \text{ CO}_2 \text{ } ^9, \text{ } 0.1300 \text{ H}_2\text{O}. \text{ C}=81.1; \text{ H}=8.4.$$

$C_{27}H_{26}O_2$ requires C = 81.3 ; H = 8.4 per cent.

The molecular weight was found by the freezing point method in glacial acetic acid solution.

0.5876 gram, in 20 grams of glacial acetic acid, gave a depression of 0.380° .

0.6250 gram, in 20 grams of glacial acetic acid, gave a depression of 0.390° .

Calculated for	
$C_{21}H_{26}O_2$.	Found.
Mol. wt. = 310.	310, 313.

The compound is optically inactive.

Oxidation of Trinitrocannabinol with Nitric Acid.

One hundred and twenty grams of trinitrocannabinol was dissolved in 300 c.c. of hot, fuming nitric acid, and gently boiled for 5 hours in a reflux apparatus, more acid being added from time to time, until in all 700 c.c. had been used. On pouring the product into water, 70 grams of a yellow, waxy precipitate separated, and from this 35 grams of nitrocannabinol-lactone (oxycannabin) were obtained on treatment with alcohol. The filtrate from the above yellow precipitate

28 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

smelt strongly of valeric acid, and contained normal caproic, valeric, and butyric acids, possibly also propionic acid, together with non-volatile acids. Substantially the same products were obtained by the oxidation of crude cannabinol with nitric acid.

Examination of the Volatile Fatty Acids.

The volatile acids were removed from the above-mentioned acid mother liquor by steam distillation, and the distillate neutralised with sodium carbonate and evaporated to dryness; on acidifying with dilute sulphuric acid and extracting with ether, 12 grams of the mixed acids were obtained. These were fractionated with the following results.

105—150° = 2·2 grams.	170—180° = 1·2 grams.
150—170° = 0·9 ,,	180—195° = 3·9 ,,
Above 195° = 1·85 grams.	

From the fraction 150—170°, *normal butyric acid* was isolated by means of its calcium salt, which was purified and analysed, with the following results.

0·0730 lost 0·0037 H₂O at 135° and gave 0·0418 CaSO₄. H₂O = 7·8 ;
Ca = 16·9.

(C₄H₉O₂)₂Ca + H₂O requires H₂O = 7·7. Ca = 17·2 per cent.

The *valeric acid* in the fraction 180—195° was separated as the valeranilide which melted at 60° (uncorr.), and on analysis gave the following results.

0·0660 gave 0·1795 CO₂ and 0·0515 H₂O. C = 74·2 ; H = 8·7.

0·1998 ,, 13·6 c.c. moist nitrogen at 20·5° and 757 mm. N = 7·8.

C₁₁H₁₅NO requires C = 74·6 ; H = 8·5 ; N = 7·9 per cent.

As the anilide of normal valeric acid has not been described, it was prepared from a sample of normal valeric acid boiling at 185—186°, and was found to melt at 61° (uncorr.). Admixture of the anilide obtained from the fraction 180—195° with the anilide from normal valeric acid did not depress the melting point of the latter. The acid in this fraction is, therefore, normal valeric acid.

The *fraction boiling above 195°* was converted into the anilide which, after many crystallisations from light petroleum, melted at 93° (uncorr.). The analytical numbers were slightly low for a caproanilide, and lack of material prevented further purification. Normal caproanilide melts at 95°, and since it has been shown that the lower acids belong to the normal series, it can hardly be doubted that the acid obtained from this fraction is normal caproic acid.

In a similar examination of a much larger quantity of the fatty

acids obtained by oxidation of crude cannabinol with nitric acid, the same acids were obtained. Normal butyric acid was identified by its calcium salt, normal valeric acid by its anilide, and caproic acid by its silver salt.

The fraction 150—170° was also examined for isobutyric acid (b. p. 155°) by the method used by V. Meyer and Hutzler (*Ber.*, 1897, 2519), but as no trace of acetic acid could be detected after oxidation with potassium permanganate, isobutyric acid is evidently absent.

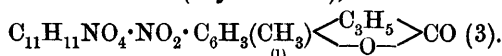
Caproic acid was also found in the product of the oxidation of crude cannabinol by chromic acid mixture, and by potassium permanganate solution.

In each case, the silver salt was recrystallised until the analytical results were constant. A. From chromic acid mixture oxidation. B. From potassium permanganate oxidation. C. From nitric acid oxidation.

- A. $\left\{ \begin{array}{l} 0.1459 \text{ gave } 0.1745 \text{ CO}_2 \text{ and } 0.0648 \text{ H}_2\text{O. } C = 32.5; H = 4.9. \\ 0.1650 \text{ ,, } 0.0800 \text{ Ag. } Ag = 48.5. \end{array} \right.$
 B. $0.1070 \text{ ,, } 0.0515 \text{ Ag. } Ag = 48.1.$
 C. $0.2383 \text{ ,, } 0.1158 \text{ Ag. } Ag = 48.6.$

$C_5H_{11}CO_2Ag$ requires $C = 32.3; H = 4.9; Ag = 48.3$ per cent.

Nitrocannabinolactone (oxycannabin),



The preparation of this substance from trinitrocannabinol has already been described; it can be obtained more conveniently by the following method. Crude cannabinol is dissolved in three times its weight of glacial acetic acid, warmed to 100°, and nitric acid (sp. gr. 1.42) slowly dropped in from a burette in the proportion of 1 c.c. of nitric acid for each gram of cannabinol; the solution is then boiled gently for half an hour, more nitric acid is added, and the boiling continued for 8—10 hours, nitric acid being added whenever the oxidation slackens, 50 grams of crude cannabinol require in all 300—400 c.c. of nitric acid. The product is then poured into water, and the nitrocannabinolactone separated as before; the yield is 15—20 per cent. of the crude cannabinol used. When purified by repeated crystallisation from alcohol, it is obtained in very faintly yellowish needles melting at 178° (uncorr.), and is not changed by sublimation. On exposure to light, it gradually assumes a reddish tinge. It is soluble in alcohol, acetic acid, benzene, and concentrated nitric acid. These properties show that it is identical with the oxycannabin of Bolas and Francis (*loc. cit.*), and of Dunstan and Henry (*loc. cit.*). Five samples were

30 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

analysed. A. Purified by sublimation. B. Precipitated from the potassium salt. C. Crystallised from dilute acetic acid. D. From alcohol. E. From trinitrocannabinol, and crystallised from alcohol.

A.	0.1478	gave 0.3225 CO ₂ and 0.0663 H ₂ O.	C = 59.5; H = 5.0.
B.	0.1313	0.2852 CO ₂ „ 0.0580 H ₂ O.	C = 59.2; H = 4.9.
C.	0.1195	0.2615 CO ₂ „ 0.0582 H ₂ O.	C = 59.7; H = 5.4.
D.	0.1330	0.2900 CO ₂ „ 0.0605 H ₂ O.	C = 59.5; H = 5.1.
	0.1615	8.8 c.c. moist nitrogen at 21° and 772 mm.	N = 6.3.
	0.1415	8.0 „ „ 17° „ 764 „	N = 6.6.
E.	0.1155	6.5 „ „ 19° „ 750 „	N = 6.4.
$C_{11}H_{11}NO_4$ requires C = 59.7; H = 5.0; N = 6.3 per cent.			
$C_{20}H_{20}N_2O_7$ (Bolas and Francis) „ C = 60.0; H = 5.0; N = 7.0 „			
$C_{10}H_{10}NO_4$ (Dunstan and Henry) „ C = 57.7; H = 4.8; N = 6.7 „			

The molecular weight was determined by the freezing point method in glacial acetic acid.

0.4313 gram, dissolved in 20 grams glacial acetic acid, lowered the freezing point 0.375°.

Mol. wt. calc. for $C_{11}H_{11}NO_4$ = 221. Found = 225.

Nitrocannabinolactone is insoluble in cold aqueous alkalis, but dissolves on boiling for a few minutes, and is not precipitated on dilution with water; the addition of mineral acids, however, precipitates it unchanged. Its salts are prepared as follows.

Potassium salt.—This salt separates in slender, pale yellow needles on mixing saturated solutions, in absolute alcohol, of the lactone and caustic potash.

0.1197 gave 0.0375 K₂SO₄. K = 14.1.

$C_{11}H_{12}NO_5K$ requires K = 14.0 per cent.

Silver salt.—Prepared by adding silver nitrate to an aqueous solution of the potassium salt.

0.1322 gave 0.0409 Ag. Ag = 30.9.

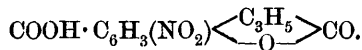
$C_{11}H_{12}NO_5Ag$ requires Ag = 31.3 per cent.

An attempt was made to obtain the ethylic salt by boiling the silver salt with ethylic iodide; silver iodide separated, but on extracting the product with boiling alcohol, nothing but unaltered nitrocannabinolactone was obtained.

The lactone was treated with aqueous ammonia, sp. gr. 0.88, and with saturated alcoholic ammonia, both at the ordinary temperature, and in sealed tubes at 100°. In each case, nothing but the unaltered lactone could be recovered. Failing to obtain an amide, an attempt was made to prepare the anilide, but this also was unsuccessful.

Oxidation of Nitrocannabino-lactone with dilute Nitric Acid.—Nitrocannabino-lactone (4 grams) was heated with 25 per cent. nitric acid (80 c.c.) at 185° for 8 hours, and the liquid, on stirring, deposited a colourless, crystalline, sparingly soluble acid; this, after recrystallisation from hot water, melted at 229—230° (uncorr.). The weight of the recrystallised acid was 1.1 grams.

Analysis shows that the substance has the formula $C_{11}H_9NO_6$, which may be derived from nitrocannabino-lactone by the oxidation of a methyl group to a carboxyl group, thus



This conclusion is strengthened by the fact that nitrocannabino-lactone, on oxidation with potassium permanganate in the cold, yields the same product. A. Was prepared by oxidation with nitric acid. B. With potassium permanganate.

- A. $\begin{cases} 0.1053 \text{ gave } 0.0360 \text{ H}_2\text{O and } 0.2033 \text{ CO}_2. & C = 52.7; H = 3.8. \\ 0.1328 \text{ „ } 6.5 \text{ c.c. moist nitrogen at } 21^\circ \text{ and } 750 \text{ mm.} & N = 5.5. \end{cases}$
 B. $\begin{cases} 0.1725 \text{ gave } 0.0612 \text{ H}_2\text{O and } 0.3300 \text{ CO}_2. & C = 52.2; H = 3.9. \\ 0.1700 \text{ „ } 8.0 \text{ c.c. moist nitrogen at } 20^\circ \text{ and } 765 \text{ mm.} & N = 5.4. \end{cases}$
 $C_{11}H_9NO_6$ requires $C = 52.6; H = 3.6; N = 5.5$ per cent.

The acid, neutralised with ammonia, was converted into silver salt. 0.1568 gave 0.0472 Ag. $Ag = 30.1$.

$C_{11}H_9NO_6Ag$ requires $Ag = 30.2$ per cent.

This acid must be regarded as the nitro-derivative of the cannabino-lactonic acid described below.

The nitric acid mother liquor, from which the sparingly soluble acid had separated, was evaporated to dryness, the residue dissolved in a very small quantity of cold water, filtered, again evaporated to dryness and extracted with ether. The syrup left on evaporating the ether gradually deposited crystals which were excessively soluble in water, alcohol, ether, glacial acetic acid, and ethylic acetate, but practically insoluble in benzene, chloroform, and light petroleum. The compound is most satisfactorily purified by recrystallisation from strong hydrochloric acid, when it is obtained as a colourless, crystalline powder, melting at 228—230° with much effervescence, but only a slight discoloration.

Three preparations were analysed.

- I. 0.0948 gave 0.0188 H_2O and 0.1478 CO_2 . $C = 42.5; H = 2.2$.
 0.0760 „ 3.5 c.c. nitrogen at 20° and 760 mm. $N = 5.5$.
 II. 0.1646 „ 0.0302 H_2O and 0.2552 CO_2 . $C = 42.3; H = 2.0$.
 III. 0.1775 „ 0.0325 H_2O „ 0.2754 CO_2 . $C = 42.3; H = 2.0$.

The formula $C_9H_5NO_4$ requires $C = 42.3; H = 2.0; N = 5.5$.

32 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

The acid is tribasic, for on titration with N/10 soda and phenolphthalein, 0.065 gram required 7.5 c.c. for neutralisation. A tribasic acid of the above formula requires 7.65 c.c.

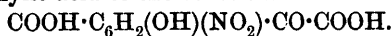
A solution of the calcium salt of the acid was prepared by neutralisation with chalk, and from this, nitrate of silver precipitated the silver salt as a primrose-yellow powder, slightly soluble in hot water. The salt is feebly explosive.

0.113 gave 0.004 H_2O and 0.079 CO_2 . $\text{C} = 19.0$; $\text{H} = 0.4$.

0.1565 „ 0.1172 AgCl . $\text{Ag} = 56.4$.

$\text{C}_9\text{H}_2\text{NO}_8\text{Ag}_3$ requires $\text{C} = 18.7$; $\text{H} = 0.3$; $\text{Ag} = 56.2$.

No attempt has been made to elucidate the constitution of the acid; it is, however, difficult to account for the formation of a tribasic acid of the formula $\text{C}_9\text{H}_5\text{NO}_8$ from nitrotolylbutyrolactone unless the acid is a hydroxyglyoxylic acid of the constitution



Amidocannabino-lactone, $\text{C}_{11}\text{H}_{11}\text{NH}_2 \cdot \text{O}_2$.—This compound can be obtained by the reduction of the nitrolactone by tin and hydrochloric acid, or by hydriodic acid and phosphorus, but the latter is more convenient.

Ten grams of the nitrolactone dissolved in 40 c.c. of glacial acetic acid was boiled with 30 c.c. of hydriodic acid of sp. gr. 1.6 and 5 grams of phosphorus for 2 or 3 hours, the colourless solution on cooling depositing crystals of the hydriodide of the base, and a further quantity of the base was obtained by pouring the strongly acid mother liquor into water. On dissolving the hydriodide thus obtained in boiling water, dissociation occurs, and the free base crystallises out on cooling.

Amidocannabino-lactone crystallises readily from hot water in long, white needles melting at 119° (uncorr.). Two preparations were analysed. A. Prepared by hydriodic acid and phosphorus. B. By tin and hydrochloric acid.

- A. $\begin{cases} 0.1260 \text{ gave } 0.3200 \text{ CO}_2 \text{ and } 0.0770 \text{ H}_2\text{O}. & \text{C} = 69.3; \text{H} = 6.8. \\ 0.1140 \text{ „ } 0.2895 \text{ CO}_2 \text{ „ } 0.0720 \text{ H}_2\text{O}. & \text{C} = 69.2; \text{H} = 7.0. \\ 0.1826 \text{ „ } 11.5 \text{ c.c. moist nitrogen at } 22^\circ \text{ and } 770 \text{ mm.} & \text{N} = 7.2. \end{cases}$
- B. $0.0795 \text{ „ } 0.2005 \text{ CO}_2 \text{ and } 0.0500 \text{ H}_2\text{O}. \quad \text{C} = 68.8; \text{H} = 7.0.$

$\text{C}_{11}\text{H}_{13}\text{NO}_2$ requires $\text{C} = 69.1$; $\text{H} = 6.8$; $\text{N} = 7.3$ per cent.

The hydriodide was also analysed.

0.1957 gave 0.1420 AgI . $\text{I} = 39.2$.

$\text{C}_{11}\text{H}_{11}\text{O}_2 \cdot \text{NH}_2 \cdot \text{HI}$ requires $\text{I} = 39.8$ per cent.

The platinochloride was prepared by dissolving the base in strong hydrochloric acid and adding platinic chloride solution. Two specimens were analysed.

0.1200 gave 0.0296 Pt. Pt = 24.7.

0.2594 „ 0.0636 Pt. Pt = 24.5.

$(C_{11}H_{11}O_2 \cdot NH_2)_2, H_2PtCl_6$ requires Pt = 24.6 per cent.

The base was readily diazotised, and an attempt was made to prepare cannabino-lactone from it by Friedländer's method, but no satisfactory product could be obtained.

Cannabino-lactone was, however, easily obtained through the iodolactone, whose preparation is given below.

Iodocannabino-lactone, $CH_3 \cdot C_6H_3I \langle \underset{O}{C_3H_5} \rangle CO$.—Ten grams of amido-cannabino-lactone was dissolved in 25 c.c. strong hydrochloric acid, 75 c.c. water added, and the solution diazotised by the addition of 4.5 grams of sodium nitrite dissolved in 15 c.c. of water, the temperature being kept within a few degrees of the freezing point. 12.5 grams of potassium iodide in 25 c.c. water was then added, and the mixture heated on the water bath until evolution of nitrogen ceased; the acid liquor was then poured off, and the solid residue, after treatment with solution of sodium thiosulphate to remove free iodine, was repeatedly crystallised from dilute acetic acid. The yield was 10 grams. The iodolactone forms almost colourless crystals melting at 137.5° (uncorr.), insoluble in water, but easily soluble in alcohol and acetic acid; it sublimes very readily.

0.2370 gave 0.3825 CO_2 and 0.0803 H_2O . C = 44.0; H = 3.8.

0.2785 „ 0.2145 AgI. I = 41.6.

$C_{11}H_{11}IO_2$ requires C = 43.7; H = 3.6; I = 42.0 per cent.

Silver Salt.—A solution of the potassium salt was obtained by saturating alcoholic caustic potash solution with the iodolactone, and after precipitating the excess of lactone by water, silver nitrate was added to the filtrate. The silver salt was precipitated as an amorphous powder which became crystalline on standing. It is soluble in hot water, but cannot be recrystallised without decomposition.

0.2430 gave 0.1315 AgI. Ag = 24.9

$C_{12}H_{12}IO_3Ag$ requires Ag = 25.3 per cent.

Cannabino-lactone, $CH_3 \cdot C_6H_4 \langle \underset{O}{C_3H_5} \rangle CO$.—The iodolactone is dissolved in hot alcoholic potash solution and the solution, diluted with water, is reduced with 2.5 per cent. sodium amalgam. No hydrogen is evolved until almost the theoretical amount of amalgam has been added, but it is found advantageous to use a considerable excess of the reducing agent in order to ensure the complete removal of iodine. After the alcohol has been removed by boiling, the alkaline solution is acidified

34 WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I.

by sulphuric acid, and steam distilled until the distillate no longer becomes turbid on adding a strong solution of potassium carbonate. The lactone is obtained by salting out the distillate with potassium carbonate, and extracting with ether; the oily residue left on evaporating the ether distilled almost to the last drop at 290.5° (uncorr.) under a pressure of 768 mm. When purified by redistillation under diminished pressure, it was obtained as a colourless, highly refracting liquid of sp. gr. at $20^{\circ}/20^{\circ} = 1.0833$, and boiling at 126° (uncorr.) (20 mm.). The yield of pure cannabino-lactone from the iodolactone amounts to 86 per cent. of the theoretical.

0.1105 gave 0.3055 CO_2 and 0.0700 H_2O . $\text{C} = 74.9$; $\text{H} = 7.0$.

$\text{C}_{11}\text{H}_{12}\text{O}_2$ requires $\text{C} = 75.0$; $\text{H} = 6.8$ per cent.

The lactone dissolves slowly in aqueous solution of caustic alkalis, and is reprecipitated by carbon dioxide. So great is the tendency to lactone formation that a current of steam slowly removes the lactone from its solution in excess of caustic potash.

Cannabino-lactonic Acid, $\text{COOH} \cdot \text{C}_6\text{H}_4 \langle \text{C}_8\text{H}_5 \rangle \text{CO}$.—11.5 grams of cannabino-lactone, dissolved in hot aqueous potash, was treated with 41.4 grams of potassium permanganate dissolved in 1000 c.c. of water, and the mixture, after being boiled for 9 hours, was decolorised by a few drops of alcohol. The filtrate from the manganese dioxide, when evaporated to 200 c.c. and acidified with hydrochloric acid, deposited 10.6 grams of a pearly-white, crystalline compound, which, after recrystallisation from hot water, was obtained in long needles melting at 203° (uncorr.). The yield is 88 per cent. of the theoretical. Two samples were analysed.

0.1371 gave 0.3205 CO_2 and 0.0635 H_2O . $\text{C} = 63.8$; $\text{H} = 5.2$.

0.1380 „ 0.3250 CO_2 „ 0.0626 H_2O . $\text{C} = 64.2$; $\text{H} = 5.0$.

$\text{C}_{11}\text{H}_{10}\text{O}_4$ requires $\text{C} = 64.1$; $\text{H} = 4.9$ per cent.

The lactonic acid is soluble in about 85 parts of boiling water, very sparingly in cold water, and easily in alcohol.

Potassium Salt.—Prepared by adding alcoholic potash to an alcoholic solution of the lactonic acid.

0.2295 gave 0.0825 K_2SO_4 . $\text{K} = 16.1$.

$\text{C}_{11}\text{H}_9\text{O}_4\text{K}$ requires $\text{K} = 16.0$ per cent.

The silver salt was found to contain 33.8 per cent. Ag. $\text{C}_{11}\text{H}_9\text{O}_4\text{Ag}$ requires 34.5 per cent.

The *ethylic salt* was prepared by boiling the lactonic acid for 5 hours with a 3 per cent. solution of hydrogen chloride in absolute alcohol. After recrystallisation from dilute alcohol, it melted at 105° (uncorr.), and, on analysis, gave the following numbers.

WOOD, SPIVEY, AND EASTERFIELD: CANNABINOL. PART I. 35

0.0861 gave 0.2095 CO_2 and 0.0484 H_2O . $\text{C} = 66.4$; $\text{H} = 6.2$.

0.1608 „ 0.3905 CO_2 „ 0.0890 H_2O . $\text{C} = 66.2$; $\text{H} = 6.1$.

$\text{C}_{11}\text{H}_9\text{O}_4 \cdot \text{C}_2\text{H}_5$ requires $\text{C} = 66.7$; $\text{H} = 6.0$ per cent.

Fusion of Cannabino-lactonic Acid with Potash.

4.4 grams of the lactonic acid was fused with 25 grams moist caustic potash at 286° (in a bath of boiling β -naphthol). The reaction is completed almost instantaneously at this temperature, but proceeds with extreme slowness at 220° . The melt, on being dissolved and acidified with dilute sulphuric acid, gave 3.4 grams of a crystalline precipitate, which, after several recrystallisations from dilute alcohol, sublimation, and a further recrystallisation, melted above 300° , and sublimed without decomposition.

0.1133 gave 0.2392 CO_2 and 0.0400 H_2O . $\text{C} = 57.6$; $\text{H} = 3.9$.

$\text{C}_8\text{H}_6\text{O}_4$ requires $\text{C} = 57.8$; $\text{H} = 3.6$ per cent.

The analysis and physical characters agree with those of isophthalic acid.

Its methylic salt melted at 64° (uncorr.), and boiled at 280 — 282° (uncorr.) (Baeyer gives 64 — 65° , *Annalen*, 1873, 166, 340). The salt, on analysis, gave the following numbers.

0.1084 gave 0.2445 CO_2 and 0.0518 H_2O . $\text{C} = 61.5$; $\text{H} = 5.3$.

0.1060 „ 0.2395 CO_2 „ 0.0510 H_2O . $\text{C} = 61.7$; $\text{H} = 5.3$.

$\text{C}_6\text{H}_4(\text{COOCH}_3)_2$ requires $\text{C} = 61.9$; $\text{H} = 5.1$ per cent.

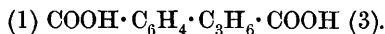
Potash Fusion of Cannabino-lactone with Potash.

The conclusions to be drawn from the fusion of cannabino-lactonic acid are supported by the potash fusion of cannabino-lactone (0.9 gram) with moist caustic potash (15 grams) at 300° to 320° , which yields metatoluic acid.

The reaction took place slowly, and the melt, which was very dark in colour, was dissolved, acidified with sulphuric acid, and extracted with ether, &c., in the usual way. After purifying the product by crystallisation from water and animal charcoal 0.3 gram was obtained. It began to melt at 108° , but was not completely melted until 200° . It was accordingly steam distilled, and the crystals, which separated in the distillate, were now found to melt at 110° (uncorr.). Jacobsen (*Ber.*, 1881, 14, 2349) gives the melting point of metatoluic acid as 110.5° . The mother liquor from which the metatoluic acid had been removed by steam distillation, on being evaporated to dryness, dried at 150° , and then recrystallised from water, gave isophthalic acid, which melted above 300° , and sublimed without decomposition; this was, no doubt, produced from the metatoluic acid by further oxidation.

Reduction of Cannabino-lactonic Acid.

The lactonic acid was reduced by heating with hydriodic acid and phosphorus in a sealed tube at 190° , and the product, after two recrystallisations, melted at about 210° . As the limited quantity of the substance did not allow of further purification, it was analysed. The result leaves no doubt that it is the expected metacarboxy-phenylbutyric acid.



0.1298 gave 0.3044 CO_2 and 0.0695 H_2O . $\text{C} = 64.0$; $\text{H} = 5.9$.

$\text{C}_{11}\text{H}_{12}\text{O}_4$ requires $\text{C} = 63.5$; $\text{H} = 5.8$ per cent.

UNIVERSITY CHEMICAL LABORATORY,
CAMBRIDGE.
