

XL.—*Charas. The Resin of Indian Hemp.*

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SEVERAL preparations of *Cannabis indica* (syn. *sativa*), differing in physiological activity and in the manner of application to the human subject, are familiar to the Eastern nations. Of these, "charas" is an Indian drug, and is regarded by the natives as the most potent substance obtainable from the plant. It is chiefly used in the Punjab, and consists essentially of the resinous exudation from the stems, leaves, and flower heads of the unfertilised female plant. By the kindness of Mr. Charles A. Silberrad, B.A., I.C.S., at present resident at Etawah, N.W.P., the authors have been provided with several pounds of the resin, the examination of which has furnished the materials for the present communication.

Cannabis indica has been employed medicinally, both in this country

and on the Continent, but the uncertain action of the drug has prevented its use from becoming general, different preparations having apparently very different effects on the organism. It was with the object of isolating the physiologically active constituent of the hemp plant that the present research was undertaken, the importance of cannabis in veterinary medicine having been pointed out to the authors by Professor F. R. Hobday, of the Royal Veterinary College, and Mr. W. A. Wood, M.R.C.V.S.

Charas was examined rather than any other preparation because the active principle appeared to be most highly concentrated in this natural exudation, and also because it contains no chlorophyll, a substance which causes much inconvenience in the examination of extracts made from the plant itself.

Now that the characteristic compound has been isolated by the authors and placed in the hands of experienced pharmacologists, the difficulties which have hitherto attended the pharmaceutical use of Indian hemp will probably disappear.

More than 40 original papers referring to *Cannabis indica* have been published; abstracts of these are to be found in a dissertation by Leib Lapin (*Zur Kenntniss der Cannabis indica*, Jurjew, 1894), and in the *Journal of the Imperial Institute*, vol. ii, No. 15, 105 (March, 1896).

The physiological action was ascribed by T. and H. Smith (*Pharm. Jour.*, 1847, **6**, 675) to a resin which they obtained by alcoholic extraction of the dry plant, previously treated with acid and alkali, evaporation with lime to destroy chlorophyll, and subsequent extraction of the mass with alcohol. No definite composition was assigned to the resin; it could evidently have contained no alkaloids.

Personne (*J. Pharm.*, 1857, **31**, 47) attributed the physiological effect to a volatile oil, whilst various observers have stated, and others have denied, that an alkaloid is present in the plant. The authors would state that their results do not agree with those obtained by any one investigator. Personne's volatile oil has been shown by Valenta (*Gazzetta*, 1889, **10**, 540), and more recently by Vignolo (*Gazzetta*, 1895, **25**, i, 110), to be an impure sesquiterpene. This substance is also present in "charas," but is comparatively inert. Smith's resin contains the active substance in large quantity, but is not a pure chemical compound. The authors have separated from charas and from Smith's resin an oil, resinous at ordinary temperatures, and having the formula $C_{18}H_{24}O_2$. This substance is present in charas to the extent of 33 per cent., and in Smith's preparation to nearly 80 per cent., and the authors have been able to isolate the same compound, not only from the ethereal and alcoholic extracts of the dry plant, but also from two commercial preparations by Merck,

of Darmstadt, known as "cannabinon" and "cannabis resin" respectively. Charas has yielded no alkaloid, but the balance of evidence is in favour of some relatively inert alkaloïdal substance being present in small quantity in Indian hemp.

Since the compound $C_{18}H_{24}O_2$ gives rise to all the symptoms of cannabis poisoning, such as is produced amongst the "haschish" smokers, the authors are of opinion that the main effects produced by the drug are due to the action of this substance, but that the presence of the terpenes and other constituents probably causes secondary effects, which to a certain extent interfere with the highly characteristic physiological action for which Indian hemp is so noted.

The ethereal extract from charas has yielded four distinct chemical compounds.

1. A terpene, boiling at 160—180°. Yield 1·5 per cent.
2. A sesquiterpene, boiling at 258—259°. Yield 2 per cent.
3. A paraffin ($C_{28}H_{60}$), m. p. 63—64°. Yield 0·15 per cent.
4. A toxic red oil, $C_{18}H_{24}O_2$, boiling at 265° under a pressure of 20 mm. Yield 33 per cent. of the charas taken.

EXPERIMENTAL.

Two kilos. of charas were extracted completely with ether, the ethereal extract concentrated to a syrup, and the product distilled until the thermometer rose to 300°; the residue was then distilled under a pressure of 15—60 mm., when the whole, with the exception of a pitchy residue, came over between 270° to 290°.

The charas was thus separated into four crude products.

- A. The portion insoluble in ether, 755 grams, that is, 38 per cent.
This was a grey powder containing much ash, and about 3 per cent. of nitrogen. On destructive distillation, it yielded ammonia, pyrroline (pine-shaving reaction), and organic bases. No alkaloid was obtainable by the usual methods of extraction, and it has not been further examined. Under the microscope it was seen to be largely composed of plant hairs.
- B. The oily distillate from the ether extract, boiling below 300°. Weight, 200 grams = 10 per cent.
- C. The red resinous portion boiling at 270—290°, under a pressure of 15—60 mm. Weight, 650 grams = 33 per cent.
- D. The pitchy residue. Weight, 160 grams = 8 per cent.; this was not further examined.

Examination of Fraction B.

1. *Terpene of Low Boiling Point.*—The oil was distilled until the temperature rose to 200°; the distillate was shaken with water, dried

with calcium chloride, and then repeatedly fractionated over sodium, and finally over phosphoric anhydride. 30 grams of an oil boiling between 160° and 180° , and mostly coming over between 165° and 175° , was thus obtained. The portion distilling between 170 and 175° was analysed.

Calculated for $C_{10}H_{16}$, C = 88.2; H = 11.8.

Found, C = 87.8; H = 12.0.

The vapour density by Victor Meyer's air displacement method was found to be 65. Calculated for $C_{10}H_{16}$ = 68.

The sp. gr. of the oil at $17^{\circ}/4^{\circ}$ was found to be 0.819, which is considerably less than that of the ordinary terpenes. It is slightly laevorotatory, but in consideration of the very doubtful purity of the substance no importance could be attached to a determination of the specific rotation. The oil has a very pleasant terebinthous odour, and resinifies with remarkable rapidity on exposure to the air. It combines with hydrogen chloride to form an oily monohydrochloride (found, 22 per cent. Cl.; calculated, 20.6), the first few bubbles of gas giving rise to a brilliant violet coloration.

The same compound, boiling at 160 — 180° , has been found by the authors in an ethereal extract of the plant supplied to them by Merck. It was isolated by steam distillation, &c.

Monoterpenes have not been previously reported amongst the products obtained from the hemp plant.

Terpene of High Boiling Point (Sesquiterpene).—That portion of fraction B which boiled above 200° was distilled with steam; a grass-green oil passed over, leaving a less volatile residue (see C below). The green oil was separated from the water by means of ether, dried with calcium chloride, and fractionated. After repeated distillation over sodium, about 35 grams of a colourless oil boiling at 258 — 259° was obtained. The substance is a sesquiterpene.

		Found.		
		I.	II.	III.
Calculated for				
$(C_{15}H_{24})x$.				
C	88.2	87.94	87.60	87.86
H	11.8	11.60	11.73	—

Two vapour density determinations by Hofmann's method at the temperature of boiling nitrotoluene (223°) gave 99.8 and 101.8. Calculated for $C_{15}H_{24}$, vapour density = 102.

The sp. gr. of the freshly distilled oil was 0.898 at 18° , the specific rotation -8.6 at the same temperature. This oil is evidently identical with that isolated by Valenta (*Gazzetta*, 1880, **10**, 540), and more recently by Vignolo (*Gazzetta*, 1895, **25**, i, 110), as a constituent of "cannabene," the oil which Personne obtained by distil-

ling the hemp plant with water. Valenta gives the boiling point as $256-258^{\circ}$, sp. gr. at $0^{\circ} = 0.9289$, and sp. rotation in chloroform solution $= -10.81$.

The sesquiterpene absorbs hydrogen chloride with production of a violet colour and separation of a brown, tarry mass. Bromine added to a chloroform solution of the compound gives rise to a violet colour, changing to red on adding more of the reagent. Sulphuric acid added to the acetic acid solution at once gives a deep red coloration. The sesquiterpene obtained by Wallach (*Annalen*, 1887, **238**, 81) from oil of cubebs gives a somewhat similar reaction.

Examination of Fraction C.—(1) *Paraffin*, $C_{29}H_{60}$?—The resinous oil which remained when fraction B was steam distilled was added to C, and the mass on standing became filled with white crystalline scales; the whole was then dissolved in boiling alcohol and allowed to cool, when the crystals again separated and were collected. After several recrystallisations from much boiling alcohol, they melted at $63.5-64^{\circ}$, and the melting point was not changed by further recrystallisation. The boiling point was $285-290^{\circ}$ under a pressure of 15 mm. Analysis indicated that the substance was a higher paraffin.

		Found.		
		Calculated for $C_{29}H_{60}$.		
		I.	II.	III.
C	85.3	85.15	84.9	84.7
H	14.7	14.54	14.7	15.0

The numbers would agree equally well for any of the higher paraffins. Since, however, the melting and boiling points coincide with those which can with a high degree of certainty be predicted by interpolation for normal nonacosane, $C_{29}H_{60}$ (Krafft, *Ber.*, 1882, **15**, 1702, *et seq.*), there is greater probability that it is this hydrocarbon than that it is any other.

By constructing a curve from the melting and boiling points given by Krafft and interpolating for the unknown members of the paraffin series, the figures obtained are

		Calculated for $C_{29}H_{60}$.	Found.
M. p.....		63—64	63.5—64
B. p. (15 mm. pressure)		285—286	285—290 (corr.).

The molecular weight by Raoult's freezing point method in naphthalene was found to be 391. Calculated for $C_{29}H_{60} = 408$.

This hydrocarbon had no action on acid solution of potassium permanganate at 80° , and in chloroform solution it did not absorb bromine from bromine water. Lack of material has prevented a more thorough investigation of the compound.

The authors have isolated the same hydrocarbon from *Resina Cannabis indicæ* as supplied by Merck; from the *Extractum Cannabis indicæ spirit. sicc.* of the German Pharmacopœia; and also from the ethereal and carbon bisulphide extracts prepared from the plant.

A paraffin whose composition and melting point agree with those of the substance under consideration has been found by Zugo (*Gazzetta*, 1889, **19**, 210) in the flowers of *Chrysanthemum cinerariæfolium*, but the authors have had no opportunity of comparing the two substances. An olefine (?) with the same melting point has been found in the flowers of *Anthemis nobilis* (*Naudin Bulletin*, **41**, 484). With the exception of normal heptane, found by Thorpe (*Annalen*, 1879, **198**, 364) in the turpentine of *Pinus sabiniana*, these appear to be the only recorded instances of the occurrence of paraffinoid hydrocarbons in the vegetable kingdom.

Personne appears to have first noticed the occurrence of a solid hydrocarbon in the hemp plant. He named it hydride of cannabene, and assigned to it the formula $C_{12}H_{14}$ (old notation). No analysis is given in the paper. The same hydrocarbon has been examined by Arutinianz, who describes it as a white substance melting at 60° . His analysis gave C = 83.81, H = 14.58, only adding up to 98.39. The authors would mention that, unless burnt with extreme care, the substance invariably gives very low results when analysed.

(2.) *Toxic Red Oil*, $C_{18}H_{24}O_2$, *Cannabinol*.—The alcoholic filtrate from the paraffin just described was concentrated, and the syrup distilled under diminished pressure; an oil, amber coloured when seen in thin layers, but ruby red when seen in mass, distilled between 270° and 290° , under a pressure of 15—35 mm. There was practically no residue. Two kilos. of charas yielded upwards of 600 grams of this oil. On redistillation, the compound was found to boil constantly at 265° (20 mm. pressure), 300° (46 mm.), and 315° (100 mm.).

When the oil was cooled below 60° , it set to a sticky, semi-solid, odourless mass, insoluble in water, but dissolving easily in alcohol, ether, benzene, glacial acetic acid, and organic solvents generally. Its solution in cold concentrated sulphuric acid is cherry red. Four different preparations were analysed.

	Calculated for $C_{18}H_{24}O_2$.	Found.			
		I.	II.	III.	IV.
C.....	79.4	78.9	79.0	79.3	79.4
H.....	8.8	9.0	9.05	8.9	9.29

Preparation I had been obtained by the use of "petroleum ether," II and III, by ether as described above. IV had been worked up from residues, and had been exposed to the air for some weeks before being analysed. The molecular weight of the oil in acetic acid

solution was found by Raoult's freezing-point method to be 273 and 278. The formula, $C_{18}H_{24}O_2 = 272$. The sp. gr. was found to be 0.9892 at 100°; 1.00925 at 65° and 1.0424 at 18°.

The substance is extremely stable, but it reacts with bromine and with phosphorus pentachloride at the ordinary temperature. Fuming hydriodic acid, with phosphorus, is apparently without action on it below 150°, whilst above this temperature, a mixture of hydrocarbons is formed. Boiling alcoholic potash does not act on the substance and no oxime or phenylhydrazine derivative has been obtained; a monacetyl and a monobenzoyl derivative, however, have been prepared. Experiments on the constitution of the compound are in progress.

The physiological effects of the substances isolated from charas, have been investigated by Dr. C. R. Marshall, assistant to the Downing Professor of Medicine. A full account of the experiments will be published elsewhere, but the following report has been kindly supplied for insertion in the present paper.

"The physiological action of the terpenes closely resembles that of the other members of this class, of which ordinary turpentine may be taken as the type. In doses of 0.5 gram they have very little effect and produce none of the characteristic symptoms of cannabis action. The red oil, on the contrary, is extremely active, and taken in doses of 0.05 gram induces decided intoxication followed by sleep. The symptoms produced by it are peculiar to *Cannabis indica*, and as none of the other products appear to possess this action, this substance must be regarded as the active constituent of the plant."

If the physiological action of hemp is really due to the red oil, it is evident that the oil must exist to a greater or less extent in all the pharmaceutical preparations which are known to exert the characteristic effects. The authors have, therefore, examined a number of such preparations and have in every case succeeded in isolating the compound in question. The approximate yields obtained together with the analytical numbers are recorded in the following table.

Source.	Charas.	Cannabin (Smith's resin).	Cannabinon (Merck).	Ethereal extract (Merck).	Cannabis resin (Merck).
Yield of red oil per cent.	33	80	50	26	20
Calculated for $C_{18}H_{24}O_2$					
C 79.4	79.15	79.3	79.4	79.9	77.7
H 8.8	9.06	9.6	9.6	9.6	9.3

The oil was also obtained in small quantity from the alcoholic extract (*Extractum Sicc. Pharm. Germanica*) supplied by Merck.

The following notes on the method of treatment pursued in each case may be of use to subsequent workers.

Cannabin (*Smith's Resin*).—The substance was merely distilled under diminished pressure and the distillate once redistilled.

Cannabinon (*Merck*).—The crude material was dissolved in ether, washed with 10 per cent. sodium carbonate solution which removed a small quantity of a non-crystalline acid, then with dilute sulphuric acid, and finally with water. The ethereal solution was concentrated, and distilled under diminished pressure. The distillate had a strong odour of tobacco which was almost entirely removed by steam distillation. The product was finally redistilled. The original cannabinon contained 1.7 per cent. of nitrogen.

Ethereal Extract (*Merck*).—Steam distillation removed the terpenes, the residue was dissolved in alcohol and evaporated with lime, the cake boiled out with spirit, and the solution concentrated and distilled under diminished pressure.

Cannabin Resin (*Merck*).—The dark-green mass was distilled under diminished pressure, and the product repeatedly redistilled. The sample of red oil thus prepared was far from pure as shown by its persistent smell, its fluidity, and the analytical figures.

The red resinous oil has not previously been isolated as a definite chemical compound, although Leib Lapin (*Dissertation Jurgew*, 1894) obtained a substance to which he assigned the formula $C_8H_{12}O$ by a tedious process of fractional precipitation from the ethereal extract of the plant. As far as can be judged from the properties as described by him, his substance may well have been an impure preparation of the red oil. The name, "cannabindon," which Leib Lapin proposes for his substance, from its similarity to "cannabinon," does not recommend itself to the authors who propose the name *cannabinol* as the compound is undoubtedly a hydroxyl derivative.

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