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# Stability, transfer and absorption of cannabinoid constituents of Cannabis (Hashish) during smoking[1]

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SUMMARY The cannabinoids of a hashish preparation were determined qualitatively and quantitatively.

A group of Cannabis smokers using this preparation obtained a 14—20 % transfer of the cannabinoids present in the hashish cigarette to the respiratory system. These results agree with experiments using tobacco cigarettes impregnated with pure cannabinoids, showing a 14—29 % transfer with the main stream smoke. While cigarette smoking made only 14—20 % of the cannabinoid constituents of hashish available to the smoker, this figure was increased to about 45 for pipe smoking. The experienced Cannabis smokers using deep inhalations absorbed over 80 % of the cannabinoids in the main stream smoke.

There is no difference in the transfer of cannabinoids using the deep inhalation technique, when compared to normal superficial smoking.

Except for decarboxylation of cannabinoid acids, there is no substantial difference between the major cannabinoids of the smoke as compared to the drug itself. That the smoking process causes only limited changes in the cannabinoid fraction was also shown by smoking pure $\Delta^1$-tetrahydrocannabinol, cannabidiol, cannabinol and cannabidiolic acid.

The present results indicated that to achieve a "normal biological high" by smoking, the absorbed dose of $\Delta^1$-tetrahydrocannabinol was in the range of 3—5 mg for the tested persons.

[1] Part VIII of Metabolism of Cannabis. Part VII. *Science 168*, 1228 (1970). Part IX. *Life Sciences 10, Part II*, 157 (1971).

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Our results further indicate a rather rapid fall in the content of $\Delta^1$-tetrahydrocannabinol in stored hashish, partly due to the transformation to cannabinol. A gas chromatographic method for the determination of cannabinoids, using triphenyl carbinol as internal standard, is presented.

Up to 1964, only three cannabinoid constituents of Cannabis were known structurally, viz. cannabidiol, cannabidiolic acid and cannabinol. Since the structural elucidation of $\Delta^1$-tetrahydrocannabinol in that year by Gaoni and Mechoulam [1], progress in the chemistry of Cannabis has been rapid and some fifteen other cannabinoids have now been isolated. For structures and further references to these compounds, we refer to Fig. 1 and to the recent reviews by Mechoulam [2], Farnsworth [3] and to the proceedings of a symposium [4]. The pharmacological, clinical and psychological effects of Cannabis have been reviewed by e.g. Weil [5] and Grinspoon [6].

Cannabis is known to have a stronger and more immediate effect when smoked than when taken orally in similar amounts [5—7]. It is obvious that, during the process of smoking, cannabinoids and other compounds are to a large extent destroyed by burning, but other chemical reactions

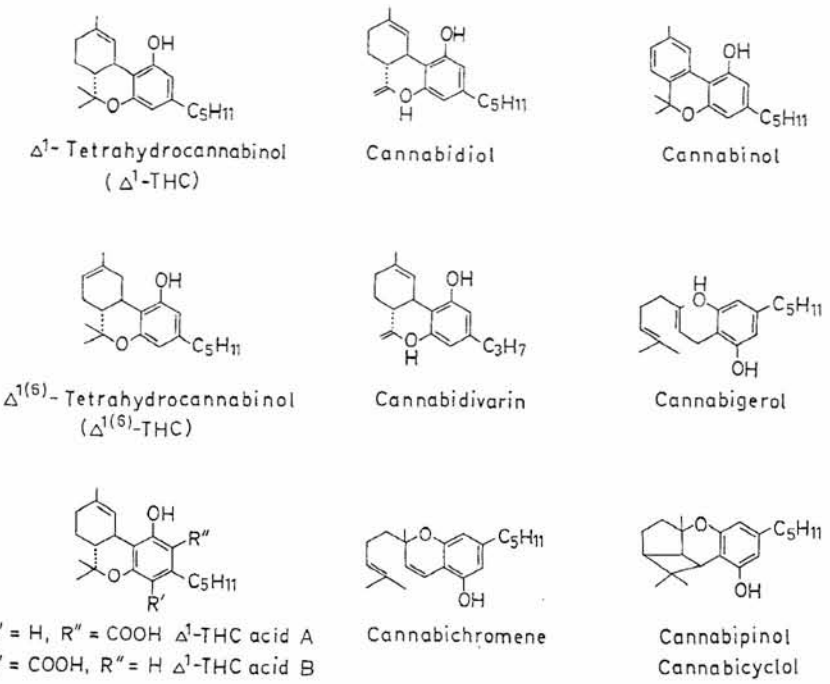


*Fig. 1. Structures of cannabinoid compounds.*

may also occur. Thus, the chemical composition and the pharmacological properties of the *drug* itself and the Cannabis *smoke* may be quite different. So far, this has generally been overlooked and, as discussed later, only a few limited investigations have been carried out concerning this problem.

The present work was initiated to answer some questions of importance for biochemical and pharmacological studies, i.e.: How many per cent of the cannabinoids in the Cannabis cigarette are transferred with the smoke to the respiratory system of the smoker and how much is absorbed? How much $\Delta^1$-tetrahydrocannabinol is absorbed in the lungs to produce a "biological high"? What chemical changes occur in the cannabinoid fraction during the smoking process?

## Experimental

Gas chromatography-mass spectrometry was performed with a Perkin-Elmer 270 instrument (electron energy 70 eV) using a 3 % JXR/Gas Chrom Q column. NMR spectra were obtained with a Varian A-60A spectrometer in $CDCl_3$ solution and with tetramethylsilane as internal standard.

### Gas chromatography

Gas chromatography was carried out with a Perkin-Elmer model 900 gas chromatograph (FID) using 180 cm×2 mm (inner diameter) glass columns with 3 % JXR on 100/120 mesh Gas Chrom Q as column packing [7]. Injector temp. 240°, detector temp. 240°, column temp. 195°. Retention times for a number of cannabinoids on this column have been published [8] and further information is given in Table 1. Also, 5 % SE-30 and 5 % XE-60 columns were used [8].

Cannabinoids were estimated quantitatively by GLC from peak area measurements using known amounts of triphenyl carbinol as internal standard. The calibration curve for cannabidiol–triphenyl carbinol is shown in Fig. 2. Pure, distilled $\Delta^{1(6)}$-tetrahydrocannabinol was shown to give a relative response of 0.82 when compared with cannabidiol in equimolar amounts. $\Delta^1$-Tetrahydrocannabinol was assumed to have the same response factor as the $\Delta^{1(6)}$-isomer. Distilled cannabinol had a response factor of 0.79 compared to cannabidiol. These response factors apparently differ from those published by Philips *et al.* [9]. Other cannabinoids were estimated as having the same response factor as cannabidiol. Some further details are given as footnotes to Table 1.

### Column separation

A Cannabis preparation (hashish) of Lebanese origin was extracted in a Soxhlet apparatus with metylene dichloride [10]. Three hours' extraction was found to be sufficient for a complete extraction of the hashish.

Table 1

*Cannabinoid compounds identified in original hashish sample before smoking.*

| Compound identified | Approx. mg/g hashish[a] | Identified by[b] | Retention times (min) at 235° 3 % JXR/ Gas Chrom O |
|---|---|---|---|
| Cannabidiol (CBD) | 90 | GLC, MS, m.p. | 3.4 |
| $\Delta^1$-Tetrahydrocannabinol (THC) | 64 | GLC, MS | 4.6 |
| $\Delta^{1(6)}$-Tetrahydrocannabinol | < 2 | GLC, MS | 4.4 |
| Cannabinol (CBN) | 21 | GLC, MS | 5.6 |
| Cannabichromene | < 2 | GLC, MS, NMR | 3.6 |
| Cannabidivarine | < 1 | MS, (GLC)[c] | 2.4 |
| Cannabigerol | < 2 | GLC, MS | 5.8 |
| Cannabipinol (Cannabicyclol) | < 1 | GLC, MS | 2.9 |

[a] Determined by gas chromatography of a methylene dichloride extract of the hashish sample. The figures for cannabidiol and $\Delta^1$-tetrahydrocannabinol also include the corresponding carboxylic acids which readily decarboxylate on heating [8, 10, 16]. These acidic compound decarboxylate in the gas chromatograph.

[b] "GLC" means GLC retention time identical with retention time of reference compound, and "MS" mass spectrum identical with published or reference mass spectrum. For literature references to spectral and chemical data for these compounds, (see refs. [2, 4 and 17]).

[c] Cannabidivarine [18] was not available as reference but the retention time suggests our compound to be the lower homologue of cannabidiol (cannabidivarine).

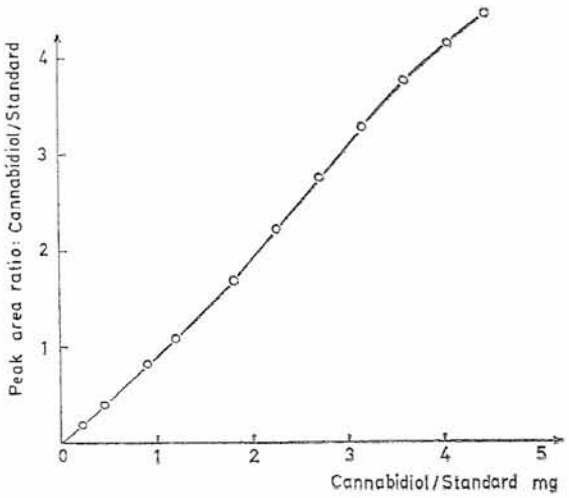


*Fig. 2*

*Standard calibration curve for cannabidiol.*

This procedure is, however, not satisfactory for marihuana type Cannabis. The components in the extract (3—4 g) were separated by chromatography on a 5×80 cm silica gel column (0.05—0.2 mm; Merck) using chloroform as eluent.

### Hashish cigarettes

Coarsely levigated hashish (1.00 g) (analysis shown in Table 1) was mixed with 1.8 g of pipe tobacco and made into a cone shaped cigarette with a small card-board tip (Fig. 3).

### Transfer of cannabinoids with smoke

The main stream smoke (resulting when air is drawn through the burning cigarette) from a Cannabis cigarette was collected by one of two different methods. Either the smoke aerosol was collected by an electrofilter (Cottrell filter) precipitating the aerosol particles on a silver cylinder [11, 12] or by a mechanical glass fiber disc filter (Cambridge filter — Fig. 3) used for determination of tar in cigarettes. The cigarette was connected to one end of the filter and smoked by volunteers as they ordinarily would smoke a Cannabis cigarette or an ordinary tobacco cigarette, respectively (Table 2). The hashish cigarettes were smoked until only the card-board tip was left. The compounds retained by the filter were eluted with methanol and the amount of cannabinoids estimated by GLC.

The amount of cannabinoids not absorbed in the respiratory system of the smoker (only chronic Cannabis users) was determined by the use of Cannabis cigarettes with no filter during the inhalation phase but letting the subject exhale through a Cambridge filter.

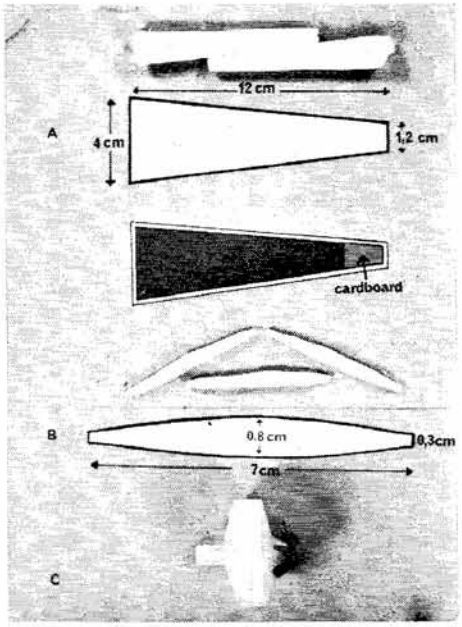


*Fig. 3*

*A. Hashish cigarette*
*B. Marihuana cigarette of the "joint"-type*
*C. Cambridge filter*

### Transfer of pure cannabinoids

Known amounts of a pure cannabinoid were dissolved in ethanol and injected into medium-sized tobacco cigarettes (John Silver®, Swedish Tobacco Co.). These cigarettes were smoked and the aerosol collected in Cambridge filters (Table 3). Pure (over 99.5 % by GLC) cannabidiol was obtained by repeated recrystallizations from light petroleum (40—60°) of cannabidiol-rich fractions from the column separation above. Cannabidiolic acid was a gift from Dr. R. Mechoulam. $\Delta^{1(6)}$-Tetrahydrocannabinol was synthesized according to Petrzilka [13] and carefully purified by column chromatography (silica gel/benzene) and distillation.

Cannabinol was prepared [13] by dehydrogenation of $\Delta^{1(6)}$-tetrahydrocannabinol and purified by column chromatography (silica gel/benzene) and distillation.

## Results and discussion

Basically, one may differentiate between two types of Cannabis. The *"hashish-type"* Cannabis, which consists of resin from the flowering tops of female plants, is the type most commonly encountered in Europe. The *"marihuana-type"* Cannabis, generally used in the United States, consists of dried flowering tops of the plants as well as considerable amounts of leaf material. Since the two types show large differences, one Cannabis preparation of each type was investigated. The results obtained from the marihuana preparation will be published in a later paper.

Whereas the chemistry of cannabinoids occurring in Cannabis now is reasonably wellknown [2—4], the chemistry of the cannabinoids in Cannabis smoke condensate has hardly been investigated at all, (cf. refs. [2—6, 10, 19]).

There may be considerable differences between the drug and the smoke due to a more ready sublimation of some cannabinoids compared to others and due to decarboxylations, cyclizations, pyrolytic, oxidative reactions etc. Cannabis is usually smoked and the pharmacologically active agent is thus the smoke and not the Cannabis preparation *per se*. The pharmacological actions may further be influenzed by synergistic or antagonistic effects due to non-cannabinoid or cannabinoid constituents present in different amounts in the Cannabis and in the smoke condensate. Such assumptions are supported by investigations which indicate that the replacement of Cannabis with the corresponding amount of pure $\Delta^1$-THC does not quantitatively or qualitatively induce the same effects (discussion in refs. [4, 9, 14]).

The knowledge [2—6] of which compounds in Cannabis that are psychotomimetically active was scanty until the recent report by Mechoulam *et al.* [15]. $\Delta^1$-Tetrahydrocannabinol is undoubtedly the predominant active compound [7, 15]. The $\Delta^{1(6)}$-isomer has apparently similar effects [2, 3] although it normally is present in small amounts [2]. Some other cannabinoids, e.g. cannabidiol and cannabinol, when tested singly have shown no hallucinogenic activity [2, 3, 15]. A recent investigation [22] has shown that minor pharmacological effects may possibly be attributed to compounds in Cannabis other than cannabinoids. In some Cannabis

preparations, a minor part of the pharmacological activity must be assigned to the propyl homologue of $\Delta^1$-tetrahydrocannabinol [22]. As a basis for further studies, e.g. for calculation of dose levels in humans and the possible use of more accurate administration forms, it was also necessary to determine the quantity of the cannabinoids in Cannabis that is transferred to and absorbed in the respiratory system of the smoker.

### Hashish — Cannabinoids

It was first necessary to determine qualitatively and quantitatively the cannabinoids in a large hashish sample to be used in the further studies. After conventional extraction [8, 10], the three major cannabinoids were identified and estimated directly by gas chromatography of the extract, whereas the minor constituents were identified and estimated after fractionation on a silica gel column (Table 1). The relative and total amounts of the three major constituents, with a $\Delta^1$-tetrahydrocannabinol content of 6.4 %, 9.0 % cannabidiol and 2.1 % cannabinol, are rather common for a Lebanese hashish sample [2]. Both the neutral compounds and the corresponding carboxylic acids (e.g. cannabidiol — cannabidiolic acid) are estimated together, since the acids readily decarboxylate at higher temperatures, e.g. by smoking [8, 10, 16]. Also small amounts of $\Delta^{1(6)}$-tetrahydrocannabinol, cannabichromene, cannabidivarine, cannabigerol and cannabipinol (cannabicyclol) were identified.

### Transfer of cannabinoids by smoking

Two groups of volunteers were used: 1) Experienced Cannabis smokers, who smoked the hashish cigarette as they would normally smoke a Cannabis cigarette, and 2) Tobacco cigarette smokers, who smoked the Cannabis cigarette as an ordinary tobacco cigarette. The four experienced Cannabis smokers had been regular users for at least one year. The reason for selecting these two groups is that the inhalation techniques are quite different. The Cannabis smokers smoked the full hashish cigarette (Fig. 3) in 15—22 puffs — each puff lasting 8—10 sec and with intervals of 20—30 sec. After each inhalation they held their breath for a few sec. The ordinary cigarette smokers consumed the cigarette in 44—54 puffs (in one case 74 puffs; Table 2, subject C.H.) with about 5 second inhalations and with 20—30 second intervals (no holding of breath).

A pronounced difference exists between the two groups also in the amount of air inhaled through the cigarette and which for the tested group of Cannabis smokers amounted to 50—175 ml/puff, in contrast to only some 35 ml/puff for the cigarette smokers.

The amount of cannabinoids in a hashish cigarette which is transferred by the main stream smoke to the filter trap placed between the cigarette and the smoker, is shown in Table 2. The results indicate that with uniform Cannabis cigarettes, there is independent of inhalation technique, only a limited variation in the amount of cannabinoids transferred from the cigarette to the respiratory system. However, such parameters as the

Table 2

*Amount of cannabinoids in smoke condensate obtained by smoking 1.00 g hashish (cigarettes contained 1.00 g hashish and 1.8 g pipe tobacco).*

| | Method of collecting cannabinoids: | | | | | |
|---|---|---|---|---|---|---|
| | Cottrell filter | | | Cambridge filter | | |
| | CBD[a] mg | THC mg | CBN mg | CBD mg | THC mg | CBN mg |
| Hashish cigarettes | | | | | | |
| *Smoked as Cannabis cigarettes*[b] | | | | | | |
| Subject B. T. | 13 | 8 | 3 | 18 | 11 | 4 |
| B. S. | | | | 14 | 9 | 3 |
| I. Q. | 15 | 9 | 4 | 16 | 10 | 4 |
| I. R. | | | | 15 | 9 | 3 |
| *Smoked as tobacco cigarettes*[c] | | | | | | |
| Subject M. I. | 15 | 9 | 3 | 17 | 11 | 4 |
| M. H. | | | | 17 | 10 | 4 |
| M. H. | | | | 13 | 8 | 3 |
| R. R. | | | | 14 | 9 | 3 |
| P. A. | | | | 16 | 10 | 4 |
| C. H. | | | | 13 | 8 | 3 |
| Cannabis pipe | | | | | | |
| *Smoked as Cannabis*[d] | | | | | | |
| Subject I. Q. | 44 | 31 | 11 | 42 | 29 | 8 |
| Cannabinoids in mg per 1.00 g of original hashish | | | | CBD 90 | THC 64 | CBN 21 |

[a] For abbreviations, see Table 1. Figures approximated to nearest mg.

[b] Smoked by experienced Cannabis smoker with the ordinary technique of a Cannabis smoker, viz. deep inhalations followed by holding the breath for a few seconds.

[c] Smoked in the normal fashion by a cigarette-smoker.

[d] Smoked by an experienced Cannabis smoker. In the first experiment (Cottrell) 500 mg of Cannabis (no tobacco) was smoked in a wooden pipe with a 40 cm long wooden stem. The second experiment (Cambridge) was carried out with an ordinary size metal pipe and 625 mg Cannabis. For comparison, the yields in Table 2 have been calculated per 1000 mg of Cannabis smoked.

length of the time interval between puffs, relative humidity and structure of cigarette will influence the yields. The results obtained with the two filters, based on different principles, were compatible (Table 2) and hence, the more convenient and safer Cambridge filter was preferred in later experiments.

Our results show (Table 2) that using a limited number of volunteers under as genuine conditions as possible, 14—20 % of the cannabinoids

(based on cannabidiol) are transferred by the main stream smoke from the hashish cigarette. For a pipe, the percentage of transfer is as high as about 45 %. These results are in contrast to some recent data by Claussen and Korte [10] who, using a smoking machine, state that 98 % of the cannabinoids in a cigarette are lost and only 2 % are transferred. Another value given in the literature states a transfer of 60 % of the cannabinoids during smoking of Cannabis under unspecified conditions [19].

**Absorption of cannabinoids**

In view of the fact that Cannabis smokers use a typical inhalation technique, it was perhaps somewhat surprising that there was no significant quantitative difference (Table 2) between the amount of cannabinoids trapped in the filter used by a Cannabis cigarette smoker *versus* that used by a tobacco cigarette smoker. Although there thus seems to be no significant difference in the amount of cannabinoids *transferred* to the lungs using the "Cannabis smokers"-technique, there is undoubtedly an increase in the amount *retained* and presumably subsequently absorbed in the lungs. It has been shown that by holding the breath for a few seconds the percentage of a drug aerosol retained in the lungs may be increased from 20 to 80 % [cf. ref. 12]. For a discussion on numerous aspects of drug administration by means of cigarettes, we refer to Holmstedt and Wallén [12].

Four experiments with hashish cigarette smokers indicate that (based on the transfer values for each subject in Table 2) less than 20 % of the cannabinoids entering the respiratory system are exhaled by a Cannabis smoker using deep inhalations. More precise determinations were not possible using hashish cigarettes due to considerable background interference from the admixed tobacco in the gas chromatographic determination. A single experiment with pipe (only hashish) smoking, showed that (based on the value of 42 mg CBD being transferred — Table 2; Cambridge filter) only 12 % was being exhaled and thus 88 % absorbed.

However, the interference from non-cannabinoid compounds was minimum when marihuana cigarettes were used. Some experiments were therefore carried out with marihuana cigarettes to determine the extent to which the cannabinoid aerosol is absorbed with the superficial smoking used by tobacco cigarette smokers compared to the deep inhalation technique practiced among Cannabis smokers. These results will be published later [20], but show that the amount of cannabinoids absorbed is considerably increased by the deep inhalation technique, thereby proving that the inhalation technique used by Cannabis smokers is indeed advantageous.

The four experienced marihuana smokers agreed that in order to obtain a "normal biological high" about one third to one half of the hashish cigarette would be required. According to Table 2, this would indicate that the amount of $\Delta^1$-tetrahydrocannabinol, absorbed by smoking, necessary to obtain the desired effects for this group of smokers would be in the range of 3—5 mg. However, they all had experienced a more "pronounced biological high" which would be roughly equivalent to some

Table 3

*Amounts of Cannabinoids in smoke condensate (Cambridge filter) obtained by smoking tobacco cigarettes impregnated with known amounts of pure cannabinoids.*

| Compound | Amount (mg) in | |
|---|---|---|
| | cigarette | smoke condensate |
| *Cannabidiol* | | |
| Subject I. Q. | 20.0 | 4.2[a] |
| B. S. | 20.0 | 3.8[a] |
| M. I. | 20.0 | 5.8[a] |
| *$\Delta^{1(6)}$-Tetrahydrocannabinol* | | |
| Subject M. J. | 22.0 | 3.5[a] |
| M. J. | 26.0 | 5.1[a] |
| I. Q. | 26.0 | 4.7[a] |
| *Cannabinol* | | |
| Subject S. I. | 23.0 | 4.3[a] |
| S. I. | 27.0 | 4.0[a] |
| H. Q. | 20.0 | 3.5[a] |
| *Cannabidiolic acid* | | |
| Subject H. Q. | 17.0 (CBDA) | 4.4 (CBD)[b] |
| H. Q. | 15.5 (CBDA) | 3.9 (CBD)[b] |

[a] Conversion to other known cannabinoids not detectable (less than 1 %) by GLC.
[b] Cannabidiolic acid (CBDA) decarboxylated to cannabidiol (CBD) during smoking. No conversion to other cannabinoids.

10 mg $\Delta^1$-tetrahydrocannabinol absorbed. Likewise, all could experience the effects of lower amounts, viz. what would be equivalent to a single mg of $\Delta^1$-tetrahydrocannabinol absorbed.

**Chemical changes during smoking**

As stated earlier, cannabinoid acids readily decarboxylate during smoking to the corresponding neutral phenols (see also Table 3). It has also previously been shown [10] that cannabidiolic acid is not cyclized to tetrahydrocannabinols during smoking (Table 3). Our experiments also show (Table 3) that pure cannabidiol is not converted to a detectable degree (less than 0.5 % of the cannabinoids recovered in condensate) to any tetrahydrocannabinol, a conversion which otherwise occurs readily during slightly acidic conditions [21]. Not is it converted to any other cannabinoid. The same stability is also shown by $\Delta^{1(6)}$-tetrahydrocannabinol which is not detectably converted to any other cannabinoids such as cannabinol or the $\Delta^1$-isomer (which, however, is less stable than the $\Delta^{1(6)}$-isomer). Korte [10] and Mechoulam [2] have recently shown the lack of conversion of $\Delta^1$-tetrahydrocannabinol to the $\Delta^{1(6)}$-isomer during smoking. The results in Table 2 also suggest there is little interconversion of the three main cannabinoids.

Fig. 4 shows gas chromatograms of A: original hashish sample, and B: the corresponding smoke condensate. It is evident that there are no pronounced differences between the cannabinoid fraction in the drug and in the smoke condensate. Although in past investigations the chemical difference between a Cannabis sample and its usual, pharmacologically active form — the smoke — has largely been ignored, it would appear [19] (Tables 2—3, Fig. 4) that except for decarboxylations, the major cannabinoids occurring in the smoke are not drastically affected chemically by the smoking process. However, this is still one important problem which has to be investigated.

The cannabinoids in hashish, particularly in hashish mixed with tobacco in cigarettes, are comparatively unstable and after 10 months' storage in a closed box at room temperature, the total cannabinoid content in the cigarettes had decreased by up to 20 %. After the same period, the original ratio of cannabidiol: $\Delta^1$-tetrahydrocannabinol: cannabinol of 1.0 : 0.71 : 0.23 had changed to 1.0 : 0.38—0.55 : 0.33—0.37 (slightly varying ratios for different cigarettes). The figures show a small decrease in cannabidiol but a preferential breakdown of $\Delta^1$-tetrahydrocannabinol with a simultaneous increase in the relative and total amounts of cannabinol. This is in agreement with some recent results obtained by Schou and Nielsen [23].

The percentage of pure cannabinoids recovered in the condensate shows (Table 3) somewhat greater variation and is slightly higher (14—29 %) than for hashish. This could be due to the fact that the pure cannabinoids injected into the cigarettes are very likely largely deposited on the surface of the tobacco particles.

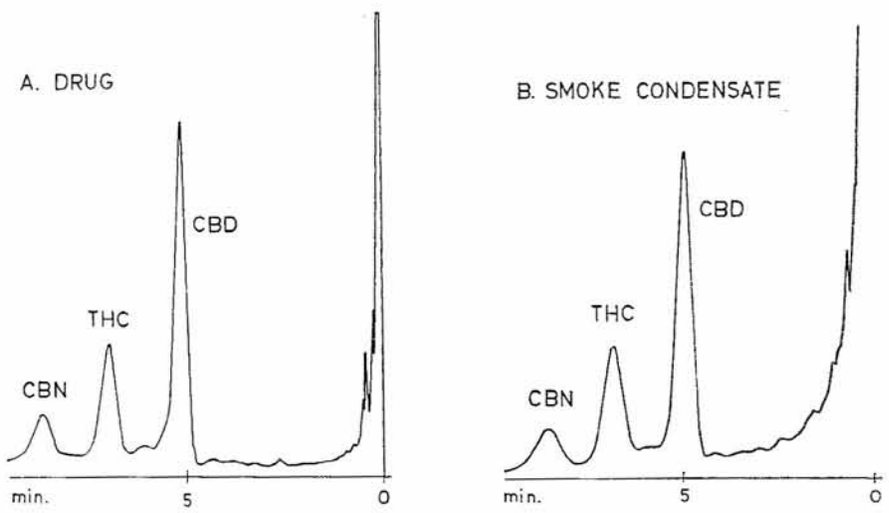


*Fig. 4. Gas chromatogram (3 % SE-30 on as Chrom Q) of: A. Original hashish sample; B. Smoke condensate from a hashish cigarette.*
CBD = cannabidiol THC = $\Delta^1$-tetrahydrocannabinol CBN = cannabinol

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