Pure & Appl. Chem., Vol. 58, No. 5, pp. 693–700, 1986.
Printed in Great Britain.

Natural products of cannabis and khat

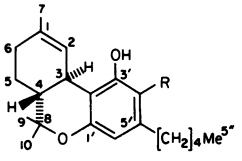
Leslie Crombie

Department of Chemistry, University of Nottingham, NG7 2RD, UK

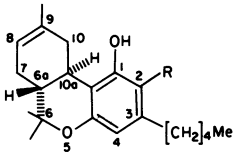
Abstract - The chemistry of two drugs of abuse is surveyed. Cannabis sativa contains two major series of natural products: first, the cannabinoid group which includes the psychotomimetic Δ^1-THC, and second, a biogenetically connected series involving bibenzyls, spiro-compounds, dihydrophenanthrenes and flavonoids. At an early biogenetic stage there are connections between these two series, and late stage 'chemical crossing' is described. The E.African drug Khat (Catha edulis) is used in Arab lands, but in contrast to Cannabis much less is known of its pharmacology. Khat contains the stimulants cathine and cathinone, but chemical interest centres particularly on a series of large alkaloids the plant contains. These are based on highly hydroxylated terpenic cores, derived from dihydroagarofuran, which are esterified with a variety of acids, some forming macrocyclic bridges.

INTRODUCTION: CANNABINOIDS

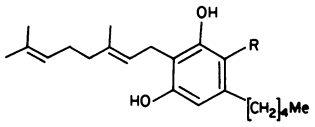
The best known group of natural products in Cannabis sativa is the so-called cannabinoid group which includes the psychotomimetic principle Δ^1-tetrahydro-cannabinol (Δ^1-THC, or Δ^9-THC in an alternative numbering), (1), $\Delta^{1,6}$-THC (2), cannabidiol (3) characteristic of fibre-type plants, and the decomposition product cannabinol (4) (Ref.1). Also included are cannabigerol (5), cannabichromen (6), cannabicyclol (7), and cannabicitran (8) (Ref.1). In the plant, these compounds appear to exist as carboxylic acids (R = CO_2H) and all of these acids (Ref.2), like their decarboxylated forms, have been synthesised.



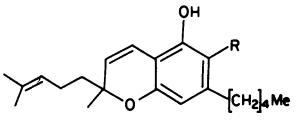
Δ^1-THC (1)
Δ^9-THC



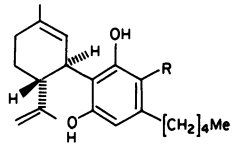
$\Delta^{1,6}$-THC (2)
Δ^8-THC



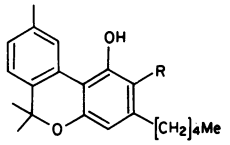
Cannabigerol (5)



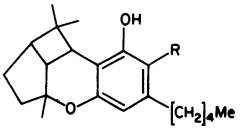
Cannabichromen (6)



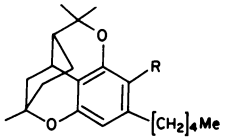
Cannabidiol (3)
R=H, CO_2H



Cannabinol (4)



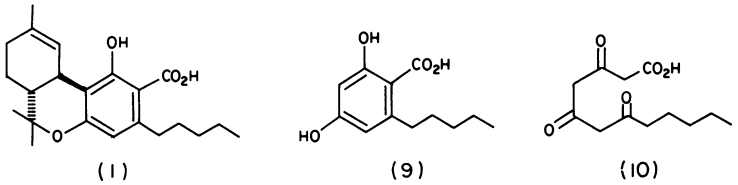
Cannabicyclol (7)



Cannabicitran (8)
R=H, R=CO_2H

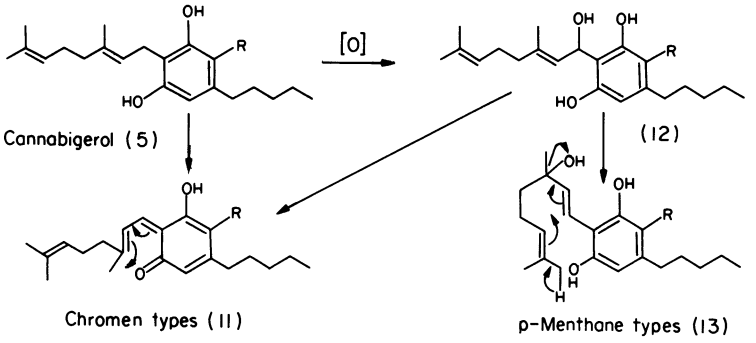
Compounds in the cannabinoid group are based on olivetolic acid (9) of apparent polyketide (10) derivation (Scheme 1), and the biosynthesis of the two sub-divisions of the cannabinoids are both considered to involve cannabigerol (5) as parent.

Scheme 1

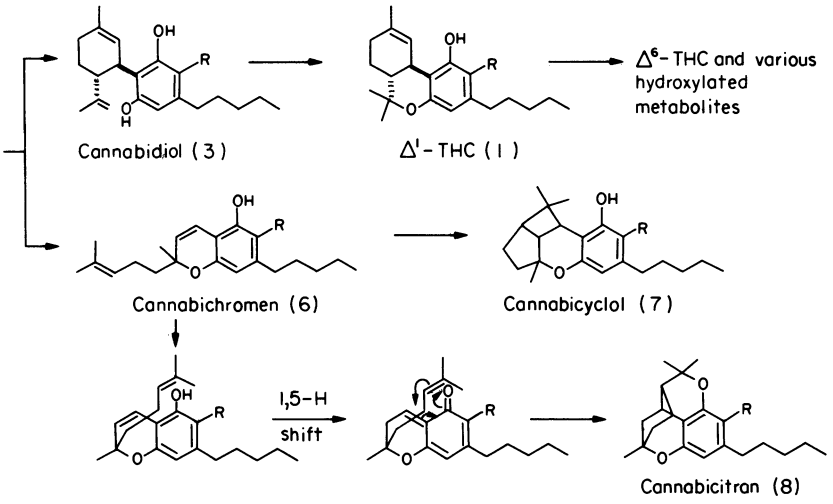


(1) (9) (10)

Scheme 2

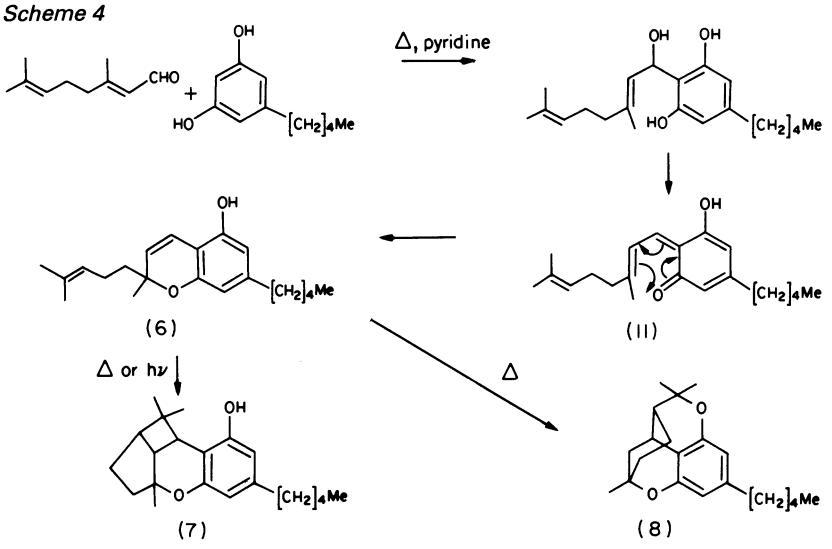


Scheme 3



Thus, formation of the dienone (11), either by direct dehydrogenation, or via (12) formed by oxidation and followed by dehydration, gives an intermediate which can electrocyclise to a chromen. Using the hydroxylated intermediate (12), allylic rearrangement and cyclisation gives the p-methane groups (13) (Scheme 2). Cannabidiol (Scheme 3) is the first-formed product leading to Δ^1-THC and then to other products sometimes found in Cannabis. The chromen (6) is considered to be the precursor of cannibicyclol and, after having undergone a 1,5-hydrogen shift, electrocyclisation gives cannabicitran from the chromen. We have shown how similar processes can be used (Scheme 4) in biomimetic synthesis of cannabichromen, generating the dienone (11) by condensation of olivetol with citral (or its acetal) (Ref.3). Photochemical $2\pi+2\pi$ cyclisation of the chromen gives cannabicyclol, whilst heating in pyridine gives cannabicitran (Scheme 4) (Ref.3).

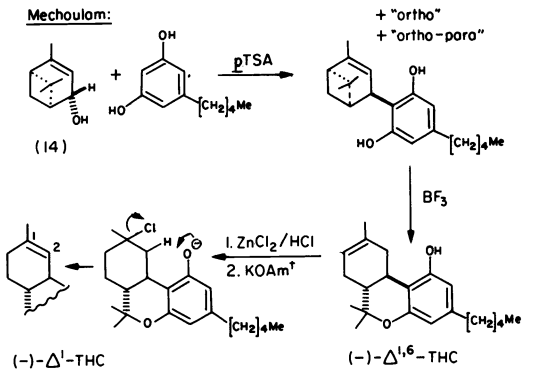
Scheme 4



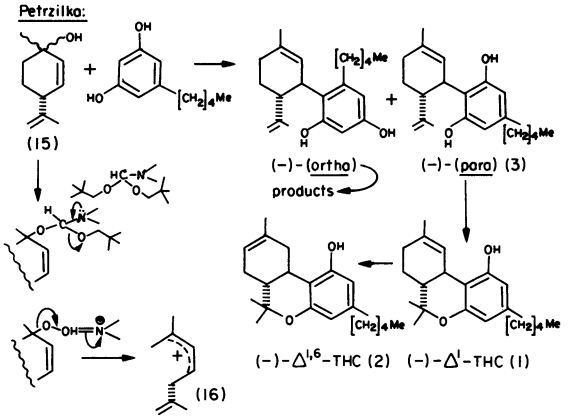
TERPENE EPOXIDE IN THC-SYNTHESIS

As only one isomer of Δ^1-THC is biologically active, its synthesis by methods employing natural optically active terpenes is highly attractive and Mechoulam's route (Ref.4) uses (-)-verbenol (14) as in Scheme 5. The product is $\Delta^{1,6}$-THC which has to be chemically converted into Δ^1-THC. Petrzilca's method (Ref.5), which uses (+)-trans- or (+)-cis-p-mentha-2,8-dien-1-ol (15) (Scheme 6) has proved to be the most flexible procedure giving predominantly cannabidiol, Δ^1-THC or $\Delta^{1,6}$-THC according to reaction conditions. The use of dimethylformamide dineopentylacetal to generate the necessary carbonium ion (16) is particularly interesting.

Scheme 5

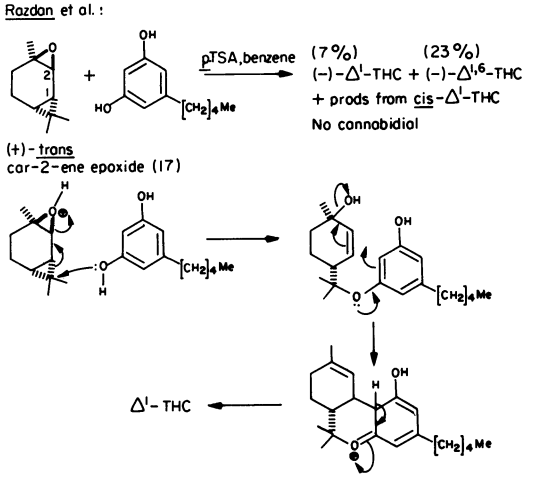


Scheme 6

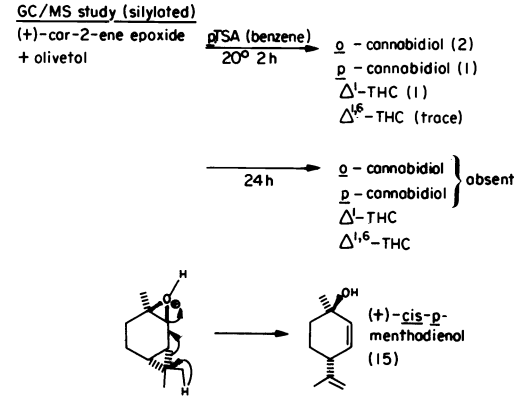


(+)-trans-Car-2-ene epoxide (17) has also been recommended as a terpenylating agent for olivetol and mainly on the grounds that no cannabidiol was detected in the reaction products, the special mechanism shown in Scheme 7 was proposed by Razdan (Ref.6). However, we have shown that o- and p-cannabidiols are in fact produced at lower temperatures and cyclisation of the latter to THC's occurs at higher temperatures (Scheme 8). In view of the known acid sensitivity of car-2-ene epoxide, leading to p-menthadienol, we regard the epoxide as essentially a surrogate for the latter, reaction proceeding through Petrzilka's carbonium ion (16).

Scheme 7

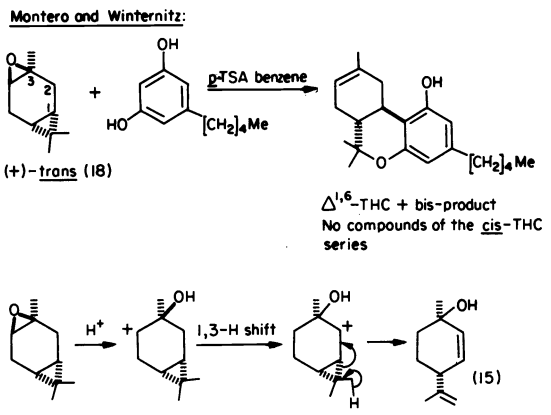


Scheme 8

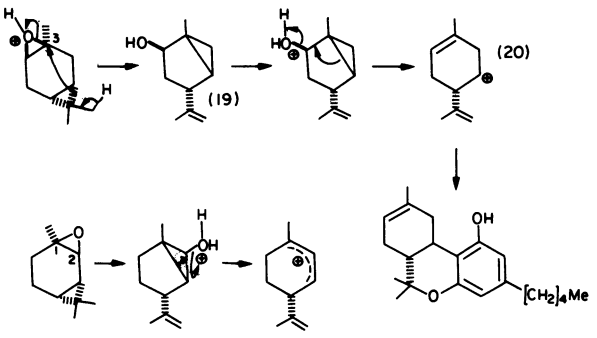


More interestingly Montero and Winternitz discovered that (+)-trans-car-3-ene epoxide (18) reacts with olivetol under acid conditions to give $\Delta^{1,6}$-THC (Ref.8). They propose (Scheme 9) that the epoxide is converted into p-menthadienol as shown but this requires epoxide opening to give a secondary in preference to a tertiary carbonium ion, followed by a 1,3-hydrogen shift. Our first thoughts were that an initial Kropp-type (Ref.9) isomerisation took place giving (19) which then led to (20) as the terpenylating species: a similar type of isomerisation might be written for car-2-ene epoxide (Scheme 10). However, when (19) was prepared independently and used in the reaction, no THC's were formed, only

Scheme 9

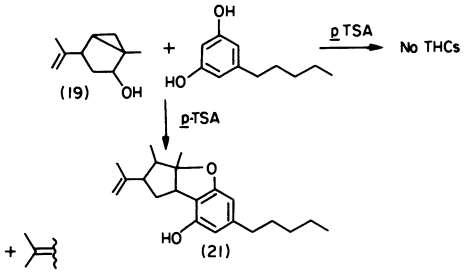


Scheme 10

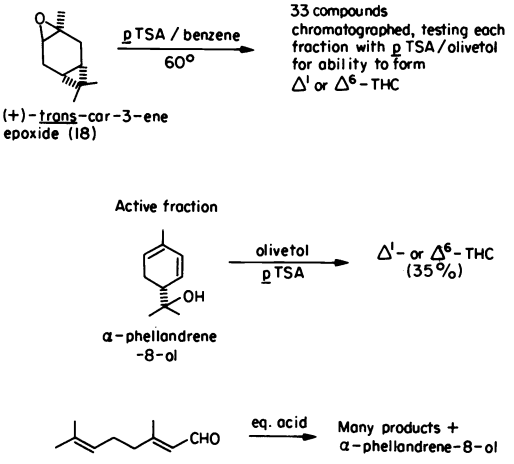


(21) and its isopropylidene isomer (Scheme 11), (Ref.7): clearly one has to look elsewhere for an explanation. (+)-trans-Car-3-ene epoxide (18) was therefore treated with acid and the products fractionated (Scheme 12). The effective product was identified as α-phellandrene-8-ol and this was verified by using a synthetic specimen made from citral (Ref.7). The mechanism for terpenylation using car-3-ene epoxide thus proceeds, as in the case of car-2-ene epoxide, via the Petrzilka carbonium ion generated as in Scheme 13. Phellandrene (22) itself is a very clean terpenylating agent under acid conditions, yielding dihydrocannabidiol.

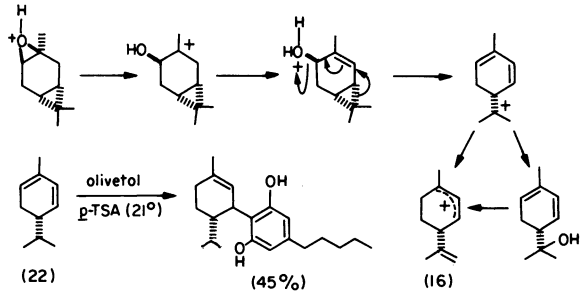
Scheme 11



Scheme 12



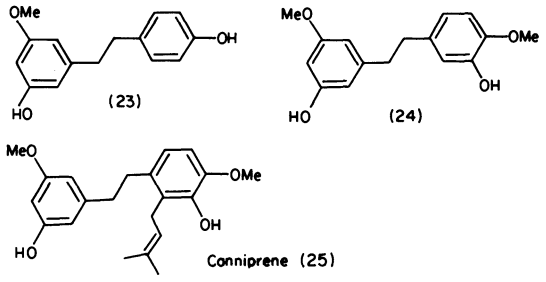
Scheme 13



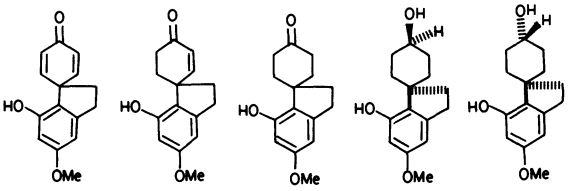
THE BIBENZYL SERIES OF *CANNABIS* NATURAL PRODUCTS

In the past few years a second group of biogenetically connected natural products of Cannabis has emerged. We have isolated three bibenzyls (23)-(25), the key spirodienone (26), the dihydrophenanthrenes (27) and (28) and the flavonoids (29) and (30) (Schemes 14-16, Ref.10): other reduction levels of the spirodienone (Scheme 15) have also been found. Schemes 17 and 18 show the way in which members of what may be termed the bibenzyl group are biogenetically linked together and we have synthesised most of the compounds involved, (Refs.11-13). The bibenzyls are partly polyketide in origin (Scheme 19), prenylation being a late stage process. Both the cannabinoid and bibenzyl series thus involve triketides (Scheme 20), the starter in the former series being hexanoic acid and in the latter cinnamic (or p-coumaric) acid, cyclisation being aldol in type. Cinnamic (or p-coumaric) acid is also the biogenetic precursor of the canniflavones, this time by Claisen cyclisation.

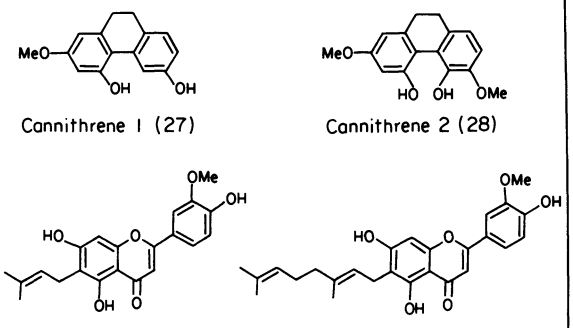
Scheme 14



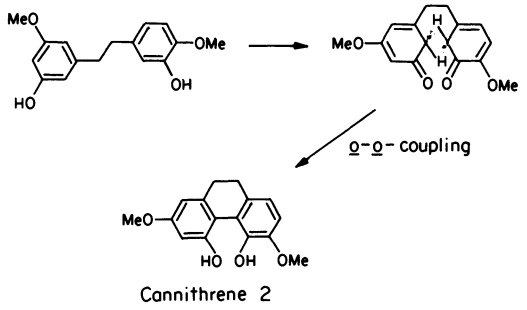
Scheme 15



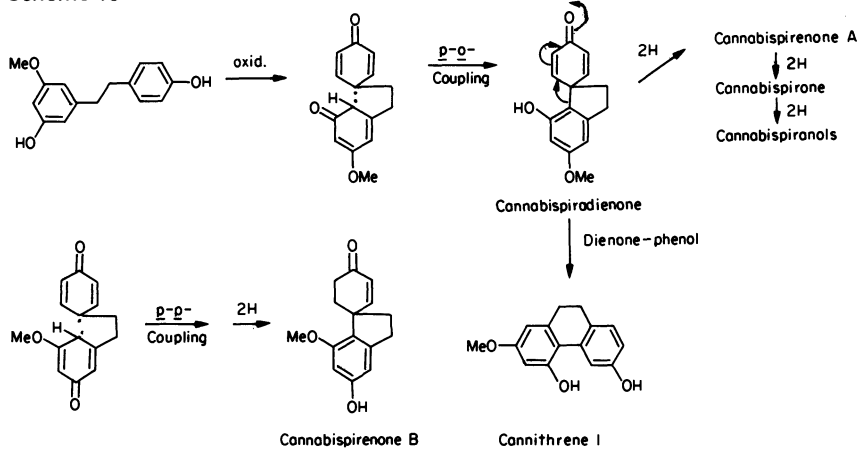
Scheme 16



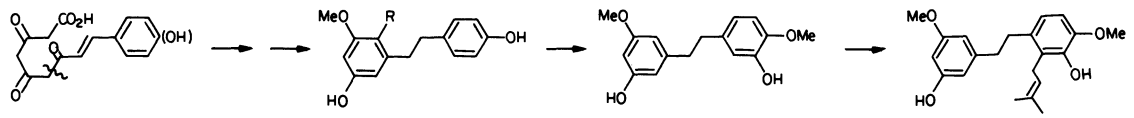
Scheme 17



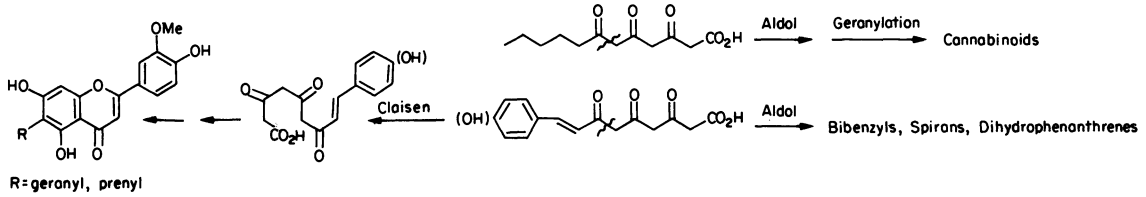
Scheme 18



Scheme 19



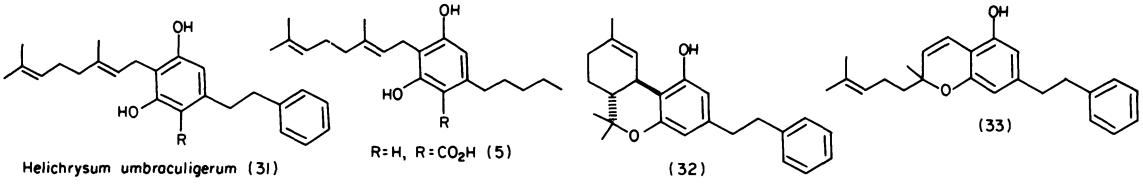
Scheme 20



The polyketide origin of olivetol (9) and one ring of the bibenzyls (23)-(25) leads one to expect that a geranylated version of bibenzyls (e.g. 31) analogous to cannabigerol (5) might be found in nature and both have indeed been found in a Helichrysum species (Scheme

21) (Ref.14). This 'crossed' molecule should, given plants having the necessary enzymes, be the biogenetic originator of a cannabinoid class of bibenzyls (cf. 1-8). The remaining members are not yet known in nature but we shall be surprised if they do not emerge and to ease the way to their recognition we have recently made the chemically crossed Δ^1-THC type (32) and the cannabichromen type (33) along with other members of the 'cannabinoid-bibenzyl' class (cannabidiol, $\Delta^{1,6}$-THC, cyclol and citran types) (Ref.15). The pharmacological activity of (32) will also be of interest.

Scheme 21

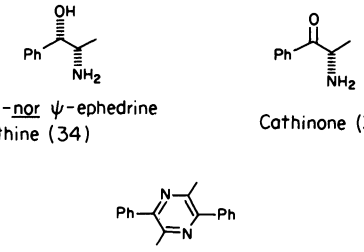


Helichrysum umbraculigerum (31)

THE KHAT ALKALOIDS

A different area of interest in psychotomimetic plants has been our work on Khat. Khat is a drug used in countries around the horn of Africa, particularly Arab lands, and is administered by chewing the fresh young branches of the tree Catha edulis. Some of its effects are doubtless due to the stimulating action of cathine (34) and cathinone (35): the anhydrodimer (36) is also found in the plant (Ref.16). We have been particularly interested in the large alkaloids this plant contains (Table 1). These have a core based on the highly hydroxylated dihydroagarofuran euonyminol (37) or the pentahydroxy relative (38) (Scheme 23) (Refs.16-19)

Scheme 22

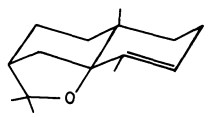


(+)-nor ψ-ephedrine Cathine (34)

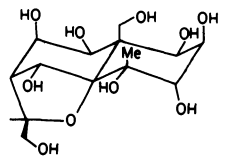
Cathinone (35)

3,6-Dimethyl-2,5-diphenyl-pyrazine (36)

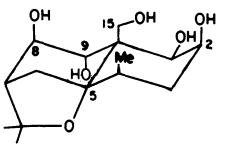
Scheme 23



α-Agarofuran



Euonyminol (37)

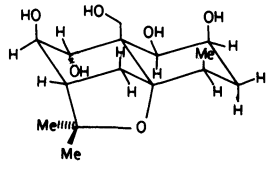


1,2,8,9,15-Pentahydroxydihydro-agarofuran (38)

Table 1 Khat Alkaloids

Catha edulis (Khat, Chat, Quat)			
Ethiopian			
M 700	Cathedulin	E-2	$C_{38}H_{40}N_2O_{11}$
1104	Cathedulin	E-3	$C_{54}H_{60}N_2O_{23}$
1062	Cathedulin	E-4	$C_{52}H_{58}N_2O_{22}$
1168	Cathedulin	E-5	$C_{59}H_{64}N_2O_{23}$
1126	Cathedulin	E-6	$C_{57}H_{62}N_2O_{22}$
595	Cathedulin	E-8	$C_{32}H_{37}NO_{10}$
Kenyan			
M 891	Cathedulin	K-1	$C_{42}H_{53}NO_{20}$
849	Cathedulin	K-2	$C_{40}H_{51}NO_{19}$
807	Cathedulin	K-6	$C_{38}H_{49}NO_{18}$
1106	Cathedulin	K-12	$C_{54}H_{62}N_2O_{23}$
765	Cathedulin	K-15	$C_{36}H_{47}NO_{17}$
(+	Cathedulin	E-3)	
1166	Cathedulin	K-17	$C_{59}H_{62}N_2O_{23}$
1102	Cathedulin	K-19	$C_{54}H_{58}N_2O_{23}$
1166	Cathedulin	K-20	$C_{59}H_{62}N_2O_{23}$

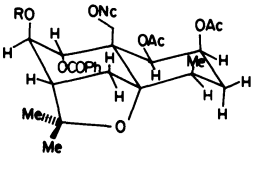
Scheme 24



Cathedulin E-2: CO· x2, PhCO· ·OAc x2

Cathedulin E-8: CO·, PhCO· ·OAc x2

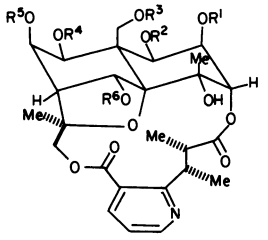
Scheme 25



Cathedulin E-2 R=Nc
E-8 R=H

The simpler alkaloids cathedulin E-2 and E-8 are based on 1,2,8,9,15-pentahydroxydihydroagarofuran and the major problem is placing the esterifying acids (Scheme 24). This has been done by nmr methods including nOe effects, combined with graded partial hydrolysis and other chemistry, leading to the structures in Scheme 25 (Ref.17). Cathedulins K-2, K-1, K-6 and K-15 are of increased complexity having an evoninate ester bridge and also hydroxy- (or acetoxy)isobutyric acid as an esterifying residue: they can be interconverted by acetylation as shown (Schme 26) (Ref.18).

Scheme 26



Cathedulin K-2 $R^1=H$; $R^3=Ac$; $R^2, R^5, R^6 = 3Ac$; $R^4 = AcO{\cdot}CMe_2CO{\cdot}$

K-1 $R^1=Ac$; $R^3=Ac$; $R^2, R^5, R^6 = 3Ac$; $R^4 = AcO{\cdot}CMe_2CO{\cdot}$

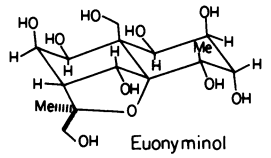
K-6 $R^1=H$; $R^3=H$; $R^2, R^5, R^6 = 3Ac$; $R^4 = AcO{\cdot}CMe_2CO{\cdot}$

K-15 $R^1=H$; $R^3=H$; $R^2, R^5, R^6 = 3Ac$; $R^4 = HOCMe_2CO{\cdot}$

Acetylation

The large alkaloids cathedulin E-3 and K-12 are both based on euonyminol and Scheme 27 shows a workshop of acids that have to be fitted into position. A combination of spectral and chemical means (up to the present X-ray crystallography has not been successful on these large structures) has led to the complete formulations shown in Scheme 28 (Ref.19). Cathedulins E-4, E-5 and E-6 belong to the same class (Scheme 29), having an evoninate bridge and either a cathate bridge or its seco-residue (Ref.19).

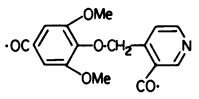
Scheme 27



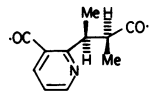
Euonyminol

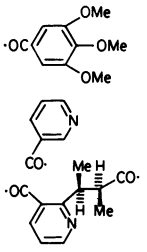
Cathedulin E-3 (M 1104) OAc x 3 $Me_2CCO{\cdot}$ OAc

Cathedulin K-12 (M 1106) OAc x 3 $Me_2CCO{\cdot}$ OAc



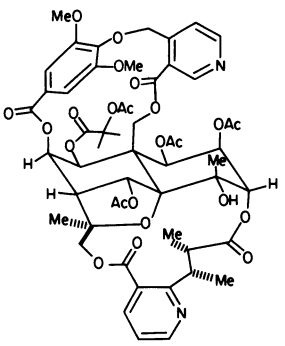
Cathic acid



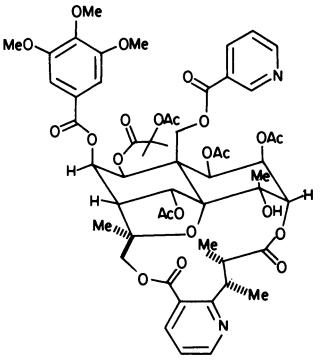


Evoninic acid

Scheme 28

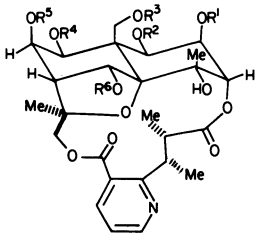


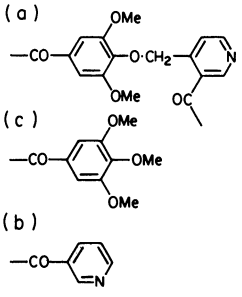
Cathedulin E-3



Cathedulin K-12

Scheme 29





Cathedulin

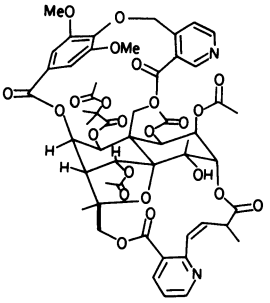
E-4 $R^1=Ac$; $R^6=H$; $R^2=Ac$; $R^4=AcO{\cdot}CMe_2CO{\cdot}$; $R^5, R^3 = (a)$

E-5 $R^1=R^6=Ac$; $R^2=PhCO$; $R^4=AcO{\cdot}CMe_2CO{\cdot}$; $R^3=(b)$; $R^5=(c)$

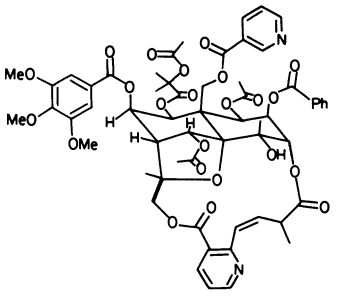
E-6 $R^1=Ac$, $R^6=H$; $R^2=PhCO$; $R^4=AcO{\cdot}CMe_2CO{\cdot}$; $R^3=(b)$; $R^5=(c)$

Very recently (Ref.20) we have isolated two further alkaloids from Kenyan khat and these, whilst being generally similar to the known types, have a new cis-olefinic decarboxylic acid replacing the customary evoninate bridge (Scheme 30). Little is known of the pharmacology of the khat alkaloids at the present time.

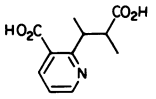
Scheme 30

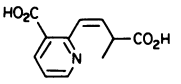


Cathedulin K-19



Cathedulin K-17





Acknowledgements

Thanks are due to Dr. W. Mary L. Crombie for her important contributions in both the cannabis and khat fields. It is also a pleasure to acknowledge the many contributions of my colleague Dr. D.A. Whiting to the khat area, and our fruitful collaboration with Dr. K. Szendrei of the U.N. Narcotics Laboratory. Finally, the efforts of my co-workers who are mentioned in the references is gratefully appreciated.

REFERENCES

1. For a review see L. Crombie and W.M.L. Crombie in 'Cannabis in Health' Ed. J.D.P. Graham; Pub. Academic Press (1976).
2. L. Crombie, W. Mary L. Crombie, R. Forbes and A. Whitaker, J.Chem.Research, (S), 114-115 (M), 1301-1345 (1977).
3. L. Crombie and R. Ponsford, J.Chem.Soc.(C), 796 (1971).
4. R. Mechoulam, P. Braun and Y. Gaoni, J.Am.Chem.Soc., 94, 6159 (1972).
5. T. Petrzilka, W. Haefliger and C. Sikemeir, Helv.Chim.Acta, 52, 1102 (1969).
6. R.K. Razdan and G.R. Handrick, J.Am.Chem.Soc., 92, 6061 (1970).
7. L. Crombie, W. Mary L. Crombie, C.J. Palmer and S.V. Jamieson, Tetrahedron Lett., 24, 3129 (1983).
8. J.-L. Montero and F. Winternitz, C.R. hebd. Seances Acad.Sci.(C), 197 (1975). J.-L. Montero, Ph.D. Thesis, Univ. of Langedoc, Montpellier, France [Chem.Abstr. 84, 44430 (1976)].
9. P.J. Kropp, J.Am.Chem.Soc., 88, 4926 (1966).
10. L. Crombie and W. Mary L. Crombie, J.Chem.Soc., Perkin Trans.1, 1455 (1982).
11. L. Crombie and S.V. Jamieson, J.Chem.Soc., Perkin Trans.1, 1467 (1982).
12. L. Crombie, P. Tuchinda and M.J. Powell, J.Chem.Soc., Perkin Trans.1, 1477 (1982).
13. L. Crombie, W. Mary L. Crombie, S.V. Jamieson, P. Tuchinda and A.J. Whitaker, J.Chem. Soc., Perkin Trans.1, 1485 (1982).
14. F. Bohlmann and E. Hoffmann, Phytochemistry, 18, 1371 (1979).
15. L. Crombie, W. Mary L. Crombie and D.F. Firth, unpublished work.
16. R.L. Baxter, L. Crombie, D.J. Simmonds, D.A. Whiting, O.J. Braenden and K. Szendrei, J.Chem.Soc., Perkin Trans.1, 2965 (1979).
17. R.L. Baxter, L. Crombie, D.J. Simmonds and D.A. Whiting, J.Chem.Soc., Perkin Trans.1, 2972 (1979).
18. L. Crombie, W. Mary L. Crombie, D.A. Whiting and K. Szendrei, J.Chem.Soc., Perkin Trans., 1, 2976 (1979).
19. R.L. Baxter, W. Mary L. Crombie, L. Crombie, D.J. Simmonds, D.A. Whiting and K. Szendrei J.Chem.Soc., Perkin Trans.1, 2982 (1979).
20. L. Crombie, D. Toplis, D.A. Whiting, Z. Rozsá, J. Hohmann and K. Szendrei, J.Chem.Soc., Perkin Trans.1, in the press.