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SPIRO-INDANS FROM *CANNABIS SATIVA*

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Key Word Index—*Cannabis sativa*; Cannabacea; cannabispiran; dehydrocannabispiran; spiro-indans; deketonization; demethylation; NMR.

Abstract—Three new spiro-indans were isolated from hashish (*Cannabis sativa*). Their chemical structures were established by spectroscopic means, and by chemical correlation with cannabispiran and iso-cannabispiran. They were found to be 7-hydroxy-5-methoxyindan-1-spiro-cyclohexane, its isomer 5-hydroxy-7-methoxyindan-1-spirocyclohexane and 5,7-dihydroxyindan-1-spiro-cyclohexane.

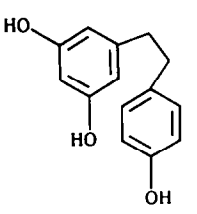
INTRODUCTION

In a previous report [1], an ethanolic extract of a locally confiscated sample of hashish (*Cannabis sativa*) yielded 3,5,4′-trihydroxybibenzyl (**1**) whose structure was confirmed by synthesis. GC-MS analysis of the mother liquor a from **1**, revealed the presence of the three spiro-indans **2**,**3** and **4**‡. This paper describes the isolation, structure elucidation and correlation of these compounds with cannabispiran (cannabispirone, **5**) and iso-cannabispiran (**6**).

RESULTS AND DISCUSSION

An ethanolic extract of a locally siezed sample of hashish followed by solvent partitioning yielded the previously reported [1] bibenzyl **1** upon chromatography then crystallization from ether–chloroform. GC-MS analysis of the mother liquor revealed the presence of three compounds **3**, **2** and **4**, with R_ts of 5.89, 6.16 and 6.58 min, and parent ion peaks at m/z 232, 232 and 218, respectively. While both **2** and **3** showed a base peak at m/z 189, that of **4** appeared at m/z 175. This fragmentation pattern was in agreement with a spiro-cyclohexane-1,1′-indan structure as the mass spectrum of iso-cannabispiran itself (**6**) showed [2] the same base peak at m/z 189, resulting from the formation of the highly stable cation of general structure **7** [2, 3]; cannabispiran (**5**), likewise, gives a similar although less prominent peak [2], due to the same fragment.

Compounds **2**, **3** and **4** were separated by flash chromatography [4] on silica gel using ether–hexane (2:3). Compound **2**, $C_{15}H_{20}O_2$, mp 112–113°, showed IR absorption bands and ^{1}H NMR and ^{13}C NMR signals



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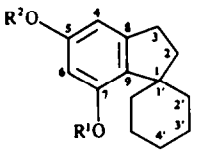

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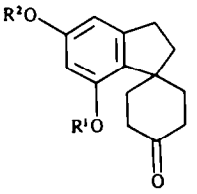
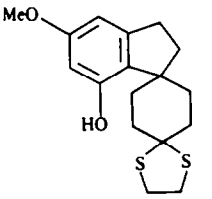
3 R^1 = Me, R^2 = H
4 R^1 = R^2 = H



5 R^1 = H, R^2 = Me
6 R^1 = Me, R^2 = H
9 R^1 = R^2 = Me



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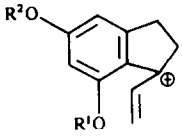

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†Part of this work was completed while on an AMIDEAST fellowship at the School of Pharmacy, University of Mississippi, University, MS 38677, U.S.A. Present address, Faculty of Pharmacy, Cairo University, Egypt.

‡Dr. Hala N. Elsohly of the Research Institute of Pharmaceutical Sciences, University of Mississippi has informed us that she detected the same three compounds in a Nepalese variant of marijuana.

similar to those reported [2] for cannabispiran (**5**) except for the absence of a carbonyl group. Its structure was unambiguously confirmed by correlation with cannabispirn (**5**) whose structure was previously established by X-ray crystallographic analysis [5]. This was accomplished by converting **5** to the thioketal **8** followed by treatment witney Ni. The product was indistinguishable from **2**.

Compound **3**, $C_{15}H_{20}O_2$, mp 175–176°, was clearly a positional isomer of **2** as based on its spectral data (see Experimental). This was confirmed as shown in Scheme 1 by deketonization* [6] of **9** to **10** by first forming its *p*-toluenesulphonylhydrazone **11** then reducing it with sodium borohydride. Demethylation of **10** using 2-methyl-2-propanethiol as the lithium salt [7] provided two monomethyl ethers: one of them was identical to **2** while the other was the same as **3**. Both monomethyl ethers could be methylated back to **10**, thus confirming the identity of **3**.

Complete characterization of **4**, which was obtained as an unstable oil, proved to be a formidable task due to its paucity and instability. Demethylation of **10** with a variety of reagents was attempted but the use of MeMgI [8] proceeded cleanly, although incompletely, to yield both **2** and **3** and a low yield of a more polar compound whose mass and IR spectra were identical to those of **4** isolated from hashish.

EXPERIMENTAL

Mps: uncorr; IR: 7–9% soln in $CHCl_3$ unless otherwise specified; ^{1}H NMR: 90 MHz, $CDCl_3$, TMS int. standard; ^{13}C NMR: 15.03 MHz, $CDCl_3$, TMS int. standard; GC using capillary column containing DB-1 (cross-linked and bonded 100% dimethylpolysiloxane) using mass selective detector (MSD) and operating at 150° with temp. prog. at 10°/min, using N_2 as carrier at 3.0 ml/min. For other information see ref. [1]. TLC was performed on silica gel using Et_2O–hexane (2:3) as solvent and visualization with *p*-anisaldehyde spray reagent [9].

Isolation of spiro-indans. The mother liquor (54 mg) left from flash chromatography of 5.0 g of the MeOH fraction of hashish [1] was further flash chromatographed [4] on silica gel using *n*-hexane–Et_2O (3:2) to give the following three compounds in order of their elution:

Spiro-indan **2**. R_f 0.65 (TLC), R_t 6.16 min (GC), crystallized from Et_2O–hexane to give fine needles (12 mg), mp 112–113°; optically inactive; UV λ_{max}^{MeOH} (log ε): 210 (4.46), 222 (4.03) and 280 (3.35); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 and 3350 (OH) and 1578 and 1618 (C=C Ar); ^{1}H NMR ($CDCl_3$): δ6.30 (1H, *d*, *J* = 1.8 Hz, Ar–H), 6.07 (1H, *d*, *J* = 1.8 Hz, Ar–H), 5.0 (1H, *br s*, exch. OH), 3.71 (3H, *s*, OMe), 2.75 (2H, *t*, *J* = 7.0 Hz, H-3), 1.98 (2H, *t*, *J* = 7.0 Hz, H-2) and 1.60–2.0 (10 H, *m*, 5 × CH_2); ^{13}C NMR ($CDCl_3$): δ159.8 (*s*, C-5), 153.3 (*s*, C-7), 146.6 (*s*, C-8), 129.5 (*s*, C-9), 102.3 (*d*, C-4), 100.9 (*d*, C-6), 55.4 (*q*, OMe), 48.9 (*s*, C-1), 35.3 (*t*, C-2), 35.1 (*t*, double intensity, C-2'), 31.1 (*t* C-3) [2], 26.0 (*t*, C-4') and 23.6 (*t*, double intensity, C-3'); MS *m/z*:232 [M]$^+$ (20%), base peak *m/z* 189. (Found: C, 77.45; H, 8.60. $C_{15}H_{20}O_2$ (232) requires: C, 77.55; H, 8.68%.)

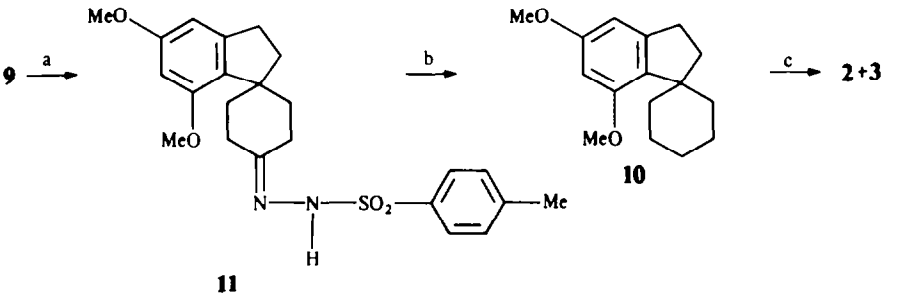
Spiro-indan **3**. R_f 0.55 (TLC), R_t 5.89 min (GC), crystallized from Et_2O–hexane to give prisms (3.5 mg), mp 175–176°, optically inactive; UV λ_{max}^{MeOH} (log ε): 210 (4.44), 222 (3.97), and 280 (3.37); IR $\nu_{max}^{CHCl_3}$ cm^{-1}:3582 and 3320 (OH) and 1605 (C=C Ar); ^{1}H NMR ($CDCl_3$): δ6.34 (2H, *s*, Ar–H), 4.76 (1H, *br s*, exch. OH), 3.83 (3H, *s*, OMe), 2.80 (2H, *t*, *J* = 7.2 Hz, H-3), 2.01 (2H, *t*, *J* = 7.2 Hz, H-2) and 1.60–2.30 (10H, *m*, 5 × CH_2); MS *m/z*: 232 [M]$^+$ (21%), base peak *m/z* 189. (Found: C, 77.32; H, 8.46. $C_{15}H_{20}O_2$ (232) requires: C, 77.55; H, 8.68%.)

Spiro-indan **4**. R_f 0.30 (TLC), R_t 6.58 min (GC), obtained as colourless oil that darkened quickly (2.0 mg), optically inactive; UV λ_{max}^{MeOH} (log ε): 210 (4.50), 222 (4.21) and 281 (3.37); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3583 and 3320 (OH) and 1605 (C=C Ar); MS *m/z*: 218 [M]$^+$ (25%), major fragments analogous [2] to those from cannabispiran (**5**) at *m/z* 147 (14%), 149 (13%) and 162 (64%). (Found: 218.2943 $C_{14}H_{18}O_2$ requires: 218.2950.)

Reduction of cannabispiran (**5**) *to* **2**. Cannabispiran (**5**, 55 mg) [10] was stirred at 0° for 20 min under N_2 with ethanedithiol (0.15 ml) and BF_3 etherate (0.15 ml). The oily product, R_f 0.55 (TLC), was purified by filtration on a bed of silica to give the thioketal **8** as a colourless oil (66 mg, 92%); MS *m/z*: 322 [M]$^+$ (9%). It was used in the next step without any further treatment.

The thioketal **8** (66 mg) obtained above was refluxed for 2 hr with 10 ml of a suspension of Raney Ni [11] in 95% EtOH. Usual work-up followed by crystallization from Et_2O–hexane provided 37 mg (78%) of colourless needles, that were indistinguishable from those of **2** (mp, mmp and spectral data).

Reducation of cannabispiran methyl ether (**9**) *to* **10**. Cannabispiran-methyl ether (**9**, 64 mg) was dissolved in THF (3 ml) along with 46 mg of *p*-toluenesulphonylhydrazine and one



(a) *p* - Toluenesulphonylhydrazine - HCl ; (b) $NaBH_4$ (c) 2 - Methyl - 2 - propanethiol - $LiAlH_4$–HMPA

Scheme 1. Synthetic methods used in structural elucidation of spiro-indans.

*Deketonization can be accomplished equally well as described in the Experimental for **5** by forming ethanedithioketal, mp 114–115°, then reducing it to **10** with Raney Ni.

drop of conc. HCl. Refluxing for 2 hr produced **11** as a white ppt that was removed by filtration, then washed with THF to give 75 mg (77%) of colourless crystals, mp 218–219°; MS *m/z*: 428 $[M]^+$ (4%). (Found: C, 64.66; H, 6.49; N, 6.43; S, 7.78. $C_{23}H_{28}N_2O_4S_4$(428) requires: C, 64.46; H, 6.59; N, 6.54; S, 7.48%.)

Compound **11** (43 mg) was dissolved in HOAc (1.5 ml) and stirred at room temp. with $NaBH_4$ (100 mg) added over 4 hr. Work-up and chromatography of the product on silica gel using CH_2Cl_2–hexane (1:1) provided a fraction, R_f 0.80 (TLC using CH_2Cl_2) that crystallized from Et_2O–hexane to give needles (17 mg, 68%), mp 92–93°; IR, ^1H NMR and ^{13}C NMR spectra were similar to those of **9** except for the absence of a CO signal; MS *m/z*: 246 $[M]^+$ (20%), base peak *m/z* 190. (Found: C, 78.23; H, 8.97. $C_{16}H_{22}O_2$ (246) requires: C, 78.01; H, 9.00%.)

Demethylation of **10** *with 2-methyl-2-propanethiol to the spiroindans* **2** *and* **3**. A suspension of LiH (500 mg) in HMPA (8 ml) and 2-methyl-2-propanethiol (1 ml) was stirred at 50° for 24 hr. A soln of **10** (50 mg) in HMPA (2 ml) was added and the mixture stirred for 2.5 hr. Work-up as before [10] yielded 20 mg (43%) of **2** and 21 mg (45%) of a product identical with **3** (mp, mmp, spectral data).

Methylation of **2** *and* **3** *back to* **10**. Compound **2** (15 mg) was dissolved in Me_2CO (5 ml) to which was added MeI (1 ml) and dry K_2CO_3 (150 mg) and the mixture refluxed for 24 hr. Upon work-up a product identical with **10** was obtained (12 mg, 75%). Compound **3** (15 mg) when treated similarly gave the same product (13 mg, 81%).

Demethylation of **10** *with methylmagnesium iodide to* **2**, **3** *and* **4**. Compound **10** (25 mg) was added to a soln of MeMgI in 3 ml of Et_2O prepared from MeI (71 mg) and Mg turnings (15 mg) with a crystal of I_2. Evapn of the mixture followed by heating at 160° for 1 hr and work-up provided a residue (25 mg) that contained (TLC) unreacted **10**, **2**, **3** and a new spot R_f 0.30 not observed with other demethylating agents (HBr, NaCN–DMSO, BBr_3, BCl_3 and BBr_3–MeSH complex). Flash chromatography as above provided **10** (5 mg), **2** (4 mg), **3** (4 mg) and 2 mg of a product with the same mass and IR spectra as **4**.

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REFERENCES

1. El-Feraly, F. S. (1984) *J. Nat. Prod.* **47**, 89.
2. Dongent, J. P. C. M. V., Heerma, W., Lousberg, R. J. J. Ch. and Kuppers, F. J. E. (1976) *Tetrahedron* **32**, 2939.
3. Elsohly, H. N. and Turner, C. E. (1982) *Experientia* **38**, 229.
4. Still, W. C., Kahn, M. and Mitra A. (1978) *J. Org. Chem.* **43**, 2923.
5. El-Feraly, F. S., Elsohyl, M. A., Boeren, E. G., Turner, C. E., Ottersen, T. and Aasen, A. (1977) *Tetrahedron* **33**, 2393.
6. Minura, T. and Nakai, T. (1981) *Chem. Letters* 1579.
7. Buchi, G., Spitzner, D., Pagliaunga, S. and Wogan, G. N. (1978) *Life Sci.* **13**, 1143.
8. Mechoulam, R. and Gaoni, Y. (1965) *J. Am. Chem. Soc.* **87**, 3273.
9. El-Feraly, F. S. and Hufford, C. D. (1982) *J. Org. Chem.* **47**, 1527.
10. El-Feraly, F. S. and Chan, Y.-M. (1981) *J. Nat. Prod.* **44**, 557.
11. Horning, E. C. (1955) *Organic Synthesis Collective*, Vol. III, p. 181. Wiley, New York.