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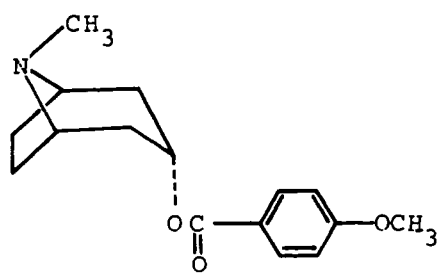
ISOLATION AND STRUCTURE OF A NEW ALKALOID DATUMETINE FROM THE LEAVES OF *DATURA METEL*

SALIMUZZAMAN SIDDIQUI,* NAHEED SULTANA, S. SALMAN AHMED, and S. IMTIAZ HAIDER

H.E.J. Research Institute of Chemistry, University of Karachi, Karachi-32, Pakistan

Datura metel L. (Solanaceae) bears an important place in the traditional systems of medicine for the treatment of a variety of human ailments. It finds particular reference in this context as a narcotic, anodyne, and antispasmodic drug (1). As far back as 1890, Dymock's *Pharmacographia Indica* noted the isolation of hyoscyamine, atropine, and hyoscine alkaloids from *Datura stramonium* (2). The presence of these alkaloids in *D. metel* was reported by E. Schmidt (3-6). Later norhyoscyamine was obtained by F.H. Carr and his co-workers (7) from this plant, but the isolation of these alkaloids was invariably achieved by extraction of dried, powdered plant materials.

As part of a general program, based on the utilization of fresh, undried plant materials for the isolation of their chemical constituents, studies on the leaves of *D. metel* have been undertaken. As a result of the present work, a new tropane alkaloid datumetine (**1**) has been isolated. This is the first tropane alkaloid isolated from *Datura* plants containing *p*-methoxybenzoic acid as an esterifying acid, although several methoxybenzoic acid derivatives of tropane alkaloids, such as, physochlaine (8), confoline (9), convoline (10), and tropan-3α-yl 3,4,5-trimethoxybenzoate (11) have been isolated from other plants.



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RESULTS AND DISCUSSION

The crude alkaloids obtained from the leaves of *D. metel* were divided into two fractions according to basic strength, followed by the isolation of individual alkaloids by preparative layer chromatography. As a result, the new alkaloid datumetine (**1**) was isolated as colorless prismatic plates on recrystallization from a mixture of $CHCl_3$-Et_2O (9:1). The uv spectrum of **1** was characteristic of a benzenoid system (12), and the ir spectrum showed an intense peak at 1700 cm^{-1} for the aryl ester, while a peak at 1580 cm^{-1} with additional aromatic peaks showed further conjugation with the benzene ring. The mass spectrum afforded the molecular ion peak at *m/z* 275 (32.8%). High resolution measurement corresponded to the molecular formula $C_{16}H_{21}NO_3$. The base peak at *m/z* 124 and other prominent peaks at *m/z* 82, 83, 94, 96, and 140 suggested that the alkaloid was an ester of tropine (13). In addition, the peaks at *m/z* 107, 135, and 151 indicated the presence of a methoxybenzoyl moiety which was supported by a three-proton singlet at δ 3.86 in the ^{1}H-nmr spectrum. The *N*-methyl appeared as a three-proton singlet at δ 2.3, while the one-proton triplet at δ 5.23 (J=5.2 Hz) was characteristic of the 3β-H in tropan-3α-ol (14,15). A two proton broad singlet resonating at δ 3.17 and a four-proton broad singlet at δ 2.08 were assigned to H-1, H-5 and H-2, H-4, respectively. H-6a and H-7a resonated as a two-proton broad doublet at δ 1.83 (J=15.0 Hz), while H-6b and H-7b were observed at δ 2.25 as double triplet (J=4.3, 8.5 and 15.0 Hz). These values are somewhat downfield as compared to

TABLE 1. ^{13}C-nmr Assignments of Tropan-3α-yl 4-methoxybenzoate

No. of Carbon	Chemical Shift[a] (δ)	Multiplicity (DEPT)
1,5	59.99	CH
2,4	36.66	CH_2
3	67.61	CH
6,7	25.88	CH_2
2′,6′	131.47	CH
3′,5′	113.79	CH
NCH_3	40.35	CH_3
OCOPh	163.40	−C−
OCH_3	55.48	CH_3

[a]All values are in ppm with respect to TMS.

those of the tropane nucleus in tropan-3α-yl 3,4,5-trimethoxybenzoate (11), due perhaps to the shielding effect of the methoxy groups in the latter. Integration of the aromatic signals showed the presence of only four protons as two sets of double doublets at δ 6.9 (2H, J=1.8 and 7.2 Hz, H-3′ and H-5′) and δ 7.9 (2H, J=1.8 and 7.2 Hz, H-2′ and H-6′). This revealed that the methoxy group is linked at C-4′, a conclusion supported by the ^{13}C-nmr spectrum in which C-2′ and C-6′ have the same chemical shift, i.e. δ 131.47 and similarly C-3′ and C-5′ resonated at δ 113.79. Further, the methoxy group resonateda at δ 55.48, while the carbonyl carbon appeared at δ 163.40. The peak at δ 40.35 has been assigned to the *N*-methyl function, whereas the signals of C-1′ and C-4′ were very weak. ^{13}C-nmr assignments (Table 1) of datumetine are based on comparison with tropan-3α-yl benzoate (16) and confirmed by gated spin echo and polarization transfer (DEPT) experiments. In the light of the above observations, structure **1** has been assigned to datumetine.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The melting points were recorded in glass capillary tubes and are uncorrected. The uv spectrum in MeOH was recorded on a Shimadzu 240 uv spectrometer and the ir spectrum (KBr disc) on a Jasco A-302. The ^{1}H-nmr spectrum was run at 300 MHz, ^{13}C-nmr at 75 MHz with TMS as internal standard on a Bruker AM-300. DEPT experiments were carried out with θ=45°, 90° and 135°. The mass spectrum was recorded on a Finnigan Mat-312 spectrometer fitted with a direct inlet system.

PLANT MATERIAL.—The leaves of *D. metel* collected in Karachi, Pakistan, in March 1985, were identified by the Department of Botany, University of Karachi, where a voucher specimen has been deposited.

ISOLATION.—The fresh, undried leaves of *D. metel* were cut into small pieces and repeatedly extracted with EtOH at room temperature. The combined extracts were concentrated under reduced pressure to a viscous liquid and kept overnight at about 20°. The gummy mass that settled was separated and triturated with 10% HOAc. The acid solution thereby obtained was gradually adjusted with dilute NH_4OH th pH 6.5 and finally to pH 8.5. The bases liberated at the two stages were separately extracted with EtOAc (fractions A and B, respectively).

The residue left on removal of solvent from fraction B was freed of residual fatty matter with Et_2O, n-hexane and then divided in $CHCl_3$ soluble and MeOH soluble components. The residue from the $CHCl_3$ soluble fraction was subjected to preparative layer chromatography (silica gel, $CHCl_3$-EtOH, 93:7) resulting in the isolation of the new base datumetine, (0.3% of total akaloids) which on recrystallization from $CHCl_3$-Et_2O (9:1) formed prismatic plates mp 84°; eims *m/z* (rel. int. %) 275.1496 M^+, calcd. for $C_{16}H_{21}NO_3$ (275.1521) (32.8), 151.0394 $(C_8H_7O_3)^+$ (6.7), 140.1073 $(C_8H_{14}NO)^+$ (33.7), 135.0442 $(C_8H_7O_2)^+$ (42.4), 124.1109 $(C_8H_{14}N)^+$ (100), 107.0496 $(C_7H_7O)^+$ (7.99), 96.0814 $(C_6H_{10}N)^+$ (15.7), 94.0653 $(C_6H_8N)^+$ (27.7), 83.0734 $(C_5H_9N)^+$ (45.7), and 82.0656 $(C_5H_8N)^+$ (46.5); ir ν max (KBr) (cm^{-1}) 1700 (aryl ester), 1600, 1580, 1500 (aromatic ring), 2840 (C-H stretching of -O-CH_3), 2820 (*N*-

CH_3); uv λ max (MeOH) (nm) 213, 251, 253, 257, and 258; ^{1}H nmr ($CDCl_3$) (δ) 3.8 (3H, s, $-OCH_3$), 2.2 (3H, s, $N-CH_3$), 5.2 (1H, t, J=5.16 Hz, H-3), 3.17 (2H, br, s, H-1, H-5), 2.08 (4H, br s, H-2, H-4), 1.83 (2H, d, J=15.0 Hz, H-6a, H-7a), 2.25 (2H, dt, J=4.29, 8.52 and 15.0 Hz, H-6b, H-7b), 6.9 (2H, dd, J=1.8, 7.2 Hz, H-2′, H-6′), 7.9 (2H, dd, J=1.8, 7.2 Hz, H-3′, H-5′).

The residue from fraction A and MeOH soluble part of fraction B yielded two bases, scopolamine (17,18) and atropine (12,19).

HYDROLYSIS OF DATUMETINE (**1**).—The alkaloid (**1**) (20 mg) in EtOH (2ml) was refluxed with $Ba(OH)_2$ (220 mg) in H_2O (5 ml) for 1 h. After cooling, it was acidified with 10 N H_2SO_4 and extracted with Et_2O. Work up of the Et_2O solution afforded white needles, mp 183-184°, lit. mp 184° (20), having identical ms and ir data to those of 4-methoxybenzoic acid. The acidic solution was basified with NH_4OH and extracted with $CHCl_3$. The oily residue, obtained on work up of the $CHCl_3$ phase was identified as tropine by comparison of its ir and ms data with those reported (13).

DATUMETINE HYDROCHLORIDE.—The hydrochloride of the base was prepared by passing HCl gas through a solution of the base in $CHCl_3$ (elongated rods from EtOH, mp 234°). It is insoluble in Et_2O, C_6H_6, and $CHCl_3$ but readily soluble in MeOH and H_2O.

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