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MINOR ALKALOIDS OF *TYLOPHORA HIRSUTA**

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Key Word Index—*Tylophora hirsuta*; Asclepiadaceae; minor phenanthroindolizidine alkaloids; 14-desoxy-13a-methyltylohirsutinidine; 5-hydroxy-*O*-methyltylophorinidine; tylohirsuticine; structural determination.

Abstract—Seven minor alkaloids have been isolated from *Tylophora hirsuta*. The known alkaloids 14-hydroxyisotylocrebrine, (+)-isotylocrebrine, (−)-tylophorine and 4-desmethylisotylocrebrine have also been isolated in addition to three new alkaloids, namely 14-desoxy-13a-methyltylohirsutinidine, 5-hydroxy-*O*-methyltylophorinidine and tylohirsuticine. Structural studies indicate that the first six alkaloids possess the dibenzo-[*f*,*h*]pyrrolo[1,2*b*]isoquinoline skeleton but differ in the number, nature and distribution of the oxygen-bearing substituents, in the presence or absence of a benzylic type hydroxyl and an angular methyl function. Tylohirsuticine possesses a related septicine-type skeleton containing four oxygen-bearing substituents on the cleaved phenanthrene nucleus and an angular methyl function.

INTRODUCTION

In a recent communication [2], we have reported the isolation and characterization of 13a-hydroxytylophorine as the principal phenanthroindolizidine alkaloid from wild populations of *Tylophora hirsuta*. This alkaloid was not isolated from the cultivated plant investigated by us earlier [3]. We further employed the mother liquor obtained after the isolation and separation of 13a-hydroxytylophorine from wild collections in search of new and potentially important members of phenanthroindolizidine series from this plant. Surprisingly, none of the five alkaloids, namely tylohirsutinine, 13a-methyltylohirsutine, 13a-methyltylohirsutinidine, tylohirsutinidine and 13a-hydroxyseptícine [3], found in the cultivated plant could be isolated.

In this communication, we report the isolation and characterization of seven minor alkaloids from *T. hirsuta*. Four alkaloids, *viz.* 14-hydroxyisotylocrebrine [4], (+)-isotylocrebrine [5], (−)-tylophorine [6] and 4-desmethylisotylocrebrine [4], have been reported earlier from other species of *Tylophora*. The other three alkaloids, 14-desoxy-13a-methyltylohirsutinidine, 5-hydroxy-*O*-methyltylophorinidine and tylohirsuticine, whose structural elucidations are described herein, are new.

RESULTS AND DISCUSSION

The total alkaloidal fraction isolated from the aerial parts of the plant collected from wild locations was fractionated into ethyl acetate soluble and insoluble fractions [2]. 13a-Hydroxytylophorine [2] was obtained from the ethyl acetate insoluble fraction as the principal alkaloid. The ethyl acetate soluble fraction (mother liquor of 13a-hydroxytylophorine) was chromatographed on basic alumina with solvents of increasing polarity. 14-Hydroxyisotylocrebrine (**1**) [4] and (+)-isotylocrebrine (**2**) [5] were obtained as a mixture from the benzene eluants. Alkaloid **1** (0.028% yield) was separated from **2** by fractional crystallization from acetone. The mother liquor upon further purification gave **2** (0.017% yield). (−)-Tylophorine (**3**) [6] and 4-desmethylisotylocrebrine (**4**) [4] were also obtained as a mixture from the benzene–ethyl acetate (9:1) eluants. (−)-Tylophorine (0.033% yield) was separated by fractional crystallization from chloroform–methanol. The mother liquor on further purification afforded **4** (0.020% yield). Further elution of the main column with the same solvent system afforded 14-desoxy-13a-methyltylohirsutinidine (**5**; 0.022% yield). 5-Hydroxy-*O*-methyltylophorinidine (**6**, 0.011% yield) and tylohirsuticine (**7**; 0.022% yield) were obtained from the benzene–ethyl acetate eluates of 3:1 and 1:1 ratios, respectively.

Compound **5** had a close resemblance to 13a-methyltylohirsutinidine [3] reported earlier by us from the cultivated plant but differed in the absence of a 14-hydroxyl group. There was an additional benzylic hydroxyl in compound **6** substituted on the *O*-methyltylophorinidine structure [5]. Base **7** had a cleaved phenanthroindolizidine nucleus as encountered earlier in the characterization of (+)-septicine [5] and 13a-hydroxysepticine [3], with an angular methyl group on the indolizidine moeity. One unmethylated benzylic hydroxyl and three methoxy groups in **7** also differed in the attachment from the four methoxy groups in (+)-septicine [5].

The physical and spectroscopic data for 14-hydroxyisotylocrebrine (**1**) [4], (+)-isotylocrebrine (**2**) [5], (−)-tylophorine (**3**) [6] and 4-desmethylisotylocrebrine (**4**) [4] agreed with those previously reported in the literature.

14-Desoxy-13a-methyltylohirsutinidine (**5**), mp 180–182°, $[M]^+$ *m/z* 393 ($C_{24}H_{27}NO_4$), $[\alpha]_D^{18}$ + 14.66 (*c* 0.2 in MeOH) closely resembled **4** in its UV and IR spectral characteristics indicating a 3,6,7-trimethoxy substituted phenanthrene skeleton. The extra oxygen is in the form of a hydroxyl group which is phenolic in nature as

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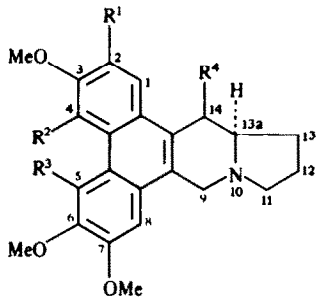
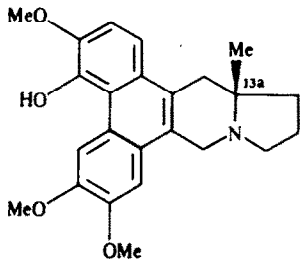


1 $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = OH$
2 $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
3 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
4 $R^1 = R^3 = R^4 = H$, $R^2 = OH$
6 $R^1 = R^2 = H$, $R^3 = R^4 = OH$



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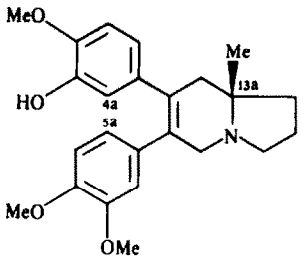

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indicated by a green colouration with ferric chloride. It showed UV maxima at 260, 284, 302 and 316 nm which shifted to 217, 257, 276 and 295 nm on addition of sodium hydroxide confirming the presence of a phenolic hydroxyl. The IR spectrum showed a strong bond at *ca* 3505 cm^{-1} typical of a hindered hydroxyl group. In its mass spectrum the base peak at *m/z* 378 arising due to the loss of 15 mu from the $[M]^+$ indicated the presence of an angular methyl group. The intense peaks at *m/z* 324 (69.5%) and *m/z* 310 (96%) were obtained from $[M-69]^+$ and $[M-83]^+$ ions, respectively, by retro-Diels–Alder reactions characteristic of phenanthroindolizidine alkaloids. The loss of methyl pyrrolidine $[M-83]^+$ along with pyrrolidine $[M-69]^+$ further confirmed the presence of an angular methyl function. Another prominent peak at *m/z* 296 (96%) arising from the loss of CO from *m/z* 324 was indicative of the presence of a benzylic hydroxyl. Overall, the fragmentation pattern of alkaloid **5** was in complete agreement with that of 13a-methyltylohirsutinidine [3] in which additional fragments due to the C-14 hydroxyl appeared. The ^1H NMR spectrum of **5** showed the presence of three methoxy groups at δ4.04, 4.00 and 3.78, four aromatic protons at δ7.56 (*d*, $J = 9$ Hz), 7.32 (*d*, $J = 9$ Hz), 7.26 (*s*) and 6.86 (*s*) assigned to C-1, C-2, C-5 and C-8, respectively, one D_2O-exchangeable proton at δ7.16 (phenolic OH) and a methyl singlet at δ1.36 indicative of an angular methyl function. In our earlier structural elucidations of 13a-methyltylohirsutine [3] and 13a-methyltylohirsutinidine [3], the angular methyl functions were encountered for the first time on a phenanthroindolizidine nucleus. However, we observed the unusual deshielding of these angular methyl functions in ^1H NMR. In a later communication Pettit *et al.* [7] reported the assignment of angular methyl groups on phenanthroindolizidine alkaloids named as hypoestestatin 1 and hypoestestatin 2 isolated from *Hypoëstes verticillaris* with values close to the similar functions in **5** and **7**.

Acetylation of **5** gave a monoacetylated product. A monomethyl ether was formed on treatment of **5** with diazomethane which could not be further acetylated proving the presence of one phenolic hydroxyl. The site of demethylation in **5** was decided by comparison of the ^1H NMR spectra of **5**, its monoacetylated product and its monomethyl ether. There was a large deshielding (by δ1.32) of the signal due to the proton at C-5 in the monomethyl ether. The monoacetylated product showed no such effect thus excluding the possibility of a phenolic hydroxyl at C-6. This effect had already been established by us in similar structural elucidations in isotylocrebrine type alkaloids [3]. Compound **5** also responded to the Gibb's test. Finally, the monomethyl ether of **5** was found to be identical with 13a-methyltylohirsutine reported by us earlier [3]. These data further substantiated structure **5** for the alkaloid named 14-desoxy-13a-methyltylohirsutinidine.

5-Hydroxy-*O*-methyltylophorinidine (**6**), mp 245–247°, $[M]^+$ at *m/z* 395 ($C_{23}H_{25}NO_5$), $[\alpha]_D^{18} + 58.97$ (*c* 0.8 in MeOH) did not resemble the isotylocrebrine-type (**1**, **2**, **4**, **5**) and tylophorine (**3**)-type alkaloids in UV and IR spectral behaviour indicating a different substitution pattern of the methoxy and hydroxyl groups. The presence of a phenolic hydroxyl was indicated by the shift in its UV maxima at 228, 272, 285, 300 and 325 (sh) nm to 218, 248, 256, 275 (sh), 296 (sh) and 325 nm on addition of sodium hydroxide. The IR spectrum showed a broad band at 3415 cm^{-1}. Its mass spectrum showed a peak at *m/z* 366 (8.5%) arising from the loss of CHO from $[M]^+$ indicative of the presence of a hydroxyl group at C-14 [3, 8]. Another peak at *m/z* 326 (17.2%) arose due to the loss of a pyrrolidine fragment from the $[M]^+$ by retro-Diels–Alder

reaction with the base peak at *m/z* 70 being due to the pyrrolidine ring. The fragments at *m/z* 297 (56.2%) and 283 (2.9%) resulted from the losses of CHO and CO from *m/z* 326 (17.2%) and 311 (7.8%), respectively. There was a further abstraction of CO from the peak at *m/z* 297 to give the fragment at *m/z* 269 (5.5%) indicating the presence of two hydroxyl groups. The ^{1}H NMR spectrum of **6** showed the presence of three methoxy groups at δ4.02, 4.00 and 3.80, four aromatic protons at δ8.12 (*d*, *J* = 9 Hz), 7.88 (*d*, *J* = 3 Hz), 7.10 (*d*, *J* = 9 Hz) and 6.92 (*s*) assigned to C-1, C-4, C-2 and C-8, respectively, two D_2O exchangeable protons at δ7.84 (phenolic OH) and 3.20 (C-14 OH) and signals at δ4.30 (*br s*) and 3.64 (*br s*) due to the protons attached to the hydroxyl at C-14 and C-13a, respectively. Compound **6** on acetylation gave a diacetylated product. A monomethyl ether was formed on treatment with diazomethane which in turn gave an acetate proving the presence of one phenolic and another hydroxyl at C-14.

The ^{1}H NMR values of the aromatic protons at C-1, C-2 and C-4 in **6** were comparable with the corresponding values in *O*-methyltylophorinidine [5]. The deshielding (by δ0.52) of the aromatic proton at C-8 in **6** from the similar signal in *O*-methyltylophorinidine [5] could be easily postulated due to the presence of a hydroxyl (C-5) at the *para* position. The evidence of the free *para* position to the hydroxyl came from the positive Gibb's test. Further, *O*-methyltylophorinidine with a (+)-rotation has been shown to exist in the structure in which the C-13a H is *trans*-diaxially disposed to the C-14 OH [5, 9]. These data led structure **6** for the alkaloid named 5-hydroxy-*O*-methyltylophorinidine.

Tylohirsuticine (**7**), mp 215–217°, $[M]^+$ at *m/z* 395 ($C_{24}H_{29}NO_4$), $[\alpha]_D^{18}$ +20.80 (*c* 0.8 in MeOH) had UV maxima at 220, 260, 316 (sh) and 340 nm. The IR spectrum showed a hydroxyl band at 3440 cm^{-1}. The hydroxyl function was shown to be phenolic by the presence of a shift in its UV maxima at 217, 257, 295 (sh) and 336 nm on addition of sodium hydroxide. Acetylation of **7** gave a monoacetylated product further confirming the presence of one hydroxyl group. Since methylation of **7** with diazomethane formed a monomethyl ether, the hydroxyl group is phenolic in nature. Its mass spectrum showed a $[M-Me]^+$ at *m/z* 380 (2%). The base peak at *m/z* 326 $[M-69]^+$ indicated the presence of a phenanthroindolizidine skeleton. The fragment at *m/z* 312 (10.8%) arose due to loss of 83 mu in the form of methylpyrrolidine from the $[M]^+$, as observed in **5** and encountered earlier in phenanthroindolizidine alkaloids with angular methyl functions [3, 7]. The intense peak at *m/z* 311 (59.3%) was due to the loss of 15 mu (Me) from the base peak. In its ^{1}H NMR the presence of six aromatic protons indicated **7** to be a cleaved phenanthrene analogue like *d*-septicine [5] and 13a-hydroxysepticine [3]. However, the position of the aromatic signals in **7** differed considerably from those in 13a-hydroxysepticine [3] indicating a different substituent pattern for the three methoxy and one hydroxyl functions. The six aromatic protons appearing at δ8.50 (*s*, 1H), 8.25 (*d*, 2H, *J* = 9 Hz), 7.33 (*d*, 2H, *J* = 9 Hz) and 6.56 (*s*) fitted well with the substitution pattern in the cleaved form of isotylocrebrine. In the light of earlier findings [3, 5], the shielded signal at δ6.56 has been assigned to C-8 in **7**. The deshielded signal at δ8.50 could be conveniently assigned to the proton adjacent to the phenolic hydroxyl. The shielded and the deshielded doublets integrating for two protons each have been assigned to the C-2, C-5 and C-1, C-5a protons, respectively. The three methoxy groups appeared at δ4.05, 3.86 and 3.82 along with a D_2O exchangeable (phenolic OH) proton at δ7.02. As in **5**, an angular methyl function was present at δ1.42. The cleaved phenanthrene alkaloid **7**, the structure for which was deduced from above data, has been named tylohirsuticine.

EXPERIMENTAL

Mps are uncorr. ^{1}H NMR δvalues are given in ppm downfield from TMS. TLC spots were detected with Dragondroff's reagent after development in C_6H_6–EtOAc–Et_2NH (6:3:1).

Isolation of alkaloids. Air-dried aerial parts of *T. hirsuta* (900 g) collected from wild populations during April 1984 were extracted and the EtOAc sol brown coloured alkaloids separated as described in refs. [2, 3]. TLC of the partially purified alkaloid extract showed 7 spots.

Separation of alkaloids. The EtOAc-sol portion was concd *in vacuo* and subjected to CC over basic Al_2O_3 after the formation of a slurry. The column was eluted with mixtures of C_6H_6, EtOAc and MeOH of increasing polarities.

14-Hydroxyisotylocrebrine (**1**). Fraction 1, eluted with C_6H_6 gave **1** (0.25 g, 0.028% yield; from Me_2CO), mp 214–215° (lit. mp 212–214°), $[\alpha]_D^{18}$ −40.29° (*c* 0.5; MeOH), MS *m/z* (rel. int.): 409 $[M]^+$ ($C_{24}H_{27}NO_5$, 10). Acetylation of **1** with Ac_2O–pyridine at room temp for 24 hr and usual work up gave a monoacetylated product, mp 197–198°; IR ν_{max}^{KBr} 1725 and 1225 cm^{-1}.

Isotylocrebrine (**2**). The concd mother liquor of **1** on chromatography in C_6H_6 gave **2** (0.15 g, 0.017% yield; from Me_2CO), mp 210–212° (lit. mp 212–214°), $[\alpha]_D^{18}$ +18.66 (*c* 0.9, MeOH) (lit $[\alpha]_D$ +22.4° (*c* 1.1, $CHCl_3$)), MS *m/z* (rel. int.): 393 $[M]^+$ ($C_{24}H_{27}NO_4$, 51.2)

Tylophorine (**3**). Fractions 2–3 from the main column eluted with C_6H_6–EtOAc (9:1) afforded **3** (0.3 g, 0.033% yield; from $CHCl_3$–MeOH), mp 290–292° (decomp) [lit. mp 287–288° (decomp)], $[\alpha]_D^{18}$ −20.90° (*c*, 0.8, MeOH), MS *m/z* (rel. int.): 393 $[M]^+$ ($C_{24}H_{27}NO_4$, 85.7).

4-Desmethylisotylocrebrine. (**4**). The dried mother liquor of **1** on chromatography in C_6H_6–EtOAc (9:1) gave **4** (0.18 g, 0.020% yield; from Me_2CO–*n*-hexane), mp 220–221° (lit. mp 222–224°), $[\alpha]_D^{18}$ −50.80 (*c* 0.7; MeOH), MS *m/z* (rel. int.): 379 $[M]^+$ ($C_{23}H_{25}NO_4$, 12.9). Methylation of **4** with CH_2N_2 gave **2**, mp and mmp 211–213°.

14-Desoxy-13a-methyltylohirsutinidine (**5**). Fractions 4–6 from the main column, eluted with C_6H_6–EtOAc (9:1) on crystallization from Me_2CO, gave **5** (0.2 g, 0.022% yield) as light yellow solid flakes, mp 180–182°, $[\alpha]_D^{18}$ +14.66 (*c* 0.2 g, MeOH); UV λ_{max}^{MeOH} nm: 260, 284, 302 and 316 (log ε 5.51, 2.06, 0.69 and 0.65) λ_{max}^{MeOH} (on addition of NaOH) nm: 217, 257, 276 and 295 (log ε 8.94, 8.27, 5.55 and 4.54). IR ν_{max}^{KBr} cm^{-1}: 3505, 2940, 1605, 1515, 1465, 1390, 1310, 1245, 1160, 1085, 1015, 885, 780. ^{1}H NMR ($CDCl_3$ + 1 drop TFA): δ7.56 (*d*, *J* = 9 Hz, *o*-coupled H, C-1), 7.32 (*d*, *J* = 9 Hz, *o*-coupled, C-2), 7.26 (*s*, *p*-coupled H, C-5), 7.16 (*br s*, D_2O exchangeable, OH), 6.86 (*s*, *p*-coupled H, C-8), 4.04 (*s*, 3H, OMe), 4.00 (*s*, 3H, OMe), 3.78 (*s*, 3H, OMe) and 1.36 (*s*, 3H, C-Me); MS *m/z* (rel. int.): 393 $[M]^+$ ($C_{24}H_{27}NO_4$, 28.6), 378 (100) $[M-15]^+$, 363 (75.9), 324 (69.5), 310 (96), 309 (99), 296 (96), 295 (99), 281 (35.7), 252 (29), 249 (35), 181 (27.5) 165 (35.4), 152 (33.3) and 70 (23.8). Acetylation of **5** with Ac_2O–pyridine at room temp. for 24 hr and usual work-up, gave a monoacetylated product, mp 187–188°; IR 1760 cm^{-1}, MS *m/z* (rel. int.): 435 $[M]^+$ ($C_{26}H_{29}NO_5$, 10). Methylation of **5** with CH_2N_2 gave a mono Me ether, mp 198–200°. This product was comparable (mmp, TLC, co-TLC, UV and IR) with 13a-methyltylohirsutine [3].

5-Hydroxy-O-methyltylophorinidine (**6**). Further elution of the main column with C_6H_6–EtOAc (3:1) gave **6** (0.1 g, 0.011% yield) from fractions 7–8 after crystallization from Me_2CO; mp 245–247°, $[\alpha]_D^{18}$ + 58.97 (*c* 0.8 g, MeOH); λ_{max}^{MeOH} nm: 228, 272, 285, 300 and 325 (sh) (log ε 1.6, 5.3, 2.2, 2.2, and 0.6); λ_{max}^{MeOH} (on addition of NaOH) nm: 218, 248, 256, 275 (sh) 296 (sh) and 325 (log ε 6.2, 7.6, 7.6, 5.3, 4.1 and 0.3). IR ν_{max}^{KBr} cm^{-1}: 3415, 2900, 1615, 1505, 1465, 1405, 1210, 1125, 915 and 720; ^1H NMR (DMSO-d_6): δ8.12 (*d*, 1H, *J* = 9, *o*-coupled, C-1), 7.88 (*d*, 1H, *J* = 3. *o,m*-coupled, C-4), 7.84 (*br s*, 1H, D_2O exchangeable; phenolic OH), 7.10 (*d*, 1H, *J* = 9, *o*-coupled, C-2), 6.92 (*s*, 1H, C-8), 4.30 (*br s*, 1H, C-14), 4.02 (*s*, 3H, OMe), 4.00 (*s*, 3H, OMe), 3.80 (*s*, 3H, OMe), 3.64 (*s*, 1H, C-13a) and 3.20 (*br s*, 1H, D_2O exchangeable, C-14 OH); MS *m/z* (rel. int.): 395 $[M]^+$ ($C_{23}H_{25}NO_5$, 3.8), 366 (8.5), 326 (17.2), 311 (7.8), 297 (56.2), 283 (2.9), 269 (5.5), 223 (6.3), 210 (7.3), 165 (5.9), 152 (6.0), 70 (100). Acetylation of **6** with Ac_2O–pyridine at room temp. gave a diacetylated product, mp 192–194°; IR ν_{max}^{KBr} cm^{-1} 1760 and 1735; MS *m/z* (rel. int.) 479 $[M]^+$ ($C_{27}H_{29}NO_7$, 25). Methylation of **6** with CH_2N_2 gave a mono Me ether, mp 218–219°, $C_{24}H_{27}NO_5$ ($[M]^+$ 409) which on acetylation gave a monoacetate (confirmed by TLC comparison).

Tylohirsuticine (**7**). Fractions 9–10 eluted with C_6H_6–EtOAc (1:1) gave light yellow beads of **7** (0.2 g, 0.022% yield) on crystallization from Me_2CO, mp 215–217°, $[\alpha]_D^{18}$ + 20.80 (*c* 0.8; MeOH), UV λ_{max}^{MeOH} nm: 220, 260, 316 (sh), and 340 (log ε 0.5, 5.2, 0.7 and 0.1), λ_{max}^{MeOH} (on addition of NaOH) nm: 217, 257, 295 (sh) 336 (log ε 3.7, 5.7, 20.2 and 1.6); IR ν_{max}^{KBr} cm^{-1} 3440, 2930, 1605, 1515, 1465, 1415, 1255, 1200, 1160, 1030, 845. ^1H NMR ($CDCl_3$): δ8.50 (*s,p*-coupled, 1H, C-4a), 8.25 (*d*, 2H, *J* = 9 Hz, *o,p*-coupled, C-1 and C-5a), 7.33 (*d*, 2H, *J* = 9 Hz, *o,p*-coupled, C-2, C-5), 6.56 (*s*, 1H, *p*-coupled, C-8), 7.02 (*br s*, 1H, D_2O exchangeable OH), 4.05 (*s*, 3H, OMe), 3.86 (*s*, 3H, OMe), 3.82 (*s*, 3H, OMe), and 1.42 (*s*, 3H, C-Me); MS *m/z* (rel. int.): 395 $[M]^+$ ($C_{24}H_{29}NO_4$, 13.6), 380 (2) $[M-15]^+$, 326 (100), 312 (10.8) 311 (59.3), 283 (12.1), 266 (6.2), 255 (8.5), 70 (99). Acetylation of **7** with Ac_2O–pyridine at room temp gave a monoacetylated product, mp 203–204°; IR ν_{max}^{KBr} 1740 cm^{-1}, $C_{26}H_{31}NO_5$ ($[M]^+$ 437). Methylation of **7** with CH_2N_2 gave a mono Me ether, mp 199–202°, $C_{25}H_{31}NO_4$ ($[M]^+$ 409).

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