METHYLENATION OF SOME LYCOCTONINE-TYPE C_{19}-DITERPENOID ALKALOIDS: PARTIAL SYNTHESIS OF DELBRULINE, AND ELATINE

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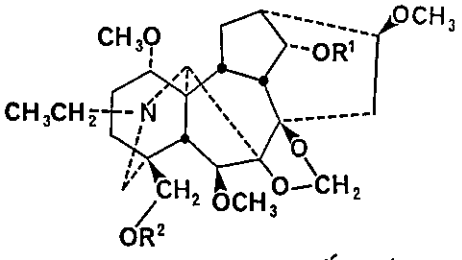
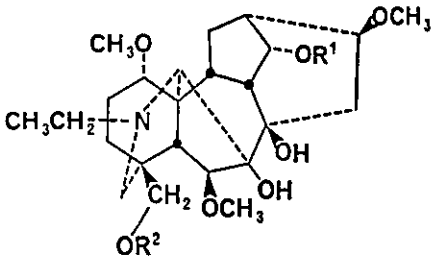
Abstract - Delbruline (5), delbrusine (6), elatine (1) and certain other alkaloids containing a methylenedioxy group at the C(7)-C(8) position have been synthesized by the reaction of formaldehyde or diethoxymethane with suitable alkaloid substrates under carefully controlled conditions.

A number of naturally occurring C_{19}-diterpenoid alkaloids, e.g. delcorine, delpheline, deltaline and dictyocarpine, contain a methylenedioxy group.[1] The structures of some of these alkaloids were established by acidic hydrolysis of the methylenedioxy group and comparison of the resulting product with alkaloids of known structures. The disadvantage of this method is that other sensitive functional groups, such as esters, are also cleaved under the experimental conditions. Synthesis of alkaloids containing the methylenedioxy group from suitable substrates would be a much more useful method for structure determination. Since methylenation of alkaloids containing *cis* diols has not been adequately studied, we undertook the present investigation.

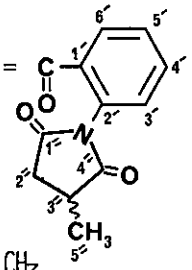
Diethoxymethane or aqueous formaldehyde in the presence of *p*-toluenesulfonic acid (*pts*) was used for the methylenation reactions. The structure of elatine (1), isolated from *Delphinium elatum* L., was originally established by heating the alkaloid with aqueous HCl and phloroglucinol at 90°C to give anthranoyllycoctonine (2), which had been correlated with lycoctonine (3).[2] In the present work treatment of methyllycaconitine (4) with 30% aqueous HCHO and *p*-toluenesulfonic acid in refluxing benzene (Dean-Stark apparatus) afforded elatine (1), mp 210-213°C (lit.[2]: 222-225°C) and $[\alpha]_D^{25}$ +2.9° ($CHCl_3$) (lit.[2]: $[\alpha]_D$ +3.4°), HRMS: m/z 694.34492 (calculated for $C_{38}H_{50}N_2O_{10}$: m/z 694.34654). The ^{13}C and ^1H nmr spectra of 1 are not available in the literature and are listed in Tables 1 and 2.

Delbruline (5) and delbrusine (6), two alkaloids isolated from *D. brunonianum* Royle[3], were partially synthesized from known substrates. Thus, treatment of 14-acetylbrowniine (7) with diethoxymethane and *p*-toluenesulfonic acid gave the methylenedioxy analog 8, mp 133-135°C, $[\alpha]_D^{29}$ +16.2° ($CHCl_3$) and EIMS: m/z 521 (M^+, $C_{28}H_{43}NO_8$). The ^{13}C and ^1H nmr data are listed in Tables 1 and 2. Alkaline hydrolysis of 8 furnished delbruline (5), mp 140-142°C. The synthetic substance showed a higher mp (lit.[3]: 129-31°C), but the ir (KBr), ^1H and ^{13}C nmr spectra were identical with those of the natural product.[3] Reaction of delphatine (9)[4] under similar conditions furnished delbrusine (6). However, the synthetic delbrusine differed from the natural product in the following ways. Mp 100-103°C (141°C)[3]; $[\alpha]_D^{25}$ 0° (+16.8°)[3]; ^1H nmr: δ 3.25,

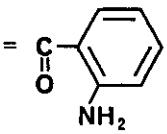




1 $R^1 = CH_3$; R^2 =

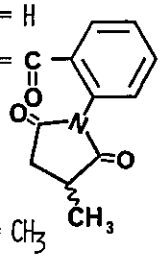


2 $R^1 = CH_3$; R^2 =



3 $R^1 = CH_3$; $R^2 = H$

4 $R^1 = CH_3$; R^2 =

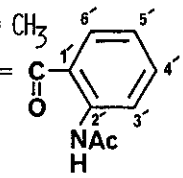


5 $R^1 = H$; $R^2 = CH_3$

6 $R^1 = R^2 = CH_3$

8 $R^1 = Ac$; $R^2 = CH_3$

16 $R^1 = CH_3$; R^2 =

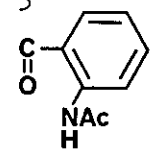


7 $R^1 = Ac$; $R^2 = CH_3$

9 $R^1 = R^2 = CH_3$

11 $R^1 = H$; $R^2 = CH_3$

12 $R^1 = CH_3$; R^2 =



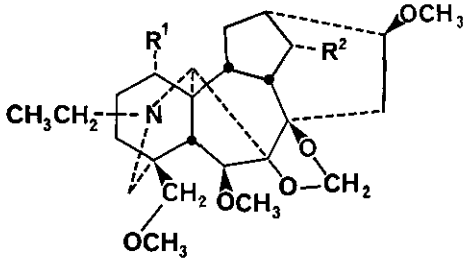
3.31, 3.33, 3.35, 3.42 (3.32, 3.33, 3.38, 3.42, 3.43)[3] and 5.06 (5.11 and 5.16)[3] for the methoxyl and methylenedioxy protons, respectively. The ir (nujol) and ^{13}C nmr spectra (Table 1) were not identical. This result led us to prepare delbrusine (**6**) by two other routes from other alkaloids of established structure. Compound **15**, prepared by methylenation of delsoline (**10**), was methylated to give compound **6**; delbruline (**5**), synthesized from 14-acetylbrowniine (**7**) (see Table 3), was methylated (as reported[3]) to give compound **6**. Thus the products obtained by three different syntheses were identical in all respects (^1H and ^{13}C nmr and ir spectra).[7] The results are shown in Table 3.

Delsoline (**10**), ajacine (**12**), 1,14-diacetyldelcosine (**13**) and 14-dehydrobrowniine (**14**) were also transformed to their methylenedioxy analogs **15**, amorphous; $[\alpha]_D^{12}$ +4.7° ($CHCl_3$); EIMS: m/z 479 (M^+, $C_{26}H_{41}NO_7$), **16**, mp 160-166°C; $[\alpha]_D^{27}$ +8° ($CHCl_3$); EIMS: m/z 640 (M^+, $C_{35}H_{48}N_2O_9$), **17**, amorphous; $[\alpha]_D^{25}$ +10.4° ($CHCl_3$); EIMS: m/z 549 (M^+, $C_{29}H_{43}NO_9$) and **18**, amporphous; $[\alpha]_D^{24}$ +14.3° ($CHCl_3$); EIMS: m/z 477 (M^+, $C_{26}H_{39}NO_9$), respectively. The ^{13}C and ^1H nmr spectra of **15**, **16**, **17** and **18** are listed in Tables 1 and 2.

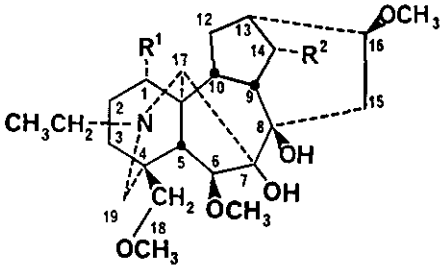
That the methylenation conditions described did not cause rearrangement was demonstrated by the following sequence of reactions. Deltaline (**19**) was hydrolysed with 10% aqueous H_2SO_4 to de-

methylenedeltamine (**20**, mp 101-103°C; the ^{13}C nmr and ^{1}H nmr spectra are listed in Tables 1 and 2). Acetylation of **20** gave demethylenedeltaline (**21**, mp 100-102°C; $[\alpha]_D^{27}$ +21.3° ($CHCl_3$); ^{13}C and ^{1}H nmr data are listed in Tables 1 and 2). The perchlorate salt of **21** under the methylenation conditions regenerated deltaline (**19**).

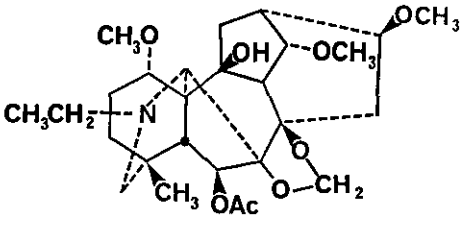
Although the yields of the products are low in some cases, the conditions described will be useful for effecting structure correlations among certain C_{19}-diterpenoid alkaloids.



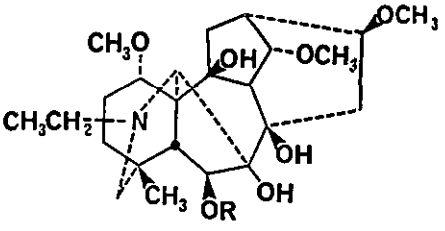
15 R^1 = OH; R^2 = OCH_3
17 R^1 = R^2 = OAc
18 R^1 = OCH_3; R^2 = O



10 R^1 = OH; R^2 = OCH_3
13 R^1 = R^2 = OAc
14 R^1 = OCH_3; R^2 = O



19



20 R = H
21 R = Ac

Table 1. ^{13}C nmr spectra of compounds **1, 6, 8, 15, 16, 17, 18, 20** and **21**[a]

	1[d]	6	6[e]	8	15	16[f]	17	18	20	21
C(1)	83.4	81.7	82.1	81.8	71.8	83.4	77.9	83.4	81.9	81.6
C(2)	28.4	26.6	26.7	26.3	26.9	26.3	27.5	24.9	26.2	26.4
C(3)	31.8	32.0	31.6	31.9	29.5	31.8	31.8	31.6	39.0	39.5 b
C(4)	37.2	37.7	39.0	37.6	37.1	37.2	37.7	38.1	34.1	34.4
C(5)	53.0	52.3	52.3	50.7	45.5	53.0	50.7	50.9	53.9 b	51.6 c
C(6)	89.4	89.2	89.5	88.3	88.8	89.5	88.0	88.1	77.4	77.4
C)7)	92.1	92.3	92.5	92.4	91.8	92.1	92.4	92.9	86.8	88.2
C(8)	83.4	83.5	84.0	82.7	84.5	83.4	82.5	89.0	76.8	74.8
C(9)	48.5	48.5	48.7	47.6	46.6	48.5	46.8	48.7	54.1 b	53.4 c
C(10)	40.0	40.0	40.2	40.0	45.5	40.0	40.0	46.1	80.5	80.5
C(11)	50.1	50.0	50.7	50.0	51.2	50.0	48.8	50.1	54.1	54.2
C(12)	27.9	27.9	28.3	27.2	30.6	27.9	27.6	24.9	36.9 c	36.6
C(13)	38.7	38.7	37.9	35.5	37.4	38.6	36.0	46.1	37.1	37.3
C(14)	81.3 b	83.3	82.1	75.4	83.7	81.2	74.9	214.0	82.8	82.0
C(15)	34.9	35.0	35.0	36.9	35.8	34.8	35.5	31.9	37.4 c	39.0 b
C(16)	81.7 b	81.7	81.9	81.2	82.6	81.6	81.9	84.4	81.9	82.9
C(17)	64.1	64.4	64.3	64.0	65.7	64.0	63.2	65.3	65.9	66.1
C(18)	69.8	78.7	79.0	78.2	78.0	69.9	76.0	78.2	25.9	25.6
C(19)	52.6	53.2	53.9	52.9	57.7	52.6	53.6	53.4	56.8	56.2
N-CH_2	50.4	50.6	50.7	50.5	49.9	50.4	50.1	50.7	51.5	51.0
CH_3	13.8	13.9	13.4	13.9	13.4	13.8	13.8	14.0	14.6	14.1
C1(OMe)	55.2	55.1	55.1	55.2	-	55.1	-	55.7	55.5	55.4
C6(OMe)	57.8	58.4	58.5	57.8	58.1	57.7	58.0	58.2	-	-
C7-O, C8-O CH_2	93.6	93.5	94.0	93.6	94.0	93.4	93.8	94.4	-	-
C14(OMe)	58.9	57.7	57.8	-	57.7	58.9	-	-	57.9	57.8
C16(OMe)	56.1	56.1	56.2	55.9	56.2	56.1	56.1	55.9	56.2	56.2
C18(OMe)	-	59.3	59.5	59.1	59.2	-	59.2	59.3	-	-
CO				171.6			171.6,170.2		-	172.5
CH_3				21.4			21.9, 21.4			21.6

a. Chemical shifts in ppm downfield from TMS; solvent is $CDCl_3$.

b,c. These may be interchanged in any vertical column.

d. ^{13}C shifts of R^2: (CO) 164.3, C(1') 127.3, C(2') 133.1, C(3') 129.4, C(4') 133.5, C(5') 131.2, C(6') 130.0, C(1") 179.8, C(2") 37.0, C(3") 35.3, C(4") 175.8, C(5") 16.4 ppm.

e. Values taken from Ref. 3.

f. ^{13}C shifts of R^2: (CO) 168.1, C(1') 114.7, C(2') 141.8, C(3') 120.6, C(4') 134.8, C(5') 122.5, C(6') 130.4, (NH-CO) 168.9, ($COCH_3$) 25.4 ppm.

Table 2. ^{1}H nmr (90 MHZ, $CDCl_3$) Spectra of Compounds **1**, **8**, **15**, **16**, **17**, **18**, **20** and **21**.

Proton	1[a]	8	15	16[b]	17	18	20	21
1β	-	-	-	-	4.85-4.62 m	-	-	-
6α	-	-	-	-	-	-	-	5.30 br
14β	3.65 t (J=4.5 Hz)	4.79 t	-	-	4.85-4.62 m	-	4.21 t	4.19 t
18	4.05 s[c]	-	-	4.14 s[c]	-	-	0.96 s[d]	0.88 s[d]
OMe[d]	3.25 s	3.22 s	3.32 s	3.27 s	3.26 s	3.29 s	3.24 s	3.25 s
	3.33 s	3.24 s	3.35 s	3.33 s	3.29 s	3.31 s	3.33 s	3.32 s
	3.34 s	3.26 s	3.36 s	3.34 s	3.34 s	3.32 s	3.43 s	3.43 s
	3.42 s	3.30 s	3.43 s	3.42 s	-	3.34 s	-	-
$-OCH_2O$[c]	5.06 s	5.03 s	5.05 s 5.10 s	5.06 s	5.07 s	5.07 s 5.12 s	-	-
$N-CH_2-CH_3$[d]	1.06 t (J=7Hz)	1.02 t	1.10 t	1.07 t	1.08 t	1.07 t	1.04 t	1.05 t
OAc[d]	-	2.03 s	-	-	2.05 s 2.04 s	-	-	2.04 s

a ^{1}H nmr shifts of R^2:δ 7.25 (1H, dd, J = 8, 2 Hz, H-3'), 7.52-7.68 (2H, m, H-4' and 5'), 8.08 (1H, dd, J = 8,2 Hz, H-6') and 1.50 (3H, d, J = 6 Hz, H-5").
b ^{1}H nmr shifts of R^2:δ 7.97 (1H, dd, J = 8.5, 2 Hz, H-3'), 7.10 (1H, ddd, J = 8.5, 8, 1 Hz, H-4'), 7.58 (1H, ddd, J = 8.5, 8, 2 Hz, H-5'), 8.70 (1H, dd, J = 8.5, 1 Hz, H-6'), 2.24 (3H, s, NHAc) and 11.0 (1H, br, NH).
c Intensity of two protons
d Intensity of three protons

Table 3. Methylenation of Some Lycoctonine-type C_{19}-Diterpene Alkaloids

Substrate	Product	Yield[a] %	Recovery of Starting Material %	Conditions[b,c]
4	**1**	30	50	CH_2O, *pts*, 3h
7	**8**	68	17	$(C_2H_5O)_2CH_2$[d], *pts*, 7h
9	**6**	22	50	CH_2O, *pts*, 8.5 h
9·$HClO_4$	**6**	50	30	$(C_2H_5O)_2CH_2$[d], *pts*,0.5 h
10	**15**	60	20	CH_2O, *pts*, 5 h
12	**16**	44	12	$(C_2H_5O)_2CH_2$[d], *pts*, 9 h
13	**17**	20	34	$(C_2H_5O)_2CH_2$[d], *pts*, 5.5 h
14	**18**	25	41	$(C_2H_5O)_2CH_2$[d], *pts*, 3 h
21·$HClO_4$	**19**	15	45	$(C_2H_5O)_2CH_2$[d], *pts*, 2 h

a Isolated yield.
b Reaction was stopped when the solution had turned dark.
c 1.3 equivalent of *pts* to the substrate concentration was used in all these reactions.
d Use of this reagent with substrates possessing a primary and secondary hydroxyl groups led to the formation of acetals of the type $RCH_2OCH_2OCH_2CH_3$ and $R_2CHOCH_2OCH_2CH_3$, respectively. The details of these compounds will be discussed elsewhere.

ACKNOWLEDGEMENT

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3. W. Deng and W. L. Sung, *Heterocycles*, 1986, **24**, 873.
4. Delphatine (**9**) isolated from *D. biternatum*[5] was crystalline, mp 105°C, $[\alpha]_D$ +38.5° ($HClO_4$ salt, mp 220-221°C). Compound **9** used in this study, isolated from *Consolida ambigua*[6], was amorphous, $[\alpha]_D^{22}$ +38.2° ($HClO_4$ salt, mp 220-221°C).
5. M. S. Yunusov and S. Y. Yunusov, *Khim. Prir. Soedin.*, 1970, 334.
6. S. W. Pelletier, R. S. Sawhney, H. K. Desai and N. V. Mody, *J. Natural Products*, 1980, **43**, 395.
7. Deng and Sung[3] have reported that delbruline (**5**) on methylation afforded delbrusine (**6**). We suggest that the name delbrusine for the alkaloid having structure **6** be retained inspite of the differences in physical and spectral properties of our samples of delbrusine and the sample of Deng and Sung.

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