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KETALISATION OF α,β-UNSATURATED KETONES. PART I

3-METHOXY-N-METHYLMORPHINAN DERIVATIVES AND 14-HYDROXYCODEINONE

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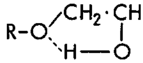
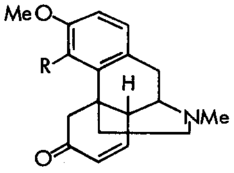
In view of the known migration of the double bond in ketalisation of α,β-unsaturated ketones, thebainone 1a was subjected to ketalisation that would give the β,γ-unsaturated ketal 3a. However, in the presence of 1.1 mol eq of p·TsOH, thebainone 1a afforded an unexpected conjugate addition ketal 2a (oil; oxalate, mp 198° dec; diacetate, mp 170-172°) (1). The structure of 2a was suggested from the following evidences: i) hydrogen-bonded hydroxyl bands at 3527 (C_4-OH) and 3602 cm^{-1} (a reasonable value for a five-membered type of hydrogen-bonding  $R\text{-}O\begin{smallmatrix}CH_2\cdot CH_2\\ \vert\\ H\text{—}O\end{smallmatrix}$ (2)), ii) no olefinic proton signal in the NMR, iii) acid-catalysed hydrolysis of 2a with N-HCl (100°, 10 min) resulted in regeneration of the parent ketone 1a quantitatively. This indicates that the configuration at C_{14} is not disturbed during ketalisation. An alternative structure 2' for the conjugate addition ketal was eliminated from the following reasons: i) In the form of 2', two sorts of hydroxyl bands would exist. One is free and the other is strongly hydrogen-bonded to the bridged ketal-oxygen atom at C_6 (2), ii) the five-membered dioxolane ring in the 2 would be more stable than the seven-membered one in the 2', iii) since it is likely to assume that SN2' type of this reaction gives rise to form an equatorial bond at C_8, 2' type ketal formation ($C_8 \rightarrow C_6$) should force the C-ring to boat-form. The minor product of this reaction was an expected unsaturated ketal 3a, mp 149-150°, which shows one olefinic proton that appears at 5.60 ppm (triplet, J = 4 Hz) in the NMR. Acid-catalysed hydrolysis of 3a followed by catalytic hydrogenation gave C_{14} epimers of dihydrothebainone 4 and 5. The ketal 3a was mainly obtained when 2.5 mol eq of the acid was used for ketalisation of 1a. These results were summarised in Table I.

Ketalisation of desoxythebainone 1b afforded an analogous results, giving the conjugate addition ketal 2b, mp 135-136°, and the unsaturated ketal 3b, mp 92-93° (Table).

The ketal 2b was converted into the ketal 3b (2.5 mol eq of p·TsOH·H_2O/ethylene glycol/dichloro-



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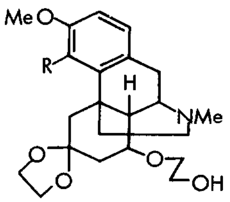

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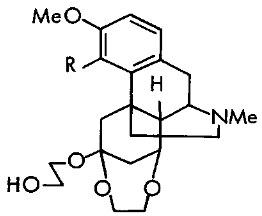
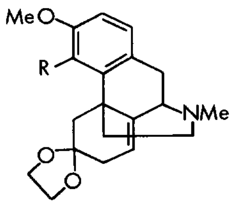


2'



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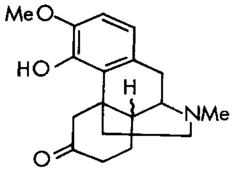
a series: R = OH
b series: R = H



4: 14β-H
5: 14α-H

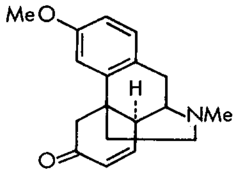


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Table I

Conj. ketone	p-TsOH H_2O (mol eq)	Conjugate addn. ketal 2 (%)		Unsaturated ketal 3 (%)	
1a	1.1	2a	64.1 a)	3a	11.9
1b	1.1	2b	72.0 b)	3b	c)
1a	2.5	2a	8.2 a)	3a	52.7
1b	2.5	2b	10.8 a)	3b	60.9
6	1.1	2b	c)	3b	74.9
6	2.5	2b	8.6 b)	3b	61.5

a) Estimated as oxlate.

b) Base with benzene as a crystal solvent.

c) Detected only by TLC.

ethane) in 62%, but the ketal 3b was entirely recovered under the ketalisation condition that affords the addition ketal. The most probable mechanism for the addition ketal formation is that initiated by Michael type addition of ethylene glycol to the conjugated ketone system.

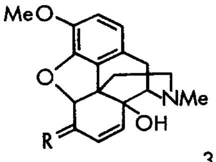
On the other hand, ketalisation of desoxy-β-thebainone 6 (B/C trans: C_{14} epimer of 1b) yielded the unsaturated ketal 3b as a major product, irrespective of quantity of the acid (Table I). Moreover, in the case of excess acid catalysis (2.5 mol eq), the conjugate addition ketal isolated was proved to be identical with 2b (B/C cis). Epimerisation of the ketone (6 → 1b) must occur under the condition used.

Next, 14-hydroxycodeinone 7 in which the conjugated ketone system is fixed was ketalised. Three products were isolated, one of which was the unsaturated ketal 8 (mp 179-180°; NMR 5.82 ppm, singlet, 2H), and the other two were the conjugate addition ketals 9 (mp 190-191°; IR 3548, 3472, and 3341 cm^{-1}) and 14 (mp 182-184°; IR 3635 sh, 3604, 3488 sh, and 3409 cm^{-1}). The results were summarised in Table II.

Table II

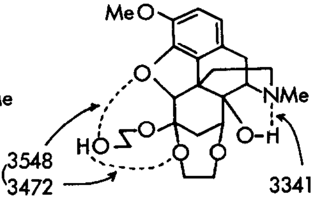
p-TsOH·H_2O (mol eq)	8 (%)	9 (%)	14 (%)
1.1	40.9	9.8	35.8
2.5	(mixture	ca 20%)	72.5

Hydrolysis of the unsaturated ketal 8 with 2N·HCl (room temp 7 hr) afforded the starting ketone 7 quantitatively. Catalytic hydrogenation of the ketal 8 gave dihydro-derivative, which was identical with the ketal 13 derived from 14-hydroxydihydrocodeinone 12. Both conjugate addition ketals 9 and 14, on treatment with 6N·HCl (100°, 3 hr), yielded a mixture of 14-hydroxycodeinone 7 and 8,14-dihydroxydihydrocodeinone 11, mp 170-171°, which was also obtained when 7 was heated under the same condition.



7: R = O

8: R = -O-CH2-CH2-O-



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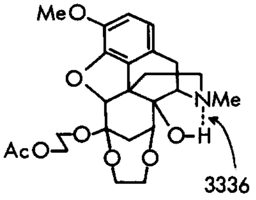

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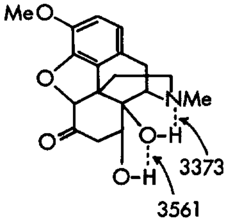

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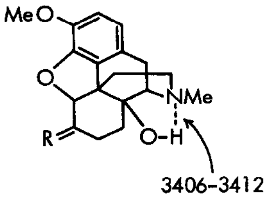
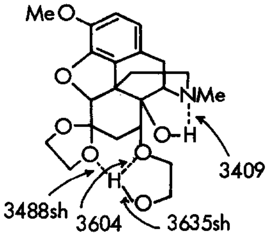
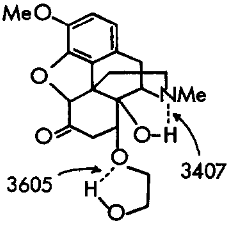


12: R = O

13: R = -O-CH2-CH2-O-



14



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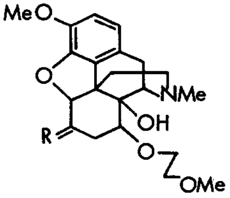

16: R = O

17: R = -O-CH2-CH2-O-

Hydrolysis of the ketal 14 with 6N·HCl (room temp 2 days) gave a new ketone 15 (87%, mp 172°), but under the same condition the ketal 9 afforded a mixture of 7 (76%) and 11 (20%). Methylation of the ketal 14 with NaH/MeI gave the mono methyl ether 17 (78%, mp 134-135°), which on treatment with 6N·HCl (room temp 2 days) yielded the ketone 16 (90%, mp 106-108°). In the NMR spectrum of 16, the methyl proton signal is still present at 3.31 ppm (3.30 ppm in 17). The structure of the ketal 14 was thus confirmed.

Hydrogen-bonding of above mentioned compounds and some reference compounds was measured in dilute CCl_4 solution. Reasonable values for hydrogen-bonding of C_{14}-OH···N were observed in the cases of the ketal 14 and the ketone 15 (cf 12 and 13) (2). Since lower shift of hydrogen-bonding of C_{14}-OH···N in the cases of the ketals 9 and 10 is owing to steric compression (and dipole repulsion) between C_8-O-CH- and C_{14}-OH, it is very probable to assume that the dioxolane ring in the ketals 9 and 10 is β-oriented.*

General procedure: A mixture of a conjugated ketone (1.0 mol eq) and ethylene glycol (10 mol eq) in benzene (20 v/w) containing p·TsOH·H_2O (1.1 or 2.5 mol eq) was refluxed with stirring for 2 hr using a modified Dean-Stark water separator (Fig. 1) (3). Neutralisation with NH_3·aq then extraction with benzene and methylene chloride furnished the crude product, which was chromatographed on neutral alumina (20 w/w) or crystallised directly.

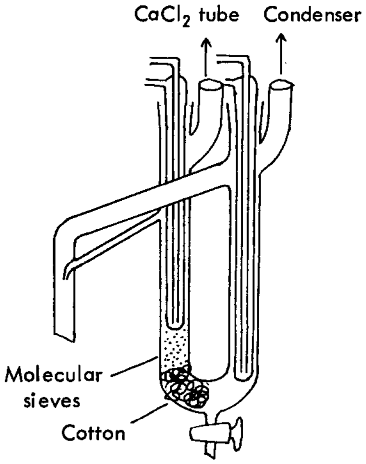

FIG. 1

REFERENCES

1. Satisfactory elemental analyses were obtained for all the crystalline compounds.
2. Y. Matsui, M. Takasuka, and T. Kubota, Ann. Rept. Shionogi Res. Lab., 15, 125 (1965); ibid., 16, 63 (1966).
3. (a) E. W. Dean and D. D. Stark, Ind. Eng. Chem., 12, 486 (1920); (b) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, J. Am. Chem. Soc., 63, 3452 (1941).

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* An examination with Dreiding model suggests that the C-ring of the molecule having ether bridge (C_4-C_5) may be stable either in chair form or in boat. If the ketal 9 is the C_8-epimer of 14, four kinds of hydrogen-bonding corresponding to C_8-O$(CH_2)_2$OH···O(C_6), C_{14}-OH···N, and C_8-O$(CH_2)_2$OH···C_{14}-OH···N must be observed.