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# REACTIONS OF THEBAINE WITH *CIS*- AND *TRANS*-DISUBSTITUTED DIENOPHILES

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**Abstract**—Thebaine has been shown to undergo Diels–Alder reactions with *trans*-disubstituted ethylenes containing relatively bulky groups. These were correlated with reactions in which the corresponding *cis*-disubstituted dienophiles were used. Reductions, Grignard reactions and base-catalyzed rearrangements of the adducts are described.

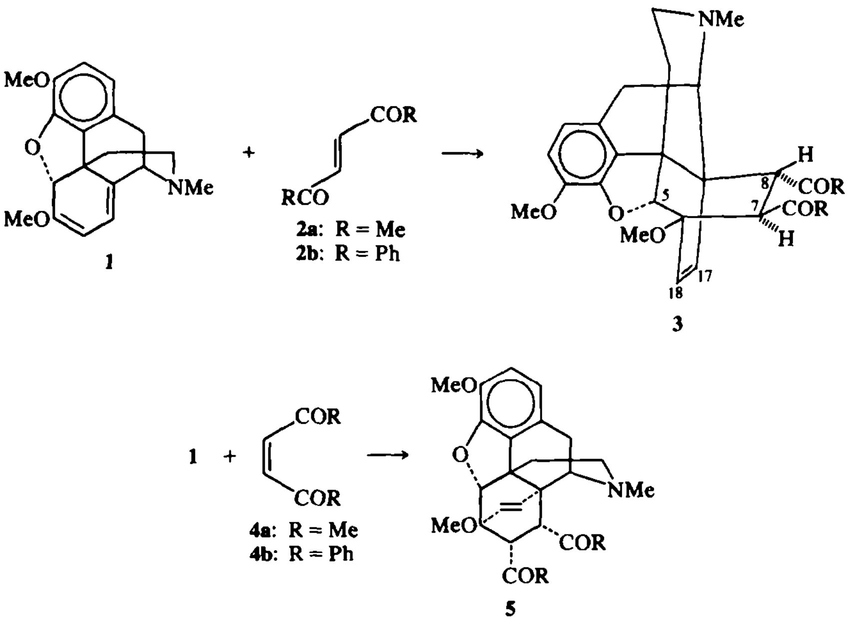
The limited usefulness and toxicity of thebaine have led to more or less successful attempts to employ the natural alkaloid as a starting material for the preparation of more efficacious medicinal agents. The more successful approaches utilize only small amounts of thebaine, e.g. only small amounts of dicodid and metopon have been manufactured and used.[1,2] Thus thebaine Diels–Alder adducts seemed amenable to further transformations.[3,4] The major contributor to this field has been Bentley with his collaborators.[4] This has led to products of such great activity compared with morphine, accompanied however by such side effects, that again the use of these products, e.g. etorphine,[5] has been minimal.

The work of Bentley's groups dealt either with monosubstituted dienophiles or 1,1-disubstituted and several *cis*-disubstituted compounds. In fact it was claimed that certain dienophiles of the *trans*-type failed to react with thebaine because of steric hindrance.[4a] This appeared reasonable until we studied the reaction of thebaine with *cis*-dibenzoylethylene. When two isomeric adducts were isolated in which the vicinal benzoyl groups were either in *cis*- or *trans*-disposition towards one another we treated thebaine with *trans*-dibenzoylethylene and obtained the previously isolated *trans*-adduct. It turned out, as is often the case, that it is apparently a matter of finding suitable conditions for effecting the reaction. We describe herein our work on a number of Diels–Alder adducts of thebaine with symmetrical and unsymmetrical *cis*- and *trans*-disubstituted dienophiles.

In principle, in the reaction of thebaine, **1**, with *trans*-diacetylethylene, **2a**, two products may be obtained, the 7$\beta$, 8$\alpha$-diacetyl compound, **3a** or its isomer having the 7$\alpha$, 8$\beta$-configuration (Scheme 1). Similarly when -thebaine reacts with *cis*-diacetylethylene **4a**, it may, in principle, give **5a** and the 7$\beta$, 8$\beta$-isomer (Scheme 1). In fact, the former reaction led to only one adduct, **3a**. In the reaction with **4a**, however, two isomeric adducts were indeed obtained but these were **5a** and **3a**, the latter being the thermodynamically more stable epimer (*vide infra* for relative stability of the 7,8-dibenzoyl adducts). It is clear from models why a bulky substituent prefers the $\alpha$-configuration at C-8 due to the proximity of the nitrogen-containing ring. This is probably the major reason for the absence of the 7$\alpha$, 8$\beta$ isomer and the 7$\beta$, 8$\beta$-isomer in the reactions with **2** and with **4**, respectively. We shall later show that a $\beta$-hydrogen atom at this position is affected by the proximity of the neighboring nitrogen atom.

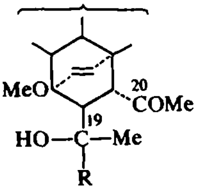
Both **3a** and **5a** show peaks due to the molecular ions, $m/e$ 423, and peaks at $m/e$ 311 corresponding to the ion-radical resulting from a retro-Diels–Alder reaction within the mass spectrometer. Since H-5 in **3a** or **5a** undergoes long-range coupling with H-18 (as part of a W array), H-15 has the $\beta$-configuration.[4g] Since the resonance for H-18 appears at relatively low field ($\tau$ 5·53 and 5·60) in **3a** and in **5a**, respectively, it also appears to have the $\beta$-configuration.[4g] The coupling constant for H-7 and H-8 corresponds to a transoid vicinal array (6Hz) in **3a** and to a cisoid arrangement in **5a** (11Hz). The resonances for H-5$\beta$ in **6a–e** are at $\tau$ 4·67, 4·53, 4·50, 4·69 and 4·50, respectively, as expected from model compounds.[4g] The resonance at 5·43 for **5a** is also normal as this has *cis*-substituents at C-7 and C-8. The anomalous resonance for **3a**, need not be taken too seriously from the diagnostic point of view. For once it undergoes Grignard reaction, in which only the 7$\beta$-acetyl group participates, and once the carbonyl group at C-7 disappears, the positions of H-5$\beta$ in all of the products **6** return to "normal", as expected for compounds having 7$\beta$-substituents.[4g]

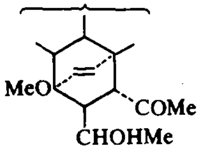
Although a great excess of Grignard reagent was used in each case only one acetyl group is attacked. This is due, at least in part, to the insolubility of the products in the reaction mixture. Lewis and Readhead[6] suggest for an analogous case the possibility that a complex forms between the reagent,


1 + 2a: R = Me; 2b: R = Ph → 3

1 + 4a: R = Me; 4b: R = Ph → 5

SCHEME 1


6a: R = Ph
6b: R = $PhCH_2$
6c: R = $Ph(CH_2)_2$
6d: R = Me
6e: R = $C_6H_{11}$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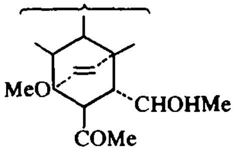
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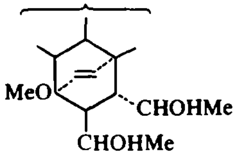
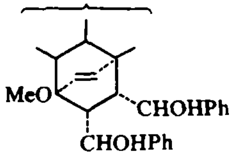

2 isomers: 9, 10

the methoxyl group at C-6 and the 7$\beta$-carbonyl group, following models used by Cram[7] and Bentley.[4b] This would explain the preferential attack by the Grignard reagent at C-19. The spectral results confirm the correctness of **6a–e**,

Reduction of **3a** with one equivalent of sodium borohydride gives keto-alcohols **7** and **8** whilst an excess of this reagent or lithium aluminium hydride affords two distinct diols **9** and **10**. Although it is of interest to determine the configuration of each in its entirety thus showing how **9** and **10** differ from one another, this was not pursued.

As already stated above both *cis*- and *trans*-dibenzoylethylenes reacted with thebaine. Whilst **2b** gave the *trans*-adduct, **3b**, exclusively, the same compound accompanied the *cis*-adduct **5b** when **4b** reacted with thebaine. Lithium aluminium hydride reduction of **5b** and **3b** gave **11** and **12**, respectively, each apparently being a single stereoisomer, although this point was not proven conclusively (m.p. ranges shown in the experimental section perhaps indicate otherwise but this was not pursued further).

Grignard reactions of the dibenzoyl adducts of thebaine with methylmagnesium iodide gave results which differ from those of the diacetyl adduct **3a**. In the case of the analogous **3b**, the reagent also attacked exclusively at C-19 but the reaction went further than to the simple analogs of the **6a–e** series and gave the phenolic **13** containing a newly formed



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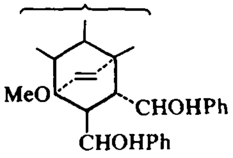

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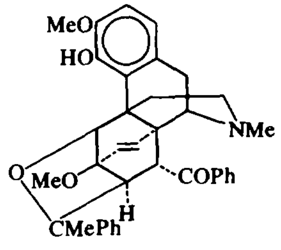
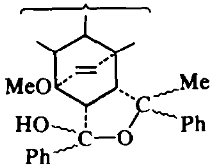


13

ether function as part of a bridge supported by C-5 and C-7 rather than by C-5 and C-4.[6] Alternatively **5b** is attacked by the reagent both at C-19 and at C-20, leading to the hemiketals **14** and **15**, respectively, in about equal amounts. But because of difficulties in isolation these account for only about one quarter of the material so that it would be unjustified to belabor the fact that some attack occurs at C-20, particularly since this is attached to $C_8$ in the $\alpha$- rather than the $\beta$-configuration.



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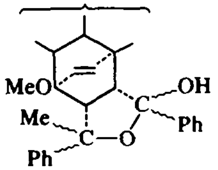


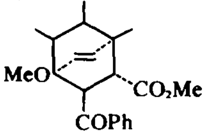
15

The isomeric *cis*- and *trans*-methyl benzoylacrylates were reacted separately with thebaine, introducing another dienophile, this time with two different substituents at the 1- and 2-positions of the pertinent ethylene. Such an unsymmetrical dienophile could, if it partially isomerized during the course of cycloaddition afford a total of eight stereoisomers. Of these, three were isolated. Thebaine with *trans*-methyl benzoylacrylate afforded the adducts **16** and **17**, both formally analogous to **3**. *cis*-Ethyl benzoylacrylate gave the *cis*-adduct **18** but not the "reverse" one (although a rigorous search for it was made), accompanied by **16** and **17**, probably again due to thermal isomerization of the dienophile during cycloaddition. In all cases the molecular ion peak was observed, *m/e* 501 accompanied by the ubiquitous fragment of retro-Diels–Alder reaction *m/e* 311. The absorption of H-5 in both **16** and **17** at relatively low field ($\tau$ 4·74 and 4·99, respectively) indicates that the configuration at C-7 is $\beta$. H-8 also appears at relatively low field (5·87 and 4·75) again indicating that it is $\beta$. In both **16** and **17** the 6Hz coupling constant between H-7 and H-8 indicates their *trans*-disposition. The NMe group is "normal" in **16** ($\tau$ 7·63) but at anomalously high field (8·01) in **17**. The aromatic ring in **17** is close enough to affect the nitrogen as in the cases of **3b** (8·07) and **5b** (7·80). These configurations received further support (*vide infra*).

In **18**, H-5$\beta$ absorbs at relatively high field ($\tau$ 5·37) indicating that there is present a 7$\alpha$-substituent. Peculiarly H-7 and H-8 form jointly a relatively low field singlet (5·70) in deuteriochloroform. However in deuterated pyridine they appear as 2 doublets with a coupling constant of 11Hz corresponding to their *cis*-disposition. The NMe is "normal" (7·76) indicating that the structure is **18** rather than the "reversed" one in which the ester group is 7$\alpha$. (For further support, see below). Reduction of **17** with LAH gave the diol **19**.

In their respective reactions with methylmagnesium iodide **16** gave **20**, **17** gave **21** and **22**. The isomer **18** gave two lactones, **23** and **24**. Compounds **20** and **21** are normal Grignard addition products and the spectral evidence supports these formulations. However, a rearrangement product **22** (55% yield) accompanies **21** (only 12% yield). There is ample precedent for such rearrangement in other 7-nitrile or 7-ester substituted products.[4f] The Grignard reagent acts as a base but the electron withdrawing properties of these groups do not suffice to cause opening of the cyclopropane ring. Thus the rearrangement ends with **22** and does not go further to an analogue of **27** as in the case of known alkali-catalyzed rearrangements.[4f,i] A phenolic absorption appears in the IR spectrum of **22** (3540 $\text{cm}^{-1}$) in addition to the ester absorption (1735 $\text{cm}^{-1}$). Also of interest is the lack of possibility for long-range coupling between H-5$\beta$ and H-18.[4f]

The *cis*-adduct **18** affords two distinct lactones **23** and **24**, in 66% and 12% yield, respectively. The isomer formed with higher stereoselectivity is presumed to be **23**.[4b,g]



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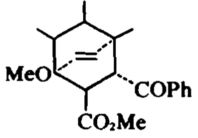

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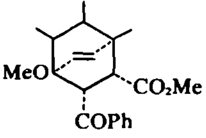
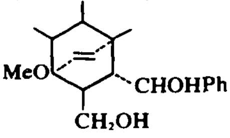


18



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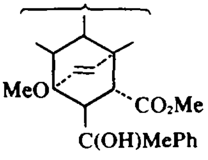
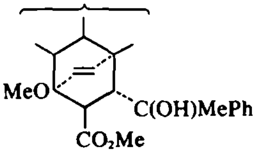
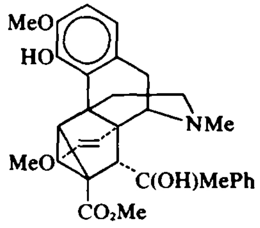


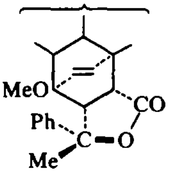
**20**



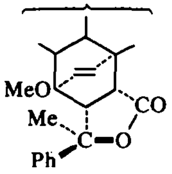
**21**



**22**



**23**



**24**

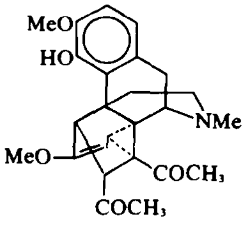
We are indebted to Prof. W. von Philipsborn for suggesting to us an excellent diagnostic tool for determining the configuration at C-8 in the 6,14-*endo*-ethenotetrahydrothebaine series. In the free base, H-8β absorbs at low field due to shielding by the nitrogen lone pair.[4g] Reduction of the electron density at nitrogen, e.g. by adding acid, causes the H-8β resonance to shift to higher field. Alternatively, increasing the electron density at nitrogen, e.g. by preparing the N-oxide, the position of H-8β should shift,[8] this time to lower field. Partial cancellation of this effect by adding acid to the N-oxide should again shift the resonance to higher field. The Table shows that these shifts occur consistently, and in the expected directions.

Upon treatment with base, **3a** undergoes rearrangement. Here, as in other cases of complex rearrangements in this series, our task was vastly simplified by the elegant work of Bentley. In this case we obtained **25** in analogy to a model case.[4i] The enol ether easily hydrolyzes in acid giving the phenolic triketone **26**.

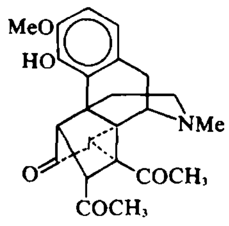
It is of interest that in the NMR spectrum of **25** the unique vinylic proton (τ 5·40) exhibits a quartet owing to vicinal coupling (7Hz) with H-8 and long-range coupling with H-5β (2Hz). The latter is shifted to rather high field (τ 6·18). Its position is confirmed by decoupling experiments. The

Table. Chemical shift of H-8β

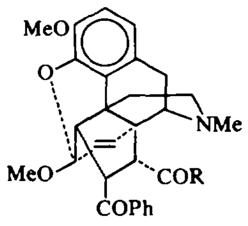
| Compound | H-8β (τ) | Δτ |
|---|---|---|
| **3a** N: | 5·53 | — |
| $\overset{+}{\mathrm{N}}$—$\overset{-}{\mathrm{O}}$ | 4·42 | −1·11 |
| $\overset{+}{\mathrm{N}}$—OH | 5·20 | +0·78 |
| **6d** N: | 6·09 | — |
| $\overset{+}{\mathrm{N}}$—$\overset{-}{\mathrm{O}}$ | 4·52 | −1·57 |
| $\overset{+}{\mathrm{N}}$—OH | 5·40 | +0·88 |
| **16** N: | 5·80 | — |
| $\overset{+}{\mathrm{N}}$—$\overset{-}{\mathrm{O}}$ | 4·55 | −1·25 |
| $\overset{+}{\mathrm{N}}$—OH | 5·39 | +0·86 |
| **17** N: | 4·75 | — |
| $\overset{+}{\mathrm{N}}$—$\overset{-}{\mathrm{O}}$ | 3·50 | −1·25 |
| $\overset{+}{\mathrm{N}}$—OH | 4·35 | +0·85 |
| **18** N: | 5·70 | — |
| $\overset{+}{\mathrm{N}}$—$\overset{-}{\mathrm{O}}$ | 4·10 | −1·60 |
| $\overset{+}{\mathrm{N}}$—OH | 5·10 | +1·00 |



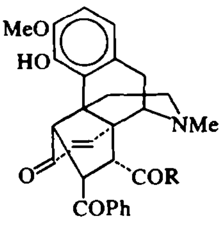
**25**



**26**



**27a**: R = Ph
**27b**: R = OMe



**28**

methoxyl at C-6 also absorbs at relatively high field ($\tau$ 6·74) owing to the C-19 carbonyl group.

Similar alkaline treatment of **5b** gave the simple product of epimerization **3b** and the hemiketal–diketone **27a** which upon acid hydrolysis afforded the phenolic triketone **28a**. This is completely analogous to the nepenthone → isonepenthone → $\psi$-nepenthone rearrangement which has been reported by Bentley.[4f,i] In a separate base-catalyzed reaction it was shown that **3b** also affords **27a**. Attempted reduction of **3a** with sodium borohydride also gave the same product, **27a**.

A completely analogous base-catalyzed rearrangement occurred with **18**. This afforded **27b**, an analog of **27a**. The epimer **16** was also isolated and when treated with base also gave **17b**. Acid hydrolysis of the latter led to **28b**, an analog of **28a**. The similarity in the behavior of **16** and **18** supports the structure of **18** as having the 7-benzoyl group rather than ester group.

Observation of models shows that much strain relief accompanies these rearrangements. It is therefore not surprising that attempts at simple epimerization are succeeded by rather complex though mechanistically-reasonable rearrangements.

## EXPERIMENTAL

IR spectra were measured using a Perkin-Elmer 237 spectrometer. UV spectra were measured using a Cary 14 or Spectronic 505 instrument. The NMR spectra were measured using a Varian A-60 or T-60 spectrometer. MW determinations were made mass spectrometrically using an Atlas CH-4 instrument.

All m.ps are uncorrected. Organic extracts were dried using $Na_2SO_4$ and solvents were removed at the water pump (25–30 torr).

*7β,8α - Diacetyl* - 6,14 - endo - *etheno* - 6,7,8,14 - *tetrahydrothebaine*, **3a**. A solution of thebaine (2·92 g) and *trans*-diacetylethylene[9] (1·05 g) in toluene (80 ml) was heated under reflux for 68 h. Removal of solvent afforded colorless crystals of the diketone **3a** (2·75 g; 75%), m.p. 218–219° (chloroform ethanol). Some thebaine (0·24 g) was recovered. (Found: C, 71·04; H, 6·99; N, 3·28; $M^+$ 423. $C_{25}N_{29}NO_5$ requires C, 76·90; H, 6·90; N, 3·31; M.W. 423·49). IR($CHCl_3$): 1702 cm$^{-1}$(CO). UV(MeOH): $\lambda_{max}$ 287 nm, $\epsilon_{max}$ 1450. NMR($CDCl_3$): $\tau$ 3·32 (d, $J_{2,1}$ = 8Hz, H-2); 3·48 (d, $J_{1,2}$ = 8Hz, H-1); 3·92 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·8Hz, H-18); 4·53 (d, $J_{17,18}$ = 9Hz, H-17) 5·33 (d, $J_{5,18}$ = 1·8Hz, H-5); 5·53 (d, $J_{8,7}$ = 6Hz, H-8); 6·17 (s, 3-OC$\underline{H}_3$); 6·34 (s, 6-OC$\underline{H}_3$); 7·63 (s, NC$\underline{H}_3$, COC$\underline{H}_3$); 7·83 (2s, COC$\underline{H}_3$).

*N-oxide*. m-Chloroperbenzoic acid (43 mg) was added to a solution of **3a** (*105 mg*) in chloroform (2 ml) and the whole was stirred at room temp for 45 min. After washing with aq sodium bicarbonate and drying, the solvent was removed, affording colorless crystals of the' *N*-oxide (80 mg; 72%), m.p. 217° (chloroform–ether). (Found. C, 65·85; H, 6·62; N, 2·89; $M^+$ 423. $C_{25}H_{29}NO_6$. $H_2O$ requires C, 65·62; H, 6·85; N, 3·06%; $M^+$ 423·49). IR($CHCl_3$): 3670 (OH), 1705 cm$^{-1}$ (CO). NMR ($CDCl_3$):$\tau$ 3·34 ($AB_q$, J = 8Hz, H-1, H-2); 3·99 (dd, $J_{18,7}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·23 (d, $J_{17,8}$ = 9Hz, H-17); 4·43 (d, $J_{8,7}$ = 7Hz, H-8); 5·01 (d, $J_{5,18}$ = 2Hz, H-5); 5·80 (m, H-9); 6·15 (s, 3-OC$\underline{H}_3$); 6·37 (s, 6-OC$\underline{H}_3$); 6·61 (s, O←NC$\underline{H}_3$); 7·30 (d, $J_{7,8}$ = 7Hz, H-7); 7·60, 8·00 (2s, COC$\underline{H}_3$). Addition of trifluoroacetic acid shifts H-8$\beta$ to higher field, $\tau$ 5·20.

*7α,8α - Diacetyl* - 6,14 - endo - *etheno* - 6,7,8,14 - *tetrahydrothebaine*, **5a**. A solution of thebaine (0·311 g) and "*cis*"-diacetylethylene[10] (66% *cis* + 34% *trans* by NMR; 0·112 g) in toluene (5 ml) was heated under reflux for 46 h. After removal of solvent, crystallization affords first the *trans*-isomer **3a** (89 mg) m.p. 216° (chloroform–ethanol) identical in all respects with the product described above. The *cis*-diketone **5a** is obtained from the mother liquor (27 mg, 9·6%), m.p. 209° (chloroform–ethanol). (Found: C, 71·03; H, 7·08; N, 3·41; $M^+$ 423). IR($CHCl_3$): 1705 cm$^{-1}$ (CO). UV(MeOH): $\lambda_{max}$ 287 nm, $\epsilon_{max}$ 1840. NMR($CDCl_3$): $\tau$ 3·28 (d, $J_{2,1}$ = 7·5Hz, H-2); 3·45 (d, $J_{1,2}$ = 7·5Hz, H-1); 3·99 (d of finely split doublets, $J_{18,17}$ = 9Hz $J_{18,5}$ = 1·8Hz, $J_{18,7\beta}$ very small, H-18); 4·25 (d, $J_{17,18}$ = 9Hz, H-17); 5·43 (d, $J_{5,18}$ = 1·8Hz, H-5): 5·60 (d, $J_{8,7}$ = 12Hz, H-8); 6·15 (s, 3-OC$\underline{H}_3$); 6·39 (s, 6-OC$\underline{H}_3$), 7·70 (s, NC$\underline{H}_3$); 7·85, 7·97 (2s, COC$\underline{H}_3$).

*Grignard reactions of* **3a**. (a) To a solution of Grignard reagent prepared in dry ether (6 ml) from bromobenzene (0·79 g) and magnesium (0·15 g) was added under nitrogen a solution of **3a** (0·17 g) in benzene (5 ml)–ether (4 ml). The whole was heated under reflux with stirring for 3·5 h. After cooling and decomposition with saturated aq ammonium chloride, separation of phases, extraction of the aqueous phase with $CH_2Cl_2$, drying ($Na_2SO_4$) and removal of solvent, the product, 7$\beta$-($\alpha$-hydroxy-$\alpha$-phenyl)ethyl-8$\alpha$-acetyl-6, 14-*endo*-etheno-6,7,8,14-tetrahydrothebaine, **6a** was obtained as a colorless foam (0·14 g). It was purified by preparative TLC on alumina with chloroform as eluent giving the pure product (0·11 g; 55%), m.p. 242° (ether). (Found: C, 73·86; H, 7·33; N, 2·65; $M^+$ 501. $C_{31}H_{35}NO_5$ requires C, 74·23; H, 7·03; N, 2·79%; $M^+$ 501·60). IR($CHCl_3$): 3460(OH), 1712 cm$^{-1}$ (CO). UV(MeOH): $\lambda\lambda_{max}$ 278 (348), 230 nm (sh, 1390). NMR($CDCl_3$): $\tau$ 2·30–2·85 (m, 5 arom, H); 3·64 (ABq, J = 8Hz, H-1, H-2); 3·75 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·67 (d, $J_{5,18}$ = 2Hz, H-5); 4·88 (d, $J_{17,18}$ = 9Hz, H-17); 5·34 (s, O$\underline{H}$, exchanged in $D_2O$); 6·18 (s, 3-OC$\underline{H}_3$); 6·34 (s, 6-OC$\underline{H}_3$); 7·73 (s, NC$\underline{H}_3$); 8·14 (s, COC$\underline{H}_3$); 8·54 (s, CC$\underline{H}_3$).

(b) To a solution of reagent prepared in dry ether (45 ml) from benzyl chloride (5·7 g) and magnesium (1·08 g) was added a solution of **3a** (1·9 g) in benzene (42 ml)–ether (90 ml). The whole was heated under reflux for 4 h and worked up as above. Purification of the product **6b**, was effected by chromatography on a column of neutral alumina containing 10% water, with benzene as eluent. The product (1·69 g; 73%) had m.p. 197° ($CH_2Cl_2$–ether). (Found: C, 74·26; H, 7·06; N, 2·84; $M^+$ 515. $C_{32}H_{37}NO_5$ requires C, 74·54; H, 7·23; N, 2·72%; $M^+$ 515·62). IR($CHCl_3$): 3450 (OH), 1710 cm$^{-1}$ (CO). UV(MeOH): 287 (1430), 240 nm (sh, 5750). NMR($CDCl_3$): $\tau$ 2·64 (m, 5 arom H); 3·27 (d, $J_{2,1}$ = 8Hz, H-2); 3·45 (d, $J_{1,2}$ = 8Hz, H-1); 3·70 (dd, $J_{18,17}$ = 8Hz, $J_{18,5}$ = 1·8 Hz, H-18); 4·53 (d, $J_{5,18}$ = 1·8Hz, H-5); 4·74 (d, $J_{17,18}$ = 8Hz, H-17): 5·82 (D, $J_{8,7}$ = 7Hz, H-8); 6·14 (s, 3-OC$\underline{H}_3$); 6·30 (s, 6-OC$\underline{H}_3$; 7·00 (br s, O$\underline{H}$, exchanged in -$D_2O$); 7·60 (s, NC$\underline{H}_3$, COC$\underline{H}_3$); 8·85 (s, CC$\underline{H}_3$).

(c) To a solution prepared in dry ether (18 ml) from $\beta$-phenethyl bromide (3·79 g) and magnesium (0·52 g) was added a solution of **3a** (0·84 g) in benzene (24 ml)–ether (60 ml). After 4 h reflux and workup as above, the product **6c** (0·6 g; 57%) had m.p. 161° (chloroform–ether). (Found: C, 74·77; H, 7·52; N, 2·61; $M^+$ 529. $C_{33}H_{39}NO_5$ requires C, 74·83; H, 7·42; N, 2·64%; $M^+$ 529·65). IR($CHCl_3$): 3430(OH), 1710 cm$^{-1}$(CO). UV(MeOH): 287 (1315), 240 nm (sh, 5380). NMR ($CDCl_3$): $\tau$ 2·74 (m, 5 arom H); 3·29 (d, $J_{2,1}$ = 8Hz, H-2); 3·45 (d, $J_{1,2}$ = 8Hz, H-1); 3·70 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·6Hz, H-18); 4·60 (d, $J_{5,18}$ = 1·6Hz, H-5); 4·77 (d, $J_{17,18}$ = 9Hz, H-17); 6·10 (br, s, O$\underline{H}$ exchanged in $D_2O$); 6·14 (s, 3-OC$\underline{H}_3$); 6·24 (s, 6-OC$\underline{H}_3$); 7·61, 7·69 (2s, NC$\underline{H}_3$, COC$\underline{H}_3$); 8·55 (s, CC$\underline{H}_3$).

(d) To a solution of methylmagnesium iodide in dry ether (5 ml) prepared from methyl iodide (0·62 g) and magnesium (97 mg) was added a solution of **3a** (0·21 g) in benzene (6 ml)–ether (12 ml). After reflux for 3·5 h and the usual workup the colorless tertiary alcohol **6d** was obtained (0·18 g; 80%), m.p. 208° ($CH_2Cl_2$-methanol). (Found: C, 71·01; H, 7·49; N, 3·25; M$^+$ 439. $C_{26}H_{33}NO_5$ requires C, 71·04; H, 7·57; N, 3·19%; M$^+$ 439·53). IR($CHCl_3$): 3430 (OH), 1705 cm$^{-1}$ (CO). UV(MeOH): 287 (1550), 240 nm (sh, 5950). NMR($CDCl_3$): $\tau$ 3·30 (d, $J_{2,1}$ = 8Hz, H-2); 3·50 (d, $J_{1,2}$ = 8Hz, H-1); 3·74 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·8Hz, H-18); 4·69 (d, $J_{6,18}$ = 1·8Hz, H-5); 4·79 (d, $J_{17,18}$ = 9Hz, H-17); 5·60–6·40 (br, O$\underline{H}$, exchanged in $D_2O$); 6·09 (d, $J_{8,7}$ = 6Hz, H-8); 6·16 (s, 3-OC$\underline{H}_3$); 6·30 (s, 6-OC$\underline{H}_3$); 7·63 (s, NC$\underline{H}_3$, COC$\underline{H}_3$); 8·63, 8·78 [2s, C(C$\underline{H}_3$)$_2$].

*N-Oxide of* **6d**. Prepared as described above for **3a**. From **6d** (0·11 g), the N-oxide was obtained as a colorless powder (53 mg; 48%), m.p. 211–212° (ether). (Found: N, 3·00; M$^+$—O, 439. $C_{26}H_{33}NO_6$ requires N, 3·08%; M$^+$ 455·53). IR($CHCl_3$): 3650, 3400 (OH), 1690 cm$^{-1}$ (CO). NMR($CDCl_3$): $\tau$ 3·31 (d, $J_{2,1}$ = 8Hz, H-2); 3·53 (d, $J_{1,2}$ = 8Hz, H-1); 3·90 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·6Hz, H-18); 4·30 (d, $J_{5,18}$ = 1·6Hz, H-5); 4·52 (d, $J_{8,7}$ = 6Hz, H-8$\beta$); 4·61 (d, $J_{17,18}$ = 9Hz, H-17) 6·16 (s, 3-OC$\underline{H}_3$); 6·45 (s, 6-OC$\underline{H}_3$); 6·58 (s, O←NC$\underline{H}_3$); 7·34 (s, COC$\underline{H}_3$); 8·00 (d, $J_{7,8}$ = 6Hz, H-7$\alpha$); 8·45, 8·67 (2s, C(C$\underline{H}_3$)$_2$). Addition of trifluoroacetic acid caused upfield shift of H-8$\beta$ to $\tau$ 5·40.

(e) To a solution in dry ether (2·5 ml) prepared from chlorocyclohexane (0·59 g) and magnesium (0·13 g) was added a solution of **3a** (0·21 g) in benzene (7 ml)–ether (12 ml) After 3·5 h reflux and the above workup, the tertiary alcohol **19** afforded colorless crystals (0·21 g; 83%), m.p. 233° ($CH_2Cl_2$–ethanol). (Found: C, 73·51; H, 8·20; N, 2·88; M$^+$ 507. $C_{31}H_{41}NO_5$ requires C, 73·34; H, 8·14; N, 2·76%; M$^+$ 507·65). IR($CHCl_3$): 3440 (OH), 1702 cm$^{-1}$ (CO). UV(MeOH): 287 (1560), 240 nm (sh, 3980). NMR($CDCl_3$): $\tau$ 3·33 (d, $J_{2,1}$ = 7Hz, H-2); 3·49 (d, $J_{1,2}$ = 7Hz, H-1); 3·75 (dd, $J_{18,17}$ = 8Hz, $J_{18,5}$ = 1·8Hz, H-18); 4·50 (d, $J_{5,18}$ = 1·8Hz, H-5); 4·79 (d, $J_{17,18}$ = 8Hz, H-17); 5·81 (d, $J_{8,7}$ = 6Hz, H-8); 6·15 (s, 3-OC$\underline{H}_3$); 6·31 (s, 6-OC$\underline{H}_3$); 6·96 (br s, O$\underline{H}$, exchanged in $D_2O$); 7·45 (d, $J_{7,8}$ = 6Hz, H-7); 7·61 (s, NC$\underline{H}_3$, COC$\underline{H}_3$); 8·90 (s, CC$\underline{H}_3$).

*Sodium borohydride reduction of* **3a**. (a) To a solution of **3a** (0·12 g) in dry ethanol (20 ml) was added sodium broohydride (9·5 mg) and the whole was stirred at room temp for 10 days. Ammonium hydroxide (25%; 15 ml) and methylene chloride were added and the whole was shaken. After separating and drying ($Na_2SO_4$) the organic layer and removal of solvent a colorless foamy residue was obtained. The two isomeric keto-alcohols were separated by TLC on alumina using chloroform as eluent. The 8$\alpha$-acetyl compound **7** (65 mg; 30%) had m.p. 199° (chloroform–ether) and the isomeric 7$\beta$-acetyl compound **8** (60 mg; 28%) had m.p. 204° (chloroform–ether). Admixture of the two caused depression of m.p.

**7**: (Found: C, 70·37; H, 7·54; N, 3·15; M$^+$ 425. $C_{25}H_{31}NO_5$ requires C, 70·56; H, 7·34; N, 3·29%; M$^+$ 425·51). IR($CHCl_3$): 3438(OH), 1710 cm$^{-1}$ (CO). UV(MeOH): 287 nm (1695). NMR($CDCl_3$): $\tau$ 3·38 (ABq, J = 8Hz, H-1, H-2); 3·81 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·6Hz, H-18); 4·74 (d, $J_{17,18}$ = 9Hz, H-17); 4·81 (s, O$\underline{H}$, exchanged in $D_2O$); 5·04 (d, $J_{5,18}$ = 1·6Hz, H-5); 6·04 (m, CH—OH), 5·80–6·30 (m, contg also H-8); 6·15 (s, 3-OC$\underline{H}_3$); 6·30 (s, 6-OC$\underline{H}_3$); 7·61, 7·64 (2s, NC$\underline{H}_3$, COC$\underline{H}_3$); 8·87 (d, J = 6Hz, HO-CHC$\underline{H}_3$). Double resonance showed that the protons at 8·87 and 6·04 are coupled.

**8**: (Found:C, 70·46; H, 7·54; N, 3·09; M$^+$ 425). IR($CHCl_3$): 3460 (OH), 1708 cm$^{-1}$ (CO). UV(MeOH): 287 nm (1340). NMR($CDCl_3$): $\tau$ 3·40 (ABq, J = 8Hz, H-1, H-2); 3·83 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·55 (d, $J_{17,18}$ = 9Hz, H-17); 5·20 (d, $J_{5,18}$ = 2Hz, H-5); 6·08 (br s, O$\underline{H}$, exchanged in $D_2O$); 6·17 (s, 3-OC$\underline{H}_3$); 6·35 (s, 6-OC$\underline{H}_3$); 6·50 (m, HO-C$\underline{H}$); 7·65 (s, NC$\underline{H}_3$, COC$\underline{H}_3$); 8·99 (d, J = 6Hz, HO-CHC$\underline{H}_3$). Here too double resonance showed the connection between protons at 8·99 and 6·50.

(b) Reduction of **3a** (1·05 g) in dry ethanol (75 ml) with sodium borohydride (0·75 g) was carried out by heating under reflux for 5 h. After workup as above a foamy residue (1·045 g; 98%) was obtained consisting of a mixture of diastereomeric diols. Fractional crystallization ($CH_2Cl_2$–ether) afforded the diol **9** (0·1 g; 9·4%), m.p. 237–238° and the isomeric diol **10** (0·2 g; 18·8%), m.p. 184°, in addition to a mxiture of the two (0·4 g; 38%).

**9**: (Found: C, 70·73; H, 7·78; N, 3·31; M$^+$ 427. $C_{25}H_{33}NO_5$ requires C, 70·23; H, 7·78; N, 3·28% M$^+$ 427·52). IR($CHCl_3$): 3600–3140 cm$^{-1}$ (OH). UV(MeOH): 276 (2930), 241 nm (sh, 5320). NMR($CDCl_3$): $\tau$ 3·25 (d, $J_{2,1}$ = 8Hz, H-2); 3·43 (d, $J_{1,2}$ = 8Hz, H-1); 3·90 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·46 (d, $J_{17,18}$ = 9Hz, H-17); 4·88 (d, $J_{5,18}$ = 2Hz, H-5); 4·90–5·15 (br, O$\underline{H}$, exchanged in $D_2O$); 5·80 (m, HOC$\underline{H}$, coupled with 8·62); 6·10 (m, HOC$\underline{H}$, coupled with 8·77); 6·60–7·10 (br, O$\underline{H}$, exchanged in $D_2O$); 6·14 (s, 3-OC$\underline{H}_3$); 6·30 (s, 6-OC$\underline{H}_3$); 7·63 (s, NC$\underline{H}_3$); 8·62 (d, J = 6Hz, HO-CHC$\underline{H}_3$, coupled with 5·80); 8·77 (d, J = 6Hz, HO-CHC$\underline{H}_3$, coupled with 6·10).

**10**: (Found: C, 70·34; H, 7·64; N, 3·32; M$^+$ 427). IR($CHCl_3$): 3600–3160 cm$^{-1}$ (OH). UV(MeOH): 285 (1280), 240 nm (sh, 4410). NMR($CDCl_3$); $\tau$ 3·25 (d, $J_{2,1}$ = 8Hz, H-2); 3·43 (d, $J_{1,2}$ = 8Hz, H-1); 3·96 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·8Hz, H-18); 4·51 (d, $J_{17,18}$ = 9Hz, H-17); 4·74 (br s, O$\underline{H}$, exchanged in $D_2O$); 4·93 (d, $J_{5,18}$ = 1·8Hz, H-5); 5·85 (m, HOC$\underline{H}$, coupled with 8·63); 6·10 (m, HOC$\underline{H}$, coupled with 8·97); 6·60–7·10 (br, O$\underline{H}$, exchanged in $D_2O$); 6·14 (s, 3-OC$\underline{H}_3$); 6·30 (s, 6-OC$\underline{H}_3$); 7·63 (s, NC$\underline{H}_3$); 8·63 (d, J = 6Hz, HO-CHC$\underline{H}_3$, coupled with 5·85); 8·97 (d, J = 6Hz, HO-CHC$\underline{H}_3$, coupled with 6·10).

A mixture of **9** and **10**, similar in NMR spectrum to that obtained above was obtained by reducing **3a** (0·21 g) with LAH (0·19 g) in dry THF (4·5 ml). After 3·5 h reflux and decomposing with moist THF, the usual workup gave the diol mixture as a colorless solid (0·21 g; 99%). It was not separated into its components.

*Addition of* cis-*dibenzoylethylene to thebaine.* A solution of thebaine (9·3 g) and *cis*-dibenzoylethylene[11] (7·08 g) in toluene (60 ml) was heated under reflux for 8 h. After 3 h some solid begins to separate. The solvent was removed in a vacuum and the residue was triturated with methanol affording 7$\alpha$,8$\alpha$-*dibenzoyl*-6,14-endo-*ethenotetrahydrothebaine*, **5b**, as colorless prisms (3·6 g; 22%), m.p. 243–244°. The analytical sample had m.p. 244° (chloroform–ethanol). (Found: C, 77·01; H, 6·04; N, 2·59; M$^+$ 547. $C_{35}H_{33}NO_5$ requires C, 76·76; H, 6·07; N, 2·56%; M$^+$ 547·62). IR($CHCl_3$): 1690 cm$^{-1}$ (CO). NMR($CDCl_3$): $\tau$ 1·90–2·80 (m, 10 arom H); 3·34 (s, H-1, H-2); 3·90 (s, H-7$\alpha$, H,-8$\alpha$); 4·82, 5·45 (ABq, $J_{18,17}$ = 11Hz, H-17, H-18); 5·20 (s, H-5); 6·17 (s, 3-OC$\underline{H}_3$); 6·38 (s, $J_{10\beta,10\alpha}$ = 20Hz, H-10$\beta$); 6·50 (s, 6-OC$\underline{H}_3$); 7·22 (d, $J_{9\alpha,10\alpha}$ = 6Hz, H-9$\alpha$); 7·77 (q, $J_{10\alpha,10\beta}$ = 20Hz, $J_{10\alpha,9\alpha}$ = 6Hz, H-10$\alpha$); 7·80 (s, NC$\underline{H}_3$).

After removal of solvent from the mother liquor and triturating with methanol the isomeric 7β, 8α- compound, **3b**, was obtained as long colorless needles (6·1 g; 37%), m.p. 159°, raised to 161° (chloroform–ethanol). (Found: C, 76·70; H, 6·01; N, 2·63; M$^+$ 547). IR(CHCl$_3$): 1670 cm$^{-1}$ (CO). NMR CDCl$_3$): τ, 1·80–2·80 (m, 10 arom H); 3·30, 3·42 (ABq J = 8Hz, H-1, H-2); 3·80 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·38 (d, $J_{17,18}$ = 9Hz, H-17); 4·70 (d, $J_{5,18}$ = 2Hz, H-5); 6·17 (s, 3-OC$\underline{H}_3$); 6·60 (s, 6-OC$\underline{H}_3$); 6·80 (d, $J_{10\beta,10\alpha}$ = 18Hz, H-10β); 6·80 (d, $J_{9\alpha,10\alpha}$ = 6Hz, H-9α); 7·66 (q, $J_{10\alpha,10\beta}$ = 18Hz, $J_{10\alpha,9\alpha}$ = 6Hz, H-10α); 8·07 (s, NC$\underline{H}_3$).Chromatography of the mother liquor on neutral alumina yielded more of **5b** (0·54 g; 3·3%) and **3b** (0·99 g; 6%).

*Addition of* trans-*dibenzoylethylene to thebaine.* A solution of thebaine (15·5 g) and *trans*-dibenzoylethylene[12] (16·8 g) in toluene (100 ml) was treated exactly as above fro the *cis*-dienophile. The *trans*-isomer **3a** was obtained (21·9 g; 68%). m.p. and mixed m.p. 160° identical in all respects with the *trans*-isomer described above.

cis-7α,8α-Bis(1-*Hydroxybenzyl*)6,14-endo-*etheno-tetrahydrothebaine*, **11**. To a mixture of LAH (3·42 g) in dry THF (45 ml) was added added a solution of the *cis*-adduct **5b** (4·92 g) in dry THF (300 ml) under nitrogen. The whole was heated under reflux with stirring for 3·5 h. After cooling to 0° and adding moist THF until excess reagent was decomposed the mixture was diluted with CH$_2$Cl$_2$ and filtered. The filtrate was concentrated in a vacuum. The residue afforded **11** as colorless crystals (3·61 g; 73%), m.p. 247–248° (ether–chloroform). (Found: C, 76·50; H, 6·71; N, 2·55; M$^+$ 551. C$_{35}$H$_{37}$NO$_5$ requires C, 76·20; H, 6·76; N, 2·54%; M$^+$ 551·65). IR(CHCl$_3$): 3480 cm$^{-1}$ (OH), unchanged on dilution. NMR (CDCl$_3$): τ 2·00–3·00 (m, 10 arom H); 3·35, 3·55 (ABq, J = 6Hz, H-1, H-2); 4·15 (d, $J_{18,17}$ = 7Hz, H-18); 4·35 (d, $J_{17,18}$ = 7Hz, H-17); 4·58 (br s, H-7, H-8); 5·50 (s, H-5); 6·20 (s, 3-OC$\underline{H}_3$); 6·00–6·80 (m, 19-O$\underline{H}$, 20-O$\underline{H}$); 7·08 (s, 6-OC$\underline{H}_3$); 8·65 (s, NC$\underline{H}_3$).

The *diacetate* was prepared by stirring a mixture of **11** (0·165 g), acetic anhydride (2 ml) and pyridine (5 ml) at room temp for 63 h. The solvents were removed at reduced pressure and the residue taken up in chloroform. After washing with aqueous sodium bicarbonate and drying the solution was concentrated and chromatographed on neutral alumina. Elution with hexane–benzene (1:1) gave a colorless oil (0·145 g; 76·5%) which formed an amorphous solid, m.p. 154–157° (carbon tetrachloride–hexane). (Found: M$^+$ 635. C$_{39}$H$_{41}$NO$_7$ requires M$^+$ 635·73). IR(CHCl$_3$): 1740, 1730 cm$^{-1}$ (CO). NMR(CDCl$_3$): τ 2·30–3·00 (m, 10 arom H); 4·00 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1Hz, H-18); 4·55 (d, $J_{17,18}$ = 9Hz, H-17); 5·50( d, $J_{5,17}$ = 1Hz, H-5); 6·19 (s, 3-OC$\underline{H}_3$); 6·88 (s, OC$\underline{H}_3$); 7·75 (s, OCOC$\underline{H}_3$); 7·85 (s, OCOC$\underline{H}_3$); 8·02 (s, NC$\underline{H}_3$).

trans-7β,8α-Bis(1-*Hydroxybenzyl*)-6,14 endo-*ethenotetrahydrothebaine*, **12**. The adduct **3b** (1·64 g) was reduced as was **5b**, with LAH (1·14 g) in dry THF (75 ml). After the same workup an amorphous diol **12** was obtained, m.p. 185–190° (isopropyl ether). (Found: C, 76·34; H, 6·72; N, 2·48%). IR(CHCl$_3$): 3380 cm$^{-1}$ (OH). NMR(CDCl$_3$): τ 2·20–3·20 (m, 10 arom, H); 3·90 (dd, $J_{18,7}$ = 9Hz, $J_{18,5}$ = 1Hz, H-18); 4·43 (d, $J_{17,18}$ = 9Hz, H-17); 4·52 (d, $J_{5,18}$ = 1·5 Hz, H-5); 5·35, 5·70 (ABq, J = 6Hz, H-7, H-8); 6·20 (s, 3-OC$\underline{H}_3$); 7·00 (s, 6-OC$\underline{H}_3$); 8·02 (s, NC$\underline{H}_3$).

*Grignard reaction of* **5b**. A solution of **5b** (1·09 g) in dry ether (1:2; 90 ml) was added under nitrogen with stirring to methylmagnesium iodide (from 0·49 g magnesium and 3·1 g methyl iodide) in dry ether (25 ml). The whole was heated under reflux for 2 h, cooled to 0° and shaken with aq ammonium chloride. The organic layer was separated and dried and the solvent evaporated, yielding a colorless oil (1·08 g). Several fractional crystallizations afforded colorless crystals of the hemiketal **14** (0·14 g), m.p. 180–182° (hexane–ether). (Found: C, 76·83; H, 6·74; N, 2·54; M$^+$ 563. C$_{36}$H$_{37}$NO$_5$ requires C, 76·71; H, 6·61; N, 2·49%; M$^+$ 563·66). IR(CHCl$_3$): 3560, 3540 cm$^{-1}$ (OH). NMR(DMSO-d$_6$): τ 2·00–3·00 (m, 10 arom H); 3·50 (s, H-1, H-2); 4·60 (d, $J_{18,17}$ = 9Hz, H-18); 5·20 (d, $J_{17,18}$ = 9Hz, H-17); 5·62 (s, H-5); 6·40 (s, 3-OC$\underline{H}_3$); 7·00 (s, 6-OC$\underline{H}_3$); 7·80 (s, NC$\underline{H}_3$); 8·32 (s, C-C$\underline{H}_3$).

Workup of the mother liquor by fractional crystallization afforded the isomeric hemiketal, **15** (9·16 g), m.p. 136–138°. (Found: C, 76·58; H, 6·48; N, 2·42%; M.W. 563). IR(CHCl$_3$): 3560 cm$^{-1}$ (OH). NMR (DMSO-d$_6$): τ 2·00–3·00 (m, 10 arom H); 3·30, 3·50 (ABq, J = 5Hz, H-1, H-2); 4·10 (d, $J_{18,17}$ = 9Hz, H-18); 4·50 (d, $J_{17,18}$ = 9Hz, H-17); 5·52 (s, H-5); 6·30 (s, 3-OC$\underline{H}_3$); 6·52 (s, 6-OC$\underline{H}_3$); 6·70 (s, NC$\underline{H}_3$); 8·28 (s, C-C$\underline{H}_3$).

*Grignard reaction of* **3b**. A solution of **3a** (0·545 g) in dry benzene–ether (1:2; 45 ml) was added under nitrogen with stirring to the Grignard reagent from magnesium (0·243 g) and methyl iodide (0·7 ml) in dry ether (15 ml). The whole was treated exactly as described above for **5a**. The residual foamy oil afforded colorless needles of the isomeric rearranged product **13** (0·32 g; 56%), m.p. 246–247°. (Found: C, 76·86; H, 6·78; N, 2·38%; M$^+$ 563). IR(CHCl$_3$); 3590, 3400 (OH), 1670 cm$^{-1}$ (CO). NMR(DMSO-d$_6$): τ 2·20–3·70 (m, 10 arom H + H − 1 + H − 2); 3·92 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1Hz, H-18); 4·25 (d, $J_{5,18}$ = 1Hz, H-5); 4·88 (d, $J_{17,18}$ = 9Hz, H-17); 5·30 (d, $J_{8,7}$ = 5Hz, H-8); 6·28 (s, 3-OC$\underline{H}_3$); 6·40 (s, 6-OC$\underline{H}_3$); 6·55 (s, NC$\underline{H}_3$); 7·10 (d, $J_{7,8}$ = 5Hz, H-7); 8·42 (s, C-C$\underline{H}_3$).

7β-*Benzoyl*-8α-*methoxycarbonyl*-6,14-endo-*etheno*-6,7,8,14-*tetrahydrothebaine*, **16**. A solution of thebaine (3·11 g) and *trans*-methyl benzoylacrylate[13] (1·90 g) in toluene (30 ml) was heated under reflux for 65 h. Removal of solvent and fractional crystallization of the residue gave **16** (2·3 g; 47%), m.p. 185–186°. The analytical sample had m.p. 191° (CH$_2$Cl$_2$–ethanol). The isomer **17** was obtained from the mother liquor (1·4 g; 28%). When analytically pure it had m.p. 153° (ethanol). A mixture of **16** and **17** still remained in the mother liquor but the isomers could not be separated by crystallization or TLC.

**16**: (Found: C, 71·85; H, 6·22; N, 2·88, M$^+$ 501. C$_{30}$H$_{31}$NO$_6$ requires C, 71·84; H, 6·23; N, 2·79% M$^+$ 501·56). IR(CHCl$_3$): 1730 (ester CO), 1680 cm$^{-1}$ (ketone). UV(MeOH): 275 (2230), 247 nm (1600). NMR(CDCl$_3$): τ 1·80–2·73 (m, 5 arom H); 3·30 (d, $J_{2,1}$ = 8Hz, H-2); 3·45 (d, $J_{1,2}$ = 8Hz, H-1); 3·80 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·40 (d, $J_{17,18}$ = 9Hz, H-17); 4·74 (d, $J_{5,18}$ = 2Hz, H-5); 5·87 (ABq, J = 6Hz, H-8β, *H*-7α); 6·17 (s, 3-OC$\underline{H}_3$); 6·39 (s, 6-OC$\underline{H}_3$); 6·59 (s, CO$_2$C$\underline{H}_3$); 7·63 (s, NC$\underline{H}_3$).

*N-oxide of* **16**. From **16** (125 mg) was obtained as above the N-oxide (106 mg; 82%), m.p. 209° (ether). (Found: N, 2·47; M$^+$—O, 501. C$_{30}$H$_{31}$NO$_7$ requires N, 2·71%; M$^+$ 517·56). IR(CHCl$_3$): 3660, 1735, 1680 cm$^{-1}$. NMR(CDCl$_3$): τ 1·87–2·77 (m, 5 arom H); 3·35 (ABq, J = 8Hz, H-1, H-2); 3·87 (dd, $J_{18,17}$ = 8Hz, $J_{8,5}$ = 2Hz, H-18); 4·21 (d, $J_{17,18}$ = 8Hz, H-17); 4·57 (d, $J_{8,7}$ = 6Hz, H-8β); 4·60 (d, $J_{5,18}$ = 2Hz, H-5); 5·47 (m, H-9); 6·15 (s, 3-OC$\underline{H}_3$); 6·30 (d, $J_{7,8}$ = 6Hz, H-7α); 6·45 (s, 6-OC$\underline{H}_3$); 6·58 (s, CO$_2$C$\underline{H}_3$); 6·64 (s, NH$\underline{H}_3$). Addition of trifluoroacetic acid in ratio 1:1·2 caused a significant change in the chemical shift of H-8β to higher field, to τ 5·39.

8α-*Benzoyl*-7β-*methoxycarbonyl*-6, 14-endo-*etheno*-6, 7,8,14 - *tetrahydrothebaine*, **17**. (See above under **16**). (Found: C, 72·00; H, 6·38; N, 2·84; $M^-$ 501). IR(CHCl$_3$): 1728 (ester CO), 1680 cm$^{-1}$ (ketone). UV(MeOH): 275 (1820), 242·5 nm (1300). NMR(CDCl$_3$): $\tau$ 1·80–2·73 (m, 5 arom H); 3·30 (d, $J_{2,1}$ = 8Hz, H-2); 3·49 (d, $J_{1,2}$ = 8Hz, H-1); 3·91 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·39 (d, $J_{17,18}$ = 9Hz, H-17); 4·75 (d, $J_{8,7}$ = 6Hz, H-8$\beta$); 4·99 (d, $J_{5,\beta}$ = 2Hz, H-5); 6·17 (s, 3-OC$\underline{H}_3$); 6·31 (s, CO$_2$C$\underline{H}_3$); 6·45 (s, 6-OC$\underline{H}_3$); 8·01 (s, NC$\underline{H}_3$); 8·01 (d, $J_{7,8}$ = 6Hz, H-7$\alpha$).

*N-oxide*. This was obtained as above from **17** (100 mg) as a colorless amorphous powder (92 mg; 89%), m.p. 216–217° (ether). (Found: N, 2·48; $M^+$ 501). IR(CHCl$_3$): 3650, 1730, 1680 cm$^{-1}$. NMR(CDCl$_3$): $\tau$ 2·00–2·70 (m, 5 arom H); 3·33 (ABq, J = 8Hz, H-1, H-2); 3·50 (d, $J_{8,7}$ = 7Hz, H-8$\beta$); 4·04 (ABq, H-17, H-18); 4·73 (br s, H-5); 5·50 (m, H-9); 6·15 (s, 3-OC$\underline{H}_3$); 6·41, 6·56 (2s, CO$_2$C$\underline{H}_3$, 6-OC$\underline{H}_3$); 6·66 (s, NC$\underline{H}_3$); 7·55 (d, $J_{7,8}$ = 7Hz, H-7$\alpha$). Addition of trifluoroacetic acid (1 : 1·2) shifted H-8$\beta$ to higher field, to $\tau$ 4·34.

*Reduction of* **17** *with LAH*. A solution of **17** (0·15 g) in dry THF (3 ml) was added to LAH (114 mg) in dry THF (1·5 ml) and the whole was heated under reflux for 3·5 h. After the usual workup, the diol **19** was obtained (85 mg; 59%) as colorless crystals, m.p. 273–274°. The analytical specimen had m.p. 278·5° (chloroform–ether). (Found: C, 73·27; H, 6·78; N, 3·19; $M^+$ 475. $C_{29}H_{33}NO_5$ requires C, 73·24; H, 7·00; N, 2·95%; $M^+$ 475·56). IR(CHCl$_3$): 3600–3100 cm$^{-1}$ (br, OH). UV(MeOH): 285(1325), 240 nm (sh, 4580). NMR(CDCl$_3$): $\tau$ 2·63 (s, 5 arom H); 3·27 (d, $J_{2,1}$ = 8Hz, H-2); 3·42 (d, $J_{1,2}$ = 8Hz, H-1); 3·80 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·47 (d, $J_{17,18}$ = 9Hz, H-17); 5·03 (d, $J_{5,18}$ = 2Hz, H-5); 5·58 (d, $J_{8,7}$ = 8Hz, H-8); 5·00–6·00 (1H, O$\underline{H}$); 6·16 (s, 3-OC$\underline{H}_3$); 6·47 (s, 6-OC$\underline{H}_3$); 7·58 (s, NC$\underline{H}_3$), 7·60 (1H, O$\underline{H}$).

7$\alpha$*-Benzoyl-8*$\alpha$*-methoxycarbonyl*-6, 14-endo-*etheno*-6, 7,8,14-*tetrahydrothebaine*, **18**. A solution of thebaine (155 mg) and *cis*-methyl benzoylacrylate[13b] (95 mg) in toluene (4 ml) was heated under reflux for 50 h. Removal of solvent and fractional crystallization afforded **18** (52 mg; 21%) which crystallized first, m.p. 258–260° (chloroform–ethanol). The already known isomers **16** and **17** crystallized from the mother liquor. (Found: C, 72·28; H, 6·56; N, 2·98; $M^+$ 501). IR (CHCl$_3$): 1740 (ester CO); 1685 cm $^1$ (ketone). UV(MeOH): 275 (3000), 245 nm (20950). NMR(CDCl$_3$): $\tau$ 1·90–2·80 (m, 5 arom H); 3·38 (ABq, J = 8Hz, H-1, H-2); 3·90 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·16 (d, $J_{17,18}$ = 9Hz, H-17); 5·37 (d, $J_{5,18}$ = 2Hz, H-5); 5·70 (s, H-7, H-8); 6·17 (s, 3-OC$\underline{H}_3$); 6·55, 6·65 (2s, CO$_2$C$\underline{H}_3$, 6-OC$\underline{H}_3$); 7·67 (s, NC$\underline{H}_3$). (Py-d$_5$): 1·60–2·85 (m, 5 arom H); 3·14 (d, $J_{2\,1}$ = 7Hz, H-2); 3·33 (d, $J_{1\,2}$ = 7Hz, H-1); 3·70 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = very small, H-18); 3·92 (d, $J_{17,18}$ = 9Hz, H-17); 5·00 (d, very small J, H-5$\beta$); 5·17 (d, $J_{8,7}$ = 11Hz, H-8$\beta$); 5·41 (d, $J_{7,8}$ = 11Hz, H-7$\beta$); 6·21 (s, 3-OC$\underline{H}_3$); 6·52, 6·65 (2s, CO$_2$C$\underline{H}_3$, 6-OC$\underline{H}_3$); 7·76 (s, NC$\underline{H}_3$).

*N-oxide*. From **18** (100 mg) this was obtained as above as a colorless amorphous powder (90 mg; 87%), m.p. 194–5° (ether). (Found: N, 2·38; $M^+$ 501). IR(CHCl$_3$): 3650, 1740, 1690 cm$^{-1}$. NMR(CDCl$_3$): $\tau$ 1·82–2·64 (m, 5 arom, H); 3·33 (ABq, J = 8Hz, H-1, H-2); 3·88 (d of finely split doublets, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·4Hz, $J_{18,7}$ very small, H-18); 4·09 (d, $J_{17,18}$ = 9Hz, H-17); 4·10 (d, $J_{8,7}$ = 11Hz, H-8$\beta$); 5·20 (d, $J_{5,18}$ = 1Hz, H-5$\beta$); 5·44 (m, H-9); 5·57 (dd, $J_{7,8}$ = 11Hz, $J_{7,18}$ very small, H-7$\beta$); 6·16 (s, 3-OC$\underline{H}$); 6·55, 6·65 (2s, 6-OC$\underline{H}_3$, CO$_2$CH$_3$, NC$\underline{H}_3$). Addition of trifluoroacetic acid (1 : 1·2) shifted H-8$\beta$ to higher field, to $\tau$ 5·10.

*Grignard reaction of* **16**. To a solution of reagent prepared in dry ether (50 ml) from methyl iodide (6·2 g) and magnesium (0·97 g) was added under nitrogen a solution of **16** (2·0 g) in dry benzene (60 ml)–ether (120 ml) and the whole was heated under reflux for 2·5 h. After workup as above a foamy residue of the tertiary alcohol **20** was obtained (2·01 g; 98%). It had m.p. 135–150° (ethanol). Even with a 30-fold excess of reagent and heating for 8·5 h the same product was obtained in similar yield. (Found: N, 2·65; $M^+$ 517. $C_{31}H_{35}NO_6$ requires N, 2·71%; $M^+$ 517·60). IR(CHCl$_3$): 3540–3200 (OH), 1730 cm$^{-1}$ (ester CO). UV(MeOH): 285(1190), 243 nm (sh, 4345). NMR(CDCl$_3$): $\tau$ 2·20–2·83 (m, 5 arom H); 3·38 (d, $J_{2,1}$ = 8Hz, H-2); 3·55 (d, $J_{1,2}$ = 8Hz, H-1); 3·79 (dd, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 2Hz, H-18); 4·75 (d, $J_{17,18}$ = 9Hz, H-17); 5·10 (d, $J_{5,18}$ = 2Hz, H-5); 5·79 (s, O$\underline{H}$ exchanged in D$_2$O); 6·20 (s, 3-OC$\underline{H}_3$); 6·27 (s, 6-OC$\underline{H}_3$); 6·59 (s, CO$_2$C$\underline{H}_3$); 7·73 (s, NC$\underline{H}_3$); 8·28 (s, CC$\underline{H}_3$).

*Grignard reaction of* **17**. Reagent from methyl iodide (1·24 g) and magnesium (0·2 g) in dry ether (5 ml) was treated under nitrogen with a solution of **17** (0·30 g) in benzene (14 ml)-ether (10 ml) and the whole was heated for 4 h. After the usual workup a colorless foam consisting of a mixture of **21** and **22** was obtained (0·30 g). Separation was effected by TLC on alumina with chloroform as eluent. The first fraction **21** (55 mg; 18%) had m.p. 217–218° (chloroform–ether). The second fraction gave the major product, **22** (170 mg; 55%), m.p. 144–145° (ethanol).

**21**: (Found: N, 2·68; $M^+$ 517. $C_{31}H_{35}NO_6$ requires N, 2·71%; $M^+$ 517·60). IR(CHCl$_3$): 3500–3160 (OH), 1730 cm$^{-1}$ (ester CO). UV(MeOH): 285 (1420), 245 nm (sh, 5000). NMR(CDCl$_3$): $\tau$ 2·43–2·89 (m, 5 arom H); 3·40 (ABq, J = 7Hz, H-1, H-2); 3·98 (dd, $J_{18,17}$ = 8Hz, $J_{18,5}$ = 2Hz, H-18); 4·47 (d, $J_{17,18}$ = 8Hz, H-17); 5·10 (d, $J_{5,18}$ = 2Hz, H-5); 6·01 (d, $J_{9,10}$ = 6Hz, H-9); 6·19 (s, 3-OC$\underline{H}_3$); 6·54 (s, 6-OC$\underline{H}_3$); 6·90 (s, CO$_2$C$\underline{H}_3$); 7·55 (s, NC$\underline{H}_3$); 8·57 (s, CC$\underline{H}_3$).

**22**: (Found: N, 2·71; $M^+$ 517). IR(CHCl$_3$): 3540 (OH), 1735 cm$^{-1}$ (ester CO). UV(MeOH): 272(1850), 235 nm (sh, 6070). NMR(CDCl$_3$): $\tau$ 1·72–2·83 (m, 5 arom H); 3·63 (ABq, J = 8Hz, H-1, H-2); 3·72 (d, $J_{18,17}$ = 9Hz, H-18); 4·27 (s, phenolic O$\underline{H}$); 4·58 (d, $J_{17,18}$ = 9Hz, H-17); 6·30 or 6·92 (s, H-5); 6·46 (s, 6-OC$\underline{H}_3$); 7·98 (s, NC$\underline{H}_3$); 8·40 (s, CC$\underline{H}_3$).

*Grignard reaction of* **18**. Reagent from methyl iodide (0·62 g) and magnesium (0·1 g) in dry ether (5 ml) was treated with a solution of **18** (0·14 g) in benzene (5·5 ml)-ether (2 ml) and the whole heated under nitrogen for 3 h. After the usual workup the foamy product (0·13 g) consisting of two lactones was obtained. Crystallization affords **23** (70 mg), m.p. 270° (chloroform–ether). The mother liquor gave a residue which was purified by TLC on alumina with benzene–chloroform (2 : 1) as eluent. Another crop of **23** was isolated (20 mg; total 66%). An isomer **24** was also obtained (16 mg; 12%), m.p. 260° (chloroform–ether).

**23**: (Found: N, 2·94; $M^+$ 485. $C_{30}H_{31}NO_5$ requires N, 2·88%; $M^+$ 485·56). IR(CHCl$_3$): 1762 cm$^{-1}$ (lactone CO). UV(MeOH): 288 nm (2300). NMR(CDCl$_3$): $\tau$ 2·67 (br s, 5 arom H); 3·40 (ABq, J = 8Hz, H-1, H-2); 4·27 (d of finely split doublets, $J_{18,17}$ = 9Hz, $J_{18,5}$ = 1·5Hz, $J_{18,7}$ small, H-18); 4·59 (d, $J_{17,18}$ = 9Hz, H-17); 5·58 (d, $J_{8,7}$ = 10Hz, H-8); 5·73 (d, $J_{5,18}$ = 1·5Hz, H-5); 5·80 (d, $J_{9,10}$ = 6Hz, H-9); 6·27 (s, 3-OC$\underline{H}_3$); 7·18 (s, 6-OC$\underline{H}_3$); 7·31 (d, $J_{7,8}$ = 10Hz, H-7); 7·54 (s, NC$\underline{H}_3$); 8·20 (s, CC$\underline{H}_3$).

**24**: (Found: C, 74·01; H, 6·40; N, 2·94, $M^+$ 485. $C_{30}H_{31}NO_5$ requires C, 74·20; H, 6·44; N, 2·88%; $M^+$ 485·56). IR(CHCl$_3$): 1762 cm$^{-1}$ (lactone CO). UV(MeOH): 288 nm (1450). NMR(CDCl$_3$): $\tau$ 2·63 (br s, 5 arom H); 3·39

(ABq, J = 9Hz, H-1, H-2); 3·78 (d of finely split doublets $J_{18,17} = 9$Hz, $J_{18,5} = 1·6$Hz, $J_{18,7}$ small, H-18); 4·50 (d, $J_{17,18} =$ 9Hz, H-17); 5·59 (d, $J_{5,18} = 1·6$Hz, H-5); 5·86 (br d, $J_{8,7} =$ 10Hz, H-8β and $J_{9,10} = 6$Hz, H-9α); 6·17 (s, 3-OC$\underline{H}_3$); 6·21 (s, 6-OC$\underline{H}_3$); 7·60 (s, NC$\underline{H}_3$); 8·23 (s, CC$\underline{H}_3$).

*Alkaline rearrangement of* **3a**. A solution of **3a** (0·63 g) and potassium hydroxide (0·6 g) in aq (0·6 ml) methanol (3 ml) was heated for 70 min at 85°. After cooling and dilution with water saturated aq ammonium chloride was added. Extraction by $CH_2Cl_2$, drying and evaporation of solvent afforded **25** as a colorless powder (0·63 g; quant). The analytical sample had m.p. 230–231° (ether). (Found: N, 3·53; M$^+$ 423. $C_{25}H_{29}NO_5$ requires N, 3·31%; M$^+$ 423·49). IR($CHCl_3$): 3450(OH), 1708, 1680(CO), 1647 cm$^{-1}$. UV(MeOH): 277(2350), 240 nm (sh, 3700). NMR($CDCl_3$): τ 3·36 (s, H-1, H-2); 4·17 (br s, phenolic O$\underline{H}$, exchanged in $D_2O$); 5·40 (dd, $J_{7,8} = 7$Hz, $J_{7,5} = 2$Hz, H-7); 6·15 (s, 3-OC$\underline{H}_3$); 6·18 (d, $J_{5,7} = 2$Hz, H-5); 6·74 (s, 6-OC$\underline{H}_3$); 7·44 (d, $J_{8,7} = 7$Hz, H-8); 7·74, 7·78 (2s, NC$\underline{H}_3$, 2COC$\underline{H}_3$).

17,18 - *Dehydro* - 7,8 - *dihydro* - 5,14 - (17,18 - *di* - *acetylethano*) - *thebaine* - *A*, **26**. A solution of **25** (0·1 g) in hydrochloric acid (2N; 0·9 ml) was allowed to stand at room temperature for 10 min. Extraction with $CH_2Cl_2$, drying and removal of solvent afforded a residue which after treatment with ether gave a colorless powder (43 mg; 46%). The analytical sample of **26** had m.p. 156° (chloroform–ether). (Found: N, 2·95; M$^+$ 409. $C_{24}H_{27}NO_5$ requires N, 3·42%; M$^+$ 409·46). IR($CHCl_3$): 3530 (OH), 1725, 1720, 1690 cm$^{-1}$ (CO). NMR($CDCl_3$): τ 3·30 (s, H-1, H-2); 5·70 (H-5, Lit. analogy[41]); 6·20 (s, 3-OC$\underline{H}_3$); 6·40–6·80 (O$\underline{H}$, exchanged in $D_2O$); 7·70, 7·73, 7·75 (3s, NC$\underline{H}_3$, 2COC$\underline{H}_3$).

*Alkaline rearrangement of* **3b**. (a) To a solution of potassium hydroxide (1·12 g) in aq methanol (1 : 1; 100 ml) was added a solution of the *trans*-adduct **3b** (5·57 g) in dioxan (300 ml). After heating under reflux under nitrogen for 4 h, $CH_2Cl_2$ and saturated ammonium chloride solution were added and the phases were separated. After another extraction with $CH_2Cl_2$ the combined organic extracts were washed with saturated salt solution, dried ($Na_2SO_4$) and the solvent removed in a vacuum. The solid residue afforded colorless crystals of **27a** (5·5 g; 99%), m.p. 220–221° ($CH_2Cl_2$–ethanol). (Found: C, 76·66; H, 6·04; N, 2·65; M$^+$ 547. $C_{35}H_{33}NO_5$ requires C, 76·76; H, 6·07; N, 2·56; M$^+$ 547·62). IR($CHCl_3$); 1670 cm$^{-1}$ (CO). NMR($CDCl_3$): τ 1·6–2·8 (m, 10 arom H); 3·40 (s, H-1, H-2); 4·20 (d, $J_{8,7} = 7$Hz, H-8); 5·08 (dd, $J_{7,8} = 7$Hz, $J_{7,5} = 2$Hz, H-7); 6·18 (s, 3-OC$\underline{H}_3$); 6·38 (s, 6-OC$\underline{H}_3$); 7·20 (d, $J_{5,7} =$ 2Hz, H-5); 7·65 (s, N-C$\underline{H}_3$).

(b) Solid **3b** (0·547 g) was added to a solution of sodium borohydride (0·38 g) in a 2-ethoxyethanol (10 ml). It dissolved as the whole was heated under reflux under nitrogen for 4 h. To the cooled solution was added 25% ammonium hydroxide and the mixture was extracted thrice with $CH_2Cl_2$. After workup as above the solid residue gave the rearranged product **27a** (0·27 g; 49%), m.p. and mixed m.p. 220° identical in all respects to the product described, under (a) above.

*Isomerization and rearrangement of* **5b**. A solution of **5b** (0·273 g) in dry dioxan (60 ml) was added to one of sodium methoxide (from 46 mg sodium) in dry methanol (5 ml) and the whole was heated under reflux for 2 h. A precipitate was observed after 30 min. After addition of water and $CH_2Cl_2$ and workup as above, **27a** (85 mg; 31%), m.p. and mixed m.p. 220° (chloroform–ethanol), was obtained, identical in all respects with the product described above. Concentration of the mother liquor afforded **3b** (obtained by simple alkaline epimerization of **5b** (95 mg; 35%), m.p. and mixed m.p. 158°, identical in all respects with **3b** described above.

cis-17, 18-*Dibenzoyl*-5, 14-*ethanothebainone*, **28a**. A mixture of **27a** (2·94 g) and hydrochloric acid (2N; 90 ml) was stirred at room temperature for 17 h. The pH was brought to 10 by adding 25% ammonium hydroxide and the whole was extracted with $CH_2Cl_2$. After workup as above the solid α,β-unsaturated ketone, **28a** was obtained (2·57 g; 90%), m.p. 269–270° (ethanol). (Found: C, 75·79; H, 5·83; N, 2·86; M$^+$ 533. $C_{34}H_{31}NO_5$ requires C, 76·53; H, 5·86; N, 2·63%; M$^+$ 533·60). IR($CHCl_3$): 3520 (OH), 1690, 1680 cm$^{-1}$ (CO). NMR($CDCl_3$): τ 1·5–2·7 (m, 10 arom H); 3·40 (s, H-1, H-2); 3·55 (d, $J_{8,7} = 9$Hz, H-8); 3·90 (d, $J_{17,18} =$ 6Hz, H-17); 4·07 (dd, $J_{7,8} = 9$Hz, $J_{7,5} = 1·6$Hz, H-7); 4·10 (s, 4-O$\underline{H}$); 5·40 (dd, $J_{18,17} = 6$Hz, $J_{18,5} = 1·6$Hz, H-18); 5·92 (m, H-5); 6·20 (s, 3-OC$\underline{H}_3$); 7·60 (s, N-C$\underline{H}_3$).

*Alkaline rearrangement of* **16**. (a) To a solution of **16** (0·3 g) in dry dioxan (7·5 ml) was added a solution of potassium hydroxide (78 mg) in dry methanol (7·5 ml) and the whole was heated under reflux for 2·5 h. After cooling, dilution with water and addition of saturated aq ammonium chloride the whole was extracted with $CH_2Cl_2$. The extract was dried and the solvent removed, affording colorless crystals of **27b** (224 mg; 75%). The analytical sample had m.p. 186° (chloroform–ether). (Found: C, 71·81; H, 6·30; N, 3·11; M$^+$ 501. $C_{30}H_{31}NO_6$ requires C, 71·84; H, 6·23; N, 2·79%; M$^+$ 501·56). IR($CHCl_3$): 1730 (ester CO), 1680 cm$^{-1}$ (ketone). UV(MeOH): 285(1965), 242·5 nm (18750). NMR ($CDCl_3$): τ 1·60–2·74 (m, 5 arom H); 3·35 (s, H-1, H-2); 3·94 (d, $J_{8,7} = 10$Hz, H-8); 4·65 (dd, $J_{7,8} = 10$Hz, $J_{7,5} = 2$Hz, H-7); 4·97 (d, $J_{17,18} = 8$Hz, H-17); 5·57 (dd, $J_{18,17} = 8$Hz, $J_{18,5} = 1·6$Hz, H-18); 7·40 (t, $J_{5,18} =$ 1·6Hz, $J_{5,7} = 2$Hz, H-5β, confirmed by decoupling experiments); 6·18 (s, 3-OC$\underline{H}_3$); 6·38 (s, $CO_2C\underline{H}_3$); 6·45 (s, 6-OC$\underline{H}_3$); 7·56 (s, NC$\underline{H}_3$).

(b) By refluxing **18** (0·1 g) in dry dioxan (3 ml) with a solution of sodium hydroxide (8 mg) in dry methanol (2·50 ml) for 2 h and workup as above, **27b** (87 mg; 87%) was obtained, identical in all respects to the product described under (a) above.

Epimerization experiments with **16** or **18** at room temperature (16 h) or reflux (30 min) carried out in solutions similar to those in (b) led to a mixture of **16**, **18** and **27b** which could be separated by TLC.

18 - *Benzoyl* - 17α - *methoxycarbonyl* - 5,14 - *ethanothebainone*, **28b**. A solution of **27b** (1 g) in hydrochloric acid (2N, 33 ml) was allowed to stand at room temperature for 16 h. After dilution with water and addition of excess 25% ammonium hydroxide, the whole was extracted with $CH_2Cl_2$, the solvent was dried and removed. The α,β-unsaturated ketone **28b** formed colorless prisms (0·72 g; 74%), m.p. 282° (chloroform-methanol). (Found: C, 70·99; H, 6·02; N, 2·88; M$^+$ 487. $C_{29}H_{29}NO_6$ requires C, 71·44; H, 6·00; N, 2·87%; M$^+$ 487·53). IR($CHCl_3$): 3530(OH), 1730 (ester CO), 1680–1690 cm$^{-1}$ (d, ketones). UV(MeOH): 280(3410), 236 nm (20500). NMR($CDCl_3$): τ 1·73–2·76 (m, 5 arom H); 3·06 (d, $J_{8,7} = 10$Hz, H-8); 3·40 (s, H-1, H-2); 4·14 (dd, $J_{7,8} = 10$Hz, $J_{7,5} = 2$Hz, H-7); 4·14 (s, phenolic O$\underline{H}$, exchanged in $D_2O$), 4·80 (d, $J_{17,18} = 7$Hz, H-17); 5·95 (dd, $J_{18,17} = 7$Hz, $J_{18,5} = 1·8$Hz, H-18); 6·06 (t, $J_{5,18} = 1·8$Hz, $J_{5,7} = 2$Hz, H-5, confirmed by decoupling experiments); 6·22 (s, 3-OC$\underline{H}_3$); 6·34 (s, $CO_2C\underline{H}_3$); 7·58 (s, NC$\underline{H}_3$).

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