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A NEW ROUTE TO THE BENZAZEPINES AND A GENERAL SYNTHESIS OF RHOEADANES[1]

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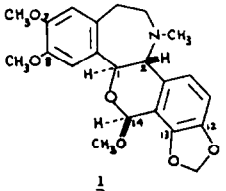
Abstract—Treatment of immonium salt **4** under Schotten–Baumann conditions yielded aldehydo amide **5** which was cyclized in base to benzazepine **6**. In an extension of this new benzazepine synthesis, immonium salt **7** was converted to the aldehydo amide **8** which was cyclized in base to the B/D-*trans* rhoedane **9**. Red-al reduction of **9** yielded hemiacetal **12**, and further Red-al reduction of methyl acetal **13** followed by HCOH-$NaBH_4$ N-methylation afforded the B/D-*trans* rhoeadane **16**.

The rhoeadine alkaloids comprise a group of about 30 dextrorotatory bases found within the genus *Papaver* of the family Papaveraceae.[3] The characteristic structural features include a tetracyclic skeleton incorporating a benzazepine system, as well as a cyclic acetal, or hemiacetal, anellated to the azepine ring as exemplified below in the case of the triad (+)-glaudine (**1**), (+)-epiglaudine (**2**) and (+)-oreodine (**3**). The rhoeadines are always substituted at C-7 and 8, and at C-12 and 13; the usual substituents being OH, OMe or methylenedioxy groups. The N atom may bear a Me or an H, and in the latter case the alkaloid is often referred to as a papaverrubine rather than as a norrhoeadine.

Three asymmetric centers are present in a rhoeadine base, and the relative and absolute configurations at these centers have been established for the natural products.[3-5] The hydrogen at C-2 is always *beta*, while treatment with very dilute mineral acid achieves isomerization at C-14. In the case of (+)-glaudine (**1**), the product would then be (+)-epiglaudine (**2**). Further treatment with hot, slightly more concentrated, mineral acid leads to isomerization at C-1 with a concomitant change of stereochemistry at C-14, so that the *cis* B/D fused (+)-oreodine (**3**) is formed from (+)-epiglaudine (**2**).



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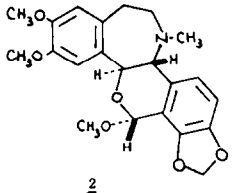

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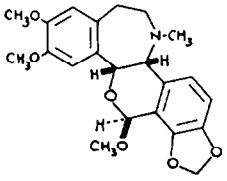

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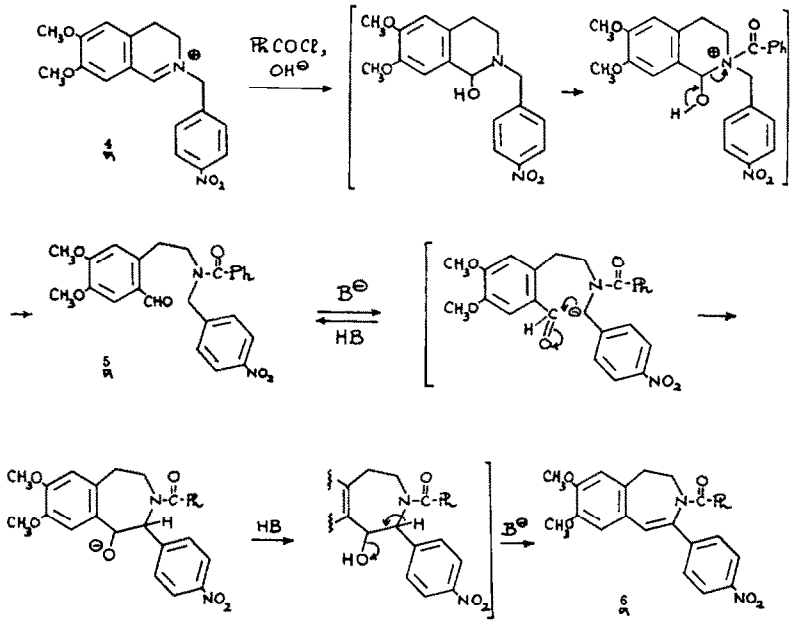
At the initiation of our work, two syntheses of the rhoeadines were available starting with alkaloidal compounds which were not available in large quantities.[6-8] We now report a novel synthetic scheme for the rhoeadane system based on starting materials obtainable in large amounts.

Our first objective was to devise a new synthetic approach to the benzazepines in a model system. To this effect, the known 6,7-dimethoxy-3,4-dihydroisoquinoline[9] was quaternized with *p*-nitrobenzyl bromide, and the resulting immonium salt **4** treated with benzoyl chloride under Schotten–Baumann conditions. The product was the crystalline aldehydo amide **5**, obtained in nearly quantitative yield, and formed through the probable intermediacy of a pseudobase as indicated in Scheme 1. Cleavage of a pseudobase by means of an acylating agent is an established but rather neglected reaction, the hetero ring of cotarnine having been opened up by such means as early as 1889.[10]

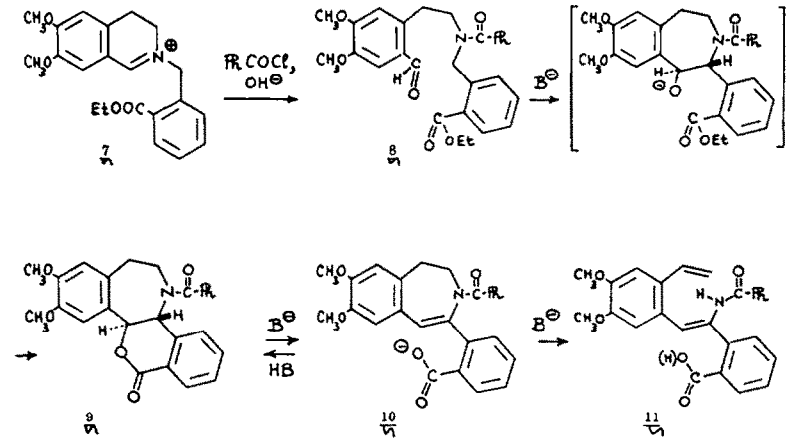
The novel feature in the present approach is the presence of an active methylene in the aldehydo amide **5**, with a consequent possibility for a base catalyzed intramolecular condensation with the aldehyde group. Indeed, sodium methoxide in methanol, or potassium t-butoxide in diglyme, could be used to effect such a cyclization, but the best results were obtained through the use of potassium t-butoxide in DMSO. The reaction mixture first turned red and then orange due to the appearance and disappearance of the benzylic carbanion, and within minutes the starting material had completely disappeared. The red crystalline product obtained in nearly quantitative yield proved to be the unsaturated benzazepine **6**, indicating that loss of hydroxide anion had followed the aldol-type condensation.

In order to apply this new benzazepine approach to the synthesis of a rhoeadine analog, it was necessary that the cyclization to the benzazepine ring proceed in the absence of the activating *p*-nitro group, and additionally that the potential be present for subsequent formation of a δ-lactone fused to the azepine system. The intermediate **8**, in which the benzylic methylene is activated by an ortho carbethoxy function, appeared to be particularly suited in this context. Base catalyzed cyclization of this species would then lead to the desired δ-lactone **9**.

The starting compounds for the preparation of the intermediate **8** were the readily available 6,7-dimethoxydihydroisoquinoline together with *o*-ethoxycarbonylbenzyl bromide. The latter could be prepared from phthalide either by the ethanol-HBr method, or alternatively and in superior fashion by using triphenylbromophosphonium bromide and subsequent ethanolic treatment of the resulting acid bromide deriva-



Scheme 1.



Scheme 2.

tive.[11] Reaction of 6,7-dimethoxydihydroisoquinoline with *o*-ethoxycarbonylbenzyl bromide supplied the immonium salt **7** in nearly quantitative yield (Scheme 2).

The next step, involving conversion under Schotten–Baumann conditions to the aldehydo amide **8**, was approached with some trepidation since an ester group is base sensitive. In fact, however, ester hydrolysis did not occur because the pseudobase was extracted into the organic benzoyl chloride phase thus protecting the ester carbonyl from hydroxide attack. The desired aldehydo amide **8** was thus obtained in excellent yield.

Initial attempts at the cyclization of **8** involved the use of such diverse bases as sodium methoxide in hot benzene or toluene, and potassium t-butoxide in hot THF or pyridine. But again the base of choice proved to be the dimsyl anion at room temperature. Under these conditions the aldehydo amide was completely converted into a water soluble, salt-like mixture of products within ten minutes. Acidification of this mixture yielded two compounds, the lactone **9** in 55–60% yield, and the vinylic amide **11** in 40% yield. These could be easily separated because of the ready solubility of **11** in dilute aqueous base or in hot ethanol. The characteristic patterns of the vinyl side chain and the enamide protons in the NMR spectrum of **11**, as well as the mass spectral fragmentation pattern, were decisive in the structural assignment of this bicyclic compound.

The NMR spectrum of lactone **9** was somewhat complicated because of the presence of two conformers in solution, in a ratio of $\approx 1:1$ in DMSO and $\approx 1:3$ in $CHCl_3$, due to geometric isomerism about the amide bond. An important conclusion that was drawn from the spectrum was that the C-1 and C-2 protons were in a *trans* relationship since $J_{1,2} = 10{\cdot}5$ Hz.

Formation of the lactone **9** from the water soluble salt **10** is a reversible process since the dimsyl anion can reconvert the lactone to the carboxylate anion **10** through β-elimination. Full characterization of the salt **10** was not possible, however, since the material was always contaminated with the salt of the vinylic amide **11** resulting from a further base catalyzed β-elimination of anion **10**. The unusual Hofmann-like elimination of anion **10** in strong

base to furnish **11** is undoubtedly due to relief of steric strain originally present in **10**.

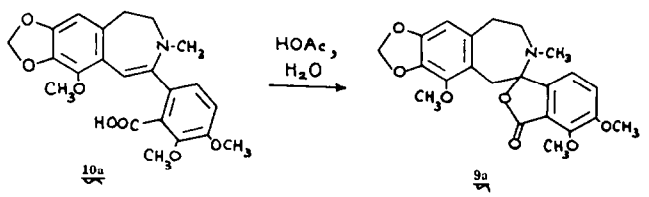
Because of these reversible processes, it can be stated that lactone **9**, with the *trans* fused B/D system, is thermodynamically more stable than its *cis* fused analog. The *trans* stereochemistry of the lactone **9**, when formed from the aldehydo amide **8**, is a result of kinetic control during the aldol-type cyclization. The alkoxide anion intermediate in this transformation is immediately converted to the lactone **9**, so that the transformation **8** to **9** is essentially irreversible. In this respect, it should be recalled that in the Klötzer–Teitel–Brossi rhoeadine synthesis,[7] acidification of the enamine **10a** had led to the γ-lactone **9***a*. In the present case, however, acidification of **10** results in formation of the δ-lactone **9** because of the presence of an amide function which precludes isomerization of the carbon–carbon double bond to an immonium linkage.

Conversion of the lactone **9** to the hemiacetal **12** was achieved using Red-al in pyridine-THF or in pyridine alone. The best results were obtained at 4° after 5 hr, when the product was obtained nearly quantitatively (Scheme 4).

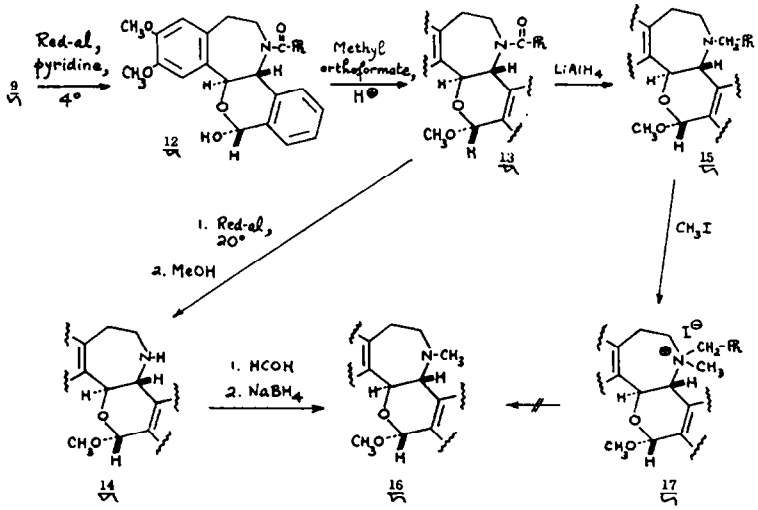
Acetal **13** was readily prepared from **12** using methyl orthoformate. As in the case of lactone **9**, NMR spectroscopy indicated the presence of two conformers in solution for the hemiacetal **12** as well as the acetal **13**; and again it was noted that the B/D junction was *trans* because of the large coupling constant (≈ 9·5 Hz) between the C-1 and C-2 protons. When a DMSO solution of the acetal **13** was heated to 110°, the analogous signals belonging to the two conformers coalesced into single peaks. Cooling down the solution regenerated the original spectrum. Using Eyring's relationship,[12] it was then calculated that the energy barrier between the two acetal conformers was about 20·1 cal/mol, a value in agreement with those found in the literature for other carboxylic acid amides.[13]

The final hurdle in the present synthesis of a *trans* rhoeadine system was the overall substitution of the N-benzoyl group of the acetal **13** with an N-Me group so as to generate the tertiary amine **16**. LAH in refluxing THF converted **13** into the N-benzylamine **15** in 90% yield. But subsequent clean N-debenzylation was not feasible using trichloroethyl chloroformate. The quaternary methyl benzyl ammonium salt **17** was, therefore, prepared from **15**. The quaternization reaction was unusually slow because of steric hindrance around the nitrogen. Worse still, N-debenzylation of the quaternary salt using Adams catalyst in neutral or acidic solution, or else using the thiophenoxide anion as nucleophile, were to no avail, again probably because of steric factors. However, in THF solution, compound **13** could be reduced slowly with an equivalent amount of LAH at 0° to a mixture containing 10% of the N-benzylamine **15**, and 80% of the desired secondary amine **14**. An even more satisfactory reducing agent proved to be Red-al. The reduction could be run for one day at room temperature in THF with a slight excess of the reducing agent to yield a 90–95% yield of the secondary amine **14**. It should be added that LAH reduction of a sterically hindered amide to afford an aldehyde and an amine is a well established process; and the present work represents an extension using Red-al.[14]

Amine **14** proved to be an oil which in acid gave a blood red color, a behavior characteristic of papaverrubines. N-Methylation of this secondary amine was achieved using the formaldehyde-$NaBH_4$ procedure. Noteworthy is the fact that the initial step in the methylation, namely the hydroxymethylation of the secondary amine, was slow as



Scheme 3.



Scheme 4.

expected due to steric hindrance, and took more than a day to effect.

The NMR spectrum of the tertiary rhoeadine base **16** showed the *trans* B/D anellation still present ($J_{1,2}$ = 9·5 Hz). The compound also belongs to the more stable epiglaudine (**2**) series bearing the C-14 OMe axial and *cis* to the C-1 hydrogen (Table 1).

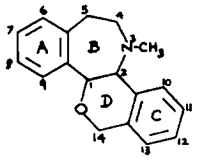
There was no change in configuration around C-14 in going from **12** to **13** to **16** since treatment of any of the compounds with 1M trifluoroacetic acid in methanol did not lead to any configurational change.

Table 1. NMR chemical shifts of rhoeadine analogs (δ)

	Compound 16	Epiglaudine	Glaudine
C-1 H	5·63	5·57	5·16
N–CH$_3$	2·30	2·30	2·24
C-14 CH$_3$O	3·57	3·56	3·69

EXPERIMENTAL

M.ps are uncorrected. IR spectra are in $CHCl_3$ soln. NMR spectra are at 60 MHz in $CDCl_3$ with TMS as internal standard unless specified otherwise. Both low and high resolution mass spectra were obtained on an AEI MS-902 instrument. Tlc was on Merck silica-gel plates 254. The rhoeadane system possesses the nucleus indicated in structure A, with the numbering system as shown. As with the other isoquinoline alkaloids, the term nor refers only to N-nor.



A

N - (p - *Nitrobenzyl*) - 6,7 - *dimethoxy* - 3,4 - *dihydroisoquinolinium bromide* (**4**)

To a soln of 6,7 - dimethoxy - 3,4 - dihydroisoquinoline (4·5 g; 23·5 mmol) in 90 ml dry ether was added *p* - nitrobenzyl bromide (5·5 g; 25·5 mmol) in 100 ml dry ether, and the mixture allowed to stand for 48 hr room temp. (TLC benzene-MeOH 8:0·4). The crystals were separated, washed with ether and air dried to yield 9·25 g (97%) of yellow prisms, m.p. 190–192° (acetonitrile); ν_{max} 1643 (–C=N<,), 1606 (arom), 1525 and 1345 cm^{-1} (NO_2); λ_{max}^{MeOH} 209, 254, 317 and 373 nm (log ϵ 4·20, 4·19, 3·89 and 3·85). NMR δ 3·21 (4H, broad m, –CH_2CH_2–), 3·90 and 3·99 (2 × 3H, s, OCH_3), 5·78 (2H, s, $ArCH_2$), 6·88 (1H, s, C-8 H), 7·62–8·30 (5H, m, ArH), and 10·25 (1H, s, C-1 H). H.R. M.S., $(M-Br)^+$: Calcd. for $C_{18}H_{19}N_2O_4$: *m/e* 327·1344. Found: 327·1336. (Found: C, 53·04; H, 4·97. Calcd. for $C_{18}H_{19}N_2O_4Br$: C, 53·08; H, 4·70%).

2 - *Formyl* - 4,5 - *dimethoxy* - N - p - *nitrobenzyl* - N - *benzoyl* - *β* - *phenylethylamine* (**5**)

To a soln of the above immonium salt (5·9 g; 14·5 mmol) in 20 ml water was added 15 ml 10% KOHaq and 5 ml benzoyl chloride at 0°. The mixture was stirred and kept at 0°. An additional 10 ml 10% KOHaq and 2 ml benzoyl chloride were added to keep the soln basic and the acid chloride in excess. About 10 ml ether was added after 10 hr to facilitate the stirring. Following 15 hr stirring (TLC benzene-MeOH 8:0·4), the liquid was decanted and the semi-solid gum stirred with 20 ml 10% HCl for 20 min. The solid was filtered, washed successively with water, 10% KOHaq, water, cold ether, and then dried. Recrystallization of the solid from benzene-hexane gave 4·51 g (69%) of pure product, m.p. 109–111°; ν_{max} 1685 (CHO), 1633 (amide), 1605 (aromatic), 1520 and 1350 cm^{-1} (NO_2); λ_{max}^{MeOH} 212, 237, 280 and 315 nm (log ϵ 4·23, 4·22, 4·05, and 3·65); NMR δ 3·46 (4H, broad m, –CH_2–CH_2–), 3·85 (6H, s with shoulder, OCH_3), 4·86 (2H, broad s, Ar–CH_2–), 7·22–8·24 (11H, m, ArH), 9·89 (1H, s, ald H). M.S. *m/e* 448 (M^+), 431, 400, 343, 312, 269, 207, 136 and 105. H.R. M.S. $(M)^+$: Calcd.: 448·1633. Found: 448·1663. (Found: C, 67·31; H, 5·48. Calcd for $C_{25}H_{24}N_2O_6$: C, 66·95; H, 5·39%).

5,6 - *Dihydro* - 7 - *benzoyl* - 8 - (p - *nitrophenyl*) - 2,3 - *dimethoxybenz(d)azepine* (**6**)

The above aldehyde (1 g; 2·25 mmol) was dissolved in 5 ml dry DMSO and the soln kept to near 10° till all t-BuOK (0·5 g; 4·4 mmol) was added. After 5 min shaking, a red solid separated (TLC $CHCl_3$: MeOH 9·7:0·3). A day later the mixture was diluted with water, and acidified with ACOH, and the yellow-red product separated, washed with water and dried, 0·90 g (93%), m.p. 246° (HOAc). ν_{max} 1651 (amide C=O), 1626 (conj. C=C), 1600 (aromatic), 1520 and 1350 cm^{-1} (NO_2); λ_{max}^{MeOH} 210, 270 and 378 nm (log ϵ 4·26, 3·93 and 3·97). NMR δ 3·32–4·33 (4H, broad m, –CH_2–CH_2–), 3·96 (6H, s, OCH_3), 6·42 (1H, s, vinylic H), 6·84, 7·13, 7·22, 7·37, 7·87, and 8·02 (11H, m, ArH). M.S. 430 (M^+), 400, 325, 309, 297, 279, 263, 251, 236, 222, 209, 189, 179 and 165. H.R. M.S. $(M)^+$: Calcd. 430·1528; Found: 430·1557. (Found: C, 69·56; H, 5·23. Calcd for $C_{25}H_{22}N_2O_5$: C, 69·76; H, 5·15%).

6,7 - *Dimethoxy* - N - (o - *ethoxycarbonylbenzyl*) - 3,4 - *dihydroisoquinolinium bromide* (**7**)

(a) Phthalide (5 g, 37·3 mmol) was suspended in 50 ml dry EtOH and the soln cooled in an ice-bath. While stirring, dry HBr gas was introduced till the soln was saturated. The mixture was diluted with 300 ml dry chloroform, and dry K_2CO_3 was added in small portions while keeping the system cold. After 1 hr the suspension was filtered off, the solid washed with chloroform. The combined filtrate and chloroform wash was evaporated *in vacuo*. The oily residue of ethyl *o*-bromomethylbenzoate was used without further purification.

(b) The ethyl *o*-bromomethylbenzoate obtained above was dissolved in 100 ml dry ether, filtered, and the filtrate poured on to an ethereal soln of 6,7 - dimethoxy - 3,4 - dihydroisoquinoline (7·6 g; 40 mmol). The solid which separated after 48 hr was washed with ether, then acetone, and dried to give 13·01 g (80%), m.p. 165° (acetonitrile); ν_{max} 1716 (ester C=O), 1650 (amide C=O and C=$\overset{\oplus}{N}$<,), 1610 (aromatic) and 1269 cm^{-1} (ester C–O); λ_{max}^{MeOH} 250, 314 and 368 nm (log ϵ 4·39, 4·12 and 4·09). NMR δ 1·37 (3H, t, J = 7 Hz, O–CH_2–CH_3), 3·28 (4H, broad m, –CH_2–CH_2–), 3·94 (6H, d, OCH_3), 4·36 (2H, q, J = 7 Hz, O–CH_2–CH_3), 5·70 (2H, s, $ArCH_2$–), 6·99–8·0 (6H, m, ArH). H.R. M.S. $(M-Br)^+$: Calcd 354·1704. Found 354·1754. (Found: C, 57·76; H, 5·62. Calcd for $C_{21}H_{24}NO_4Br$ (434·32) C, 58·07; H, 5·57%).

(c) A mixture of phthalide (13·4 g; 0·1 mol) and triphenylbromophosphonium bromide (46·4 g; 0·11 mol) was heated at 170–180° for 5 hr under N_2. The homogeneous oily product was cooled to 70°, and 0·2 mol dry EtOH added dropwise while shaking. After cooling to room temp. 0·3 mol dry ether was added, the triphenylphosphine oxide filtered off, and the filtrate washed three times with dry ether. The combined etheral soln was taken to dryness, and the oily residue dissolved again in dry ether. An ether soln of 6,7 - dimethoxy - 3,4 - dihydroisoquinoline[9] (19·1 g; 0·1 mol) was added. After 48 hr standing, the yellow ppt of **7** was filtered off, washed with ether, with acetone, and dried, yield 30·4 g (70%) based on phthalide.

N - *Benzoyl* - N - (o - *ethoxycarbonylbenzyl*) - 2 - *formyl* - 4,5 - *dimethoxy* - *β* - *phenylethylamide* (**8**)

To an ice-cooled mixture of the above immonium salt (10·8 g; 25 mmol) and benzoyl chloride (18 ml; 141 mmol), was added NaOH (14 g; 0·33 mol) as a 10% aq soln, in small portions with cooling and stirring over a period of 4 hr (the mixture *must* be kept basic). The oil consisting of benzoyl chloride and the pseudobase solidified. After 10 hr standing without stirring, the solid was collected, washed successively with 5% NaOH aq, water, 2% HCl, water, and finally ether, and then dried to afford 11·6 g (97%), m.p. 101° (EtOH); ν_{max} 1710 (ester C=O), 1675 (aldehyde C=O), 1635

(amide C=O), and 1605 cm^{-1} (aromatic); λ_{max}^{MeOH} 235, 283, and 318 (log ϵ 4·56, 4·09 and 3·84). NMR δ 1·35 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 3·50 (4H, broad m, $-CH_2-CH_2-$), 3·95 (6H, s, OCH_3), 4·32 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 5·00 (2H, broad, $ArCH_2$), 7·1–8·0 (11H, m, ArH), and 10·21 (1H, broad s, ArCHO). M.S. *m/e* 475 (M^+), 370, 312, 296, 193, 179 and 105. H.R. M.S. $(M)^+$: Calcd 475·1994. Found 475·1955. (Found: C, 70·29; H, 6·21; N, 2·95. Calcd for $C_{28}H_{29}NO_6$: C, 70·72; H, 6·15; N, 2·95%).

(±) - 1αH,2βH - 3 - *Benzoyl* - 14 - *oxo* - 7,8 - *dimethoxynorrhoeadane* (**9**) *and* 1 - β - o - *carboxylphenyl* - β - *benzoylamino* - 2 - *vinyl* - 4,5 - *dimethoxystyrene* (**11**)

Aldehyde **8** (0·4 g, 0·84 mmol) was dissolved portionwise in 3 ml dry DMSO at 5°, and t-BuOK (0·11 g; 1 mmol) was added while cooling and shaking. The mixture was shaken till all the base was dissolved. After 24 hr standing, the solid-containing mixture was diluted with water, and acidified with 1:1 conc HCl–HOAc. The solid was filtered after a day's standing, washed with water and dried. The crude product (0·41 g) was boiled with 2 ml EtOH. The insoluble white solid was filtered off and dried to afford 0·20 g (56%) of lactone, m.p. 232° (DMF); ν_{max} 1740 (lactone C=O), 1645 (amide C=O) and 1260 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-O-$); λ_{max}^{MeOH} 213, 235 and 285 nm (log ϵ 4·49, 4·37 and 3·70). NMR showed two rotamers in 2:1 ratio; major rotamer δ 3·09 (4H, broad m, $-CH_2-CH_2-$), 3·90 and 3·92 (2 × 3H, s, OCH_3), 4·81 (1H, d, J = 10 Hz, C-2 H), 5·55 (1H, d, J = 10 Hz, C-1 H), and 6·88–8·09 (11H, m, ArH); minor rotamer δ 3·09 (4H, broad m, $-CH_2CH_2-$), 3·84 (2 × 3H, s, OCH_3), 5·56 (1H, d, J = 9 Hz, C-2 H), 5·71 (1H, d, J = 9, C-1 H), and 6·88–8·09 (11H, m, ArH). M.S. *m/e* 429 (M^+), 308, 296, 237, 193 and 191. H.R. M.S. $(M)^+$: Calcd 429·1575. Found 429·1573. (Found: C, 72·54; H, 5·47; N, 3·46. Calcd for $C_{26}H_{23}NO_5$: C, 72·76; H, 5·39; N. 3·26%).

From the alcoholic mother liquor, 0·15 g white crystals of **11** precipitated on standing, m.p. 165–166° (EtOH); ν_{max} 3400 (NH), 3400–2800 (COOH), 1730 (carboxylic C=O), 1640 (amide C=O and NH deformation), and 1605 cm^{-1} (aromatic); λ_{max}^{MeOH} 212, 255 and 332 nm (log ϵ 4·51, 4·22 and 4·30). NMR (DMSO-d_6) δ 3·42 and 3·69 (2 × 3H, s, OCH_3), 5·06, 5·25, 5·38 and 5·67 (2H, m, $=C\begin{matrix}H\\H\end{matrix}$), 6·19 (1H, s, enamide vinylic H), 6·78–7·23 (1H, m, $-CH=CH_2$), 6·92 (2H, s, ArH dimethoxybenzene ring), 7·0–8·0 (9H, m, ArH) and 9·43 (1H, NH). M.S. *m/e* 429 (M^+), 411, 308, 252 and 177. H.R. M.S., $(M)^+$: Calcd 429·1575. Found 429·1568. (Found: C, 72·28; H, 5·20. Calcd for $C_{26}H_{23}NO_5$: C, 72·71; H, 5·40%).

(±) - 1αH,2βH - 3 - *Benzoyl* - 7,8 - *dimethoxy* - 14α - *hydroxynorrhoeadane* (**12**)

Lactone **9** (0·4 g, 0·93 mmol) was dissolved in 8 ml dry pyridine, and ice-cooled. A Red-al soln (3·2 ml) was added (made from 2 ml 70% sodium bis(2-methoxyethoxy) aluminum hydride in benzene, diluted with 20 ml toluene) over a period of 1 hr under N_2 (TLC benzene: MeOH 8:0·2). After two more hours of mixing, 2 ml of methanol was added, and the solvent evaporated *in vacuo*. Water was added, and the suspension extracted with chloroform. The chloroform extract was dried, and the solvent evaporated to yield 0·4 g (100%) white crystals, m.p. 223° (MeOH); ν_{max} 3570 (monomeric OH), 3450–3200 (polymeric OH), and 1635 (amide C=O); λ_{max}^{MeOH} 210, 235 and 284 nm (log ϵ 4·62, 4·19 and 3·63). NMR showed two rotamers in 3:1 ratio; major rotamer δ 3·11 (3H, broad m, C-4 and C-5 H), 3·90 and 3·97 (2 × 3H, s, OCH_3), 4·50 (1H, broad m, C-4 or C-5 H), 4·55 (1H, d, J = 9 Hz, C-2 H), 5·32 (1H, d, J = 9 Hz, C-1 H), 6·15 (1H, s, C-14 H), and 6·77–7·70 (11H, m, ArH); minor rotamer δ 3·11 (3H, broad m, C-4 and C-5 H), 3·90 and 3·97 (2 × 3H, s, OCH_3); 4·50 (1H, broad m, C-4 or C-5 H), 5·35 (1H, d, J = 10 Hz, C-2 H), 5·55 (1H, d, J = 10 Hz, C-1 H), 6·3 (1H, s, C-14 H), and 6·77–7·70 (11H, m, ArH). M.S. *m/e* 431 (M^+), 413, 326, 308, 292, 193, 163 and 105. H.R. M.S., $(M)^+$: Calcd 431·1732. Found 431·1726. (Found: C, 72·31; H, 6·10. Calcd for $C_{26}H_{25}NO_5$: C, 72·37; H, 5·84%).

(±) - 1αH,2βH - 3 - *Benzoyl* - 7,8,14α - *trimethoxynorrhoeadane* (**13**)

A soln of **12** (0·4 g; 0·93 mmol) in 20 ml dry MeOH and 5 ml methyl orthoformate was made acidic (pH 2) with H_2SO_4, and allowed to stand overnight (TLC benzene: MeOH 8:0·2). The soln was made neutral with NaOMe, and the solvent evaporated *in vacuo*. The residue was taken up in chloroform, and washed with water. The organic layer was dried and evaporated to furnish 0·37 g (90%) crystals, m.p. 201° (MeOH); ν_{max} 1630 cm^{-1} (broad, amide C=O); λ_{max}^{MeOH} 214, 235 and 284 nm (log ϵ 4·48, 4·22 and 3·69). NMR two rotamers in 3:1 ratio, major rotamer δ 3·05 (3H, broad m, C-4 and C-5 H), 3·53 (3H, s, C-14 OCH_3), 3·89 and 3·91 (2 × 3H, s, $ArOCH_3$), 4·45 (1H, broad m, C-4 or C-5 H), 4·55 (1H, d, J = 9 Hz, C-2 H) 5·16 (1H, d, J = 9 Hz, C-1 H) 5·62 (1H, s, C-14 H), and 6·62–7·65 (11H, m, ArH); minor rotamer δ 3·05 (3H, broad m, C-4 and C-5 H), 3·60 (1H, s, C-14 OCH_3), 3·91 and 3·93 (2 × 3H, s, $ArOCH_3$), 4·45 (1H, broad m, C-4 or C-5 H), 5·18 (1H, d, J = 10 Hz, C-2 H), 5·60 (1H, d, J = 10 Hz, C-1 H), 5·79 (1H, s, C-14 H), and 6·62–7·65 (11H, m, ArH). NMR in DMSO-d_6 showed the ratio of the two rotamers to be ≈ 1:1, M.S. *m/e* 445 $(M)^+$, 430, 413, 431, 322, 308, 292, 193 and 105. H.R. M.S. $(M)^+$: Calcd: 445·1888. Found: 445·1887. (Found: C, 72·74; H, 6·16. Calcd for $C_{27}H_{27}NO_5$: C, 72·79; H, 6·11%).

(±) - 1αH,2βH - 3 - *Benzyl* - 7,8,14α - *trimethoxynorrhoeadane* (**15**)

Amide **13**, (0·4 g; 0·9 mmol), was dissolved in dry THF, and the soln heated to boiling. Excess LAH in THF was added under N_2. After 1 hr boiling and stirring, the mixture was cooled and the excess reagent decomposed with MeOH. Following evaporation to dryness, 1 ml H_2O was added and the suspension extracted with $CHCl_3$. The $CHCl_3$ soln was dried and evaporated to leave 0·38 g (97%) prisms, mp 161° (MeOH); ν_{max} 1605 cm^{-1} (aromatic) and 1450 (benzyl CH_2); λ_{max}^{MeOH} 213, 240 sh and 285 nm (log ϵ 4·14, 3·58 and 3·41). NMR δ 3·74 (3H, s, C-14 OCH_3), 4·03 and 4·07 (2 × 3H, s, C-7 and C-8 OCH_3), 4·43 (1H, d, J = 9 Hz, C-2 H), 5·92 (1H, d, J = 9 Hz, C-1 H), 5·88 (1H, s, C-14 H), 6·98 (1H, s, C-9 H); 7·55 (5H, m, C_6H_5). M.S. *m/e* 431·2095 (M^+), 416, 340, 193 (base), and 127. H.R. M.S. (M^+): Calcd. 431·2095. Found: 431·2114. (Found: C, 75·24; H, 7·04. Calcd for $C_{27}H_{29}NO_4$: C, 75·15; H, 6·77%).

The methiodide salt melted 190–200° (dec) (water). Four days boiling of the free base in 1 M TFA in MeOH gave, after work-up, recovered free base in high yield.

(±) - 1αH,2βH - 7,8,14α - *Trimethoxyrhoeadane* (**16**)

A. *Reduction.* To a soln of **13** (0·445 g; 1 mmol) in dry, peroxide free THF, a slight excess of 70% Red-al in benzene (0·3 ml) was added under N_2, and the soln kept at ~ 15° for 24 hr till the starting material had disappeared (TLC). If an insufficient amount of Red-al was used, more was added as required. The excess reducing agent was decomposed with MeOH, and the soln evaporated to dryness. Water was added, and the suspension extracted in $CHCl_3$. The organic layer was dried and evaporated to leave the secondary amine **14** as an oil.

B. N-*Methylation.* The oily residue was dissolved in 10 ml EtOH, and 5 ml of 36% formalin added. The mixture was heated to reflux under N_2 till the secondary amine had disappeared (2 days). After cooling, 1 g $NaBH_4$ was added in small portions over 20 min. The next day the soln was evaporated, and the residue taken up in water and chloroform. The organic layer was dried and evaporated to leave a white solid, 0·3 g (90%), which was recrystallized from MeOH, m.p. 130°; ν_{max} 1605 cm^{-1} and 1105 cm^{-1}; λ_{max}^{MeOH} 213, 238 and 285 nm (log ϵ 4·06, 3·70 and 3·53). NMR δ 2·30 (3H, s, N–CH_3), 3·57 (3H, s, C-14 OCH_3), 3·88 and 3·92 (2 × 3H, s, C-7 and C-8 OCH_3), 4·08 (1H, d, J = 9 Hz, C-2 H), 5·59 (1H, s, C-14 H), 5·63 (1H, d, J = 9 Hz, C-1 H), 6·70 (1H, s, C-6 H), 7·39 (1H, s, C-9 H). M.S. *m/e* 355 (M^+), 340, 324, 312, 280, 251, 206 and 193 (base). H.R. M.S., (M^+): Calcd: 355·1784. Found: 355·1808. (Found: C, 71·44; H, 7·46. Calcd for $C_{21}H_{25}NO_4$: C, 70·96; H, 7·09%).

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