A RELATIVE OF PUMMERER'S KETONE AS A SOURCE OF MORPHINE ANALOGUES[1]

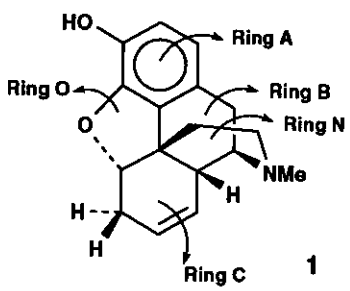
John M. Cave and Richard M. Scrowston*
School of Chemistry, The University, Hull HU6 7RX, U.K.
Peter D. Kennewell and Robert Westwood
Roussel Scientific Institute, Covingham, Swindon SN3 5BZ, U.K.

Abstract - An analogue (**3**) of Pummerer's ketone has been prepared in low yield by intermolecular oxidative coupling of methyl 4-hydroxyphenylacetate. Its key structural feature is the presence in the 9b-position of a CH_2CO_2Me group. Conjugate addition of hydrogen cyanide to the αβ-unsaturated ketone system inserts in the 1-position a cyano group *trans* to the 9b-substituent. Suitable protection of the 3-oxo group, followed by reduction of the 1-cyano group affords a lactam (**9**), which may be regarded as an analogue of morphine, in which ring B has been ruptured.

The quest for clinically useful analogues of morphine (**1**) continues unabated. Relatively little work, however, has been reported on compounds in which ring B of the morphine skeleton (*i.e.* the cyclohexane ring fused to the benzenoid ring) has been ruptured. Our present work relates to such ACNO analogues.[2]

One of us (R.W.) has previously noted[3] that Pummerer's ketone (**2**) may be used as a "pharmacophoric synthon" for morphine derivatives, since its three rings bear a close similarity to rings A, O, and C in morphine. More significantly, the O,C-ring junction in **2** has the same *cis* stereochemistry as the corresponding ring junction in morphine.[4] In the present work we wished to construct a 6-membered nitrogen ring bridging the 1- and 9b-positions in Pummerer's ketone (*cf.* ring N in morphine). Since elaboration of the 9b-methyl group is not practicable, we chose to prepare the analogue (**3**) of Pummerer's ketone, in which the 9b-side chain is already functionalised (*Note*: In order to simplify the ensuing discussion, the ring atoms in **3** and in related structures

will be numbered as for Pummerer's ketone itself. *Chemical Abstracts* nomenclature will, however, be used in the Experimental section).



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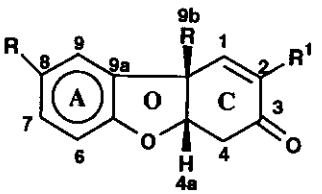
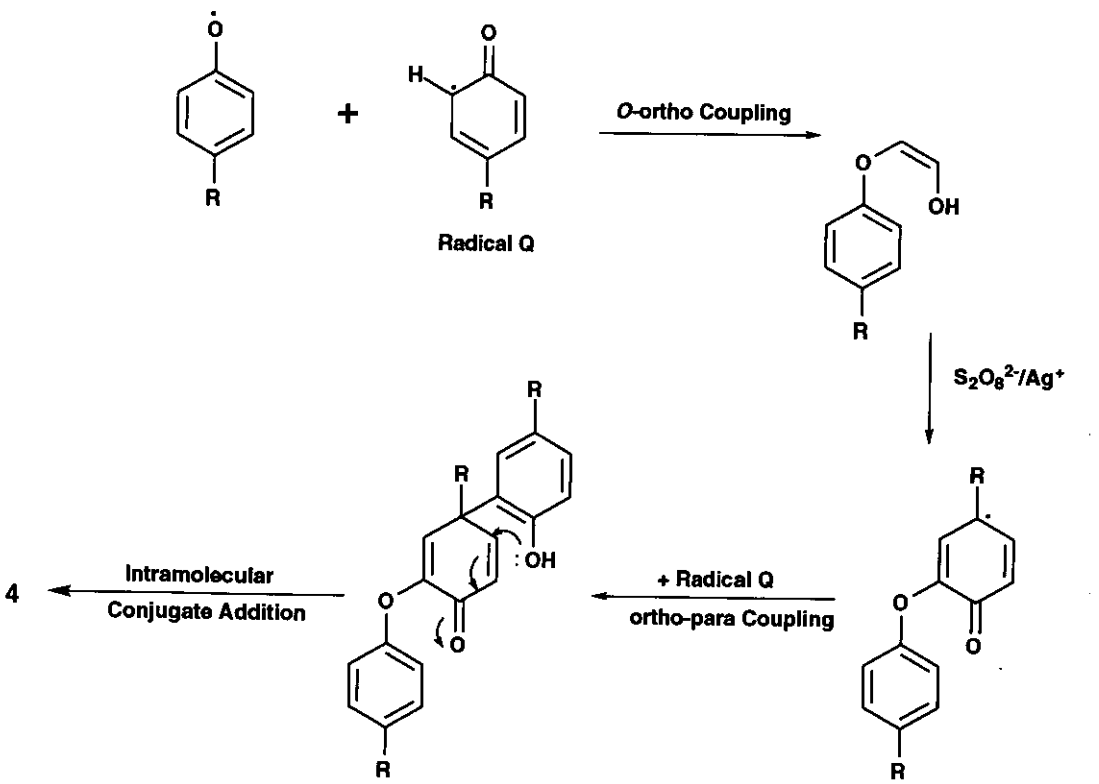


2; R = Me, R^1 = H

3; R = CH_2CO_2Me, R^1 = H

4; R = CH_2CO_2Me, R^1 = $OC_6H_4CH_2CO_2Me$-4

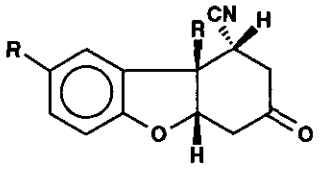


Scheme: Proposed Mechanism for the Formation of the By-product (**4**) (R = CH_2CO_2Me)

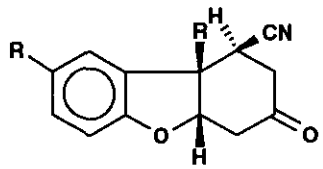
Intermolecular oxidative coupling of methyl 4-hydroxyphenylacetate was attempted with a range of oxidising agents; the optimum yield (albeit only 8%) of **3** was obtained by use of a mixture of sodium persulphate and silver nitrate in aqueous solution. The ^1H and ^{13}C nmr spectra of Pummerer's ketone (**2**) and its analogue (**3**)

were closely similar, thus confirming the structure and stereochemistry of **3**; in particular, each showed long range coupling (*J* 2.0 Hz) between 1-H and the bridgehead proton, 4a-H. Irradiation of the 4a-H signal in each case caused nuclear Overhauser enhancement of the 9b-methyl or 9b-methylene signal, as would be expected for *cis*-fusion of the OC-rings.

In addition to the required compound (**3**), one further product (300 mg from 250 g of starting material!), containing an extra phenoxy group (nmr and mass spectrum), was isolated from the complex mixture which resulted from the oxidative coupling reaction of methyl 4-hydroxyphenylacetate. Its ^{1}H nmr spectrum showed no 2-H signal; the 1-H signal lacked the vicinal coupling with 2-H and had now moved upfield (from δ 6.55 in **3** to δ 5.95). The upfield shift of 1-H (a similar shift for C-1 was evident in the ^{13}C nmr spectrum) was clearly due to electron donation from the oxygen atom of a vinylic ether, thus locating the extra phenoxy group in the 2-position and hence establishing the structure as **4**. A likely mechanism for the formation of **4** is shown in the Scheme.



5; R = CH_2CO_2Me



6; R = CH_2CO_2Me

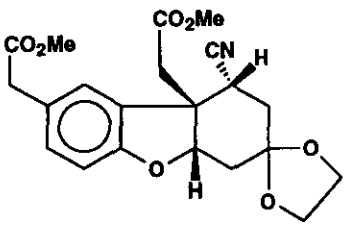
In order to construct a nitrogen-containing ring linking the 1- and 9b-positions in **3** and in order to ensure that the stereochemistry of the ring junction is analogous to that of the N,C-ring junction in morphine, we required the cyano compound (**5**), in which the 9b-CH_2CO_2Me and 1-CN substituents are *trans* with respect to each other (*Note*: we shall refer to this as the α-isomer; the alternative *cis* stereoisomer (**6**) will then be the β-isomer). Conjugate addition of hydrogen cyanide to **3** was achieved by the use of acetone cyanohydrin in aqueous methanolic sodium carbonate. After a short reaction period (1.5 h), the required α-isomer (**5**) predominated in the product; continued heating (24 h) increased the proportion of the β-isomer (**6**). At this point it was essential to establish as conclusively as possible the stereochemistry of each of the two cyano compounds (**5**) and (**6**). We examined rigorously the ^{1}H nmr spectra of the cyanide addition products of Pummerer's ketone (**2**) (we shall report this study elsewhere), as well as those of its analogue (**3**). These studies led us to believe that ring C in **5** and **6** exists in a preferred chair conformation (rather than as an alternative skew-boat conformation). This conclusion is confirmed by computer modelling experiments,[5] which reveal clearly the lower energy of the chair conformation. However, we feel that X-ray crystallographic studies may be necessary in order to resolve the problem unambiguously.

Assuming that ring C adopts a chair conformation, the magnitude of the coupling between 4a-H and the two H-4 protons in the ^{1}H nmr spectrum (see Experimental section) shows that 4a-H is equatorial in **5** and **6**. Since the O,C-ring junction in Pummerer's ketone (and therefore in the analogue **3**) is *cis*,[4] the same stereochemistry should be preserved in the cyano compounds (**5**) and (**6**). This means that the 9b-substituent in **5** and **6** must be axial, and that in the required *trans*-1,9b-isomer (**5**), the 1-cyano substituent should also be axial. The ^{1}H nmr spectrum of **5** confirmed this reasoning by showing clearly that 1-H was equatorial (eq-ax and eq-eq coupling between 1-H_{eq} and the two 2-H protons). On the other hand, the *cis* (β-)-isomer (**6**) showed ax-ax and ax-eq coupling between 1-H_{ax} and the two 2-H protons.

The photoinduced addition of methanol to Pummerer's ketone gives a product in which the 1-methoxy group and the angular 9b-methyl group are *cis* with respect to each other.[6] Its ^{1}H nmr spectrum is closely similar to that of our 1β-cyano isomer (**6**), thus confirming the stereochemistry which we assign to **5** and **6**.

The fact that the α-isomer (**5**) is formed under mild conditions indicates that this is the kinetically controlled product. Other workers have shown that the kinetically controlled addition of cyanide ion to a cyclohexenone derivative yields a mixture of products in which the one with an axial cyano group predominates.[7] As expected, and as observed, **5** is converted into the thermodynamically controlled β-product (**6**) after a longer reaction period. The use of diethylaluminium cyanide in an aprotic solvent is said to increase the proportion of the axial cyano isomer formed in the cyanide addition reaction.[7] However, this reagent proved less useful than acetone cyanohydrin in the present case.

We now wished to reduce the cyano function in the 1-α product (**5**) in the hope that the resulting primary amine might cyclise on to the 9b-ester function to afford the target lactam (**9**). First, however, we protected the 3-oxo function as the ethylene acetal (**7**). Mass spectrometry showed that the ethane-1,2-diol used in the preparation of the cyclic acetal underwent partial transesterification with one or both of the ester functions in **5**, with the result that the yield of **7** was disappointingly low (44%). When the 1-α-cyano function in **7** was reduced with Raney nickel in aqueous dioxan, cyclisation took place spontaneously to afford the lactam (**8**) (63%). Removal of the protecting acetal function under acidic conditions proceeded smoothly, to give the target ACNO lactam (**9**), in which the nitrogen containing ring is *trans*-fused with ring C (as in natural morphine).



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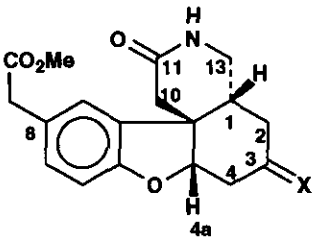

8; X = -OCH_2CH_2O-

9; X = O

We have demonstrated the potential of compounds related to Pummerer's ketone as starting materials for the synthesis of morphine analogues. Future experiments will be designed to alter the nature and positions of the substituents in rings A and C of the Pummerer's ketone analogues. The results of the biological tests on the compounds described here will be communicated when they are available.

EXPERIMENTAL

General Experimental Details.

^1H and ^{13}C Nmr spectra were determined in deuteriochloroform solution at 270 and 68 MHz respectively on a JEOL JNM-GX-FT-NMR spectrometer. Chemical shifts are recorded in parts per million (ppm) downfield from tetramethylsilane. All of the proton signals could usually be assigned (often with the aid of spin decoupling or nuclear Overhauser enhancement experiments), but for simplicity only significant signals are listed here. An asterisk * signifies that the assignments relating to similar protons may be interchanged. Protons and carbon atoms are numbered as shown in the structures in the Discussion section. Ir spectra were determined for KCl discs on a Perkin-Elmer PE 783 spectrophotometer. Mass spectra were determined on a Finnigan-MAT 1020 automated GC/MS instrument.

Light petroleum refers to the fraction of bp 40-60 °C.

Dimethyl [6,7-*Dihydro*-7-*oxodibenzofuran*-2,9a(5aH)*di-yl*]*diethanote* **(3)** and *Dimethyl* {6,7-*Dihydro*-8-[4-*methoxycarbonylmethyl*]*phenoxy*]-7-*oxodibenzofuran*-2,9a(5aH)*di-yl*}*diethanoate* **(4)**.

Methyl 4-hydroxyphenylacetate (250 g, 1.5 mol) was dissolved in hot (*ca.* 60 °C) water (50 l), then sodium persulphate (358 g, 1.5 mol) and silver nitrate (26 g, 0.15 mol) were added successively to the cooled solution. The mixture was stirred at room temperature for 24 h, then extracted with ethyl acetate/ether (1:1) (1 x 10 l, then 1 x 5 l). The combined extracts were washed with 2M sodium hydroxide (10 l) and water (10 l), then dried over

$MgSO_4$. Removal of solvent gave a brown solid which was separated into its components by preparative hplc [eluent: dichloromethane/ethyl acetate (93:7)], to give a yellow solid which, on attempted crystallisation from methanol gave the diester **(3)** as a white powder (19.5 g, 8%), mp 96-97 °C (Calc.for $C_{18}H_{18}O_6$: C, 65.45; H, 5.5%; *M*, 330. Found: C, 65.3; H, 5.55%; M^+, 330); $\nu_{max.}$ 1738, 1728 (ester C=O) and 1670 cm^{-1} (αβ-unsaturated C=O); δ_H 6.55 (dd, 1-H, $J_{1,2}$ 10.0, $J_{1,4a}$ 2.0 Hz), 6.02 (d, 2-H, $J_{1,2}$ 10.0 Hz), 3.10 (2H, d, 4-α– and 4-β-H, $J_{4a,4\alpha}$ and $J_{4a,4\beta}$ 3.5 Hz), 5.08 (sextet, 4a-H, $J_{4a,4\alpha/\beta}$ 3.5, $J_{4a,1}$ 2.0 Hz), 3.58 (s, 8-CH_2CO_2Me), 2.99 (ABq, 9b-CHH'CO_2Me, $J_{H,H'}$ 15.0 Hz), and 3.69 (s, 6H, 2 x OMe); δ_C 195.23 (C-3), 146.48 (C-1), 124.17 (C-2), and 38.69 (C-4).

Rigorous purification by hplc [eluent: dichloromethane/ethyl acetate (93:7), then ethyl acetate/hexane (50:50)] of the product remaining from the above separation gave a yellow oil (300 mg), which crystallised after being set aside for several months. Compound **(4)** formed needles (280 mg), mp 131-132 °C (from ethanol-water) (Calc. for $C_{27}H_{26}O_9$: C, 65.6; H, 5.3%; *M*, 494. Found: C, 65.7; H, 5.45%; M^+, 494); $\nu_{max.}$ 1735, 1730 (ester C=O) and 1670 cm^{-1} (αβ-unsaturated C=O); δ_H 5.95 (d, 1-H, $J_{1,4a}$ 2.0 Hz), 5.05 (ddd, 4a-H, $J_{4a,4\alpha}$ *4.0, $J_{4a,4\beta}$ *, 3.0, $J_{1,4a}$ 2.0 Hz), 3.28 (dd, 4α-H*, $J_{4\alpha,4\beta}$ 17.0 Hz), 3.15 (dd, 4β-H*,$J_{4a,4\beta}$ * 3.0, $J_{4\alpha,4\beta}$ 17.0 Hz), 3.74 (s, 3H, OMe), 3.70 (s, 6H, 2 x OMe) [the extra 1,4-disubstituted benzene ring in the 2-position showed the expected coupling between the pairs of adjacent protons (*J* 7.5 Hz)]; δ_C 123.78 (C-1), 147.29 (C-2), 189.61 (C-3), and 39.89 (C-4) [additional aromatic signals were observed due to the benzene ring in the 2-position].

Dimethyl [9α*–Cyano*-6,7,8,9-*tetrahydro*-7-*oxodibenzofuran*-2,9a(5aH)*di-yl*]*diethanoate* **(5)**.

METHOD A

A mixture of the αβ-unsaturated ketone **(3)** (10.5 g, 32 mmol), acetone cyanohydrin (10.8 ml, 96 mmol), aqueous 10% sodium carbonate (7.5 ml, 7.1 mmol), and methanol (50 ml) was stirred under reflux for 1.5 h, then the methanol was removed *in vacuo*. A suspension of the residue in ethyl acetate (50 ml) was washed successively with aqueous 10% acetic acid (50 ml), 2M sodium hydroxide (50 ml) and water (2 x 50 ml). Removal of the solvent from the dried ($MgSO_4$) solution gave a pale yellow oil which crystallised when triturated with methanol-ether (1:1). Recrystallisation from methanol gave white crystals of the *9α-isomer* **(5)**(5.1 g, 45%), mp 144-145 °C (Calc. for $C_{19}H_{19}NO_6$: C, 63.9; H, 5.4; N, 3.9%; *M*, 357. Found: C, 63.6; H, 5.4; N, 3.8%; M^+, 357); $\nu_{max.}$ 2240 (C≡N), 1748 (ester C=O), and 1725 cm^{-1} (saturated ketone C=O); δ_H 3.85 (dd, 1-H, $J_{1eq,2ax}$ 5.0, $J_{1eq,2eq}$ 3.0 Hz), 2.64 (dd, 2eq-H*, $J_{2eq,2ax}$ 18.0 Hz), 2.25 (dd, 2ax-H*, $J_{1eq,2ax}$ 5.0, $J_{2eq,2ax}$

18.0 Hz), 3.15 (dd, 4α-H*, $J_{4\alpha,4\beta}$ 17.5, $J_{4\alpha,4a}$ 3.0 Hz), 3.01 (dd, 4β-H*,$J_{4\beta,4a}$ 3.0, $J_{4\alpha,4\beta}$ 17.5 Hz), and 5.12 (t, 4a-H,$J_{4a,4\alpha/4\beta}$ 3.0 Hz); δ_C 34.06 (C-1), 38.18 (C-2*), 203.01 (C-3), 40.41 (C-4*), and 119.38 (C≡N).

METHOD B

A solution of diethylaluminium cyanide (1.0M in toluene; 6.2 ml, 6.2 mmol) was added at 0 °C under nitrogen to a solution of the unsaturated ketone **3** (500 mg, 1.52 mmol) in benzene (40 ml). The stirred mixture was kept at 0 °C for 0.75 h, allowed to attain room temperature during 1.5 h, then poured into ice/water (100 ml) containing 2M sodium hydroxide (20 ml). Extraction with trichloromethane in the usual way gave a pale yellow oil, from which the 9α-isomer (**5**) (150 mg, 28%) was isolated as in Method A.

Dimethyl [9β–*Cyano*-6,7,8,9-*tetrahydro*-7-*oxodibenzofuran*-2,9a(5aH)*di-yl*]*diethanoate* (**6**)

This was prepared by Method A described for the α-isomer, except that the reaction was carried out under reflux for 24 h. Recrystallisation of the product from ethyl acetate gave *rhombs* (32%), mp 122-123 °C (Calc.for $C_{19}H_{19}NO_6$: C, 63.9; H, 5.4; N, 3.9%; *M*, 357. Found: C, 63.7; H, 5.4; N, 3.9%; M^+, 357); $\nu_{max.}$ 2255 (C≡N), 1740 (ester C=O), and 1730 cm^{-1} (saturated ketone C=O); δ_H 3.99 (dd, 1-H, $J_{1ax,2ax}$ 13.5, $J_{1ax,2eq}$ 3.0 Hz), 2.62 (dd, 2eq-H*, $J_{2eq,2ax}$ 18.0,$J_{1ax,2eq}$ 3.0 Hz), 2.20 (dd, 2ax-H*, $J_{1ax,2ax}$ 13.5, $J_{2eq,2ax}$ 18.0 Hz), 3.24 (dd, 4α-H*, $J_{4\alpha,4\beta}$ 17.0,$J_{4\alpha,4a}$ 3.0 Hz), 3.00 (dd, 4β-H*,$J_{4\beta,4a}$ 3.0, $J_{4\alpha,4\beta}$ 17.0 Hz), and 5.09 (t, 4a-H, $J_{4a,4\alpha/4\beta}$ 3.0 Hz); δ_C 31.55 (C-1), 38.16 (C-2*), 203.60 (C-3), 40.44 (C-4*), and 117.71 (C≡N).

Dimethyl [9α–*Cyano*-7,7-*(ethylenedioxy)*-6,7,8,9-*tetrahydrodibenzofuran*-2,9a(5aH)*di-yl*]*diethanoate* (**7**)

A stirred suspension of the cyano ketone (**5**) (5.0 g, 14 mmol), ethane-1,2-diol (3.5 g, 56 mmol), toluene-4-sulphonic acid (200 mg), and toluene (100 ml) was heated under reflux for 24 h with azeotropic removal of water. The cooled solution was washed (aqueous 10% sodium hydrogencarbonate and water), then dried ($MgSO_4$) and evaporated. The resulting oil was chromatographed on silica [eluent: light petroleum/ethyl acetate (1:1)] to give an oil, which was triturated with ether. The resulting solid formed *microcrystals* (2.47 g, 44%) (from ethyl acetate), mp 108.5-109.5 °C (Calc. for $C_{21}H_{23}NO_7$: C, 62.8; H, 5.8; N, 3.5%; *M*, 401. Found: C, 62.5; H, 5.85; N, 3.4%; M^+, 401); $\nu_{max.}$ 2245 (C≡N), 1745, 1728 (C=O), and 1205 cm^{-1} (ether C-O-C); δ_H 3.95 (m, 4H, OCH_2CH_2O), 3.28 (dd, 1-H, $J_{1eq,2ax}$ 9.0, $J_{1eq,2eq}$ 6.0 Hz), and 1.95 (dd, 2H, 2ax- & 2eq-H, $J_{1eq,2ax}$ 9.0, $J_{1eq,2eq}$ 6.0 Hz); δ_C33.45 (C-1), 34.30 (C-2*), 105.73 (C-3), 35.12 (C-4*), 64.52, 65.12 (ethyleneacetal), and 119.15 (C≡N).

Methyl (6,6-*Ethylenedioxy*-1,2,3,4,4a,5,6,7,7a,12b-*decahydro*-2-*oxobenzofuro*[3,2-e]*isoquinol*-11-*yl*)-*ethanoate* **(8)**

An aqueous slurry of Raney nickel (*ca.* 50% w/v; 10 g) was added to a solution of the acetal **(7)** (1.0 g, 2.5 mmol) in dioxan (100 ml), then the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 4 h. Filtration through Hyflo and removal of solvent gave a white solid. Further material was obtained by Soxhlet extraction of the nickel/Hyflo residues with dioxan for 15 h. The combined material was triturated with light petroleum/ether (1:1), to give *needles* (590 mg, 63%), mp 210-212 °C (from ethyl acetate) (Calc. for $C_{20}H_{23}NO_6$: C, 64.35; H, 6.2; N, 3.75%; *M*, 373. Found: C, 64.5; H, 6.15; N, 3.8; M^+, 373); $\nu_{max.}$ 3420 (NH of sec. amide), 1740 (ester C=O), and 1662 (sec. amide C=O) cm^{-1}; δ_H 5.82 (br s, 1H, NH), 3.65 (q, 13α-H*, $J_{13\alpha,13\beta}$ 12.5, $J_{13\alpha,1}$ 13.0 Hz), 3.01 [m, 13β-H*, $J_{13\beta,1}$ 4.0 Hz (there was an unassigned additional coupling of 1.5 Hz)], and 2.57 (ABq, 2H, 10α-H and 10β-H, $J_{10\alpha,10\beta}$ 18.0 Hz); δ_C32.91 (C-1), 44.61 (C-9b), 43.64 (C-10), 172.31 (C-11), and 40.52 (C-13); *m/z* 314 (*M* - CO_2Me).

Methyl (1,2,3,4,4a,5,6,7,7a,12b-*Decahydro*-2,6-*dioxobenzofuro*[3,2-e]*isoquinol*-11-*yl*)*ethanoate* **(9)**

A solution of the lactam acetal **(8)**(50 mg, 0.13 mmol) in aqueous 10% hydrochloric acid/tetrahydrofuran (1:2; 20 ml) was stirred at room temperature overnight, then saturated aqueous sodium hydrogencarbonate (20 ml) was added and organic material was extracted into ethyl acetate in the usual way. Evaporation of the dried ($MgSO_4$) extracts gave a clear oil, which formed a *solid* (30 mg. 68%) on treatment with ether. It had mp 183-185 °C (from ether) (Calc, for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.8; N, 4.25%; *M*, 329. Found: C, 65.8; H, 5.85; N, 4.1%; M^+, 329); $\nu_{max.}$ 3380 (NH of sec. amide), 1740 (ester C=O), and 1662sh (ketone and sec. amide C=O) cm^{-1}; δ_H 3.65 (q, 13α-H*, $J_{13\alpha,13\beta}$ 12.5, $J_{13\alpha,1}$13.0 Hz), 3.00 [m, 13β-H*, $J_{13\beta,1}$ 4.0 Hz (there was an unassigned additional coupling of 1.5 Hz)], and 2.56 (ABq, 2H, 10α-H and 10β-H, $J_{10\alpha,10\beta}$ 18.0 Hz) (the NH signal was not observed); δ_C202.45 (C-3); *m/z* 270 (*M* - CO_2Me).

ACKNOWLEDGEMENTS

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REFERENCES

1. This paper is dedicated to Professor A.R. Katritzky, F.R.S., on his 65th birthday. May he remain in good voice for many years to come!
2. It is convenient to refer to the five rings in morphine as A, B, C, N, and O (*cf.* W.H. Moos, R.D. Gless, and H. Rapoport, *J. Org. Chem.*, 1981, **46**, 5064).
3. S.S. Matharu, D.A. Rowlands, J.B. Taylor, and R. Westwood, *J. Med. Chem.*, 1977, **20**, 197.
4. G.W. Kirby and H.P. Tiwari, *J. Chem. Soc.*, 1964, 4655.
5. We thank Miss R.P. Tuffin and Dr. P. Styring for these experiments, which were performed on a Silicon Graphics IRIS Indigo XS24 4000 work station using QUANTA/CHARMm software.
6. E. Dunkelblum, H. Hart, and M. Jeffares, *J. Org. Chem.*, 1978, **43**, 3409.
7. H.O. House, 'Modern Synthetic Reactions,' 2nd. edn., W.A. Benjamin, Inc., Menlo Park, California, 1972, pp. 623-628.

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