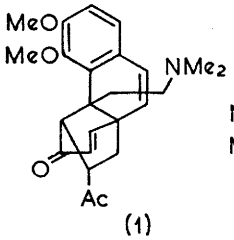
SECTION C
Organic Chemistry

Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. Part IX.[1] A Novel Aromatisation during Hofmann Degradation

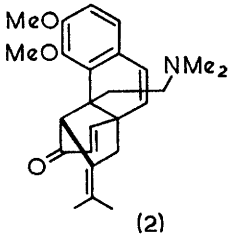
By **K. W. Bentley,* H. P. Crocker,** and **R. Walser,** Reckitt and Sons Ltd., Research Laboratories, Kingston upon Hull
W. Fulmor and **G. O. Morton,** Lederle Laboratories, Pearl River, New York 10965, U.S.A.

Hofmann degradation of the methohydroxide of the thebainone-derived methine base (2) affords an optically active neutral product, (−)-1,2-dimethoxy-7-(4-hydroxy-2-isopropylphenyl)-8-vinylnaphthalene (12). At higher temperatures the racemate and its methyl ether are obtained. Structures were assigned to these products after consideration of their n.m.r. spectra. The mechanism of the rearrangement is discussed.

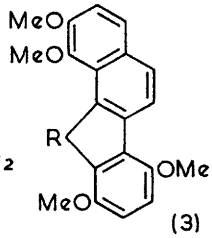
QUATERNARY salts of the base (1) have been found to be very resistant to Hofmann degradation.[2] The methiodide of the related base (2) was recovered unchanged after prolonged boiling with potassium hydroxide in aqueous solution. When the methiodide was heated with potassium t-butoxide in t-butyl alcohol, or when the methohydroxide was distilled *in vacuo* at 80°, trimethylamine was readily eliminated. The product of degradation was separated into the methine base (2) and a neutral fraction, further separated into two components having the compositions $C_{23}H_{24}O_3$ (*i.e.* methohydroxide $-H_2O - NMe_3$) and $C_{24}H_{26}O_3$. The i.r. spectra of these two neutral substances were virtually identical apart from the presence of a hydroxy-group absorption band in the spectrum of the C_{23} component. The n.m.r. spectra of the two were similar apart from the appearance of an extra methoxy-group in the C_{24} component. The solubility of the C_{23} component in aqueous sodium hydroxide but not in sodium carbonate showed this substance to be a phenol and it



(1)



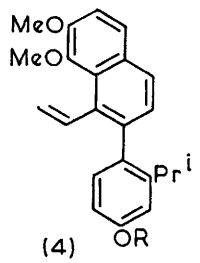
(2)



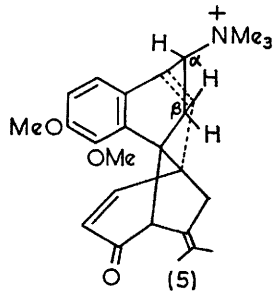
(3)

was converted into its methyl ether, identical with the C_{24} component, on methylation with methyl iodide and potassium carbonate.

The i.r. spectra of the phenol $C_{23}H_{24}O_3$ and its methyl ether showed no bands attributable to a carbonyl but did show bands at 910 and 990 cm.$^{-1}$ attributable to a vinyl group. The u.v. spectra were generally similar to those of β-phenylnaphthalenes and the benzofluorenes (3; R = H, Me, Ac, Et, or CH=CH_2) obtained by the degradation of derivatives of flavothebaone trimethyl ether methine,[3,4] which is structurally analogous to the base (2). The application of reaction mechanisms similar to those involved in the conversion of the flavothebaone methine into neutral products, however, failed to lead to tenable structures for C_{23} and C_{24} compounds, the structures of which were finally elucidated by analysis of their n.m.r. spectra.



(4)
C_{23}; R = H
C_{24}; R = Me



(5)

The n.m.r. spectrum of (4; R = Me) (Figure 1) established the presence of an isopropyl group subject to steric hindrance: a three-line pattern was observed (δ 1·10) rather than the usual two-line pattern. The isopropyl methine signal was at δ 2·77, the additional methoxy-group absorption was at δ 3·80, and the existence of the vinyl methylene group was signalled by the presence of two sets of four lines each assigned as H_a (δ 4·72) and H_b (δ 5·098) respectively (see Figure 1).

The aromatic region was thoroughly analysed by two-fold expansion of the spectrum of the complex aromatic and olefinic region (see Figure 1). By careful

[1] Part VIII, K. W. Bentley, D. G. Hardy, J. W. Lewis, M. J. Readhead, and W. I. Rushworth, *J. Chem. Soc.* (*C*), 1969, 826.
[2] K. W. Bentley, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Amer. Chem. Soc.*, 1967, **89**, 3312.
[3] K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, 1957, **22**, 409.
[4] K. W. Bentley and J. P. Ringe, *J. Org. Chem.*, 1957, **22**, 424.

measurement of the J values and consideration of the line intensities, the vinyl proton H_g (δ 7·37) was located and in addition, two AB pairs (labelled H_h and H_i, and H_f and H_j) (see Figure 1) were found at δ 7·33, 7·63, and 7·24, respectively. Consideration of the structure

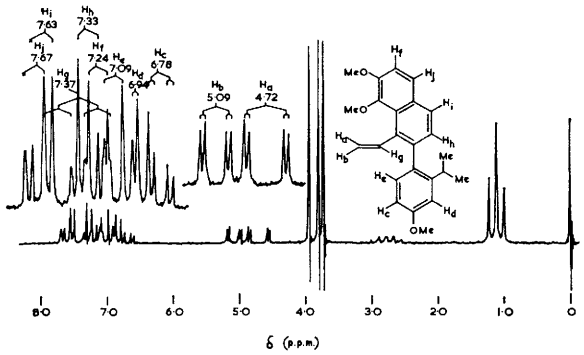


FIGURE 1 N.m.r. spectrum of (4; R = Me)

of the methine base (2) implied that these two AB pairs in the n.m.r. of (4) could have originated from H-1 and H-2, and H-9 and H-10 in (2). The assignment of these AB pairs could be reversed but that does not affect the structure.

The remaining three aromatic protons were found to comprise an ABC system which showed both *ortho*- and *meta*-coupling. Thus the H_c (δ 6·78) pattern was comprised of four lines, J_{ce} 8·4 Hz (*ortho*) and J_{cd} 2·5 Hz (*meta*). The H_d (δ 6·94) absorption consisted of two lines as did that of H_e (δ 7·09). These three signals suggested a trisubstituted benzene ring. The isopropyl methine fitted as an aromatic substituent, as did the new aromatic methoxy-group which could be a free hydroxy-group in (4; R = H), thus leaving the point of attachment to the naphthalene as the third substituent. The isopropyl substituent was assigned to the position adjacent to the naphthalene to account for the restricted rotation of the isopropyl group.[5] That an *ortho*-hydroxy-group is insufficient was shown by the thymol n.m.r. spectrum in which the isopropyl resonance was observed as the usual two lines. To determine the location of the free hydroxy-group, the spectrum of (4; R = H) was run before and after *in situ* acetylation with trichloroacetyl isocyanate.[6] Signals for H_c, H_d, and H_e all shifted downfield, by 21, 17, and 13 Hz respectively, thus showing the hydroxy-group to be on the benzene ring. The low resolution mass spectra contained molecular ions at *m/e* 348 and 362 for (4; R = H) and (4; R = Me) respectively; this fact, combined with the n.m.r. proton integrals, fitted the assigned formulae.

Chemical shifts [a] and coupling constants for the aromatic and olefinic protons in (4) [b]

H_a	4·72	J_{ab} 2,3, J_{ag} 18·0
H_b	5·09	J_{bg} 11·7
H_c	6·78	J_{cd} 2·5, J_{ce} 8·4
H_d	6·94	J_{de} <0·5
H_e	7·09	
H_f	7·24	J_{fj} 8·7
H_h	7·33	J_{hi} 9·0
H_g	7·37	
H_i	7·63	
H_j	7·67	

[a] Spectra run on an A60 spectrometer equipped with a variable temperature probe. Solutions were 20% (w/v) in deuteriochloroform. Tetramethylsilane was used as an internal reference, and the accuracy of the measurements is within 0·03 p.p.m. for the chemical shifts and 0·5 Hz for the coupling constants. [b] The data on (4) and its acetylation product were obtained at Lederle Laboratories, Pearl River, New York.

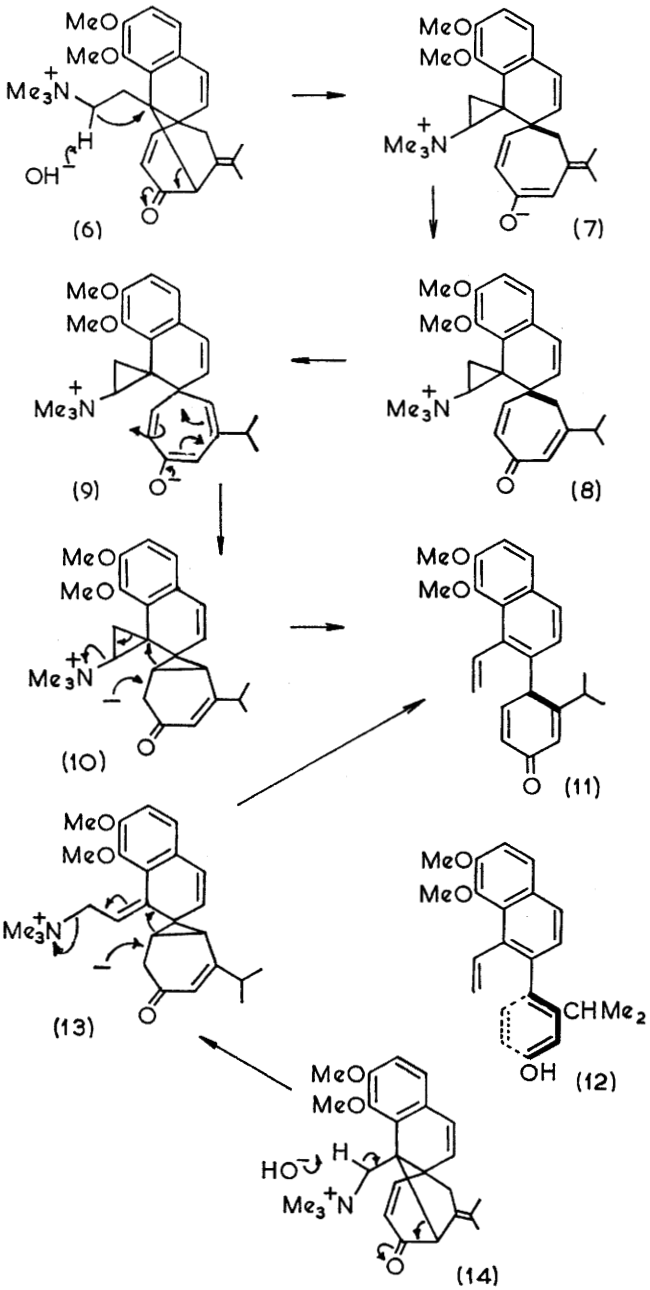
The phenol (4; R = H) which is the primary nitrogen-free product, arises as a result of a rearrangement of a novel type, which is clearly dependent upon the elimination of the quaternary nitrogen atom, since the methine base is recovered unchanged from the reaction and from attempts to effect its rearrangement under more vigorous conditions. The reaction results from a sequence of processes the initiation of which cannot be precisely defined on the available evidence.

The hydrogen atoms attached to the carbon atoms α and β to the nitrogen are potential sites of attack by hydroxide, but the examination of molecular models shows (5) that there is considerable steric hindrance to attack at the β but not at the α position. Attack at the α position must necessarily subsequently result in the formation of a cyclopropane ring, and the energy barrier to such a ring closure would be expected to be high, although such rings are formed in other reactions in this series with surprising ease when the geometry is favourable. (The formation of an ylide by removal of a proton from the $\overset{+}{N}Me_3$ group does not initiate processes that can lead by a rational route to the observed end product.)

Whichever site is involved in the initial attack by hydroxide the subsequent stages of the reaction must be similar, and must first involve displacement of the C(13)–C(5) bond (6), with the carbonyl group acting as the electron sink. This would lead, on the assumption of α attack by hydroxide, to the spirocycloheptenone enolate ion (7), in which migration of the exocyclic double bond into the ring to give the dienone (8) would be an expected process under the strongly basic conditions of the reaction. Enolisation of the dienone (8) to the ion (9) could be followed by cyclisation to a spirobicyclo[4,1,0]heptenone anion (10), in which the cyclopropane ring could be opened in either of two ways. One of these is a reversal of its formation and leads back to the enolate ion (9), but the other involves irreversible aromatisation of the naphthalene system and elimination of trimethylamine, to give the dienone (11), aromatisation of which would afford the neutral product (4; R = H). Attack by hydroxide at the β-hydrogen atom would analogously lead (14) through the intermediate (13) to the same dienone (11). In both cases completion of the sequence of changes is dependent upon elimination of trimethylamine.

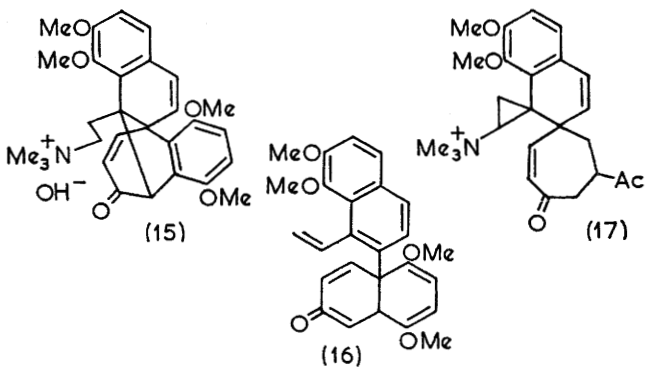
[5] W. D. Ollis and I. O. Sutherland, *Chem. Comm.*, 1966, 402.
[6] V. W. Goodlett, *Analyt. Chem.*, 1965, **37**, 431.

The intermediates (10) and (9) are related to each other, as are norcaradiene and cycloheptatriene, and it is the irreversible elimination reaction represented by (10) or (13) ⟶ (11), that determines the outcome of the reaction. Such a process cannot occur with norcaradiene, though conversion of derivatives of that hydrocarbon into benzene derivatives by acid-catalysed or thermal rearrangement has been observed.[7,8]



Models of the compounds (4; R = H) and (4; R = Me) indicate that there is a considerable hindrance to rotation about the naphthalene–phenyl bond and that the compounds might therefore be expected to exist in (+)- and (−)-forms. As isolated from the products of pyrolysis of the methohydroxide both the phenol and its ether were optically inactive, but the methohydroxide underwent slow spontaneous loss of trimethylamine at room temperature to give, in good yield, an optically active form ($[\alpha]_D$ −21·2°) of the phenol (4; R = H), which was rapidly racemised by heating at 70°. On the basis of the proposed mechanism and the known stereochemistry of the starting material (5), this laevorotatory phenol should have the precise configuration shown in (12). The production in this way of the phenol only confirms that, as represented in the proposed mechanism, this is the primary nitrogen-free product of the rearrangement and that the methyl ether is produced at higher temperature as a result of methylation of the phenol by some of the quaternary hydroxide, which is itself consequently converted into the methine base, also recovered under such conditions. Methylation of hydroxy-groups in this way during Hofmann degradation is well documented.

The remarkable ease with which this rearrangement and degradation can be accomplished contrasts markedly with the difficulty of effecting degradation of other such methine salts in the morphine group, where temperatures in the region 170—200° are frequently required. Many compounds do not contain the bridged ring system necessary to permit such a reaction as that represented in (4), whereas others such as flavothebaone trimethyl ether methine methohydroxide (15), in which such a process is possible, would give intermediates that would be expected to resist conversion into products such as (16). Similarly the diketone (17), which could arise from a salt of the methine base (1), would not be expected readily to isomerise to the keto-alcohol necessary for completion of a reaction pathway analogous to (6)—(12). In such cases other pathways, which can be followed to completion, take preference.



Methylation of the phenol (4; R = H) with methyl sulphate and potassium hydroxide, during the final stages of which the mixture became acid to litmus, afforded a neutral compound isomeric but not identical with the methyl ether (4; R = Me). The u.v. spectrum of this compound closely resembled those of the benzofluorenes (3) obtained from the flavothebaone series,

[7] M. J. S. Dewar and A. R. Ganellin, *Chem. and Ind.*, 1959, 458.
[8] E. Ciganek, *J. Amer. Chem. Soc.*, 1967, **89**, 1458.

and the i.r. spectrum no longer showed bands at 990 and 910 cm.$^{-1}$. These facts suggested that the vinyl group had been modified in some way, and the n.m.r. spectrum (Figure 2) of the compound is consistent

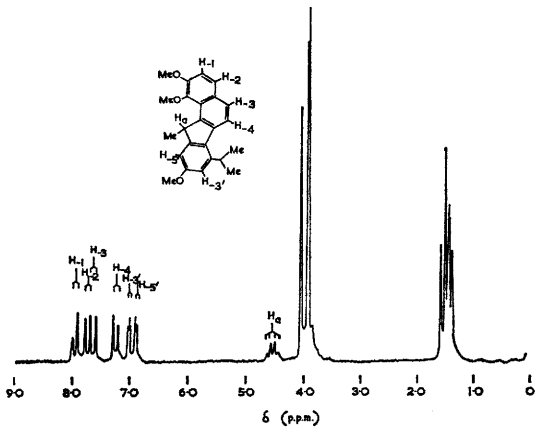
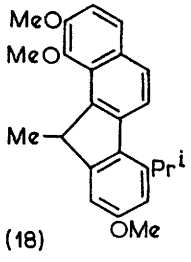
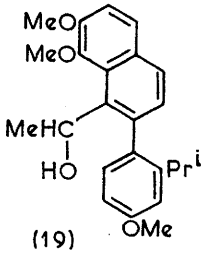


FIGURE 2 N.m.r. spectrum of (18)

with the structure (18), showing two AB pairs (labelled H-1 and H-2, and H-3 and H-4) at δ 7·95, 7·75, 7·65, and 7·25 (J_{ab} 9 Hz for all four pairs), which could have originated from the protons of the naphthalene system, and two doublets centred at δ 7·03 and 6·91 (J 2 Hz) indicative of *meta*-coupling only and assigned to the protons H-3′ and H-5′. The spectrum further showed signals due to three methyl groups as overlapping doublets centred at δ 1·54, 1·47, and 1·41, three methoxy-groups (δ 6·03, 5·93, and 5·91) and the proton H_a (δ 4·53, q, J 7·5 Hz). This compound (18) presumably arises by hydration of the vinyl group and cyclisation of the resulting intermediate (19). Such cyclisation must occur *meta* to a methoxy-group, but the position can be activated by the transmitted effect of one of the methoxy-groups in the naphthalene system.



(18)



(19)

EXPERIMENTAL

N.m.r. spectra were determined for solutions in deuteriochloroform with tetramethylsilane as internal standard at 60 Hz with a Varian A60 spectrometer, except for the compound (18) which was studied at 100 Hz with a JEOL JNM-4H-100 spectrometer.

Hofmann Degradation of 5,14-*Ethano*-18-*isopropylidene*-4-O-*Methylthebainone Methine Methohydroxide* (5).—(*a*) The methine methiodide (10·7 g.) was converted into the methohydroxide by stirring in water (100 ml.) with silver oxide (2·54 g.) for 1 hr. on a steam-bath. Charcoal (1 g.) was added, and the mixture was cooled, filtered, and evaporated under reduced pressure. The residual white solid was heated for 7 hr. at 80°/0·2 mm. The brown solid so obtained was dissolved in ether and water. The aqueous layer on evaporation afforded the undegraded methine methocarbonate (4·6 g.), identified by conversion into the methine methiodide. The ether layer was extracted with N-hydrochloric acid and the extract on basification gave the undegraded methine base (1·2 g.), m.p. 154°. Evaporation of the ether solution gave a cream-coloured solid (2 g.), which was dissolved in benzene (50 ml.), and the solution was passed down a column of Florisil (40 × 2 cm. i.d.). Elution with benzene gave (±)-1,2-*dimethoxy*-7-(2-*isopropyl*-4-*methoxyphenyl*)-8-*vinylnaphthalene* (4; R = Me), (0·64 g.) as a colourless gum, crystallising as prisms, m.p. *ca.* 0° on cooling in a freezing mixture (Found: C, 79·3; H, 7·2. $C_{24}H_{26}O_3$ requires C, 79·5; H, 7·2%), $\lambda_{max.}$ 240 mμ, $\nu_{max.}$ 990 and 910 cm.$^{-1}$ (CH=CH_2), $[\alpha]_D^{20}$ 0·0°.

Elution of the column with 1 : 1 ether–benzene afforded (±)-1,2-*dimethoxy*-7-(4-*hydroxy*-2′-*isopropylphenyl*)-8-*vinylnaphthalene* (4; R = H) (0·6 g.), obtained as colourless prisms, m.p. 202° (from methanol) (Found: C, 78·9; H, 6·9. $C_{23}H_{24}O_3$ requires C, 79·3; H, 6·9%), $\lambda_{max.}$ (EtOH) 240 mμ; $\lambda_{max.}$ (0·1N-NaOH) 240 and 290 mμ, $[\alpha]_D^{20}$ 0·0°.

(*b*) The methine methiodide (2·67 g.) in water (50 ml.) was converted into the methohydroxide by passage through a column of Amberlite IRA 400 resin. The solution was evaporated to dryness under nitrogen (to prevent formation of the methocarbonate) and the residue was kept under nitrogen at 12 mm. and at room temperature for 9 weeks. The product was purified as in (*a*) and yielded undegraded quaternary salt (1·6 g. as methiodide) and (−)-1,2-*dimethoxy*-7-(4-*hydroxy*-2-*isopropylphenyl*)-8-*vinylnaphthalene* (12) (0·46 g.), prisms, m.p. 202°, $[\alpha]_D^{20}$ −21·2° (*c* 1·35 in $CHCl_3$), identical in i.r. absorption ($CHCl_3$) with the racemic material obtained as in (*a*) and by racemisation of the (−)-form at 70° for 2 hr.

Methylation of the Phenol (4; R = H).—(*a*) A mixture of the phenol (0·172 g.), anhydrous potassium carbonate (0·138 g.), methyl iodide (0·085 g.), and acetone (25 ml.) was heated under reflux for 2·5 hr. The mixture was filtered and the solution evaporated to leave an orange residue, which was dissolved in benzene and purified by passage through Florisil; the ether (4; R = Me) was obtained as a gum, identical in i.r. absorption with material obtained by the degradation of the quaternary salt (5).

(*b*) The phenol (0·348 g.) was dissolved in methyl sulphate (1 g.) at 60°, and potassium hydroxide (0·67 g.) in water (5 ml.) was added with stirring. The mixture was stirred at 70—80° for 2 hr., during which time it became acid to litmus. Ether extraction afforded a yellow gum which crystallised on trituration with light petroleum (b.p. 60—80°). 7-*Isopropyl*-1,2,9-*trimethoxy*-11H-*benzo*[a]*fluorene* (18) was obtained as prisms, m.p. 97° (Found: C, 79·7; H, 7·1. $C_{24}H_{26}O_3$ requires C, 79·5; H, 7·2%), $\lambda_{max.}$ 272, 279, 302, and 326 mμ (ε 48,000, 61,000, 17,000, and 11,000).

We thank Dr. D. E. Webster, Hull University, for the determination of the spectrum of (18).

[9/469 *Received, March* 18*th*, 1969]