Anal. Calcd for $C_{25}H_{29}NO_4$: C, 75.8; H, 6.6. Found: C, 75.6; H, 6.5.

In a similar manner, the following ketones were prepared in poor yield from *o*- and *p*-tolylmagnesium bromide: 6,14-*endo*-etheno-7α-(2-methylbenzoyl)tetrahydrothebaine (prisms, mp 223°, ν_{max} 1690 cm^{-1}. *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8. Found: C, 75.7; H, 7.1); 6,14-*endo*-etheno-7α-(4-methylbenzoyl)tetrahydrothebaine (prisms, mp 196°, ν_{max} 1690 cm^{-1}. *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8. Found: C, 75.8; H, 6.7).

7α,7′α-Bis(1-hydroxy-1-methyl-3-oxopropano)-6,14-*endo*-ethenotetrahydrothebaine (IX, R = H). 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me) (5 g) in anhydrous benzene (20 ml) was added with vigorous stirring to a solution of anhydrous magnesium iodide (3.6 g) in ether (50 ml) and benzene (20 ml) at room temperature. A white precipitate formed almost immediately. After 15 min the mixture was decomposed by the addition of aqueous ammonium chloride. The ether–benzene layer was separated, dried, and evaporated, when a viscous gum was obtained. Chromatographic separation of this product on silica plates using a system of a 7:4:1 mixture of ethyl acetate, 2-propanol, and water showed it to contain three components in the ratio of approximately 3:6:1. Preparative plate chromatography using the same system afforded specimens of the two major components. The component with greatest R_f value (30%) was identified as 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me). The 60% component (intermediate R_f value) was obtained as off-white prisms, mp 150–151°, from methanol, ν_{max} 1715 and 3490 cm^{-1}, and was identified as 7α,7′α-bis(1-hydroxy-1-methyl-3-oxopropano)-6,14-*endo*-ethenotetrahydrothebaine (IX, R = H).

Anal. Calcd for $C_{46}H_{54}N_2O_8$: C, 72.4; H, 7.1. Found: C, 72.3; H, 7.0.

Separation of this ketol was also achieved on alumina plates using ether as solvent, and from these plates the minor component (10%) was also isolated. This has been identified as a product of rearrangement of the ketone II (R = Me) and is described in detail in another publication.[7]

7α,7′α-Bis(1-methyl-3-oxoprop-1-eno)-6,14-*endo*-ethenotetrahydrothebaine. Repeated chromatographic purification of the ketol XVI on alumina plates in ether solution led to the isolation also of a small quantity of a new base, mp 234°, ν_{max} 1690 cm^{-1}. This was also obtained by heating the ketol (70 mg) with 98–100% formic acid (1 ml) at 100° for 10 min. The solution was diluted with water, basified with ammonia, and extracted with ether, when the unsaturated ketone (50 mg) was obtained as white prisms, mp 234°, from methanol.

Anal. Calcd for $C_{46}H_{52}N_2O_7$: C, 74.2; H, 7.0. Found: C, 74.0; H, 7.1.

Charge-Transfer Complex, Thebaine Methiodide–Benzoquinone. Thebaine methiodide (5 g) and benzoquinone (1.5 g) were heated on the water bath in chloroform (25 ml) until separation of an orange crystalline solid began. The mixture was cooled, and the orange complex was collected (5.0 g), mp 205–206°, on rapid heating (lit.[11] mp 205°).

Reduction of Complex. A solution of sodium borohydride (0.1 g) in water (2 ml) was added to a warm stirred solution of the complex (1 g) in ethanol (15 ml). A transient violet color developed, and the solution rapidly became almost colorless. On cooling the solution, thebaine methiodide (0.6 g), mp 224°, was recovered, and on filtration and dilution of the solution with dilute ammonium chloride hydroquinone (0.12 g), mp 170°, was obtained.

Similar results were obtained when the complex in aqueous ethanol was reduced with sulfur dioxide.

Acknowledgments. The authors wish to thank Dr. D. E. Webster of the University of Hull, England, for the determination of nmr spectra, Mr. A. C. Young for chromatographic studies on thin and thick layer plates, and the following for experimental assistance: Mr. J. Fulstow, Mr. J. F. Saville, Mr. N. M. Scollick, Mrs. E. W. Walker, Mr. G. R. Young, and the late Mr. S. R. Duff.

Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. II.[1] Alcohols Derived from 6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine

K. W. Bentley, D. G. Hardy, and B. Meek

Contribution from the Research Laboratories, Reckitt and Sons Ltd., Kingston-upon-Hull, England. *Received September 26, 1966*

Abstract: A series of secondary and tertiary alcohols have been prepared by the reduction and reaction with Grignard reagents of the aldehyde I (R = H), the ketones I (R = Me, Et, *n*-Pr, and Ph), and their 6,14-ethano analogs. The stereospecificity of the reactions is explained. In this way analgesics of very high potency, up to 500 times that of morphine, have been obtained.

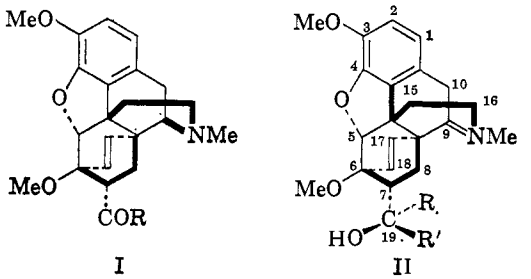
The high analgesic activity of the ketone I (R = Me) and its C-7 epimer, reported in the preceding paper, contrasts with the inactivity of the related esters I (R = OMe or OEt). The effects on the activity of further modifications of the keto group, involving removal of the electron deficiency at the carbon atom, were accordingly studied. Reduction of the ketone I (R = Me) with aluminum isopropoxide affords a product consisting of 95% of one isomer of the secondary alcohol II (R = H, R′ = Me), whereas reduction with sodium borohydride yields an approximately 1:1 mixture of this and the diastereoisomeric alcohol II (R = Me, R′ = H), which was resolved into its components by preparative thin layer chromatography. Since there is more or less free rotation about the bond linking the carbonyl group to C-7, both sides of this group are almost equally accessible to attack by a hydride ion, but in the Meerwein–Pondorff reduction, which proceeds through hydrogen transfer in a cyclic transition state,[2] steric hindrance in the transition state results in the preferential transfer of hydrogen to one

(1) (a) Part I: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967). (b) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963). (c) This work is covered by British Patent 925,723.

(2) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 2641 (1949).

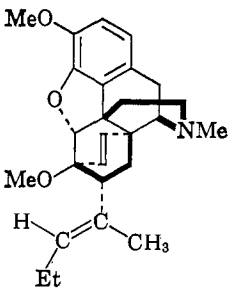
side of the carbonyl group. The examination of models of such a six-membered transition state (see below) shows that steric hindrance is least in the arrangement that leads to the alcohol II (R = H, R^1 = Me).

An excess of methylmagnesium iodide converts the ketone I (R = Me) in high yield into the tertiary alcohol II (R = R′ = Me), which is also readily prepared from the esters I (R = OMe or OEt), and the nmr spectrum of this alcohol shows that the stereochemical disposition of groups at C-7 is the same as that in the parent ketone.[3a] The tertiary alcohol epimeric at C-7 with II (R = R′ = Me) was prepared in the same way from the 7β isomer of the ketone I (R = Me). The carbinols prepared in this way were all found to be potent analgesics. Accordingly, the variation in analgesic activity within a series of alcohols of general structure II was studied, and during the course of this work many compounds were obtained with analgesic activities never previously approached in the morphine series, in which hitherto the most active members have been 14-acetoxydihydrocodeinone[4] and 5-methyldihydromorphinone,[5] both of which are about 12 times as active as morphine.



I

II



III

The alcohols of general structure II were prepared by the action of Grignard reagents or lithium alkyls on the aldehyde I (R = H), the ketones I (R = Me, Et, *n*-Pr, and Ph), and the ester I (R = OEt). The reactions of the ketones I with Grignard reagents R′MgX are generally complex and lead to the formation of a number of products resulting from the following processes: (a) normal Grignard reaction with R′MgX to give the tertiary carbinol II (major reaction); (b) normal Grignard reaction with R′MgX to give the tertiary alcohol diastereoisomeric with II (minor reaction); (c) Grignard reduction where possible, *i.e.*, when R′ contains a β-hydrogen atom, to give the secondary alcohol II (R′ = H) (major reaction in many cases);[6a] (d) Grignard reduction to give the diastereoisomeric secondary alcohol II (R = H) (minor reaction); and (e) base-catalyzed rearrangement of the ketone followed by Grignard reaction at the carbonyl group (minor reaction). Of these processes the base-catalyzed rearrangement is of minor importance and will be discussed in detail together with other topics in a subsequent communication.[6b]

The normal Grignard reaction in this series shows a remarkably high degree of stereoselectivity, and in those cases in which Grignard reduction does not compete with the normal reaction a high yield of an almost pure diastereoisomer of the tertiary carbinol is obtained. For example, the ketone I (R = Me) with phenylmagnesium bromide afforded almost entirely the alcohol II (R = Me, R′ = Ph), whereas the diastereoisomeric alcohol II (R = Ph, R′ = Me) was the almost sole product of the action of methylmagnesium iodide on the phenyl ketone I (R = Ph). The presence of a trace of the second isomer in the product in each case was demonstrated by thin layer chromatography. The stereochemical assignments of structures to these isomeric carbinols, at first tentatively made after a study of models, were rigorously confirmed by nmr spectroscopic studies.[3a]

Similarly the tertiary carbinol II (R = Me, R′ = *n*-Pr), resulting from the normal Grignard reaction of *n*-propylmagnesium iodide with the methyl ketone I (R = Me), is diastereoisomeric with the principal product II (R = *n*-Pr, R′ = Me) of the interaction of methylmagnesium iodide and the *n*-propyl ketone I (R = *n*-Pr). The seat of the isomerism was clearly shown in this case to be the alcoholic group since both carbinols were dehydrated to the same olefin III, which gave propionaldehyde on ozonolysis.[7] The structure of the carbinol II (R = Me, R′ = *n*-Pr) has been confirmed by X-ray crystallographic analysis of the hydrobromide.[3b]

Grignard reduction is, where possible, a process seriously competitive with the normal Grignard reaction, and in some cases accounts for up to 30% of the total product. Like the normal reaction, it shows a remarkably high degree of stereoselectivity, and the product consists almost entirely of the alcohol II (R′ = H), though the presence of about 5% of the diastereoisomer II (R = H) can be detected on thin layer chromatographic plates. Both the Grignard and Meerwein–Pondorff reduction processes are generally believed to proceed by hydrogen transfer in similarly constituted transition states,[2,8] IV and V, and might thus in the case of the ketone I (R = Me) be expected to lead to the same product. This expectation is not borne out in practice.

Grignard reduction of the ketone with *n*-propyl- or isobutylmagnesium halides affords the secondary alcohol diastereoisomeric with that obtained in the Meerwein–Pondorff reduction, and identical with the

(3) (a) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. H. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3322 (1967); (b) J. H. van den Hende and R. Nelson, private communication; *J. Am. Chem. Soc.*, **89**, 2901 (1967).

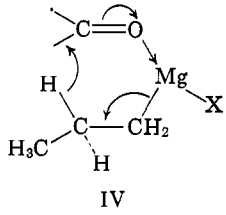
(4) R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939).

(5) L. F. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936); G. Stork and L. Bauer, *ibid.*, **75**, 4373 (1953).

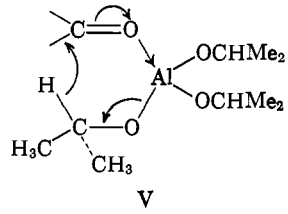
(6) (a) This reaction was first reported to us by C. F. Howell, J. J. Brown, W. Fulmor, G. O. Morton, and R. A. Hardy, Jr., of Lederle Laboratories, Pearl River, N. Y., whom we thank also for much helpful discussion of the mechanisms of the reaction of the ketones I with Grignard reagents. (b) Part VI: K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Am. Chem. Soc.*, **89**, 3312 (1967).

(7) Part IV: K. W. Bentley, D. G. Hardy, and B. Meek, *ibid.*, **89**, 3293 (1967).

(8) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable and Co. Ltd., London, 1954, p 147.



IV



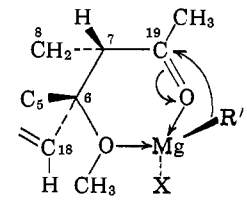
V

second component of the product of reduction of the ketone with sodium borohydride. If the Meerwein–Pondorff reduction leads, as postulated above, to the alcohol II (R = H, R′ = Me), the product of Grignard reduction must have the structure II (R = Me, R′ = H), and these structural assignments have been confirmed in the following way. The Meerwein–Pondorff reaction product in chloroform solution shows hydroxyl absorption at 3504 cm^{-1}, indicating strong hydrogen bonding between the hydroxyl and the spatially proximate C-6 methoxyl group, which results in an arrangement involving disposition of the hydrogen atom in the carbinol system of the alcohol II (R = H, R′ = Me) "downward" toward the 6,14-etheno bridge. In agreement with such a representation, in which steric hindrance of the etheno bridge is minimal, this alcohol is very readily hydrogenated at room temperature and pressure. Hydrogen bonding of a similar kind in the isomeric alcohol II (R = Me, R′ = H) would, however, involve disposition of the larger CH_3 group "downward" toward the etheno bridge, and this would be expected to result in some hindrance to hydrogenation of the bridge and also to a weakening of the hydrogen bond or even to the establishment of an alternative arrangement with a weak bond between the hydroxyl group and the π orbitals of the etheno bridge. In agreement with this, the Grignard reduction product of the ketone I (R = Me) is resistant to hydrogenation at room temperature, and shows hydroxyl absorption at 3540 cm^{-1} (weaker hydrogen bond than in the isomeric carbinol) and also at 3605 cm^{-1} (feeble bond to the etheno bridge)

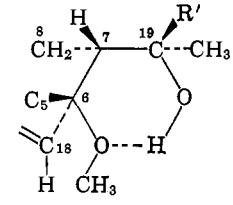
Thus, both Grignard reaction with and Grignard reduction of the ketone I (R = Me) afford products belonging to the same stereochemical series II (R = Me). This asymmetric induction may be explained on the basis of a model similar to those outlined by Cram and his co-workers.[9] If the Cram five-membered transition state is replaced in this series by a six-membered intermediate in which a complex is formed by coordination of the magnesium atom with oxygen atoms of both C-7 carbonyl and C-6 methoxyl groups (thus completing the outer electron shell of the magnesium), then an inspection of models shows that "top-side" approach of the group R′ to the carbonyl carbon, as depicted in VI, leading to VII is much less hindered than approach from below (the vicinity of the 6,14-etheno bridge). In the same complex, if the group R′ is one in which β-hydrogen transfer can occur then Grignard reduction (VIII) would lead to alcohol IX [identical with the complete structure II (R = Me, R′ = H)] belonging to the same stereochemical series as the products of the normal reaction.

In the Meerwein–Pondorff reduction, however, the aluminium atom can complete its valency shell by co-

(9) D. J. Cram, F. Ahmed, and A. Elhatez, *J. Am. Chem. Soc.*, 74, 5828 (1952).



VI



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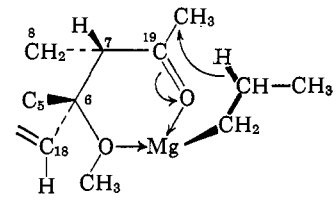
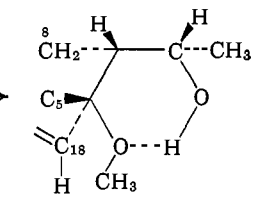
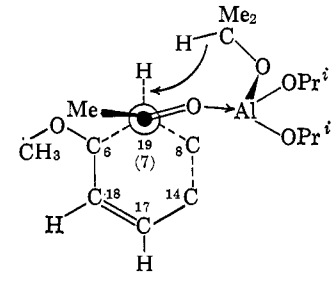


VIII

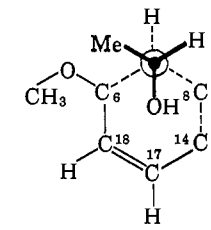


IX

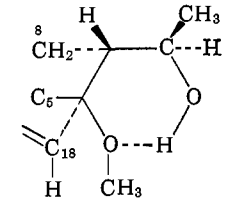
ordination with the carbonyl oxygen atom alone, and the establishment of a more rigid cyclic arrangement involving the C-6 methoxyl group is not necessary. In such a case, free rotation about the carbonyl–C-7 bond is still possible and hydrogen transfer in the complex would be expected to occur with the groups in the disposition involving least steric hindrance. This arrangement is that in which the coordinated carbonyl group is most remote from the group with the greatest effective size, namely the C-6 methoxyl group. This arrangement is shown in part structure X, which is a Newman projection of part of the ketone I (R = Me) looking along the line of the carbonyl–C-7 bond, and least hindered hydrogen transfer to the carbonyl group would occur as shown, from above, to give the secondary alcohol XI which is identical with XII. This alcohol is diastereoisomeric with that obtained by Grignard reduction, and is represented in full by structure II (R = H, R′ = Me).



X



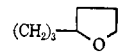
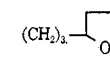
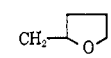
XI



XII

The reaction of the ketone I (R = Me) with lithium alkyls involves, in the cases studied, more base-catalyzed rearrangement than does the reaction with Grignard reagents, but this still remains a minor side reaction (<10%), and the formation of tertiary carbinol is somewhat less stereoselective. Secondary alcohol formation is not observed, however, and in those cases in which Grignard reduction is troublesome the use of the corresponding lithium alkyl is to be preferred.

Table I. Alcohols of Structure II

R	R′	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mp, °C, HCl	Molar potency[a]
H	Me	82	$C_{23}H_{29}NO_4$	72.1	7.6	72.0	7.5	210	1.0
Me	H	81	$C_{23}H_{29}NO_4$	72.1	7.6	71.8	8.0	240	0.9
H	Et	...	$C_{24}H_{31}NO_4 \cdot HBr \cdot 3H_2O$[b]	54.3	7.1	54.6	7.1	90[b]	0.8
H	*n*-Pr	...	$C_{25}H_{33}NO_4 \cdot C_4H_6O_6 \cdot 3H_2O$[c]	56.5	7.1	56.4	7.1	176[c]	5.3
H	*n*-C_5H_{17}	78	$C_{30}H_{43}NO_4$	74.9	8.9	74.6	8.6	155[c]	0.2
H	Ph	210	$C_{28}H_{31}NO_4$	75.4	7.1	75.6	7.1		0.01
H	CH_2Ph	95	$C_{29}H_{33}NO_4$	75.8	7.2	75.6	7.3	125[c]	7.6
H	CH_2CH_2Ph	80	$C_{30}H_{35}NO_4$	76.0	7.4	75.6	7.4	166	80
H	$(CH_2)_3OEt$	...	$C_{27}H_{37}NO \cdot C_4H_6O_6 \cdot 3H_2O$[c]	56.9	7.5	56.8	7.2	100[c]	12
H		114	$C_{29}H_{39}NO_5$	69.8	8.2	70.0	8.1		24
H		98	$C_{29}H_{37}NO_4$	74.4	8.3	74.1	8.3		9.0
Me	Me	166	$C_{24}H_{31}NO_4$	72.5	7.9	72.5	7.7	221	2.7
Me	Et	74 (132)	$C_{25}H_{33}NO_4$	73.1	8.1	72.9	8.1	245	20
Et	Me	165	$C_{25}H_{33}NO_4$	73.1	8.1	72.9	8.2		
Me	*n*-Pr	176	$C_{26}H_{35}NO_4$	73.3	8.2	73.3	8.2	217	96
n-Pr	Me	148	$C_{26}H_{35}NO_4$	73.3	8.2	73.2	8.4		
Me	*i*-Pr	165	$C_{26}H_{35}NO_4$	73.3	8.2	73.0	8.3	218	10
Me	*n*-Bu	150	$C_{27}H_{37}NO_4$	73.8	8.4	73.9	8.4		24
Me	*i*-Bu	150	$C_{27}H_{37}NO_4$	73.8	8.4	73.8	8.6	188	2.5
Me	*t*-Bu	216	$C_{27}H_{37}NO_4$	73.8	8.4	73.8	8.5		0.1
Me	*n*-Am	103	$C_{28}H_{39}NO_4$	74.1	8.6	73.8	8.4	250	15
Me	*i*-Am	126	$C_{28}H_{39}NO_4$	74.1	8.6	74.0	8.4	258	30
Me	*t*-Am	...	$C_{28}H_{39}NO_4 \cdot HCl \cdot 2H_2O$	64.0	8.4	63.8	8.2	188	0.6
Me	*n*-C_6H_{13}	...	$C_{29}H_{41}NO_4 \cdot HCl \cdot 3H_2O$	63.0	8.7	62.7	8.7	270	2.0
Me	*n*-C_7H_{15}	...	$C_{30}H_{43}NO_4 \cdot HCl \cdot 2H_2O$	64.9	8.6	65.0	8.6	256	1.2
Me	*n*-C_8H_{17}	...	$C_{31}H_{45}NO_4$	75.5	9.1	75.3	8.9	262	0.3
Me	Ph	208	$C_{29}H_{33}NO_4$	75.8	7.2	75.5	7.2	194	0.07
Ph	Me	152	$C_{29}H_{33}NO_4$	75.8	7.2	75.6	7.2	230	0.09
Me	CH_2Ph	187	$C_{30}H_{35}NO_4$	76.1	7.4	76.1	7.3		150
Me	$(CH_2)_2Ph$	146	$C_{31}H_{37}NO_4$	76.4	7.6	76.1	7.8	236	500
Me	$(CH_2)_3Ph$	94	$C_{32}H_{39}NO_4 \cdot 2H_2O$	72.3	8.0	72.5	7.9	235	2.1
Me	*o*-Tolyl	239	$C_{30}H_{35}NO_4$	76.1	7.4	76.1	7.3	190	0.15
Me	*p*-Tolyl	197	$C_{30}H_{35}NO_4$	76.1	7.4	76.0	7.4	250	0.10
Me	$CH_2C_6H_4F$-*p*	148	$C_{30}H_{34}FNO_4$	73.3	7.0	73.0	7.3		
Me	$CH_2C_6H_4Cl$-*p*	180	$C_{30}H_{34}ClNO_4$	70.9	6.1	70.7	6.9		
Me	$CH_2C_6H_4OMe$-*p*	117	$C_{31}H_{37}NO_5 \cdot H_2O$	71.6	7.5	71.8	7.3		1.5
Me	$CH_2{=}CHPh$	92	$C_{31}H_{35}NO_4 \cdot HCl$	71.2	7.1	71.2	6.9	248	4.0
Me	$CH{=}CH_2$	155	$C_{28}H_{31}NO_4$	73.3	7.6	73.3	7.6		1.4
Me	$C{\equiv}CH$	186	$C_{23}H_{29}NO_4$	73.7	7.1	73.6	7.2		0.2
Me	$CH_2CH{=}CH_2$	160	$C_{23}H_{33}NO_4$	73.6	7.8	73.6	7.8	260	0.41
Me	Cyclohexyl	201	$C_{29}H_{39}NO_4$	74.8	8.4	74.8	8.3	202	59
Me	Cyclopentyl	86	$C_{28}H_{37}NO_4$	74.6	8.2	74.3	8.0	240	1.0
Me	$(CH_2)_2OEt$	107	$C_{28}H_{39}NO_5 \cdot 2H_2O$	66.5	8.5	66.3	8.3	248	6.0
Me	$(CH_2)_2OPh$	221	$C_{33}H_{41}NO_40 \cdot 5H_2O$	73.3	7.8	73.1	7.5	260	0.05
Me		128	$C_{30}H_{41}NO_5$	72.5	8.6	72.6	8.4	185	92
Me		140	$C_{28}H_{37}NO_5$	71.1	8.1	71.0	8.0		
Et	Et	152	$C_{26}H_{35}NO_4$	73.3	8.1	73.0	8.0	130	2.5
Et	Ph	166	$C_{30}H_{35}NO_4$	76.1	7.4	76.2	7.4		
n-Pr	*n*-Pr	209	$C_{28}H_{39}NO_4$	74.2	8.7	73.9	8.7	186	3.1
n-Bu	*n*-Bu	...	$C_{30}H_{43}NO_4 \cdot C_4H_6O_6 \cdot 2H_2O$[c]	61.1	7.9	61.2	7.8	62[c]	3.0
CH_2Ph	CH_2Ph	190	$C_{36}H_{39}NO_4$	78.7	7.2	78.5	7.2	190	0
Ph	Ph	220	$C_{34}H_{35}NO_4$	78.2	6.7	77.9	6.7	266	0
Ph	*n*-Pr	177	$C_{31}H_{37}NO_4$	76.5	7.6	76.2	7.6	210	0.2
Ph	CH_2Ph	210	$C_{35}H_{37}NO_4$	78.5	6.9	78.3	7.0	220	0
Ph	Cyclohexyl	232	$C_{34}H_{41}NO_4$	77.6	7.8	77.3	7.9	239	0.04
Ph	$CH_2CH{=}CH_2$	217	$C_{31}H_{35}NO_4$	76.6	7.2	76.5	7.0		0.53

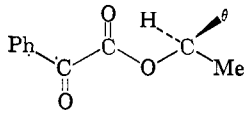
[a] Morphine = 1. [b] Hydrobromide. [c] Bitartrate.

The alcohols of general structure II prepared in this way are listed, together with their analgesic potencies, in Table I. The analgesic activities were determined by the tail pressure method in rats, with administration of the compounds usually as their hydrochlorides in aqueous solution by the subcutaneous route, and this work will be reported in detail elsewhere, together with the results of other pharmacological studies.[10] The highest activities are observed in those alcohols in which there is a moderate disparity in size between R and R′,

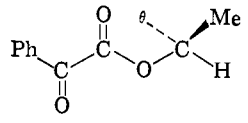
(10) Some details are briefly given by R. E. Lister, *J. Pharm. Pharmacol.*, 16, 364 (1964).

and in homologous series in which the group R remains constants as a hydrogen atom or a methyl group peak activity is reached when R′ has a size equivalent to that of a three to five carbon chain, and further lengthening of the chain results in a steady decrease in activity. The preferred constant substituent R is a methyl group, and the most potent analgesic in this series is the alcohol II (R = Me, R′ = CH_2CH_2Ph).

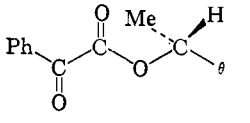
The alcoholic hydroxyl group of the secondary alcohols was readily esterified, but this modification has little effect on the analgesic potency. The tertiary alcohols, however, are very resistant to esterification. The two diastereoisomeric secondary alcohols II (R = H, R′ = Me and R = Me, R′ = H) were esterified with phenylglyoxalyl chloride and, following Prelog's method,[11] the resulting esters were treated with methylmagnesium iodide and the products hydrolyzed to atrolactic acid. With the alcohol II (R = H, R′ = Me), the three conformations of the phenylglyoxalyl ester are XIII, XIV, and XV, in which θ represents the tetrahydrothebaine unit, and in these the size of groups is in the order θ > Me > H and, as in the cases studied by Prelog, attack by the Grignard reagent on XIII would be from below and on XIV and XV would be from above. However, the examination of models of



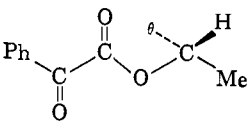
XIII



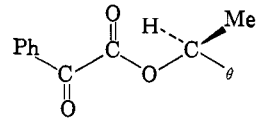
XIV



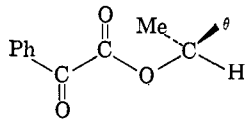
XV



XVI



XVII

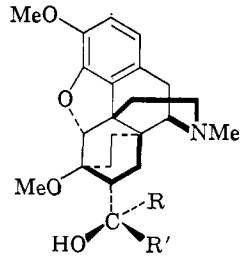


XVIII

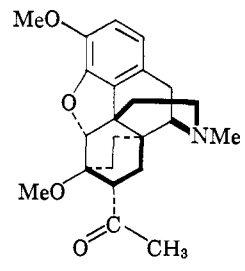
these three conformations reveals that nonbonded interactions are very much less in the form represented by XIII than in the other two, and the ester would be expected to adopt predominantly this form, attack of which by the Grignard reagent would lead, after hydrolysis, to an excess of (+)-atrolactic acid. With the ester from the diastereoisomeric alcohol II (R = Me, R′ = H) the conformation XVI would be expected to be heavily favored over XVII and XVIII, and the same process with this ester would be expected to lead to an excess of (−)-atrolactic acid. In this event this sequence of reactions on the alcohol obtained by Meerwein–Pondorff reduction of the ketone I (R = Me) gave atrolactic acid, $[\alpha]^{20}D$ +4.8°, whereas the product of Grignard reduction of the ketone in the same way afforded atrolactic acid, $[\alpha]^{20}D$ −5.4°, and these results support the structures assigned above to these bases.

O-Alkylation of the tertiary alcohols was also very difficult, but the base II (R = R′ = Me) was methylated with potassamide and methyl iodide in liquid ammonia to its methyl ether. Other attempted alkylations of this base and the methylation of other tertiary alcohols in the series proved unsuccessful.

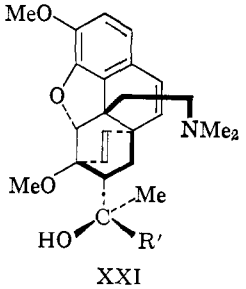
Catalytic reduction of the tertiary alcohols was in all cases achieved only at elevated temperature and pressure. Hydrogen bonding between the hydroxyl and C-6 methoxyl groups results in conformations in which one or the other of the alkyl groups R and R′ in structure II is disposed in the direction of the 6,14-etheno bridge, with consequent hindrance of the approach of this bridge to the catalyst surface. Reduction is achieved over Raney nickel catalyst at 160–170° (200 atm) to give bases of general structure XIX. These 6,14-etheno alcohols are also preparable from the 6,14-ethano ketone XX which is obtained from the etheno ketone I (R = Me) by reduction under milder conditions. The effect of the $COCH_3$ group in the ketone I (R = Me) in shielding the etheno bridge is much less than the effect of the alcoholic group in the hydrogen-bonded alcohols II, and since the shielding effect on the etheno bridge of the smaller CHO group is even less than that of the $COCH_3$ group, the aldehyde I (R = H) can be reduced under even milder conditions. In the 7β-acetyl compound, the $COCH_3$ group is disposed on the side of the molecule opposite to the etheno bridge, hydrogenation of which is accordingly unhindered, and this base can be rapidly reduced at room temperature. The Grignard reaction with the 6,14-ethano ketone XX in general follows the same pattern as that with the etheno analog II (R = Me), giving rise to tertiary carbinol XIX, secondary carbinol as a result of Grignard reduction, and base-catalyzed rearrangement. Base-catalyzed rearrangement is generally more important in this than in the etheno series, and on occasions accounts for up to 30% of the product.[6b] The normal Grignard reaction displays the same stereospecificity as in the 6,14-etheno series. The 6,14-ethano alcohols XIX prepared by these methods are listed in Table II.



XIX



XX



XXI

As in the parent Diels–Alder adducts I (R = Me and OEt), quaternary salt formation with the alcohols II proceeded only very slowly, good yields being obtained only after several days under reflux with methyl iodide in acetone. In the cases examined, Hofmann degra-

(11) V. Prelog, *Helv. Chim. Acta*, 36, 308 (1953).

Table II. Alcohols of Structure XIX

R	R′	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Molar potency[a]
H	H	124	$C_{22}H_{29}NO_4$	71.1	7.9	71.0	8.0	
H	Me	51	$C_{23}H_{31}NO_4$	71.6	8.1	71.5	8.2	
Me	Me	142	$C_{24}H_{33}NO_4$	72.1	8.3	71.9	8.2	2.9
Me	Et	146	$C_{25}H_{33}NO_4$	72.6	8.5	72.6	8.3	
Me	*n*-Pr	187	$C_{26}H_{37}NO_4$	73.1	8.7	72.8	9.1	
Me	*i*-Pr	158	$C_{26}H_{37}NO_4$	73.1	8.7	73.4	8.7	34
Me	*n*-Bu	147	$C_{27}H_{39}NO_4$	73.4	8.9	73.5	8.9	240
Me	*sec*-Bu	164	$C_{27}H_{39}NO_4$	73.4	8.9	73.1	8.8	
Me	*i*-Bu	170	$C_{27}H_{39}NO_4$	73.4	8.9	73.3	8.9	20
Me	*t*-Bu	188	$C_{27}H_{39}NO_4$	73.4	8.9	73.2	9.0	30
Me	*n*-Am	113	$C_{28}H_{41}NO_4$	73.8	9.1	73.6	9.6	36
Me	*i*-Am	126	$C_{28}H_{41}NO_4$	73.8	9.1	73.6	9.0	150
Me	CH_2Ph	146	$C_{30}H_{37}NO_4$	75.8	7.8	75.6	8.0	110
Me	Ph	202	$C_{29}H_{35}NO_4$	75.5	7.6	75.0	7.7	0
Me		195	$C_{29}H_{41}NO_4$	74.5	8.8	74.4	9.1	15

[a] Morphine = 1.

dation of the quaternary salts proceeded very readily to give the expected methine bases XXI.

Nomenclature. The systematic nomenclature for the bases in this series, based on the 6,14-*endo*-ethenotetrahydrothebaine system, is cumbersome and, since many degradation and rearrangement products of thebaine, codeine, and morphine already have simple trivial names, a simpler system, based on a trivial name for a key intermediate, would be an advantage. The trivial name nepenthone was assigned to the phenyl ketone I (R = Ph) in order to facilitate the naming of derivatives. The intermediates that have been most widely used in this work are the aldehyde I (R = H) and the ketones I (R = Me and Ph) and of these the ketone I (R = Me) is much the most active as an analgesic and gives rise to a very wide series of alcohols of structure II (R = Me) of high activity. These alcohols are more easily prepared and of much greater pharmacological interest than the corresponding bases II (R ≠ Me). Accordingly, a trivial name has been assigned to the ketone I (R = Me). This ketone is the adduct of thebaine and methyl vinyl ketone and by a suitable selection of syllables from the names of these compounds the name *thevinone* emerges for the ketone I (R = Me). The related secondary alcohol II (R = Me, R′ = H) then becomes *thevinol*, and the other bases in the series II (R = Me), being obviously homolog of II (R = Me, R′ = H), may be named as alkylthevinols, *e.g.*, the alcohol II (R = Me, R′ = *n*-Pr) becomes *propylthevinol* and II (R = Me, R′ = CH_2CH_2-Ph) becomes *phenethylthevinol*.

As will be seen in the following paper, most of the alcohols of the series II have been demethylated to phenolic 3-hydroxy analogs, and bases of this series corresponding to those of structure II (R = Me), being derivatives of tetrahydrooripavine rather than tetrahydrothebaine, can be termed alkylorvinols, *e.g.*, the 3-hydroxy analog of the base II (R = Me, R′ = cyclohexyl) would be *cyclohexylorvinol*.

The acid I (R = OH), being an oxidized form of thevinone, can be named *thevinoic acid* and the ester I (R = OEt) then becomes *ethyl thevinoate* and the acid chloride I (R = Cl) *thevinoyl chloride*. (The term thevinic acid is avoided as this leads to the acid chloride being named thevinyl chloride, which should be reserved for the halide corresponding to thevinol.) Since a series of 6,14-ethano alcohols XIX derived from the ketone XX is known, this last base can be termed *hydrothevinone* and the alcohols thus become *alkylhydrothevinols*, or hydroorvinols after O-demethylation. Relatively simple extensions of this nomenclature permit rational names to be assigned to other bases resulting from transformations of the ketone I (R = Me) and the alcohols II (R = Me), and these will be discussed where necessary in subsequent publications.

Experimental Section

Examples only of representative Grignard reactions and reductions are given in this section to show the general processes used.

7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine (19-Methylthevinol) (II, R = R′ = Me). a. A solution of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (thevinone) (I, R = Me) (10 g) in dry ether (500 ml) or in dry benzene (50 ml) was added slowly with vigorous stirring to a refluxing solution of methylmagnesium iodide, prepared from magnesium (1.67 g) and methyl iodide (9.9 g) in ether (100 ml), and the mixture was stirred and heated under reflux for 2 hr. The mixture was then shaken with aqueous ammonium chloride, and the organic layer was separated, dried, and evaporated, leaving a crystalline base (10 g), which was recrystallized from ethanol. The base was obtained in this way as plates, mp 166°.

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.5; H, 7.9. Found: C, 72.5; H, 7.7.

b. 6,14-*endo*-Etheno-7α-ethoxycarbonyltetrahydrothebaine (ethyl thevinoate) (I, R = OEt) (10 g) was extracted from a Soxhlet extractor into a boiling stirred solution of methylmagnesium iodide (from 1.67 g of magnesium and 9.9 g of methyl iodide) in ether (100 ml). The mixture was boiled under reflux for 3 hr, and the product isolated as in a above, when it was obtained (9.8 g) as white prisms, mp 166°, alone or mixed with material prepared from the ketone.

7β-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine (19-Methyl-β-thevinol) (C-7 Epimer of II, R = R′ = Me). a. A solution of 7β-acetyl-6,14-*endo*-ethenotetrahydrothebaine (0.5 g) in ether (100 ml) was added to a stirred refluxing solution of methylmagnesium iodide (from 0.17 g of magnesium and 1 g of methyl iodide), and the mixture was boiled under reflux for 1 hr. Isolation of the product in the usual way afforded a mixture of two nonketonic products. These were separated on thick alumina plates, and the base, having the greater R_f value, was obtained as prisms, mp 190°, on recrystallization from ethanol. It was identified as the alcohol epimeric at C-7 with II (R = R′ = Me) by its nmr and infrared spectra, which were very similar to but not identical with those of II (R = R^1 = Me).

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.5; H, 7.9. Found: C, 72.5; H, 7.7.

The second product, of lower R_f value, was phenolic and has been identified as a product of base-catalyzed rearrangement of the

parent ketone followed by Grignard reaction and is described in detail in a later paper.[6b]

Reduction of 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (Thevinone) (I, R = Me). a. The ketone I (R = Me) (10 g) was boiled with aluminum isopropoxide (10 g) and 2-propanol (100 ml) with slow distillation of the solvent through a 36-plate fractionating column until the distillate no longer gave a precipitate with a solution of 2,4-dinitrophenylhydrazine in aqueous hydrochloric acid. On completion of the reaction, the mixture was evaporated to small bulk and poured into dilute hydrochloric acid. The acid solution was saturated with potassium sodium tartrate and basified with ammonia, and the precipitated base was isolated by ether extraction, when the carbinol II (R = H, R′ = Me) was obtained as a viscous gum that was crystallized from aqueous methanol, being then obtained as white prisms, mp 78–80°, raised to 82° by further recrystallization from aqueous methanol or ether at low temperatures.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.1: H, 7.6. Found: C, 72.0; H, 7.5.

Thin layer chromatographic studies showed that the base, mp 78–80°, first obtained contained about 5% of the isomeric carbinol II (R = Me, R′ = H), which is the main product of Grignard reduction of the ketone.

The O-formyl ester was prepared by heating the alcohol with 98–100% formic acid at 100° for 1 hr and was obtained as plates, mp 110°, from aqueous methanol.

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.1; H, 7.1. Found: C, 70.3; H, 7.2.

The O-acetyl ester, prepared from the alcohol and acetic anhydride in pyridine, was obtained as plates, mp 170°, from aqueous ethanol.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.7; H, 7.3. Found: C, 70.9; H, 7.5.

b. The ketone I (R = Me) (10 g) was boiled under reflux in methanol (50 ml) with sodium borohydride (1 g) for 30 min. The solution was concentrated by evaporation and poured into water and the precipitated base was isolated by ether extraction, when it was obtained as a viscous gum, shown by thin layer chromatography to consist of an approximately 1:1 mixture of the products of Meerwein–Pondorff and Grignard reduction of the ketone.

7α-(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine (19-Propylthevinol) (II, R = Me, R′ = *n*-Pr)a nd Grignard Reduction of the Ketone I (R = CH_3). 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (I, R = CH_3) (50 g) in dry benzene (250 ml) was added to a vigorously stirred refluxing solution of *n*-propylmagnesium iodide (from 8.35 g of magnesium and 58.5 g of 1-iodopropane) in ether (500 ml), and the mixture was boiled under reflux for 2 hr. The product, isolated in the usual way, was a viscous gum which crystallized on trituration with methanol (100 ml). The solid was collected and recrystallized from ethanol, when the alcohol II (R = Me, R′ = *n*-Pr) was obtained as white prisms, mp 176° (24.0 g).

Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.3; H, 8.2. Found: C, 73.2; H, 8.2.

The mother liquors were diluted with methanol (50 ml) and water was added until precipitation of gummy material began. The solution was allowed to stand for 15 min, decanted from the gummy material, and then kept in the refrigerator, when the Grignard reduction product, 7α-(1-(*S*)-hydroxyethyl)-6,14-*endo*-ethenotetrahydrothebaine (thevinol) (II, R = Me, R′ = H) (12 g) was obtained as needles, mp 76–78°, raised to 81° on recrystallization from aqueous methanol.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.1; H, 7.6. Found: C, 71.8; H, 8.0.

The O-formyl ester, prepared by heating the secondary alcohol with 98–100% formic acid at 100° for 1 hr, was obtained as prisms, mp 148°, from aqueous methanol.

Anal. Calcd for $C_{24}H_{29}NO_5 \cdot 0.5H_2O$: C, 68.6; H, 7.2. Found: C, 68.7; H, 7.3.

The O-acetyl ester, prepared from the alcohol, acetic anhydride, and pyridine, was obtained as prisms, mp 120°, from aqueous methanol.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.7; H, 7.3. Found: C, 70.8; H, 7.5.

A third base has been isolated from the residues of separation of the Grignard reduction product. This was a phenol, mp 201–203°, and is a product of base-catalyzed rearrangement of the parent ketone followed by normal Grignard reaction with propylmagnesium iodide; it is described fully in a later paper.[6b]

7α-(1-(*S*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine (II, R = *n*-Pr, R′ = Me). 7α-Butyryl-6,14-*endo*-ethenotetrahydrothebaine (I, R = *n*-Pr) (15 g) in ether (500 ml) was added to a stirred solution of methylmagnesium iodide (from 2 g of magnesium and 6 ml of methyl iodide) in ether (150 ml), and the mixture was boiled under reflux for 1 hr. Isolation of the product in the usual way afforded 10.1 g of a base containing about 10% of the alcohol II (R = Me, R′ = *n*-Pr). After several recrystallizations from methanol the alcohol II (R = *n*-Pr, R′ = Me) was obtained almost pure, as prisms, mp 144–145°, and a pure specimen, mp 148–149°, for spectral studies was obtained by layer chromatographic separation on alumina.

Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.3; H, 8.2. Found: C, 73.2; H, 8.4.

7α-(1-(*R*)-Hydroxy-1-methylpropyl)-6,14-*endo*-ethenotetrahydrothebaine (19-ethylthevinol) (II, R = Me, R′ = Et) was obtained by the above general method from the ketone I (R = Me) and ethylmagnesium bromide as prisms, mp 74°, with resolidification and final melting at 135°.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 73.1; H, 8.1. Found: C, 72.9; H, 8.1.

It was also obtained by the reduction of the vinylcarbinol II (R = Me, R′ = CH=CH_2); see below.

7α-(1-(*S*)-Hydroxy-1-methylpropyl)-6,14-*endo*-ethenotetrahydrothebaine (II, R = Et, R′ = Me) was prepared by the general method from the ketone I (R = Et) and methylmagnesium iodide, when it was obtained as prisms, mp 165°.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 73.1; H, 8.1. Found: C, 72.9; H, 8.2.

It was also obtained by the reduction of the acetylenic carbinol II (R = C≡CH, R′ = Me); see below.

7α-(1-(*R*-Hydroxy-1-methylprop-2-enyl)-6,14-*endo*-ethenotetrahydrothebaine (19-Vinylthevinol) (II, R = Me, R′ = CH=CH_2). A solution of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (I, R = Me) (19 g) in dry tetrahydrofuran (30 ml) was added to a refluxing solution of vinylmagnesium bromide (from 3.0 g of magnesium and 13.4 g of vinyl bromide) in tetrahydrofuran, and the mixture was boiled under reflux for 2 hr. Saturated aqueous ammonium chloride was added, and the organic layer was separated, dried, and evaporated. The residual brown gum was crystallized from methanol when the alcohol was obtained as white prisms, mp 155°.

Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.3; H, 7.6. Found: C, 73.3; H, 7.6.

Reduction. The alcohol II (R = Me, R′ = CH=CH_2) (5 g) in ethanol (100 ml) was shaken under hydrogen at 22° (750 mm) in the presence of platinum oxide (100 mg). Hydrogen (300 ml) was absorbed over 30 min, after which reduction ceased. Filtration and evaporation of the solution gave 5.0 g of material which on crystallization from ethanol gave prisms, mp 74 and 135°, unaltered on mixing with the alcohol II (R = Me, R′ = Et), obtained from the action of ethylmagnesium bromide on the ketone I (R = Me). The infrared spectra and chromatographic behavior on alumina plates of the bases from the two sources were also identical.

7α-(1-(*S*)-Hydroxy-1-methylprop-2-ynyl)-6,14-*endo*-ethenotetrathebaine (19-Ethynylthevinol) (II, R = C≡CH, R′ = Me). 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (I, R = Me) (38 g) in dry tetrahydrofuran (200 ml) was added with stirring to a solution of lithium acetylide–ethylenediamine complex (10 g) under an atmosphere of argon. The mixture was stirred at 35° for 3 hr and poured into water (200 ml). The mixture was extracted three times with ether, and the combined extracts were dried and evaporated. The residue crystallized in part on trituration with methanol (20 ml), and the solid (10.5 g) was collected and recrystallized from methanol when the alcohol II (R = C≡CH, R′ = Me) was obtained as prisms, mp 185–186°.

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.7; H, 7.1. Found: C, 73.6; H, 7.2.

A further 4.1 g of material, mp 183–184°, was obtained on concentration of the mother liquors. Final evaporation of these liquors afforded a gum shown by thin layer chromatography to consist of an approximately 1:1 mixture of the above base and a second compound, presumably the diastereoisomeric alcohol II (R = Me, R′ = C≡CH), since the infrared spectrum of the mixture was almost identical with that of the pure base, mp 185–186°.

Reduction. The acetylenic alcohol II (R = C≡CH, R′ = Me) (4.0 g) was hydrogenated over platinum oxide (100 mg) in ethanol at 22° (760 mm). Hydrogen (449 ml, 2 moles) was absorbed over 20 min, and isolation of the product afforded the alcohol II (R = Et, R′ = Me), mp 165°, identical in melting point, mixture melting point, infrared absorption, and R_f value with the product of the action of methylmagnesium iodide on the ketone I (R = Et).

Study of the Stereochemistry at C-19 of the Alcohols II (R = H, R′ = Me and R = Me, R′ = H). A solution of 7α-(1-(*R*)-hydroxy-

ethyl)-6,14-*endo*-ethenotetrahydrothebaine (II, R = H, R′ = Me) (5 g) and phenylglyoxalyl chloride (6 g) in pyridine (12 ml) was kept at room temperature overnight. Ice water was then added until separation of solid matter occurred. The solid was isolated by ether extraction, and the viscous gum so obtained was crystallized by trituration with methanol. The solid was collected (3.5 g) and recrystallized from methanol when the phenylglyoxalyl ester was obtained as off-white plates, mp 206°.

Anal. Calcd for $C_{31}H_{33}NO_6 \cdot H_2O$: C, 69.85; H, 6.7. Found: C, 70.0; H, 7.0.

A solution of methylmagnesium iodide (from 0.95 g of magnesium and 25 ml of methyl iodide) in ether (30 ml) was added to a solution of the phenylglyoxalyl ester (5 g) in dry benzene (100 ml), and the mixture was kept at room temperature for 3 hr and then boiled under reflux for 3 hr. The mixture was poured into aqueous ammonium chloride; the organic layer was separated and the aqueous layer extracted twice with chloroform. The combined ether–benzene and chloroform solutions were evaporated, and the residue was boiled under reflux with 5% methanolic potassium hydroxide (200 ml) for 5 hr. Most of the methanol was evaporated, and the mixture was diluted with water (200 ml) and extracted four times with ether to remove the organic base. The aqueous layer was acidified with hydrochloric acid and extracted continuously with ether for 3 days. The ether extract on evaporation afforded a gum from which atrolactic acid, mp 114–115°, $[\alpha]^{20}D$ +4.8°, was obtained as white needles on extraction with light petroleum (bp 80–100°).

Repetition of the above reactions using 7α-(1-(*S*)-hydroxyethyl)-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me, R^1 = H) as starting material afforded the phenylglyoxalyl ester as prisms, mp 96 and 170°, and atrolactic acid, mp 114–115°, $[\alpha]^{20}D$ −5.4°.

Anal. Calcd for $C_{31}H_{33}NO_6 \cdot H_2O$: C, 69.85; H, 6.7. Found: C, 70.2; H, 7.0.

7α-Acetyl-6,14-*endo*-ethanotetrahydrothebaine (Dihydrothevinone) (XX). 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (I, R = Me) (5 g) in ethanol (200 ml) was shaken with 10% palladium on charcoal (0.5 g) under hydrogen at 58 psi at 50° for 10 hr. The mixture was filtered from the catalyst and evaporated. The residue was crystallized from ethanol when the 6,14-*endo*-ethano-7α-ketone (3.8 g) was obtained as white prisms, mp 134–136°, ν_{max} 1710 cm^{-1}.

Anal. Calcd for $C_{23}H_{28}NO_4$: C, 72.0; H, 7.6. Found: C, 71.6; H, 7.6.

7β-Acetyl-6,14-*endo*-ethanotetrahydrothebaine (β-Dihydrothevinone) (C-7 Epimer of XX). 7β-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (0.38 g) was hydrogenated over 10% palladium on charcoal (0.20 g) in ethanol (100 ml) at 22° (755 mm). Hydrogen (22 ml) was absorbed over 7 min. The solution was filtered and evaporated, and the residue was crystallized from ethanol when the 6,14-ethano-7β-ketone was obtained as prisms, mp 166°.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6. Found: C, 71.8; H, 7.6.

6,14-*endo*-Ethano-7α-formyltetrahydrothebaine (XX, CH_3 = H). 6,14-*endo*-Etheno-7α-formyltetrahydrothebaine (I, R = H) (1.84 g) was hydrogenated over 10% palladium on charcoal (0.3 g) in ethanol (50 ml) at 22° (760 mm). Hydrogen (112 ml) was absorbed over 2.5 hr. The isolated product was crystallized from ethanol when the 6,14-*endo*-ethano-7α-aldehyde was obtained as prisms, mp 98°, ν_{max} 1740 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4. Found: C, 71.2; H, 7.2.

6,14-*endo*-Ethano-7α-(1-(*R*)-hydroxyethyl)tetrahydrothebaine (XIX, R = H, R′ = Me). 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxyethyl)tetrahydrothebaine (II, R = H, R′ = Me) (25 g) (from the Meerwein–Pondorff reduction of the ketone I, R = Me) was hydrogenated at 22° (760 mm) in ethanol (100 ml) over 10% palladium on charcoal (1 g). Hydrogen (1500 ml) was absorbed over 50 min. The product was isolated as prisms, mp 49–51°, from aqueous methanol.

Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.6; H, 8.1. Found: C, 71.5; H, 8.2.

The O-*p*-toluenesulfonate was obtained as prisms, mp 157°, from benzene–methanol.

Anal. Calcd for $C_{30}H_{37}NO_6S \cdot 0.5H_2O$: C, 65.6; H, 7.0; S, 5.8. Found: C, 65.3; H, 7.0; S, 5.7.

The diastereoisomeric alcohol II (R = Me, R′ = H), from the Grignard reduction of the ketone I (R = Me), was resistant to hydrogenation under the above conditions and at temperatures up to 60°.

6,14-*endo*-Ethano-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (Dihydro-19-methylthevinol) (XIX, R = R′ = Me). a. 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (II, R = R′ = Me) (40 g) was hydrogenated in ethanol (300 ml) over W4 Raney nickel (10 g) at 160–165° (164–182 atm) for 4 hr. The solution was filtered and concentrated to yield the 6,14-ethano alcohol as white prisms, mp 142°, after recrystallization from ethanol.

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.2; H, 8.3; N, 3.5. Found: C, 71.8; H, 8.2; N, 3.5.

b. The same base was obtained by the action of methylmagnesium iodide (from 0.83 g of magnesium and 5.2 g of methyl iodide) on 7α-acetyl-6,14-*endo*-ethanotetrahydrothebaine (dihydrothevinone) (4.8 g) in ether solution.

Hofman Degradation of the Alcohols II (R = Me, R′ = *n*-Pr and R = Me, R′ = Ph). 19-Propylthevinol (II, R = Me, R′ = *n*-Pr) and 19-phenylthevinol (II, R = Me, R^1 = Ph) (2 g) were separately boiled under reflux with methyl iodide (10 ml) and acetone (20 ml) for 7 days. The solvent was evaporated, and the residue was recrystallized from ethanol to give 19-propylthevinol methiodide (white prisms, mp 188–190°. *Anal.* Calcd for $C_{27}H_{38}NO_4I \cdot 0.5H_2O$: C, 56.3; H, 6.8. Found: C, 56.4; H, 5.8) and 19-phenylthevinol methiodide (white prisms, mp 194–196°. *Anal.* Calcd for $C_{30}H_{36}NO_4I \cdot 0.5H_2O$: C, 59.0; H, 6.1. Found: C, 58.7; H, 6.1).

The methiodides (1 g) were degraded by boiling under reflux with 20% aqueous potassium hydroxide for 15 min. The solution was diluted and the product collected at the pump and recrystallized from aqueous ethanol to give 19-propylthevinol methine (XXI, R′ = *n*-Pr; white needles, mp 90–95°, λ_{max} 230, 279, 308, 318 mμ (ϵ_{max} 12,000, 7000, 3000, 2300). *Anal.* Calcd for $C_{28}H_{37}NO_4 \cdot H_2O$: C, 70.9; H, 8.5. Found: C, 71.2; H, 8.3) and 19-phenylthevinol methine (XXI, R′ = Ph, white plates, mp 160°, λ_{max} 279 and 310 mμ (ϵ_{max} 8050 and 3500). *Anal.* Calcd for $C_{30}H_{35}NO_4 \cdot H_2O$: C, 73.4; H, 7.5. Found: C, 73.2; H, 7.6).

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