Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. III.[1] Alcohols of the 6,14-*endo*-Ethenotetrahydrooripavine Series and Derived Analogs of N-Allylnormorphine and -norcodeine

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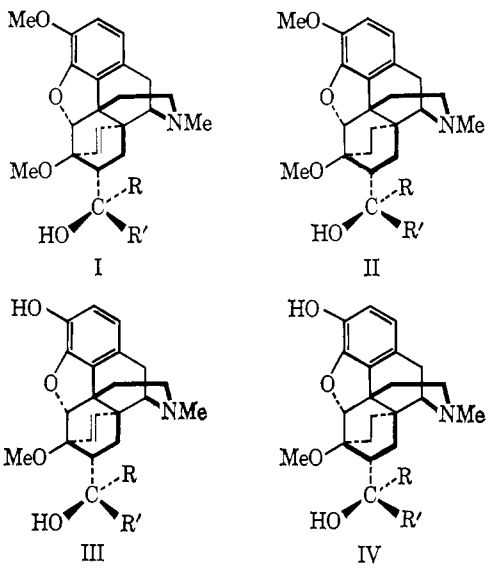
Abstract: Secondary and tertiary alcohols of general structures IV and V have been prepared by the demethylation of the corresponding bases I and II described in part II of this series. The phenols so obtained are analgesics of extremely high potency, up to an unprecedented 12,000 times that of morphine. The bases of this and earlier series have been converted into analogs of N-allylnormorphine and N-allylnorcodeine of general structures XI and XII *via* the N-cyanonor compounds and *via* novel N,N′-methylenebis compounds XIII resulting from the reaction of the bases I and II with methyl azodicarboxylate. Some bases of the series XII are morphine antagonists of unprecedented potency, up to 150 times that of N-allylnormorphine.

In the preceeding paper the preparation of two series of codeine derivatives of general structures I and II was reported, many of the members of which were considerably more active as analgesics than any base previously prepared in the morphine–thebaine group. Since the demethylation of codeine derivatives to the corresponding derivatives of morphine almost always results in an appreciable increase in analgesic activity, most of the alcohols of structures I and II were converted into the related phenols. The O-demethylation cannot be accomplished without decomposition by acidic reagents owing to the extreme ease with which the alcohols undergo acid-catalyzed rearrangement,[1c] but was effected in most cases by heating the bases with potassium hydroxide in diethylene glycol at 200–220°. Demethylation of the methyl ethers to the phenols to a very small extent was occasionally observed during the Grignard reactions leading to the alcohols of structure I. The demethylating action of Grignard reagents is well known,[2] but the method has little preparative value.

The alkaline demethylations affected only the methoxyl group attached to C-3, that at C-6 remaining undisturbed. From the point of view of analgesic activity, however, the retention of the C-6 methoxyl group is advantageous, since methylation of the hydroxyl group at this position in morphine and codeine enhances the activity. The demethylation of the C-3 methoxyl group in the codeine–thebaine group under alkaline conditions appears to have been first observed during the Huang-Minlon reduction of thebenone.[3] The 4,5-oxygen bridge in these bases, which is unaffected under the conditions of the demethylation, also represents the ether of a phenolic hydroxyl group, but fission of this bridge during simple demethylations in the morphine series has never been observed, though fused potassium hydroxide converts methylmorphenol into 3,4,5-trihydroxyphenanthrene.[4]



The bases obtained in this way, having structures III and IV, are listed in Tables I and II, respectively. In all cases it is found that demethylation of the C-3 methoxyl group results in an increase in analgesic potency, but the increase is by no means uniform throughout the series. The most potent compounds in this series do not correspond to the most potent of the methyl ethers, but, in a simple screening procedure in which analgesia is determined at a fixed time after administration of the compounds, comparisons are not always meaningful, since no account is taken of speed of onset, time of peak action, or duration of analgesia. The most potent analgesics in the morphine series reported prior to this work are about 12 times as active as morphine, but in other groups higher activities than this have frequently been encountered. The highest well-documented activities are reported in a series of benzimidazoles, of which the most active is about 1000 times as potent as morphine.[5] Of the oripavine

(1) (a) Part II: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3273 (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) Part IV: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3293 (1967).

(2) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable and Co. Ltd., London, 1954, p 1029.

(3) K. W. Bentley and R. Robinson, *Experientia*, **6**, 353 (1950); K. W. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

(4) E. von Gerichten and O. Dittmer, *Ber.*, **39**, 1718 (1906).

(5) A. Hunger, J. Kebrele, A. Rossi, and K. Hofmann, *Helv. Chim. Acta*, **43**, 1032, 1046 (1960).

Table I. Alcohols of Structure III

R	R′	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mp, °C HCl	Molar potency[a]
H	H	219	$C_{21}H_{25}NO_4$	71.0	7.1	71.1	7.2	287	17
H	Me	298	$C_{22}H_{27}NO_4$	71.4	7.3	71.2	7.5	272	37
Me	H	280	$C_{22}H_{27}NO_4$	71.4	7.3	71.6	7.6	290	15
H	Ph	160	$C_{27}H_{29}NO_4 \cdot H_2O$	72.8	6.7	72.6	6.7	300	4.2
H	CH_2CH_2Ph	120	$C_{29}H_{33}NO_4$	75.7	7.2	75.8	7.3	290	1100
Me	Me	266	$C_{23}H_{29}NO_4$	72.1	7.6	72.4	7.5	290	63
Me	Et	268	$C_{24}H_{31}NO_4$	72.6	7.8	72.5	8.1	282	330
Et	Et	157	$C_{25}H_{33}NO_4 \cdot 0.5H_2O$	71.4	8.1	71.5	8.1	310	55
Me	*n*-Pr	215	$C_{25}H_{33}NO_4 \cdot H_2O$	70.0	8.1	70.0	7.9	267	3200
Me	*n*-Bu	174	$C_{26}H_{35}NO_4 \cdot H_2O$	70.4	8.3	70.6	8.5	272	5200
Me	*i*-Bu	217	$C_{26}H_{35}NO_4 \cdot H_2O$	70.4	8.3	70.7	8.6	292	10
Me	*n*-Am	106	$C_{27}H_{37}NO_4 \cdot 0.5H_2O$	72.3	8.5	72.6	8.6	278	4500
Me	*i*-Am	132	$C_{27}H_{37}NO_4$	73.6	8.2	73.4	8.1	258	9200
Me	*n*-$C_{16}H_{13}$	288	$C_{28}H_{39}NO_4$	74.1	8.6	74.6	8.6	265	58
Me	Ph	252	$C_{28}H_{31}NO_4 \cdot H_2O$	72.7	7.2	72.9	7.4	286	34
Me	CH_2CH_2Ph	226	$C_{30}H_{35}NO_4$	76.1	7.5	75.9	7.6	255	2200
Me	Cyclopentyl	302	$C_{27}H_{35}NO_4$	74.1	8.1	74.0	7.9	248	70
Me	Cyclohexyl	242	$C_{28}H_{37}NO_4$	74.5	8.2	74.2	8.2	263	3400

[a] Morphine = 1.0.

Table II. Alcohols of Structure IV

R	R′	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Molar potency[a]
Me	*n*-Pr	116 (205)	$C_{25}H_{35}NO_4$	72.6	8.5	72.8	8.8	12,000
Me	*i*-Am	180	$C_{27}H_{39}NO_4$	73.5	8.9	73.4	8.9	11,000

[a] Morphine = 1.

Table III. 3-O-Acetyl Esters of Alcohols of Structure III

R	R′	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mp, °C HCl	Molar potency[a]
Me	Me	191	$C_{25}H_{31}NO_5$	70.5	7.3	70.5	7.2	261	55
Me	Et	154	$C_{26}H_{33}NO_5$	71.0	7.5	71.2	7.6	252	
Me	*n*-Pr	196	$C_{27}H_{35}NO_5$	71.5	7.7	71.3	7.7	206	8700
Me	*i*-Bu	152	$C_{28}H_{37}NO_5$	71.9	7.9	72.0	8.1	238	
Me	*i*-Am	126	$C_{29}H_{39}NO_5$	72.3	8.1	73.1	8.1	244	1300
Me	Cyclohexyl	193	$C_{30}H_{39}NO_5 \cdot H_2O$	70.5	8.1	70.8	8.2	262	1700
Et	Et	179	$C_{27}H_{35}NO_5$	71.5	7.7	71.2	7.6		

[a] Morphine = 1.

derivatives listed in Tables I and II, many are more active than any of the benzimidazoles, and in particular the alcohol IV (R = Me, R′ = *n*-Pr), which is about 12,000 times as active as morphine, is the most potent analgesic so far reported. The very high potency of the phenols of structures III and IV makes them eminently suitable for use in large animals and the base III (R = Me, R′ = *n*-Pr) is already widely used for the immobilization of wild animals for game conservation and veterinary purposes.[6,7]

Several of the bases of the tetrahydrooripavine series III and IV have proved to be inaccessible. Bases of either of these structures in which one of the groups R or R′ contains the system CHC=C or CH—aryl directly attached to the hydroxyl-bearing carbon atom fail to survive the vigorous conditions necessary for the alkaline demethylation process, owing to the ease with which they suffer base-catalyzed dehydration to polymerizable derivatives.

Esterification of the phenolic hydroxyl group of the tetrahydrooripavine derivatives is very easily accomplished by the conventional methods and, in general, results in some reduction in analgesic activity, though the 3-O-acetyl derivative of the base III (R = Me, R′ = *n*-Pr) is more than twice as active as the parent phenol. The esters are very readily hydrolyzed even on heating aqueous solutions of their salts. The esters prepared are listed in Table III.

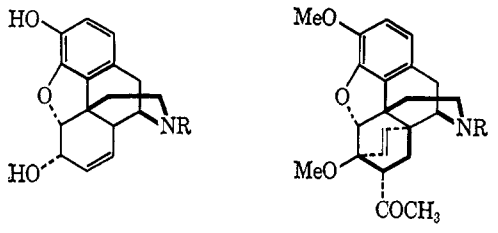
Derivatives of Nor Bases

It has been shown that N-allylnormorphine[8] (nalorphine) (V, R = $CH_2CH{=}CH_2$) antagonizes the action of morphine (V, R = Me) in animals and in man,[9] and that its administration to narcotics addicts precipitates withdrawal symptoms. Physical dependence on the drug does not appear to develop after prolonged administration, and it is widely believed to be nonaddicting.[10] Although the compound does not show

(6) J. M. King and B. H. Carter, *East African Wild Life J.*, **3**, 19 (1965).
(7) A. M. Harthoorn and J. Bligh, *Res. Vet. Sci.*, **6**, 290 (1965); A. M. Harthoorn, *J. S. African Vet. Med. Assoc.*, **36**, 45 (1965).
(8) J. Weijlard and A. E. Erickson, *J. Am. Chem. Soc.*, **64**, 869 (1942).
(9) K. Unna, *J. Pharmacol. Exptl. Therap.*, **79**, 27 (1943).
(10) H. Isbell, *Federation Proc.*, **15**, 442 (1956).

up as an analgesic when tested by the conventional techniques in laboratory animals, it has been shown to be an analgesic effective against natural pain in man, and to have a potency in such conditions about equal to that of morphine itself.[11] It has been very widely studied in clinical investigations, but has been found to produce bizarre and often distressing mental effects in a number of patients, with the result that it has found little clinical use as an analgesic.

The series of alcohols of general structures III and IV, and their 3-O-methyl ethers described in the previous paper, having a very wide range of morphine-like activity, provide a large number of starting materials, and many of these have been converted into analogs of nalorphine. Normorphine (V, R = H), from which other tertiary bases in the morphine series are prepared, is obtained from diacetylmorphine by treatment with cyanogen bromide and hydrolysis of the resulting N-cyanonor compound with dilute hydrochloric acid.[8] Cyanogen bromide reacts with the ketone VI (R = Me) and its analogs, the phenols of general structures III and IV, and their methyl ethers to give the corresponding N-cyanonor compounds in very good yield. Since the rate of quaternization of all of the bases in this series is very low, quaternary salt formation with liberated methyl bromide is not a complicating factor in the reaction.



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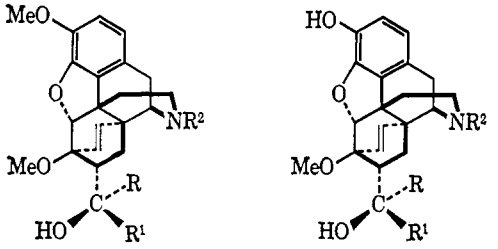
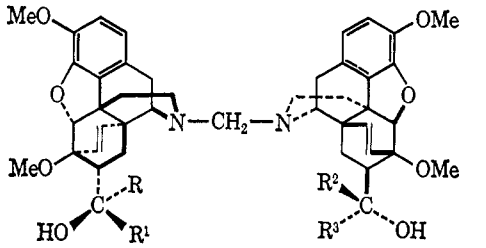
VI



VII

VIII



IX

The alcohols of general structures VII and VIII and the corresponding 6,14-ethano compounds, being very readily rearranged by acids, can only be hydrolyzed at the N-cyano group under alkaline conditions, most conveniently by heating with potassium hydroxide in diethylene glycol at 160° for 5–10 min, or at 200–220° for longer periods if the simultaneous O-demethylation of VII to VIII is also required. The ketones of structure VI are, however, unstable to alkalis, and hydrolysis of the N-cyano group of the cyanamide VI (R = CN) must be effected with dilute mineral acid, to which the ring structure is stable. The hydrolysis is, however, incomplete, and the principal product is the substituted urea VI (R = $CONH_2$). The required secondary base VI (R = H) is, however, preparable by the action of nitrous acid on the urea in 50% yield.

The preferred method of preparation of the ketonic secondary base VI (R = H) is the reaction of the tertiary base VI (R = Me) with methyl azodicarboxylate. The initial product of this reaction, which is presumably the substituted hydrazo ester VI (R = $CH_2N(COOMe)$—NHCOOMe), is very readily hydrolyzed by cold aqueous 1 *N* hydrochloric acid, with the separation of the sparingly soluble hydrochloride of the secondary base VI (R = H) and the liberation of formaldehyde and methyl hydrazodicarboxylate. Norcodeine has been prepared by this general process, but the yield is poor.[12,13] The application of this reaction to the alcohols of general structure VII (R^2 = Me) and their 6,14-ethano analogs does not lead directly to the production of the corresponding secondary bases VII (R^2 = H). These alcohols react readily with methyl or ethyl azodicarboxylate in acetone solution, but the hydrolysis of the primary reaction products with mineral acid in the cold affords solutions from which no salt separates. The basification of these solutions affords products that initially are very soluble in methanol, but are rapidly converted in hot methanol into sparingly soluble, high-melting bases. Similar results are obtained, though more slowly, when the primary reaction products are hydrolyzed with aqueous methanol instead of acid.

The final high-melting products are not carbinolamines VII (R^2 = CH_2OH), as these are lower melting, more soluble bases preparable by the action of formaldehyde on the secondary bases, but they are obtained from the carbinolamines by heating these alone, or better with secondary base, in solution. Whereas on heating with an aqueous acid solution of 2,4-dinitrophenylhydrazine, the carbinolamines give 1 molecular equiv of formaldehyde dinitrophenylhydrazone, the high-melting products under similar conditions afford only 0.5 equiv of the hydrazone. It is clear from these facts that the high-melting bases are N,N′-methylenebisnor bases of general structure IX, and nmr spectral studies support this conclusion. The spectra of the base VII (R = R^1 = R^2 = Me) and the bis compound IX (R = R^1 = R^2 = R^3 = Me) are identical in all important respects apart from the absence from the spectrum of the latter base of the characteristic signal due to NCH_3.

Unsymmetrical bis compounds of structure IX can be prepared by the interaction of carbinolamines VII (R^2 = CH_2OH) and secondary bases VII (R^2 = H) differing in the nature of the $HOCRR^1$ substituent at C-7; for example, the same unsymmetrical base is obtained by heating the carbinolamine VII (R = R^1 = Me, R^2 = CH_2OH) with the secondary base VII (R = Me, R^1 = CH_2CH_2Ph, R^2 = H) or the carbinolamine VII

(11) L. Lasagna and H. K. Beecher, *J. Pharmacol. Exptl. Therap.*, **112**, 356 (1954); A. S. Keats and J. Telford, *ibid.*, **117**, 190 (1956).

(12) O. Diels and M. Paquin, *Ber.*, **46**, 2000 (1913).

(13) O. Diels and E. Fischer, *ibid.*, **47**, 2043 (1914).

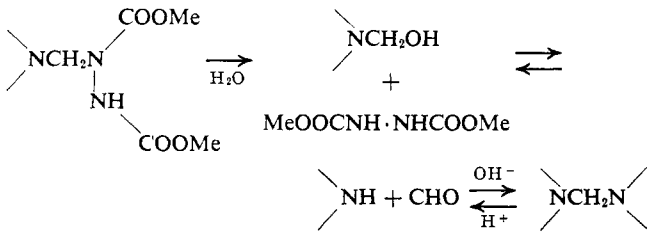
Table IV. N,N′-Methylenebis Compounds of Structure IX

R	R^1	R^2	R^3	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H
Me	Me	Me	Me	286	$C_{47}H_{58}N_2O_8$	72.5	7.4	72.3	7.5
Me	Et	Me	Et	252	$C_{49}H_{62}N_2O_8$	73.0	7.7	73.1	7.8
Me	*n*-Pr	Me	*n*-Pr	269	$C_{51}H_{66}N_2O_8$	73.4	8.0	73.2	8.4
Me	*i*-Bu	Me	*i*-Bu	224	$C_{53}H_{70}N_2O_8$	73.8	8.1	73.7	8.3
Me	*n*-Am	Me	*n*-Am	186	$C_{55}H_{74}N_2O_8$	74.1	8.4	74.2	8.2
Me	*i*-Am	Me	*i*-Am	200	$C_{55}H_{74}N_2O_8$	74.1	8.4	74.0	7.9
Me		Me		228	$C_{57}H_{74}N_2O_8$	74.8	8.2	75.1	8.0
Me	CH_2CH_2Ph	Me	CH_2CH_2Ph	243	$C_{61}H_{70}N_2O_8$	76.4	7.4	76.4	7.8
Me	Me	Me	CH_2CH_2Ph	220	$C_{54}H_{64}N_2O_8$	74.6	7.4	74.3	7.2

Table V. Ketones of Structure VI

R	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mp, °C, HCl
H	74	$C_{22}H_{25}NO_4 \cdot H_2O$	68.8	7.0	68.8	7.2	350
CN	236	$C_{23}H_{24}N_2O_4$	70.4	6.2	70.2	6.2	...
$COCH_3$	101	$C_{24}H_{27}NO_5 \cdot H_2O$	67.4	6.8	67.3	6.8	...
$CH_2CH_2CH_3$	...	$C_{25}H_{31}NO_4 \cdot HCl \cdot H_2O$	64.7	7.3	64.4	7.2	263
$CH_2CH{=}CH_2$	...	$C_{25}H_{29}NO_4 \cdot HCl \cdot 22.5H_2O$	61.3	7.1	61.3	7.1	233
$CH_2C{\equiv}CH$	...	$C_{25}H_{27}NO_4 \cdot HCl$	68.1	6.4	67.6	6.3	225
CH_2CHMe_2	...	$C_{26}H_{33}NO_4 \cdot HCl \cdot H_2O$	65.2	7.5	65.4	7.5	305
$CH_2CH{=}CMe_2$	...	$C_{27}H_{33}NO_4 \cdot HCl \cdot 1.5H_2O$	65.0	7.5	65.0	7.5	256
$CH_2CMe{=}CH_2$	...	$C_{26}H_{31}NO_4 \cdot HCl \cdot 1.5H_2O$	64.5	7.2	64.5	7.0	308
CH_2CH_2Ph	137	$C_{30}H_{33}NO_4 \cdot 0.5\,H_2O$	75.0	7.1	75.3	7.0	245
CO—◁	197	$C_{26}H_{29}NO_5$	71.7	6.7	71.8	6.8	...

(R = Me, R^1 = CH_2CH_2Ph, R^2 = CH_2OH) with the secondary base VII (R = R^1 = Me, R^2 = H). The symmetrical bis compounds IX (R = R^2, R^1 = R^3) presumably arise in this way after hydrolysis of the substituted hydrazo ester as follows.



In the hydrolysis of the hydrazo ester derived from the ketone VI (R = Me) the secondary base VI (R = H) is obtained rather than the bis compound as a result of the low solubility of its hydrochloride. The bis compounds are soluble in aqueous acids in which they are converted into carbinolamines and secondary bases which revert to the bis compounds on standing or heating in solution. When the compounds are heated in solution in dilute acetic acid, formaldehyde is slowly lost, and the secondary bases may be recovered from the solution; mineral acid solutions cannot be used for this purpose owing to the ease with which the alcohols of these series are rearranged in warm solutions of strong acids. The bis compounds of general structure IX prepared by these processes are listed in Table IV.

The secondary base VI (R = H) has been converted into a series of analogs of nalorphine V (R = $CH_2CH{=}CH_2$) by treatment with alkyl, alkenyl, or alkynyl halides RX under reflux in inert solvents. Quaternary salt formation with the 6,14-etheno and ethano tetrahydrothebaine derivatives is so slow that excellent yields of tertiary bases may be obtained without difficulty. A list of ketones of general structure VI and corresponding 6,14-ethano compounds is given in Table V.

Nonphenolic and phenolic alcohols of general structures VII and VIII in which R^2 is other than methyl or hydrogen, which also are analogs of nalorphine, have been prepared by one or other of the following general processes.

(a) Conversion of the appropriate N-substituted nor ketone VI, in which R has the desired value, into alcohols by reduction with sodium borohydride or aluminum isopropoxide, or treatment with the appropriate Grignard reagent or lithium alkyl: in general, this process leads to mixtures of alcohols containing, in many cases, appreciable quantities of the product of Grignard reduction (see preceding paper), and the separation of pure products is frequently tedious. It does not give phenols directly.

(b) Alkylation, alkenylation, or alkynylation of the appropriate secondary bases VII (R^2 = H) and VIII, (R^2 = H) may be achieved by heating under reflux with the desired halide R^2X or alternatively by acylation with an acyl halide R^3COCl, followed by reduction of the resulting amide with lithium aluminum hydride. These processes readily afford pure isomers of the alcohols, since the separation of pure starting materials VII (R^2 = Me) and VIII (R^2 = Me) may be accomplished relatively easily before N-demethylation to secondary base. Phenolic bases are readily obtained in this way.

(c) Tertiary bases are obtained by heating the N,N′-methylenebisnor compounds of general structure IX (R = R^3, R^1 = R^2) with the appropriate halide and, since the bis compounds are prepared from pure al-

cohols of the N-methyl series, this process also affords stereochemically pure products. However, this process is generally less satisfactory than the alkylation of the secondary bases since only the most reactive halides react readily with the bis compounds; in other cases prolonged periods of heating with the halide is necessary and some quaternization of the resulting tertiary base takes place under these conditions. Alternatively, tertiary bases are obtainable from the bis compounds by reaction of these with acyl halides, which proceeds readily, followed by reduction of the resulting amides with lithium aluminum hydride. Neither of these alternatives yields phenols directly since the phenolic bis compounds are not accessible by the action of methyl azodicarboxylate on the phenolic N-methyl bases VIII (R^2 = Me).

Phenolic bases of general structure VIII, when not prepared directly as in b above, may be obtained by the O-demethylation of the corresponding base VII as previously described in the case of the N-methyl compounds.

Bases corresponding to those of series VII and VIII but containing a 6,14-ethano instead of an etheno bridge may be prepared by analogous processes to those set out above, starting from the corresponding 6,14-ethano ketone or alcohols.

Bases prepared by these methods are listed in Tables VI–IX. The pharmacological testing of the compounds listed in Tables V–IX presents certain difficulties, since nalorphine-like substances are not revealed as analgesics by the conventional screening techniques in experimental animals, and the results of pharmacological studies are being and will be reported in detail elsewhere.[14] It may, however, be stated here that the structure–activity relationships in the various series are complex, and that the physiological activity of each base is dependent on the nature of the substituents on the nitrogen atom, the C-3 oxygen atom, and in the alcoholic group. No group has been found that, when substituted for methyl attached to the nitrogen atom, convers morphine-antagonist properties on all of the bases, and each of the series represented in Tables VI–IX contains potent morphine-like analgesics, as well as morphine antagonists and also several bases resembling morphine in some and nalorphine in other respects. For example, the base VIII (R = Me, R^1 = *n*-Pr, R^2 = $CH_2CH{=}CMe_2$) is a potent morphine-like agent, the base VIII (R = R^1 = Me, R^2 = $CH_2C_3H_5$, 6,14-ethano) is the most potent morphine antagonist so far reported, being some 150 times more potent than nalorphine. The base VIII (R = Me, R^1 = *i*-Am, R^2 = $CH_2C_3H_5$), however, shows morphine-like analgesic properties which are reversed by nalorphine only if the antagonist is given very soon after the drug, but, like nalorphine, it causes an increase in urinary output (morphine causes a decrease) and a decrease in locomotor activity in mice (morphine causes an increase). The physiological activity of the last mentioned base persists in animals for up to 3 days.

(14) Some information concerning certain of the bases of this group has already been published: D. Campbell, R. E. Lister, and G. W. McNicol, *Clin. Pharmacol. Therap.*, **5**, 193 (1964); R. E. Lister, *J. Pharm. Pharmacol.*, **16**, 364 (1964); K. W. Bentley, A. L. Boura, A. E. Fitzgerald, D. G. Hardy, A. McCoubrey, M. L. Aikman, and R. E. Lister, *Nature*, **206**, 102 (1965); A. L. A. Boura and A. E. Fitzgerald, *Brit. J. Pharmacol.*, **26**, 307 (1966).

Even the secondary bases in the series have been found to be unusual. Many of them are morphine-like analgesics, and this is without precedent in the morphine, morphinan, benzomorphan, and pethidine series; indeed secondary bases in general are inactive in the conventional tests.

The unprecedented potency of some members of the series I, II, III, and IV requires some comment. The bases would not be expected to be more acceptable than morphine at the receptor surface depicted by Beckett[15] since the added portions of the molecule would be expected to project outside the limited area of such a surface. Two alternative explanations of the high activities are possible. Either the receptor surface is more extensive than that depicted by Beckett and has additional points of possible attachment by which the more extensive molecules of the bases I–IV, but not morphine or simpler bases, can be bound, or the molecules are no more acceptable than morphine at the receptor but arrive there in vastly greater numbers as a result of selective concentration in the tissues of the central nervous system. There is some evidence from preliminary distribution studies using labeled material that relatively high concentrations of the base III (R = Me, R^1 = *n*-Pr) are found in the brain about 0.5 hr after intramuscular or subcutaneous injection, but this alone cannot account for the very high potency of the base, and the problem clearly requires further study.

Experimental Section

The O-demethylation of the alcohols of general structures I and II were effected by the following general method.

7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrooripavine (III, R = R^1 = Me). 7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine (I, R = R^1 = Me) (8 g) was added to a solution of potassium hydroxide (60 g) in diethylene glycol (150 ml) boiling under reflux at 200–210°. The mixture was boiled and stirred vigorously under reflux until a test portion on dilution with ten times its volume of water gave a homogeneous solution. The mixture was then diluted with five times its volume of water and a solution of ammonium chloride was added until precipitation of the phenol ceased. The product was isolated by ether extraction and recrystallized from aqueous 2-ethoxyethanol with charcoal treatment, when the oripavine derivative was obtained as elongated plates, mp 266° (4.2 g).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.1; H, 7.6. Found: C 72.4; H, 7.5.

The 3-O-acetyl ester was precipitated on the addition of acetic anhydride to a solution of the phenol in aqueous sodium hydroxide and was obtained as white prisms, mp 191°, from ethanol.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.5; H, 7.3. Found: C, 70.5; H, 7.2.

7α-(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrooripavine (III, R = Me; R^1 = *n*-Pr). 7α-(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine (I, R = Me; R^1 = *n*-Pr) (50 g) was demethylated with potassium hydroxide (360 g) and diethylene glycol (950 ml) at 205–215° until a test portion of the reaction mixture on dilution with ten times its volume of water gave a homogeneous solution. The mixture was diluted with water (4500 ml), and the solution was filtered through charcoal and aqueous ammonium chloride was added until precipitation of the phenol ceased. The solid (32 g) was collected, washed well with water, and recrystallized from aqueous 2-ethoxyethanol, when it was obtained as off-white prisms, mp 215–216°.

Anal. Calcd for $C_{25}H_{33}NO_4 \cdot H_2O$: C, 70.0; H, 8.1. Found: C, 70.0; H, 7.9.

The 3-O-acetyl ester was prepared by heating the phenol under reflux with acetic anhydride and anhydrous sodium acetate and was obtained as off-white prisms, mp 196°, from ethanol.

Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.5; H, 7.7. Found: C, 71.3; H, 7.7.

(15) A. H. Beckett, *Progr. Drug Res.*, **1**, 527 (1959).

Table VI. Alcohols of Structure VII[a]

R	R^1	R^2	Mp, °C	Composition	—Calcd, %— C	H	—Found, %— C	H	Mp, °C, HCl
H	H	H	131	$C_{21}H_{25}NO_4$	71.0	7.1	71.0	7.4	
H	Me	H	...	$C_{22}H_{27}NO_4 \cdot HCl$	65.2	6.9	65.0	6.6	275
H	Me	CN	200	$C_{23}H_{26}N_2O_4$	70.0	6.6	70.2	6.9	...
H	Me	$CH_2CH{=}CH_2$	...	$C_{25}H_{31}NO_4 \cdot HCl \cdot H_2O$	64.7	7.3	64.8	7.3	293
H	Me	CO–	185	$C_{26}H_{31}NO_5$	71.4	7.1	71.3	7.4	...
H	Me	CH_2–	...	$C_{26}H_{33}NO_4 \cdot HCl$	67.9	7.5	67.6	7.7	254
Me	H	H	102	$C_{22}H_{27}NO_4$	71.6	7.3	71.3	7.3	218
Me	H	CN	208	$C_{23}H_{26}N_2O_4$	70.0	6.6	70.2	6.5	...
Me	H	$CH_2CH_2CH_3$	...	$C_{25}H_{33}NO_4 \cdot HCl$	67.1	7.6	67.6	7.9	315
Me	H	CH_2CHMe_2	...	$C_{26}H_{35}NO_4 \cdot HCl$	67.6	7.8	67.5	7.9	300
Me	H	$CH_2CH{=}CH_2$	...	$C_{25}H_{31}NO_4 \cdot HCl \cdot H_2O$	64.7	7.3	64.6	7.4	277
Me	H	$CH_2C{\equiv}CH$	...	$C_{25}H_{29}NO_4 \cdot HCl \cdot H_2O$	65.0	6.9	64.9	7.1	260
Me	H	CO–	180	$C_{26}H_{31}NO_5$	71.4	7.1	71.3	7.4	
Me	H	CH_2–	...	$C_{26}H_{33}NO_4 \cdot HCl$	67.9	7.5	67.6	7.7	254
Me	H	$CH_2CH{=}CMe_2$	115	$C_{27}H_{35}NO_4$	74.1	8.0	74.3	7.7	230
Me	Me	H	79 (163)	$C_{23}H_{29}NO_4$	72.1	7.6	72.3	7.8	290
Me	Me	CN	228	$C_{24}H_{28}N_2O_4$	70.9	7.1	70.7	7.1	...
Me	Me	Et	142	$C_{25}H_{33}NO_4$	73.0	8.0	72.6	7.8	
Me	Me	*n*-Pr	157	$C_{26}H_{35}NO_4$	73.4	8.2	73.6	8.3	286
Me	Me	*n*-Bu	124	$C_{27}H_{37}NO_4 \cdot 0.5MeOH$	72.5	8.6	72.0	8.8	
Me	Me	*i*-Bu	76	$C_{27}H_{37}NO_4$	73.7	8.4	73.5	8.5	294
Me	Me	*n*-Am	135	$C_{28}H_{39}NO_4$	74.1	8.7	74.3	8.7	
Me	Me	$CH_2CH{=}CH_2$	104	$C_{26}H_{33}NO_4$	73.7	7.9	74.0	8.0	
Me	Me	$CH_2C{\equiv}CH$	163	$C_{26}H_{31}NO_4 \cdot 1.5H_2O$	72.5	7.4	72.7	7.5	276
Me	Me	$CH_2CMe{=}CH_2$	...	$C_{27}H_{35}NO_4 \cdot HCl$	68.4	7.6	68.3	7.7	248
Me	Me	$CH_2CH{=}CMe_2$	...	$C_{28}H_{37}NO_4 \cdot HCl$	68.8	7.8	69.0	8.1	172
Me	Me	CH_2COPh	170	$C_{31}H_{35}NO_5$	74.2	7.0	73.7	6.9	
Me	Me	CO–	214	$C_{27}H_{33}NO_5$	71.7	7.3	71.9	7.3	...
Me	Me	CH_2–	124	$C_{27}H_{35}NO_4 \cdot HCl$	68.4	7.6	68.4	7.8	266
Me	Me	CH_2–	179	$C_{28}H_{37}NO_4$	74.8	8.3	74.3	8.2	
Me	Et	H	155	$C_{24}H_{31}NO_4$	72.5	7.8	72.3	7.8	
Me	Et	CN	198	$C_{25}H_{30}N_2O_4$	71.1	7.2	70.8	7.5	...
Me	Et	Et	150	$C_{26}H_{35}NO_4$	73.4	8.3	73.2	8.3	
Me	Et	*n*-Pr	142	$C_{27}H_{37}NO_4$	73.7	8.4	73.8	8.2	282
Me	Et	*n*-Bu	100	$C_{28}H_{39}NO_4$	71.1	8.7	74.5	8.7	
Me	Et	*i*-Bu	...	$C_{28}H_{39}NO_4 \cdot HCl \cdot H_2O$	66.1	8.3	66.5	8.5	268
Me	Et	$CH_2CH{=}CH_2$	...	$C_{27}H_{35}NO_4 \cdot HCl$	68.5	7.6	68.8	7.9	286
Me	Et	$CH_2C{\equiv}CH$	158	$C_{27}H_{33}NO_4$	74.4	7.6	74.2	7.7	293
Me	Et	$CH_2CMe{=}CH_2$	124	$C_{28}H_{37}NO_4$	74.5	8.2	74.7	8.1	277
Me	Et	$CH_2CH{=}CHMe$	...	$C_{28}H_{37}NO_4 \cdot C_4H_6O_6 \cdot H_2O$[b]	62.0	7.3	61.7	7.5	242[b]
Me	Et	$CH_2CH{=}CMe_2$	126	$C_{29}H_{39}NO_4$	74.8	8.4	74.7	8.4	...
Me	Et	CO–	212	$C_{28}H_{35}NO_5$	72.2	7.6	72.0	7.6	...
Me	Et	CH_2– 	113	$C_{28}H_{37}NO_4$	74.5	8.3	74.1	8.3	...
Me	Et	CH_2COCH_3	160	$C_{27}H_{35}NO_5$	71.5	7.8	71.5	7.7	125
Me	Et	CH_2COPh	166	$C_{32}H_{37}NO_5$	74.5	7.2	74.4	7.1	155
Me	*n*-Pr	H	173	$C_{25}H_{33}NO_4$	73.0	8.0	73.2	8.2	260
Me	*n*-Pr	CN	200	$C_{26}H_{32}N_2O_4$	71.6	7.3	71.6	7.3	
Me	*n*-Pr	Et	...	$C_{27}H_{37}NO_4 \cdot HCl$	68.1	8.0	68.1	8.2	189
Me	*n*-Pr	*n*-Pr	...	$C_{28}H_{39}NO_4 \cdot C_4H_6O_6 \cdot H_2O$[b]	61.8	7.2	61.3	7.6	254[b]
Me	*n*-Pr	*n*-Bu	110	$C_{29}H_{41}NO_4$	74.5	8.9	74.1	8.8	
Me	*n*-Pr	*i*-Bu	174	$C_{29}H_{41}NO_4$	74.5	8.9	74.7	8.7	310
Me	*n*-Pr	*n*-Am	123	$C_{30}H_{43}NO_4$	74.8	9.1	74.5	9.0	
Me	*n*-Pr	$CH_2CH{=}CH_2$	118	$C_{28}H_{37}NO_4$	74.5	8.2	74.2	8.1	163
Me	*n*-Pr	$CH_2C{\equiv}CH$	162	$C_{28}H_{35}NO_4$	74.8	7.8	75.1	8.0	
Me	*n*-Pr	$CH_2CMe{=}CH_2$	...	$C_{29}H_{39}NO_4 \cdot HCl$	69.4	8.0	69.0	8.3	277
Me	*n*-Pr	$CH_2CH{=}CMe_3$	106	$C_{30}H_{41}NO_4$	75.1	8.5	75.0	8.7	160
Me	*n*-Pr	CO–	185	$C_{29}H_{37}NO_5$	72.6	7.7	72.6	7.8	
Me	*n*-Pr	CH_2–	130	$C_{29}H_{39}NO_4$	74.9	8.4	74.7	8.6	
Me	*i*-Pr	CN	230	$C_{26}H_{32}N_2O_4$	71.5	7.4	71.1	7.5	
Me	*i*-Pr	H	169	$C_{25}H_{33}NO_4$	73.0	8.1	73.1	8.0	
Me	*i*-Pr	CO–	177 (191)	$C_{29}H_{37}NO_5$	72.6	7.8	73.0	7.9	
Me	*i*-Pr	CH_2–	132	$C_{29}H_{39}NO_4$	84.7	8.4	74.0	8.6	
Me	*n*-Bu	H	110	$C_{26}H_{35}NO_4$	73.4	8.3	73.4	8.6	285

Table VI (*Continued*)

R	R[1]	R[2]	Mp, °C	Composition	—Calcd, %— C	H	—Found, %— C	H	Mp, °C, HCl
Me	*n*-Bu	CN	144	$C_{27}H_{34}N_2O_4$	71.9	7.5	72.2	7.7	
Me	*n*-Bu	$CH_2CH{=}CH_2$	102	$C_{29}H_{39}NO_4 \cdot 0.5H_2O$	73.4	8.5	73.2	8.7	255
Me	*n*-Bu	$CH_2C{\equiv}CH$	152	$C_{29}H_{37}NO_4$	75.1	8.0	75.1	8.1	267
Me	*i*-Bu	H	131	$C_{26}H_{35}NO_4$	73.4	8.3	73.5	8.4	284
Me	*i*-Bu	CN	170	$C_{27}H_{34}NO_4$	71.9	7.5	72.0	7.6	
Me	*i*-Bu	$CH_2CH{=}CH_2$	102	$C_{29}H_{39}NO_4$	74.8	8.4	74.5	8.5	277
Me	*n*-Am	H	135	$C_{27}H_{37}NO_4$	73.8	8.4	73.6	8.6	238
Me	*n*-Am	CN	129	$C_{28}H_{36}NO_4$	72.4	7.8	72.5	7.9	
Me	*n*-Am	$CH_2CMe{=}CH_2$	100	$C_{31}H_{43}NO_4$	74.5	8.8	75.2	8.8	
Me	*n*-Am	$CH_2CH{=}CMe_2$	...	$C_{32}H_{45}NO_4 \cdot HCl \cdot H_2O$	68.5	8.5	68.4	8.6	230
Me	*n*-Am		118	$C_{32}H_{45}NO_4$	75.7	8.9	75.6	8.8	
Me	*i*-Am	H	134	$C_{27}H_{37}NO_4$	73.8	8.4	73.7	8.5	
Me	*i*-Am	CN	164	$C_{28}H_{36}N_2O_4$	72.4	7.8	72.6	8.0	
Me	*i*-Am	Et	110	$C_{29}H_{41}NO_4$	74.5	8.8	74.0	8.8	
Me	*i*-Am	*n*-Pr	90	$C_{30}H_{43}NO_4$	74.8	9.0	74.7	9.0	220
Me	*i*-Am	*n*-Bu	...	$C_{31}H_{45}NO_4 \cdot HCl$	70.0	8.7	70.1	8.5	201
Me	*i*-Am	*i*-Bu	72	$C_{31}H_{45}NO_4$	75.2	9.1	75.0	9.4	301
Me	*i*-Am	*n*-Am	101	$C_{32}H_{47}NO_4$	75.5	9.3	75.8	9.2	
Me	n-C_8H_{17}	H	...	$C_{30}H_{43}NO_4 \cdot C_4H_6O_6 \cdot H_2O$[b]	62.9	7.9	62.5	8.2	286[b]
Me	n-C_8H_{17}	CN	108	$C_{31}H_{42}N_2O_4$	73.5	8.3	73.6	8.6	
Me	n-C_8H_{17}	$CH_2CH{=}CMe_2$	96	$C_{35}H_{51}NO_4$	76.5	9.3	76.8	9.5	
Me		H	110	$C_{27}H_{35}NO_4$	74.1	8.0	74.2	7.9	
Me		CN	210	$C_{28}H_{34}N_2O_4$	72.7	7.4	72.5	7.6	
Me		$CH_2CH{=}CMe_2$	112	$C_{32}H_{43}NO_4 \cdot H_2O$	73.4	8.6	73.5	8.8	
Me		H	203	$C_{28}H_{37}NO_4$	74.5	8.3	74.7	8.5	288
Me		CN	213	$C_{29}H_{36}N_2O_4$	73.1	8.6	73.2	8.5	
Me		Et	171	$C_{30}H_{41}NO_4$	75.2	8.6	74.9	8.8	
Me		*n*-Pr	180	$C_{31}H_{43}NO_4$	75.4	8.8	75.4	8.8	
Me		*n*-Bu	157	$C_{33}H_{45}NO_4 \cdot 0.5H_2O$	74.4	9.0	74.6	8.8	
Me		*n*-Am	151	$C_{34}H_{47}NO_4$	76.0	9.1	76.1	9.0	
Me		$CH_2CH{=}CH_3$	204	$C_{31}H_{41}NO_4 \cdot 0.5H_2O$	74.4	8.4	74.4	8.4	219
Me		$CH_2C{\equiv}CH$	172	$C_{31}H_{39}NO_4$	76.0	8.0	75.8	8.2	
Me		$CH_2CMe{=}CH_2$	203	$C_{32}H_{43}NO_4 \cdot 0.5H_2O$	74.7	8.6	74.7	8.5	
Me		$CH_2CH{=}CMe_2$	190	$C_{33}H_{45}NO_4$	76.1	8.7	76.0	8.8	
Me			220	$C_{32}H_{41}NO_5$	73.9	7.9	73.7	8.1	
Me			228	$C_{32}H_{43}NO_4 \cdot H_2O$	73.5	8.6	73.5	8.4	
Me			258	$C_{33}H_{43}NO_5$	74.2	8.1	74.0	8.2	
Me			98	$C_{33}H_{45}NO_4$	76.3	8.7	76.3	8.5	
Me	CH_2Ph	CN	216	$C_{30}H_{32}N_2O_4$	74.4	6.6	74.5	6.9	
Me	CH_2Ph	H	85	$C_{29}H_{33}NO_4$	75.8	7.2	75.7	7.3	
Me	CH_2Ph	$CH_2CH{=}CH_2$	78	$C_{32}H_{37}NO_4 \cdot HCl \cdot H_2O$	70.5	7.2	70.2	7.4	148
Me	CH_2CH_2Ph	H	138	$C_{30}H_{35}NO_4$	76.1	7.4	76.3	7.6	
Me	CH_2CH_2Ph	CN	98	$C_{31}H_{34}N_2O_4$	74.6	6.8	74.7	6.8	
Me	CH_2CH_2Ph	Et	159	$C_{32}H_{39}NO_4$	76.6	7.8	76.1	8.0	
Me	CH_2CH_2Ph	*n*-Pr	122	$C_{33}H_{41}NO_4$	76.9	8.0	76.8	8.0	
Me	CH_2CH_2Ph	*n*-Bu	...	$C_{34}H_{43}NO_4 \cdot HCl \cdot H_2O$	69.9	7.9	69.9	7.9	195
Me	CH_2CH_2Ph	$CH_2CH{=}CH_2$	127	$C_{33}H_{39}NO_4$	77.2	7.7	76.7	7.6	

Table VI (*Continued*)

R	R[1]	R[2]	Mp, °C	Composition	—Calcd, %— C	H	—Found, %— C	H	Mp, °C, HCl
Me	CH_2CH_2Ph	$CH_2CH{=}CMe_2$	...	$C_{35}H_{43}NO_4 \cdot HCl$	72.7	7.7	72.6	7.6	210
Me	$(CH_2)_3Ph$	H	138	$C_{31}H_{37}NO_4$	76.4	7.7	76.3	7.7	
Me	$(CH_2)_3Ph$	CN	212	$C_{32}H_{36}N_2O_4$	74.9	7.0	74.9	7.0	
Me	$(CH_2)_3Ph$	$CH_2CH{=}CMe_2$	189	$C_{36}H_{45}NO_4$	77.9	8.1	78.1	8.3	
Me	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	...	$C_{25}H_{35}NO_4 \cdot HCl$	69.2	7.4	69.0	7.7	275
Me	$(CH_2)_3OEt$	$CH_2CH{=}CH_2$	...	$C_{30}H_{41}NO_5 \cdot HCl \cdot H_2O$	65.5	8.0	65.2	8.3	130
Me	$(CH_2)_4OPh$	$CH_2CH{=}CH_2$	136	$C_{35}H_{43}NO_5$	75.5	7.7	75.6	7.9	285
Me	*p*-Tolyl	H	190	$C_{29}H_{33}NO_4$	75.8	7.2	75.7	7.1	
Me	*p*-Tolyl	CN	210	$C_{30}H_{32}N_2O_4$	74.4	6.6	74.6	6.3	
Me	*p*-Tolyl	$CH_2CN{=}CH_2$	201	$C_{32}H_{37}NO_4$	76.9	7.4	76.9	7.7	

[a] For bases where R^2 = Me, see Table I, ref 1a. [b] Bitartrate.

The 3-O-propionyl ester was obtained (from the phenol, propionic anhydride, and sodium propionate) as off-white prisms, mp 130°, from aqueous ethanol.

Anal. Calcd for $C_{28}H_{37}NO_5$: C, 71.9; H, 7.9. Found: C, 71.8; H, 7.9.

N-Cyano-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = CN). 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (VI, R = Me) (50 g) was heated under reflux with cyanogen bromide (16 g) in dry alcohol-free chloroform (350 ml) for 12 hr. The chloroform was evaporated, and the residue was recrystallized from 2-ethoxyethanol, when the N-cyanonor compound (48 g) was obtained as colorless prisms, mp 236°, ν_{max} 2250 and 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.4; H, 6.2. Found: C, 70.2; H, 6.4.

N-Aminocarbonyl-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = $CONH_2$). N-Cyano-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = CN) (40 g), finely powdered, was boiled under reflux with 2 *N* hydrochloric acid (400 ml), in the presence of a small amount of a neutral wetting agent to minimize frothing, until all the solid had dissolved (~2 hr). The solution was cooled, and a small portion was neutralized with ammonia, when a viscous gum was obtained, from which the crystalline N-aminocarbonyl compound was obtained with difficulty on crystallization from methanol as prisms, mp 220°.

Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.3; H, 6.4; N, 6.8. Found: C, 67.1; H, 6.4; N, 6.8.

7α-Acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = H). **a.** The acid solution obtained by the hydrolysis of N-cyano-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = CN) (40 g) as above was cooled to 0°, and an aqueous solution of sodium nitrite (8 g) was slowly added with vigorous stirring. When evolution of gas ceased, the mixture was made alkaline with ammonia and extracted with chloroform. Evaporation of the extract gave a viscous gum, which was converted into the crystalline hydrochloride with methanolic hydrogen chloride. The salt (25 g) was obtained as plates, mp 350°, from hot water

Anal. Calcd for $C_{22}H_{25}NO_4 \cdot HCl \cdot 0.5H_2O$: C, 64.0; H, 6.6. Found: C, 63.9; H, 6.3.

The base recovered from the hydrochloride was obtained as needles, mp 73°, from water.

Anal. Calcd for $C_{22}H_{25}NO_4 \cdot H_2O$: C, 68.8; H, 7.0. Found: 68.8; H, 7.2.

The picrate was obtained as yellow prisms, mp 273°, from ethanol.

Anal. Calcd for $C_{28}H_{28}N_4O_{11}$: C, 56.4; H, 4.7; N, 9.4. Found: C, 56.0; H, 4.7; N, 9.4.

The N-acetyl compound was prepared by heating the base with acetic anhydride and was obtained as prisms, mp 101°, from aqueous methanol.

Anal. Calcd for $C_{24}H_{27}NO_5 \cdot H_2O$: C, 67.4; H, 6.8. Found: C, 67.3; H, 6.8.

The N-cyclopropylcarbonyl compound, from the base and cyclopropylcarbonyl chloride and anhydrous potassium carbonate in ether, was obtained as prisms, mp 197°.

Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.7; H, 6.7. Found: C, 71.8; H, 6.8.

b. A solution of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (10 g) (VI, R = Me) and methyl azodicarboxylate (3.84 g) in acetone (75 ml) was evaporated to dryness over about 30 min. The viscous yellow residue was dissolved in 1 *N* hydrochloric acid (40 ml) with vigorous stirring and the solution set aside until separation of solid matter ceased (~1 hr). The hydrochloride (8.2 g) was collected and washed with ice water, and a portion was recrystallized from water when the nor base (X, R = H) hydrochloride was obtained as prisms, mp 350°, identical in infrared absorption and R_f value with material prepared as in part a.

N-Allyl-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = $CH_2CH{=}CH_2$). 7α-Acetyl-6,14-*endo*-ethenotetrahydronorthebaine (VI, R = H) (20 g), allyl bromide (6 g), anhydrous sodium carbonate (10 g), and ethanol (100 ml) were heated together under reflux for 18 hr. The mixture was filtered and evaporated leaving the base as an uncrystallizable glass giving a crystalline hydrochloride (22 g) as plates, mp 233°, on treatment with ethanolic hydrogen chloride.

Anal. Calcd for $C_{25}H_{29}NO_4 \cdot HCl \cdot H_2O$: C, 65.0; H, 6.9. Found: C, 64.8; H, 7.1.

Other N-substituted nor bases of general structure VI were prepared from the secondary base VI (R = H) by similar methods and are listed in Table V.

N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (VII, R = R^1 = Me; R^2 = CN). 7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine (VII, R = R^1 = R^2 = Me) (15 g), cyanogen bromide (5.3 g), and dry methylene chloride (50 ml) were boiled together under reflux for 24 hr. The solution was evaporated to dryness, and the solid residue was finely powdered and stirred for 10 min with cold 1 *N* hydrochloric acid, then collected, washed well with water, and recrystallized from aqueous 2-ethoxyethanol, when the N-cyanonor compound (14.8 g) was obtained as colorless prisms, mp 228°, ν_{max} 2250 cm^{-1}.

Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.6; H, 6.9. Found: C, 70.7; H, 7.1.

N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronororipavine (VIII, R = R^1 = Me; R^2 = CN). A solution of cyanogen bromide (5.3 g), 7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrooripavine (VIII, R = R^1 = R^2 = Me) (15 g) in dry methylene chloride was boiled under reflux for 24 hr. The product (14.8 g) isolated by evaporation of the solution and acid washing of the powdered residue was obtained as prisms, mp 275°, from aqueous 2-ethoxyethanol.

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.1; H, 6.6. Found: C, 70.1; H, 6.4.

7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (VII, R = R^1 = Me; R^2 = H). N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (VII, R = R^1 = Me; R^2 = CN) (57 g) was added to a vigorously stirred solution of potassium hydroxide (5.7 g) in diethylene glycol (400 ml) at 165–170°, and the mixture was heated at that temperature until evolution of ammonia ceased (~10–15 min). The mixture was then poured into vigorously stirred water (1500 ml) containing crushed ice, and the precipitated solid was collected and recrystallized from water, when the secondary base (41 g) was obtained as prisms, mp 163°. (A low-melting form, needles, mp 79°, was obtained in initial experiments, and can be recovered from a hot aqueous solution by rapid cooling.)

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.1; H, 7.6. Found: C, 72.3; H, 7.8.

The hydrolysis of other N-cyano compounds to the corresponding secondary bases was effected in the same way. Secondary bases that did not crystallize on dilution of the reaction mixture with water were isolated by ether extraction. In such cases, trituration with organic solvents of the residue after evaporation of the ether

Table VII. Alcohols of Structure VIII[a]

R	R[1]	R[2]	Mp, °C	Compositon	—Calcd, %— C	H	—Found, %— C	H	Mp, °C, HCl
H	H	H	...	$C_{20}H_{23}NO_4 \cdot HCl \cdot H_2O$	60.7	6.7	60.5	6.6	264
H	H	$CH_2CH{=}CH_2$	...	$C_{23}H_{27}NO_4 \cdot HCl \cdot 2H_2O$	60.9	7.1	60.8	7.2	281
H	Me	H	296	$C_{21}H_{25}NO_4$	71.0	7.1	71.2	7.4	
H	Me	$CH_2CH{=}CH_2$	265	$C_{24}H_{29}NO_4$	72.8	7.3	72.8	7.5	
H	Me	CH_2—◁	92	$C_{25}H_{31}NO_4 \cdot HCl \cdot H_2O$	64.6	7.3	64.6	7.2	251
Me	Me	H	284	$C_{22}H_{27}NO_4$	71.5	7.3	71.3	7.4	308
Me	Me	Et	228	$C_{24}H_{31}NO_4$	72.5	7.8	72.0	7.9	
Me	Me	*n*-Bu	172	$C_{26}H_{35}NO_4$	73.4	8.3	73.3	8.2	
Me	Me	*n*-Am	...	$C_{27}H_{37}NO_4 \cdot HCl \cdot 0.5H_2O$	66.9	8.1	67.0	8.0	196
Me	Me	$CH_2CH{=}CH_2$	120 (210)	$C_{25}H_{31}NO_4$	73.3	7.6	73.0	7.4	248
Me	Me	$CH_2C{\equiv}CH$	120	$C_{25}H_{29}NO_4$	73.6	7.1	73.7	7.4	240
Me	Me	$CH_2CH{=}CMe_2$	...	$C_{27}H_{35}NO_4 \cdot HCl \cdot 2H_2O$	63.6	7.9	63.4	8.0	212
Me	Me	CO—◁	290	$C_{26}H_{31}NO_5$	71.4	7.1	71.5	7.3	
Me	Me	CH_2—◁	234	$C_{26}H_{33}NO_4$	73.6	7.8	73.6	7.9	248
Me	Et	H	277	$C_{23}H_{29}NO_4$	72.0	7.6	71.5	7.7	
Me	Et	Et	260	$C_{25}H_{33}NO_4$	73.0	8.0	72.5	8.0	
Me	Et	*n*-Pr	187	$C_{26}H_{35}NO_4$	73.4	8.3	73.5	8.4	
Me	Et	*n*-Bu	162	$C_{27}H_{37}NO_4$	73.7	8.5	73.4	8.5	
Me	Et	$CH_2CH{=}CMe_2$	208	$C_{28}H_{37}NO_4$	74.5	8.3	74.9	8.2	
Me	Et	CO—◁	254	$C_{27}H_{33}NO_5$	71.8	7.4	71.7	7.6	
Me	Et	CH_2—◁	117	$C_{27}H_{35}NO_4$	74.1	8.1	73.8	8.1	
Me	*n*-Pr	H	260	$C_{24}H_{31}NO_4$	72.5	7.8	72.2	8.2	305
Me	*n*-Pr	Et	219	$C_{26}H_{35}NO_4$	73.4	8.3	73.0	8.3	
Me	*n*-Pr	*n*-Pr	214	$C_{27}H_{37}NO_4$	73.7	8.5	74.0	8.3	
Me	*n*-Pr	*n*-Bu	136	$C_{28}H_{39}NO_4$	74.1	8.7	73.9	8.6	
Me	*n*-Pr	*n*-Am	141	$C_{29}H_{41}NO_4$	74.5	8.9	74.4	9.2	
Me	*n*-Pr	$CH_2CH{=}CH_2$	126	$C_{27}H_{35}NO_4$	74.1	8.0	74.0	8.1	254
Me	*n*-Pr	$CH_2CH{=}CMe_2$	190	$C_{29}H_{39}NO_4$	74.8	8.4	74.5	8.2	
Me	*n*-Pr	CO—◁	270	$C_{28}H_{35}NO_5$	72.2	7.5	72.0	7.8	
Me	*n*-Pr	CH_2—◁	180	$C_{28}H_{37}NO_4$	74.4	8.2	74.7	8.5	262
Me	*n*-Bu	H	210	$C_{25}H_{33}NO_4$	73.0	8.0	72.9	8.2	
Me	*n*-Bu	$CH_2CH{=}CH_2$	122	$C_{28}H_{37}NO_4$	74.5	8.3	74.4	8.0	263
Me	*n*-Am	CO—◁	236	$C_{30}H_{39}NO_5$	73.0	8.0	72.8	7.8	
Me	*n*-Am	CH_2—◁		$C_{30}H_{41}NO_4$	75.1	8.6	74.9	8.6	
Me	*i*-Am	H	262	$C_{26}H_{35}NO_4$	73.4	8.3	73.6	8.2	
Me	*i*-Am	Et	179	$C_{28}H_{39}NO_4$	74.1	8.7	74.0	8.6	
Me	*i*-Am	*n*-Pr	175	$C_{29}H_{41}NO_4$	74.5	8.9	74.5	8.9	
Me	*i*-Am	*n*-Bu	141	$C_{30}H_{43}NO_4 \cdot 0.5H_2O$	73.5	9.0	73.8	9.0	
Me	*i*-Am	*n*-Am	122	$C_{31}H_{45}NO_4 \cdot 0.5H_2O$	73.8	9.2	74.3	9.4	
Me	*i*-Am	$CH_2CH{=}CMe_2$	225	$C_{31}H_{43}NO_4$	75.4	8.8	75.4	8.8	
Me	*i*-Am	CO—◁	240	$C_{30}H_{39}NO_5$	73.0	7.9	73.2	8.1	
Me	*i*-Am	CH_2—◁	110	$C_{30}H_{41}NO_4$	75.1	8.6	75.3	8.8	258
Me	⬡	H	310	$C_{27}H_{35}NO_4$	74.1	8.0	74.3	8.2	
Me	⬡	*n*-Pr	...	$C_{30}H_{41}NO_4 \cdot HCl$	69.8	7.9	69.9	8.1	275
Me	⬡	$CH_2CH{=}CH_2$	...	$C_{30}H_{39}NO_4 \cdot HCl$	70.1	7.6	70.0	7.9	251
Me	⬡	$CH_2C{\equiv}CH$	...	$C_{30}H_{37}NO_4 \cdot HCl$	70.3	7.2	70.0	7.5	202
Me	⬡	CO—◁	268	$C_{31}H_{39}NO_5$	73.6	7.7	73.8	7.9	
Me	⬡	CH_2—◁	134 (198)	$C_{31}H_{41}NO_4$	75.6	8.4	75.5	8.6	180

[a] For bases where R^2 = Me, see Table I, ref 1a.

generally resulted in crystallization of the product, but a few secondary bases could not be induced to crystallize and were characterized as the hydrochloride or acid tartrate.

7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronororipavine (VIII, R = R[1] = Me; R[2] = H). a. N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (VII, R = R[1] = Me; R[2] = CN) (100 g) was added to a vigorously stirred solution of potassium hydroxide (250 g) in diethylene glycol (1200 ml) at 200° under an atmosphere of nitrogen. The mixture was heated at 200–220° until a test portion on

Table VIII. 6,14-Ethano Analogs of Alcohols of Structure VII[a]

R	R^1	R^2	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mp, °C, HCl
H	H	CH_2—◁	107	$C_{25}H_{33}NO_4$	73.0	8.1	73.4	8.5	
Me	Me	H	146	$C_{23}H_{31}NO_4$	71.6	8.1	72.1	8.3	
Me	Me	CN	205	$C_{24}H_{30}N_2O_4$	70.2	7.4	69.6	7.0	
Me	Me	CH_2—◁	123	$C_{27}H_{37}NO_4$	73.8	8.5	73.4	8.5	
Me	Et	H	143	$C_{24}H_{33}NO_4$	72.1	8.3	72.0	8.1	
Me	Et	CN	170	$C_{25}H_{32}N_2O_4$	70.7	7.6	70.8	7.7	
Me	Et	CH_2—◁	100	$C_{28}H_{29}NO_4$	72.1	8.3	72.0	8.1	
Me	*n*-Pr	H	168	$C_{25}H_{35}NO_4 \cdot HCl \cdot 0.5H_2O$	65.4	8.1	64.9	7.8	265
Me	*n*-Pr	CN	199	$C_{26}H_{34}N_2O_4$	71.2	7.8	71.4	7.9	
Me	*n*-Pr	CH_2—◁	99	$C_{29}H_{41}NO_4$	74.5	8.8	74.4	8.6	
Me	*n*-Bu	H	136	$C_{26}H_{37}NO_4$	73.1	8.7	73.0	8.7	
Me	*n*-Bu	CN	153	$C_{27}H_{36}N_2O_4$	71.6	8.0	72.1	8.0	
Me	*n*-Bu	CH_2—◁	102	$C_{30}H_{43}NO_4$	74.8	9.0	74.9	9.0	
Me	*i*-Bu	H	128	$C_{26}H_{37}NO_4$	73.1	8.7	72.6	8.5	
Me	*i*-Bu	CN	180	$C_{27}H_{36}N_2O_4$	71.6	8.0	71.5	8.3	
Me	*t*-Bu	H	199	$C_{26}H_{37}NO_4$	73.1	8.7	72.6	8.6	
Me	*t*-Bu	CN	207	$C_{27}H_{36}N_2O_4$	71.6	8.0	71.3	8.2	
Me	*t*-Bu	CO—◁	176	$C_{30}H_{41}NO_5$	72.7	8.3	72.7	8.3	
Me	*t*-Bu	CH_2—◁	109	$C_{30}H_{43}NO_4$	74.8	9.0	74.5	9.0	
Me	*n*-Am	H	...	$C_{27}H_{39}NO_4 \cdot HCl$	67.8	8.4	68.1	8.5	241
Me	*n*-Am	CN	142	$C_{28}H_{38}N_2O_4$	72.0	8.2	71.5	8.5	
Me	*n*-Am	CH_2—◁	78	$C_{31}H_{45}NO_4$	75.1	9.2	74.5	9.6	
Me	*i*-Am	CN	152	$C_{28}H_{38}N_2O_4$	72.0	8.2	71.9	8.4	
Me	⬡	H	174	$C_{28}H_{39}NO_4$	74.1	8.7	74.3	8.5	
Me	⬡	CN	216	$C_{29}H_{38}N_2O_4$	72.8	8.0	72.9	8.1	
Me	⬡	CO—◁	235	$C_{32}H_{43}NO_5$	73.7	8.3	74.0	8.3	

[a] For bases where R^2 = Me, see Table II, ref 1a.

Table IX. 6,14-Ethano Analogs of Alcohols of Structure VIII

R	R^1	R^2	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H
Me	Me	CH_2—◁	185	$C_{26}H_{35}NO_4$	73.4	8.3	72.8	8.3
Me	*n*-Pr	H	239	$C_{24}H_{33}NO_4$	72.1	8.3	72.1	7.9
Me	*n*-Pr	CH_2—◁	179	$C_{28}H_{39}NO_4$	74.1	8.7	74.1	8.5
Me	*n*-Bu	CH_2—◁	178	$C_{29}H_{41}NO_4$	74.5	8.9	74.5	8.8

dilution with ten times its volume of water gave a homogeneous solution (~30–40 min). The mixture was rapidly cooled and poured with vigorous stirring into ice–water (2500 ml), and the phenol was then precipitated by the addition of saturated aqueous ammonium chloride. The product (80 g), mp 280–282°, was collected, washed well with water, and recrystallized from methanol, when the phenolic base XII (R = R^1 = Me, R^2 = H) was obtained as prisms, mp 284°.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.3. Found: C, 71.3; H, 7.4.

b. N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronororipavine (VIII, R = R^1 = Me; R^2 = CN) (5 g) was hydrolyzed with potassium hydroxide (5 g) and diethylene glycol (40 ml) at 160–170° for 10 min. The mixture was poured into water (250 ml) and the phenol was precipitated with ammonium chloride, collected, washed, and recrystallized from aqueous 2-ethoxyethanol, when it was obtained (3.1 g) as prisms, mp 284°, identical in infrared absorption, mixture melting point, and R_f value with material obtained as in part a above.

c. 19-Methylnorthevinol (VII, R = R^1 = Me; R^2 = H) (2 g) was O-demethylated by heating with potassium hydroxide (2.5 g) and diethylene glycol (12.5 ml) at 210° until a test portion gave a homogeneous solution on dilution with water. The mixture was then diluted with water (65 ml), and the product was p ecipitated with ammonium chloride, when 19-methylnororvinol (VIII, R = R^1 = Me; R^2 = H) (0.8 g) was obtained as prisms, mp 284°, from 2-ethoxyethanol, identical with the base obtained in a and b above.

Other phenolic secondary bases of structure VIII, (R^2 = H) were prepared by the combined hydrolysis and O-demethylation of N-cyano compounds of the tetrahydrothebaine series VII, (R^2 = CN) by the process given in part a above.

N-Allyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (VII, R = R^1 = Me; R^2 = $CH_2CH{=}CH_2$) (N-Allyl-19-methylnorthevinol). a. 19-Methylnorthevinol (VII, R = R^1 = Me; R^2 = H) (3.4 g), allyl bromide (1 g), anhydrous sodium carbonate (2 g), and ethanol (40 ml) were boiled together under reflux for 18 hr. The mixture was filtered and evaporated, leaving a viscous gum that crystallized on standing. It was recrystallized from petroleum ether (bp 40–60°), when N-allyl-19-methylnororvinol was obtained (3.0 g) as white prisms, mp 104°.

Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.7; H, 7.9. Found: C, 74.0; H, 8.0.

b. N-Allyl-7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (N-allylnorthevinone, VI, R = $CH_2CH{=}CH_2$) (10 g) in ether (350 ml) was slowly added to a vigorously stirred solution of methylmagnesium iodide (from 1.67 g of magnesium and 9.9 g of methyl iodide) in ether (200 ml). The mixture was stirred and heated under reflux for 2 hr and poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, leaving a residue that crystallized on standing. Recrystallization of the product from petroleum ether (bp 40–60°) afforded N-allyl-19-methylnorthevinol (8.9 g) as white prisms, mp 104°, identical in infrared absorption, mixture melting point, and R_f value with the base prepared as in part a above.

c. The base was also obtained from N,N′-methylenebis(19-methylnorthevinol) (IX, R = R^1 = R^2 = R^3 = Me) and allyl bromide (see below).

Other N-substituted nor bases of the general formula VII were prepared from the corresponding secondary bases by heating with the appropriate alkyl, alkenyl, or alkynyl halide, sodium carbonate, and a solvent, generally ethanol, though acetone or methyl ethyl ketone was the preferred solvent for 3,3-dimethylallyl bromide since solvolysis of the halide appeared to occur when ethanol was used.

N-Allyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronororipavine (VIII, R = R^1 = Me; R^2 = $CH_2CH{=}CH_2$) (N-Allyl-19-methylnororvinol). a. 7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronororipavine (VIII, R = R^1 = Me; R^2 = H) (19-methylnororvinol) (3.4 g), allyl bromide (1 g), anhydrous sodium carbonate (2 g), and ethanol (80 ml) were boiled together under reflux for 18 hr. The mixture was filtered and evaporated, and the residue was recrystallized from methanol, when the N-allyl compound (3.0 g) was obtained as white prisms, mp 120° on slow heating, 210° on plunging into a bath heated above 200°.

Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.3; H, 7.6. Found: C, 73.0; H, 7.4.

b. N-Allyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (N-allyl-19-methylnorthevinol, VII, R = R^1 = Me; R^2 = $CH_2CH{=}CH_2$) (2 g) was demethylated by heating with potassium hydroxide (2.5 g) and diethylene glycol (12.5 ml) at 200–210° until a homogeneous solution was obtained on dilution of a test portion with ten times its volume of water. The mixture was then poured into aqueous ammonium chloride, and the product was isolated by ether extraction, when it was obtained, after recrystallization from methanol, as white prisms (0.8 g), mp 120 and 210°, identical with material prepared as in part a above.

Other N-substituted nor bases of the phenolic series VIII were prepared as in a by the action of alkyl, alkenyl, or alkynyl halides on the appropriate secondary base VIII (R^2 = H), though with 3,3-dimethylallyl bromide acetone was used as the solvent.

N-Cyclopropylcarbonyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (N-Cyclopropylcarbonyl-19-methylnorthevinol, VII, R = R^1 = Me; R^2 = cyclopropylcarbonyl). The secondary base 19-methylnorthevinol (VII, R = R^1 = Me; R^2 = H) (5 g) was stirred in dry ether (150 ml) with anhydrous potassium carbonate (5 g) and cyclopropyl carbonyl chloride (1.4 g) for 6 hr. Water and dilute hydrochloric acid were then added, and the ether layer was separated, washed with water, dried, and evaporated, leaving the nonbasic amide as prisms, mp 212° (3.5 g) raised to 214°, ν_{max} 1640 cm^{-1}, on recrystallization from methanol.

Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.7; H, 7.3. Found: C, 71.9; H, 7.3.

N-Cyclopropylmethyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (N-Cyclopropylmethyl-19-methylnorthevinol, VII, R = R^1 = Me; R^2 = cyclopropylmethyl). The amide N-cyclopropylcarbonyl-19-methylnorthevinol (VII, R = R^1 = Me; R^2 = cyclopropylcarbonyl) (2 g) in tetrahydrofuran (40 ml) was stirred and heated under reflux with lithium aluminum hydride (1 g) for 5 hr. The excess of hydride was cautiously destroyed by the addition of an aqueous solution of potassium sodium tartrate, and the tetrahydrofuran layer was separated. The aqueous layer was extracted with ether, and the combined organic solutions were dried and evaporated, when the tertiary base was obtained as a gum, which slowly crystallized. Recrystallization of the product from methanol afforded 1. 4 g of colorless prisms, mp 124°.

Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.2; H, 8.0. Found: C: 74.1; H, 7.8.

The hydrochloride was obtained by treating an ethanolic solution of the base with ethanolic hydrogen chloride and adding dry ether. It formed prisms, mp 266°.

Anal. Calcd for $C_{27}H_{35}NO_4 \cdot HCl$: C, 68.4; H, 7.6. Found, C, 68.4; H, 7.8.

Other tertiary bases of general structure VII could be prepared *via* the amide and reduction with lithium aluminum hydride in a similar manner to the above.

N-Cyclopropylcarbonyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronororipavine (N-Cyclopropylcarbonyl-19-methylnororvinol, VIII, R = R^1 = Me; R^2 = cyclopropylcarbonyl). The phenolic secondary base 19-methylnororvinol (VIII, R = R^1 = Me; R^2 = H) (5 g) was stirred in dry ether (150 ml) with anhydrous potassium carbonate (5 g) and cyclopropylcarbonyl chloride (2.4 g) for 6 hr. The solution was stirred with 1 *N* hydrochloric acid (100 ml) for 5 min, the ether layer was separated, washed, dried, and evaporated, leaving the amide as a solid residue. This was recrystallized from ethanol, when it was obtained as white prisms, mp 290°, giving a blue color with ferric chloride and instantly soluble when an ethanolic solution was added to an excess of cold aqueous sodium hydroxide.

Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.4; H, 7.1. Found: C, 71.5; H, 7.3.

N-Cyclopropylmethyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (N-Cyclopropylmethyl-19-methylnororvinol, VIII, R = R^1 = Me; R^2 = cyclopropylmethyl). The amide VIII (R = R^1 = Me; R^2 = cyclopropylcarbonyl) (4 g) was reduced with lithium aluminum hydride (2.15 g) in tetrahydrofuran under reflux over 5 hr. The product was isolated by the cautious addition of an aqueous solution of potassium sodium tartrate and ether extraction, when the tertiary base was obtained as white prisms, mp 234°, on recrystallization from methanol.

Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.6; H, 7.8. Found: C, 73.6; H, 7.9.

Other N-substituted bases of the phenolic series VIII were prepared *via* the amide and reduction with lithium aluminum hydride by the same method described above.

N,N′-Methylenebis(7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine) (N,N′-Methylenebis(19-methylnororvinol), IX, R = R^1 = R^2 = R^3 = Me). a. A solution of 19-methylorvinol (I, R = R^1 = Me) (10 g) and methyl azodicarboxylate (3.64 g) in acetone (75 ml) was evaporated to dryness over 30 min. The viscous yellow product was dissolved in cold 1 *N* hydrochloric acid (100 ml) and the solution kept at room temperature for 45 min. The base was precipitated with ammonia and rapidly extracted with ether. The undried extract was evaporated, the viscous residue dissolved in methanol (50 ml), and the solution heated to boiling. A white solid (8.4 g) rapidly separated and was collected and recrystallized from 2-ethoxyethanol, when the N,N′-methylenebis compound was obtained as white prisms, mp 286°.

Anal. Calcd for $C_{47}H_{58}N_2O_8$: C, 72.5; H, 7.4. Found: C, 72.3; H, 7.5.

b. Aqueous formaldehyde (30%, 1 ml) was added to a solution of 19-methylnororvinol (VII, R = R^1 = Me; R^2 = H) (2 g) in ethanol (15 ml). The mixture was kept at the room temperature for 45 min, diluted with water, and extracted with ether. The ether extract on evaporation yielded a viscous gum (2.01 g), 1 g of which on heating under reflux in methanol (5 ml) gave 0.85 g of the above N,N′-methylenebis compound (IX, R = R^1 = R^2 = R^3 = Me). The remaining 1 g on heating with 19-methylnororvinol (1 g) in methanol (10 ml) afforded 1.8 g of the same N,N′-methylenebis compound, mp 286°.

N-Hydroxymethyl-7α-(1-(*R*)-hydroxy-1-methyl-3-phenylpropyl)-6,14-*endo*-ethenotetrahydronorthebaine (N-Hydroxymethyl-19-phenethylnorthevinol, VII, R = Me; R^1 = CH_2CH_2Ph; R^2 = CH_2OH). Aqueous formaldehyde (30%, 1 ml) was added to a warm solution 19-phenethylnorthevinol (VII, R = Me; R^1 = CH_2CH_2Ph; R^2 = H) (2 g) in ethanol (15 ml) and the mixture kept at 45° for 30 min during which time a crystalline solid separated. The mixture was cooled, and the solid (1.9 g) was collected and recrystallized from methanol containing 10% of aqueous 30% formaldehyde, when the carbinolamine (1.6 g) was obtained as white prisms, mp 123°.

Anal. Calcd for $C_{31}H_{37}NO_5$: C, 74.1; H, 7.4. Found: C, 74.6; H, 7.8.

N,N′-Methylenebis(7α-(1-(*R*)-hydroxy-1-methyl-3-phenylpropyl)-6,14-*endo*-ethenotetrahydronorthebaine) (N,N′-Methylenebis(19-phenethylnorthevinol), IX, R = R^2 = Me; R^1 = R^3 = CH_2CH_2Ph). a. A solution of 19-phenethylthevinol (60 g) and ethyl azodicarboxylate (24 g) in acetone (450 ml) was boiled under reflux for 1 hr. The acetone was then evaporated, and the residue was dissolved in methanol (600 ml) and water (75 ml) added. The solution was heated to boiling when a crystalline solid rapidly separated. The mixture was cooled, and the solid (42 g) was collected and a portion recrystallized from 1-propanol, when the N,N′-methylenebis compound was obtained as white prisms, mp 241–243°.

Anal. Calcd for $C_{61}H_{70}N_2O_8$: C, 76.4; H, 7.4; N, 2.9. Found: C, 76.4; H, 7.8; N, 2.9.

b. N-Hydroxymethyl-19-phenethylnorthevinol (VII, R = Me; R^1 = CH_2CH_2Ph; R^2 = CH_2OH) (1 g) was heated in boiling ethanol (20 ml) until separation of crystalline material appeared to have ceased. The mixture was cooled and the solid (0.8 g) collected, when the N,N′-methylenebis compound was obtained as prisms, mp 238–240°, raised to 241–242° on recrystallization from 1-propanol.

c. N-Hydroxymethyl-19-phenethylnorthevinol (VII, R = Me; $R^1 = CH_2CH_2Ph$; $R^2 = CH_2OH$) (1 g) and 19-phenethylnorthevinol (VII, R = Me; $R^1 = CH_2CH_2Ph$; R^2 = H) (0.93 g) were heated together in ethanol (25 ml) until separation of crystalline material appeared to have ceased. The mixture was cooled and the N,N′-methylenebis compound (1.7 g) was collected and recrystallized from 1-propanol, when it was obtained as white prisms, mp 241–243°.

N,N′-Methylene-7α-(1-hydroxy-1-methylethyl)-7′α-(1-(*R*)-hydroxy-1-methyl-3-phenylpropyl)bis(6,14-*endo*-ethenotetrahydronorthebaine) (N,N′-Methylene-19-methyl-19′-phenethylbis(northevinol), IX, R = R^1 = R^2 = Me; R^3 = CH_2CH_2Ph). a. N-Hydroxymethyl-19-phenethylnorthevinol (VII, R = Me; $R^1 = CH_2CH_2Ph$; $R^2 = CH_2OH$) (1 g) and 19-methylnorthevinol (VII, R = R^1 = Me; R^2 = H) (0.76 g) were heated together in boiling ethanol until separation of the solid ceased. The mixture was cooled, and the product was collected (1.41 g) and recrystallized from 1-propanol, when it was obtained as white prisms, mp 218–220°.

Anal. Calcd for $C_{54}H_{64}N_2O_8$: C, 74.6; H, 7.7. Found: C, 74.3; H, 7.2.

b. Aqueous formaldehyde (30%, 1 ml) was added to a solution of 19-methylnorthevinol (VII, R = R^1 = Me; R^2 = H) (1 g) in ethanol (10 ml), and after 30 min the solution was diluted with water (50 ml) and rapidly extracted with ether. The ether extract was evaporated at 20° *in vacuo*; the residue was dissolved in ethanol (20 ml) and heated with 19-phenethylnorthevinol (VII, R = Me, $R^1 = CH_2CH_2Ph$; R^2 = H) (1.24 g) until precipitation of solid ceased. The mixture was cooled and the above unsymmetrical bis compound (1.9 g) was collected and obtained as prisms, mp 218–220°, after recrystallization from 1-propanol.

Hydrolysis of N,N′-Methylenebis(7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine) (IX, R = R^1 = R^2 = R^3 = Me). a. The N,N′-methylenebis compound (500 g) was dissolved in 1 *N* hydrochloric acid (5 ml), and the solution was added to a solution of 2,4-dinitrophenylhydrazine (500 mg) in 3 *N* hydrochloric acid (10 ml). The mixture was warmed until separation of solid matter ceased. The solid was collected, washed with water, and dried (125 mg). On recrystallization from aqueous ethanol, it was obtained as orange needles, mp 165°, undepressed on mixing with formaldehyde 2,4-dinitrophenylhydrazone, mp 166°.

b. A solution of dimedone (0.2 g) in ethanol (5 ml) was added to a hot solution of the N,N′-methylenebis compounds (1 g) in 6% acetic acid. Methylenedimedone (0.19 g) was precipitated almost at once and was collected, when it was obtained as white prisms, mp 189° undepressed on mixing with an authentic specimen prepared from formaldehyde. The filtrate, after removal of this derivative, was basified with ammonia, and the precipitated base was collected and recrystallized from aqueous methanol, when the the secondary base (VII, R = R^1 = Me; R^2 = H) (0.8 g) was obtained as needles, mp 163°, identical with material prepared by the hydrolysis of the N-cyanonor compound (VII, R = R^1 = Me; R^2 = CN) as described above.

Reaction of N,N′-Methylenebis(7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine) (IX, R = R^1 = R^2 = R^3 = Me) with Alkyl and Acyl Halides. a. The N,N′-methylenebis compound (1 g), methyl iodide (2 ml), anhydrous potassium carbonate (1 g), and ethanol (20 ml) were boiled together under reflux for 6 hr. Filtration and concentration of the solution afforded 19-methylthevinol (I, R = R′ = Me) (1 g), mp 166° alone or mixed with an authentic specimen.

b. The bis compound (1 g), allyl bromide (2 ml), anhydrous potassium carbonate (1 g), and ethanol (20 ml) were boiled together under reflux for 16 hr. Filtration and evaporation of the solution yielded N-allyl-19-methylnorthevinol (VII, R = R^1 = Me; $R^2 = CH_2CH{=}CH_2$) (1 g), mp 104° on recrystallization from petroleum ether (bp 40–60°).

Other N-alkenylations and alkynylations of this and other methylenebis compounds using reactive halides such as propargyl bromide, allyl bromide, and dimethylallyl bromide were achieved under similar conditions. Less reactive alkyl halides, however, such as ethyl bromide, *n*-propyl iodide, etc., reacted less readily, and reflux periods of up to 3 days were necessary for complete reaction, and under such conditions quaternary salt formation was also observed.

c. The N,N′-methylenebis compound (1 g), anhydrous potassium carbonate (1 g), and cyclopropylcarbonyl chloride (0.5 g) were stirred together in dry ether (50 ml) for 6 hr. Water (10 ml) and 2 *N* hydrochloric acid (20 ml) were added, and the ether layer was separated and evaporated, when N-cyclopropylcarbonyl-19-methylnorthevinol (VII, R = R^1 = Me; R^2 = cyclopropylcarbonyl) (1.0 g) was obtained after recrystallization from methanol, mp 214°, undepressed on mixing with an authentic specimen prepared from the secondary base VII (R = R^1 = Me, R^2 = H).

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