activity for the series I as was found with the dimethanesulfonates II at $n = 4$.[2]

The activity against Leukemia L1210 shown by I (n = 3 to 5) suggests that similar mustards from other diamines or polyamines, such as spermine and spermidine, may be interesting candidates for antitumor study.

Experimental[12]

1,5-Di(benzylideneamino)pentane (V, $n = 5$).—A 10-g. portion (0.098 mole) of 1,5-diaminopentane was added slowly to a solution of 20.8 g. (0.196 mole) of benzaldehyde in 30 ml. of absolute ethanol. The solution was kept at room temperature for 20 min., at reflux temperature for 25 min., and was evaporated *in vacuo* to a sirup which crystallized on cooling to give 26.8 g. (99%) of V ($n = 5$), m.p. 30–31.5. This was sufficiently pure for the next step. Three recrystallizations from Skellysolve B gave the analytical sample of V ($n = 5$), with unchanged melting point; λ_{max}^{Nujol} 3.28, 3.32 (C–H of N=CH— and phenyl), 6.05 (C=N) μ.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 82.0; H, 7.97; N, 10.1. Found: C, 81.7; H, 7.82; N, 9.93.

1,5-Di(benzylamino)pentane (VI, $n = 5$) Dihydrochloride.—Excess sodium borohydride (14.0 g., 0.37 mole) was added in small portions over a period of 1 hr. to a stirred solution of 23.8 g. (0.0856 mole) of V ($n = 5$) in 230 ml. of methanol cooled in an ice bath. The solution was stirred for 40 min. more at room temperature, heated at reflux on a steam bath for 15 min., then evaporated *in vacuo* at 50° to leave a semisolid. This was taken up in 360 ml. of water, and the oil which separated was extracted with two 200-ml. portions of methylene chloride. The dried extract was evaporated to leave 23.9 g. (99%) of VI ($n = 5$), as a yellow oil sufficiently pure for the next step.

A portion of the oil in ethanol was converted to the dihydrochloride with gaseous hydrogen chloride. The precipitated salt was crystallized twice from 90% aqueous ethanol to give the dihydrochloride salt of VI (see Table II).

N,N′-Bis(2-hydroxyethyl)-N,N′-dibenzyl-1,5-diaminopentane (VII, $n = 5$).—An ice-cooled solution of 10.0 g. (0.035 mole) of the dibenzylamine VI ($n = 5$) in 130 ml. of methanol was treated with 35.2 ml. (0.71 mole) of freshly distilled ethylene oxide. The flask was capped and the mixture was stirred overnight with the temperature allowed to rise gradually to about 25°. The solution was evaporated *in vacuo* (bath, 35°) to leave 14.8 g. of sirup. This was taken up in 30 ml. of methylene chloride; the solution was washed with four 30-ml. portions of water, dried, filtered, and evaporated *in vacuo*, finally at 55° (0.1 mm.), to give 9.07 g. (69%) of analytically pure light yellow, sirupy VII ($n = 5$).

N,N′-Bis(2-chloroethyl)-N,N′-dibenzyl-1,4-diaminobutane Dihydrochloride (IX, $n = 4$).—A solution of 61.5 g. (0.143 mole) of the bishydroxyethylamine VII ($n = 4$) in 200 ml. (2.78 moles) of thionyl chloride was heated at reflux for 1 hr., then poured into 2 l. of petroleum ether (b.p. 30–60°). The precipitate was collected, washed with petroleum ether, then benzene, and dried to give 65 g. (98%) of crude product. Recrystallization from 95% ethanol (1 g./50 ml.) gave 40.4 g. (60.6%) of product, m.p. 206–219° dec., of sufficient purity for the hydrogenolysis step.

N,N′-Bis(2-chloroethyl)-1,4-diaminobutane Dihydrochloride (I, $n = 4$).—A mixture of 15.0 g. (0.032 mole) of the dibenzyl mustard IX ($n = 4$) and 1.88 g. of 5% palladium-on-carbon in 250 ml. of 95% acetic acid was hydrogenated in a Parr apparatus at room temperature (initial pressure 3.5 kg./cm.²). The theoretical amount of hydrogen was taken up in 30–40 min.; no further uptake was noted after a total of 4.5 hr. The reaction mixture was filtered through a Celite pad, the catalyst was washed well with methanol, and the combined filtrate and washes were evaporated *in vacuo* at 60° to leave 9.1 g. (99%) of product, m.p. 235–241° dec. Recrystallization from methanol gave 6.8 g. (74%) of I ($n = 4$), m.p. *ca.* 240–245° dec. (varies with heating rate).

N,N′-Bis(2-hydroxyethyl)-1,4-diaminobutane (VIII, $n = 4$) Dihydrochloride.—A mixture of 1.00 g. (2.4 mmoles) of the dibenzylamine dihydrochloride VII·2HCl ($n = 4$) and 100 mg. of 5% palladium-on-charcoal in 50 ml. of 2-methoxyethanol (or 35 ml. of 6 *N* hydrochloric acid), was hydrogenated 75–80° and 3.15 kg./cm.² (initial) to give 0.50 g. (87%) of product, m.p. 128–133°.

(12) Melting points were obtained with the Fisher–Johns apparatus and are corrected. The solvent Skellysolve B is essentially hexane (b.p. 60–68°). The general experimental procedures are illustrated by one example each. The physical data and analyses for all the compounds are listed in Table II. The infrared spectra of all the compounds were compatible with their structures.

Acknowledgment.—The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and his staff for the infrared spectra and some analyses. They also wish to thank Mr. O. P. Crews and his staff for the large-scale preparation of some intermediates.

Transformation of Codeine to an Analog of the Potent Analgesic Phenazocine

LEWIS J. SARGENT AND J. HARRISON AGER

Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Maryland

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Codeine has been transformed to an analog IX of phenazocine incorporating the 4,5-oxygen bridge originally present in the parent alkaloid. The analgesic activity of IX was found to be approximately twice that of morphine.

The high analgesic effectiveness of phenazocine [(±)-2′-hydroxy-2-phenethyl-5,9-dimethyl-6,7-benzomorphan] (X) has been well demonstrated.[1] One may view this substance as being related to the morphine system in which the 4,5-oxygen bridge has been abolished and ring "III" opened and partially degraded. Although the pronounced analgesic properties of the morphinans[2] demonstrate that the oxygen bridge apparently is not essential for activity, it nevertheless was a matter of theoretical interest to prepare an analog of phenazocine incorporating the oxygen bridge to determine its effect on pharmacological activity. It was evident at the outset of this investigation that the most promising way to the system envisaged (IX) would be through degradation of an appropriate morphine derivative utilizing reactions that would reasonably ensure the integrity of the 4,5-oxygen system.

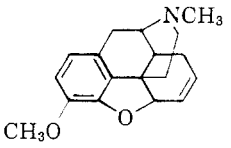
The feasibility of oxidative cleavage of ring III in the morphine series was first demonstrated in this Laboratory some years ago in degradation studies with dihydrothebaine.[3] In essence this involved osmic acid hydroxylation of an unsaturated center followed by lead tetraacetate oxidation of the resulting glycol.

(1) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959), and references cited therein.

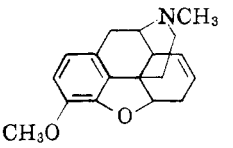
(2) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

(3) L. J. Sargent and L. F. Small, *J. Org. Chem.*, **16**, 1031 (1951).

Of the two morphine congeners (*i.e.*, desoxycodeine-C, and desoxycodeine-E) possessing the structural features required for our studies, desoxycodeine-E was



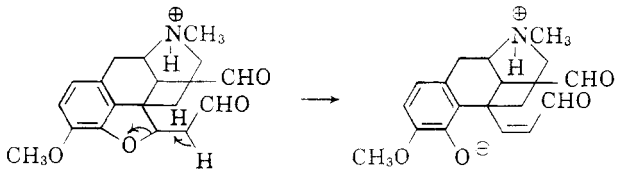
Desoxycodeine-C



Desoxycodeine-E

chosen because of its ready preparation from codeine.[4] It should be mentioned, however, that two exploratory lead tetraacetate cleavage experiments were initially carried out with 7-hydroxydihydrocodeine[5] (prepared by hydroxylation of desoxycodeine-C). Although the deep yellow, resinous oxidation product was immediately reduced with lithium aluminum hydride, virtually no alkaloidal material could be recovered. This suggested that the intermediate dialdehyde had undergone extensive polymerization to nonbasic material, despite the fact that all operations were carried out as rapidly as possible in a nitrogen atmosphere.

Rapoport, *et al.*,[6] recently reported on related periodate oxidation studies with 7,8-dihydroxydihydrodesoxycodeine. Their experiments were carried out in dilute aqueous, buffered (pH < 6) media and, while they were unable to isolate any crystalline product, they did recover a *basic* oil, in good yield, which not only gave a positive phenolic reaction with diazotized sulfanilic acid (indicative of 4,5-oxide cleavage) but whose infrared and ultraviolet spectral characteristics pointed to the presence of an α,β-unsaturated carbonyl system. It was suggested that these results could be accommodated by postulating a β-elimination in the expected oxidation product, presumably as follows



The isolation of a *basic* substance from the periodate oxidation of 7,8-dihydroxydihydrodesoxycodeine is in marked contrast to our lead tetraacetate experiments with 7-hydroxydihydrocodeine (above). These divergent results may perhaps be attributed to Rapoport's having operated in aqueous acidic solution (where the nitrogen would be protonated), whereas our *basic* glycol was oxidized in benzene solution in which internal, base-catalyzed polymerization of the resulting aminodialdehyde was possible. The instability of comparable dialdehydes has been observed in colchicine studies by Tarbell.[7]

From a consideration of these points it was apparent that, in order to circumvent loss of product through polymerization of the intermediate dialdehyde, the basicity of the glycol would have to be masked before treatment with lead tetraacetate.[8] Because it was eventually planned to substitute a phenethyl group for methyl on the heterocyclic nitrogen atom (*via* phenacylation of the nor-compound), it occurred to us that this would conveniently afford the means for temporarily neutralizing the basicity of the compound during the oxidation reaction. This, in fact, turned out to be the key step of the investigation, and the sequence of reactions that ultimately led to the desired product IX is shown in Chart I.

Tosylation of codeine followed by lithium aluminum hydride reduction gave Δ^7-desoxycodeine,[4b] which was converted to the nor-cyano derivative I.[4b] Hydroxylation of the latter with osmic acid to give II followed by acid hydrolysis afforded nor-7,8-dihydroxydihydrodesoxycodeine (III). After selective phenylacylation of the secondary amine, the glycol IV was oxidized with lead tetraacetate[9] and the resulting amidodialdehyde V (not isolated) reduced with lithium aluminum hydride to the corresponding N-phenethylaminodicarbinol (VI).[10]

Tosylation of the latter yielded an amorphous ditosylate VII in 85% yield. This high yield was taken as evidence that little, if any, internal displacement of either tosyl group by the nitrogen electron pair to form a (presumably water-soluble) quaternary salt occurred – a possibility that was suggested by the work of van Tamelen.[11] Lithium aluminum hydride reduction of VII afforded VIII (isolated as the perchlorate) whose infrared spectrum was devoid of hydroxyl absorption.[12] Hydrogen bromide demethylation of VIII (either as the perchlorate or the hydrochloride) gave IX, characterized as the hydrobromide. There is ample precedent in the morphine series for demethylating the 3-methoxyl group without concomitant cleavage of the 4,5-oxygen bridge.[13] Moreover, the enhanced analgesic activity of IX compared with that of morphine and codeine further supports the view that the integrity of the oxygen bridge has been maintained. In general, opening of the latter results in a marked decrease in activity, *e.g.*, tetrahydrodesoxymorphine and tetrahydrodesoxycodeine.[2]

It was of further interest to compare the positions of the infrared hydroxyl absorption bands of the salts of certain morphine congeners with that of IX and these data are given in Table I with catechol included as a reference. It will be noted that tetrahydrodesoxymorphine, with free hydroxyls at positions 3 and 4, shows a doublet characteristic of the catechol type, while dihydrodesoxymorphine-D, heterocodeine, and IX show single hydroxyl peaks. It appears, then, that the absorption band due to a hydroxyl at the 3-position occurs

(4) (a) P. Karrer and G. Widmark, *Helv. Chim. Acta*, **34**, 34 (1951); (b) H. Rapoport and R. M. Bonner, *J. Am. Chem. Soc.*, **73**, 2872 (1951).

(5) L. J. Sargent, L. H. Schwartzman, and L. F. Small, *J. Org. Chem.*, **23**, 1247 (1958).

(6) H. Rapoport, M. S. Chadha, and C. H. Lovell, *J. Am. Chem. Soc.*, **79**, 4694 (1957).

(7) H. R. V. Arnstein, D. S. Tarbell, G. P. Scott, and H. T. Huang, *ibid.*, **71**, 2448 (1949).

(8) *Cf.* ref. 3 where acceptable yields of dialdehyde (which was subsequently reduced) were obtained from a *neutral* glycol.

(9) It is essential to use lead tetraacetate of better than 90% assay for satisfactory results.

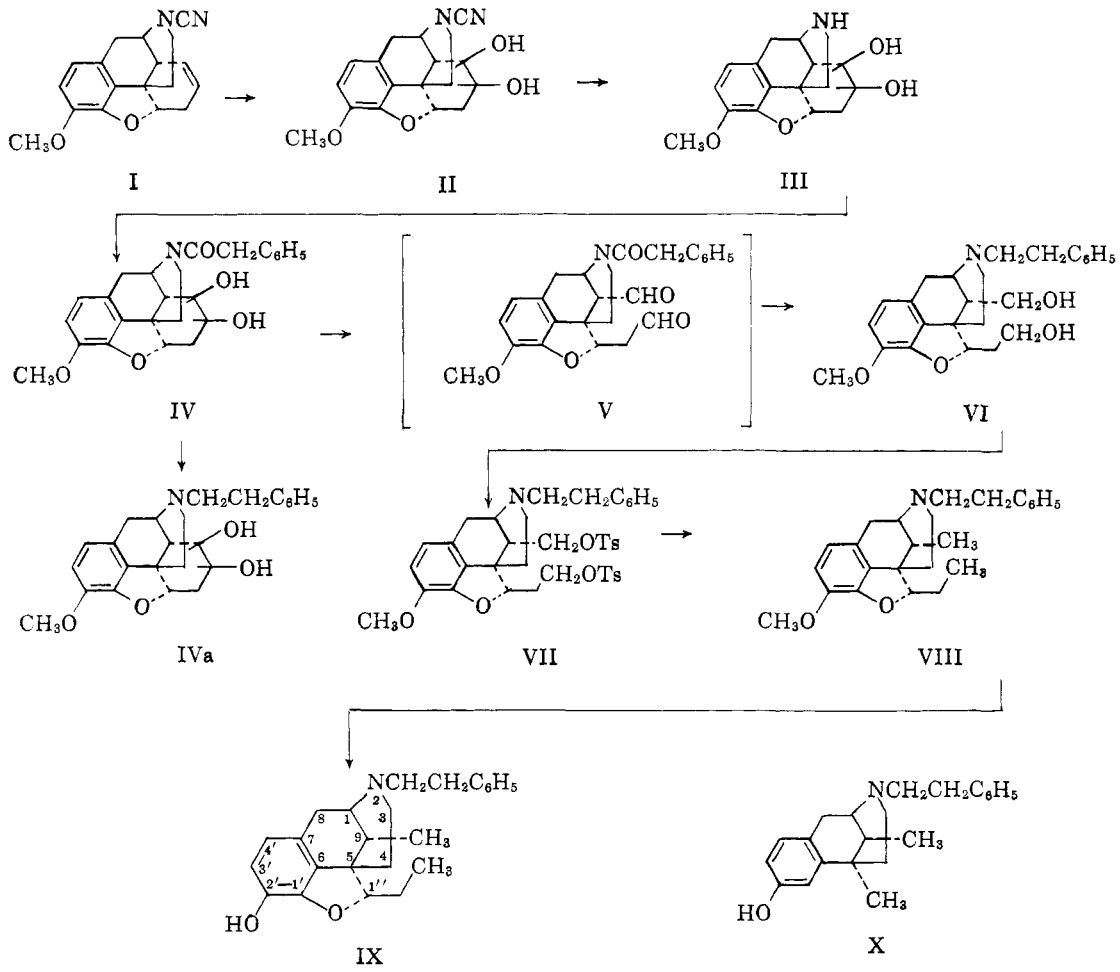
(10) The diazosulfanilic acid test, of great utility in detecting a free phenolic hydroxyl group at position 4 in morphine alkaloids (indicative of 4,5-ether cleavage), was negative (*cf.* ref. 4b).

(11) E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 6214 (1959).

(12) For comparative purposes, tetrahydrodesoxycodeine perchlorate was prepared for the first time and recrystallized from acetone–ether, m.p. 225–227° (corr.). *Anal.* Calcd. for $C_{18}H_{26}ClNO_6$: C, 55.74; H, 6.76. Found: C, 55.80; H, 6.49. Its infrared spectrum (Nujol) showed a strong hydroxyl band at 3400 cm.$^{-1}$.

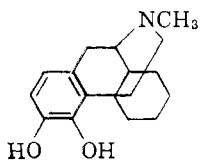
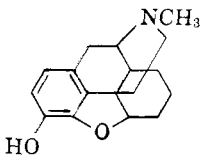
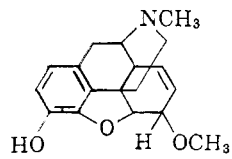
(13) (a) L. F. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936); (b) U. Weiss, *ibid.*, **77**, 5891 (1955).

CHART I



at *lower* frequencies than that arising from a 4-(*cryptophenolic*)hydroxyl group in this series.

TABLE I

Substance	Hydroxyl absorption bands (μ)	
Catechol	2.87	3.0
	2.96	3.25
Tetrahydrodesoxymorphine·HCl		
		3.20
Dihydrodesoxymorphine·HBr		
		3.12
Heterocodeine·HBr		
IX·HBr		3.12

In mice (subcutaneous administration) 1′1″-epoxy-2′-hydroxy-2-phenethyl-5-*n*-propyl-9-methyl-6,7-benzomorphan (IX) hydrobromide showed ED_{50} 0.98 mg./kg. which is somewhat more than twice the potency of morphine (*cf.* ref. 1 for testing details).

TABLE II

COMPARATIVE ANALGESIC ACTIVITIES IN MICE

Compound	ED_{50}, mg./kg.
Morphine sulfate	2.1
Codeine sulfate	14.2
(±)-Phenazocine hydrobromide	0.25
(−)-Phenazocine hydrobromide	0.11
IX·hydrobromide	0.98

Experimental[14]

nor-Cyano-Δ⁷-desoxycodeine (I).—Following the procedure of Rapoport, *et al.*,[4b] 22.5 g. of Δ⁷-desoxycodeine afforded 22 g. of the nor-cyano derivative, m.p. 148.5–150°.

nor-Cyano-7,8-dihydroxydihydrodesoxycodeine (II).—To a solution of I (12.8 g., 43 mmoles) in 150 ml. of pyridine, 10 g. (39 mmoles) of osmic acid was added and the system stirred magnetically for 2 hr. Following the addition of 18 g. of sodium bisulfite, 300 ml. of water, and 200 ml. of pyridine, stirring was continued for 45 min. and the orange solution thoroughly extracted with chloroform.[15] Concentration of the dried extracts (Na_2SO_4) *in vacuo* yielded a foamy residue which crystallized when triturated with methanol; yield 11.3 g., m.p. 223–225°. The analytical sample was recrystallized from methanol (Norit), m.p. 226–228°, $[\alpha]^{20}D$ −93.0° (*c* 0.71).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.8; H, 6.14. Found: C, 66.1; H, 6.26.

(14) The elemental analyses and rotations (in 95% ethanol) were carried out by J. G. McCann and his associates of the Analytical Services Unit of the Laboratory of Chemistry. Melting points are corrected.

(15) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

nor-7,8-Dihydroxydihydrodesoxycodeine (III).—A suspension of II (11.3 g., m.p. 223–225°)in 160 ml. of 6% hydrochloric acid was refluxed for 18 hr., cooled, made basic with a slight excess of cold 10 *N* sodium hydroxide, and thoroughly extracted with chloroform. The latter, after drying and concentration *in vacuo*, afforded a pale yellow solid which crystallized in slender prisms from methanol (Norit); yield 10.7 g., m.p. 225–227°. A specimen, recrystallized from ethyl acetate, had m.p. 228–230° $[\alpha]^{20}D$ −12.4° (*c* 0.344).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.3; H, 6.98. Found: C, 67.0; H, 7.14.

N-Phenacetyl-7,8-dihydroxydihydrodesoxycodeine (IV).—To a magnetically stirred solution of 11.9 g. (40 mmoles) of III in a mixture of acetone (240 ml.) and water (45 ml.), potassium carbonate (20 g., 144 mmoles) in 75 ml. of water was added and the system treated with 15.1 ml. (114 mmoles) of phenylacetyl chloride during 1 hr. After stirring 15 hr. at room temperature, the mixture was concentrated *in vacuo* (steam bath) and the resulting yellow gum washed with water and taken up in chloroform. The latter was washed twice with 30-ml. portions of 1.5 *N* hydrochloric acid, then dried and concentrated *in vacuo* to a gum which was triturated with 250 ml. of dry ether, and kept under this solvent for 24 hr. during which interval crystallization occurred; yield 13.8 g., m.p. 172–175°. An additional 1.4 g. was obtained from the mother liquor. A specimen was recrystallized twice from ether, m.p. 174–176°, $[\alpha]^{25}D$ −111° (*c* 0.88).

Anal. Calcd. for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46. Found: C, 71.42; H, 6.74.

N-Phenethyl-7,8-dihydroxydihydrodesoxycodeine (IVa).—Lithium aluminum hydride (0.8 g., 21 mmoles) was added to a magnetically stirred solution of IV (2.6 g., 6.2 mmoles) in 25 ml. of dry tetrahydrofuran, the system refluxed for 4 hr., and worked up according to Mićović's general procedure.[16] Evaporation of the solvent *in vacuo* gave a sirup which was taken up in chloroform and the solution extracted with five 30-ml. volumes of 0.5 *N* hydrochloric, followed by fifteen 50-ml. portions of *N* acid. The combined, cooled extracts were made basic with a slight excess of 10 *N* sodium hydroxide and shaken with ether which, after drying and concentration *in vacuo*, left 1.4 g. of a pale yellow sirup. The latter slowly (3 days) crystallized from a concentrated solution in ether; yield 0.58 g. The substance crystallizes best from slightly moist ether and the resulting small prisms retain water of crystallization; m.p. 143–146° (froth), $[\alpha]^{20}D$ −53° (*c* 0.97).

Anal. Calcd. for $C_{25}H_{29}NO_4 \cdot 0.25\,H_2O$: C, 72.9; H, 7.21; H_2O, 1.09. Found: C, 72.9; H, 7.16; H_2O, 1.15.

1′,1″-Epoxy-2′-methoxy-2-phenethyl-5-(3-hydroxypropyl)-9-hydroxymethyl-6,7-benzomorphan (VI).[17]—To a magnetically stirred solution of 12.4 g. (30 mmoles) of IV in 360 ml. of dry benzene, maintained at 15–18° (nitrogen atmosphere), 5.6 g. (40 mmoles) of potassium carbonate (dried at 110°) was added. Powdered lead tetraacetate (14.4 g., 33 mmoles; 92% assay) was introduced during 30 min. and the system stirred for 80 min. longer. After filtration, the deep yellow solution was dried for 10 min. (sodium sulfate) and concentrated *in vacuo* (below 40°; under nitrogen). The residual orange sirup was taken up in 240 ml. of dry tetrahydrofuran, filtered rapidly through a thin Celite mat, and the solution added dropwise (during 20 min.) to a stirred solution of 75 ml. (excess) of 2.7 *M* lithium aluminum hydride in tetrahydrofuran (under nitrogen). After heating the system at 40–45° for 3.5 hr., excess reductant was decomposed, as previously described,[15] and the suspension stirred rapidly with a small quantity of Celite for 30 min. Solids were removed by filtration and the precipitate digested twice with 50-ml. portions of boiling tetrahydrofuran which were combined with the main solution and concentrated *in vacuo* to a pink sirup (*ca.* 12 g.). The latter was dissolved in 175 ml. of chloroform and extracted successively with fifteen 25-ml. portions of 0.5 *N* hydrochloric acid and ten 25-ml. volumes of *N* acid.[18] The combined extracts were washed twice with ether, cooled in ice, made basic with a slight excess of 10 *N* sodium hydroxide, and extracted with ether which yielded 4.1 g. (37%) of crystalline product, m.p. 148–151°. The diazosulfanilic acid test[5b] was negative. A sample, recrystallized twice from ether, had m.p. 152–154°, $[\alpha]^{20}D$ −149.0° (*c* 1.15).

Anal. Calcd. for $C_{25}H_{31}NO_4$: C, 73.3; H, 7.63. Found: C, 73.1; H, 7.68.

Ditosylate (VII).—A magnetically stirred, ice-cooled solution of 3.6 g. (8.8 mmoles) of VI (m.p. 148–151°) in 9 ml. of dry pyridine was treated during 15 min. with a solution of 3.55 g. (18.5 mmoles) of recrystallized tosyl chloride in the same solvent. After keeping at 5° for 18 hr., the pink solution was added dropwise to a stirred slurry of ice and water. The light pink, amorphous precipitate was washed several times with water (by decantation), collected, and thoroughly dried in a vacuum desiccator; yield 5.3 g.

Anal. Calcd. for $C_{39}H_{43}NO_8S_2$: S, 8.93. Found: S, 8.48.

1′,1″-Epoxy-2′-methoxy-2-phenethyl-5-*n*-propyl-9-methyl-6,7-benzomorphan (VIII) Perchlorate.—To a solution of VII 5.4 g.) in 50 ml. of dry tetrahydrofuran (nitrogen atmosphere, magnetic stirring), 22 ml. (excess) of 1.27 *M* lithium aluminum hydride solution in tetrahydrofuran was gradually added and the system refluxed for 3.5 hr. After cooling, 250 ml. of dry ether was added and the excess reductant carefully decomposed with ice–water. The addition of a small quantity of Celite to the stirred mixture facilitated subsequent filtration from inorganic material. The latter was triturated with four 50-ml. volumes of boiling ether and the extracts were combined with the main filtrate which, after drying and concentration *in vacuo*, yielded 2.8 g. of a sirup. A solution of this in 8 ml. of methanol containing 1.3 g. (5% excess) of 60% perchloric acid was diluted with ether to light turbidity and scratched. After 4 days at room temperature, 2 g. (in two crops) of crude perchlorate, m.p. 224–226° was obtained. Recrystallization from a concentrated solution in methanol, using a little ether, gave 1.07 g. of colorless, triangular plates, m.p. 233–235°. The analytical sample, recrystallized once again, had the same melting point; $[\alpha]^{25}D$ −111.6° (*c* 0.484). The infrared spectrum was devoid of hydroxyl absorption.

Anal. Calcd. for $C_{25}H_{32}ClNO_6$: C, 62.8; H, 6.75. Found: C, 62.5; H, 6.64.

1′,1″-Epoxy-2′-hydroxy-2-phenethyl-5-*n*-propyl-9-methyl-6,7-benzomorphan (IX) Hydrobromide.—A suspension of VIII perchlorate (0.4 g.) in 3 ml. of 48% hydrobromic acid was placed in an oil bath (preheated to 160°) and the system refluxed for 20 min. The cooled solution was diluted with 10 ml. of water, made basic with a slight excess of concentrated ammonium hydroxide, and the product taken up in chloroform. The latter yielded a sirup which was treated, in ether, with ethereal hydrogen bromide to give 0.27 g. of the hydrobromide, m.p. 290–293° dec. A specimen, recrystallized from absolute ethanol, had m.p. 292–294° dec., $[\alpha]^{25}D$ −78.7 ± 2° (*c* 0.82).

Anal. Calcd. for $C_{24}H_{30}BrNO_2$: C, 64.9; H, 6.80; Br, 17.9. Found: C, 64.6; H, 7.09; Br, 17.6.

(16) V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

(17) For an explanation of this numbering system *cf.* E. L. May and J. G. Murphy, *ibid.*, **20**, 257 (1955), and succeeding papers.

(18) That the low solubility of VI in dilute hydrochloric acid was not due to intramolecular hydroxyl proton bonding with the nitrogen electron pair was demonstrated by an infrared study of VI in the 4000 to 2000 cm.$^{-1}$ region. The intensity of the absorption band at 3362 cm.$^{-1}$ (-N:-H-O bonding region) was quite weak compared to the free hydroxyl absorption band at 3638 cm.$^{-1}$. We are indebted to Mr. H. K. Miller for these data.