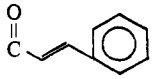
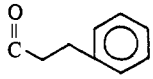
Table I *(Continued)*

No.	R	Formula	Analyses[a,b]	Mp, °C	Recrystn solvent	Rel C_{50}[c] $\left(\frac{C_{50}\text{ ester}}{C_{50}\text{ helenalin}}\right)$ (H.Ep.-2)
18		$C_{22}H_{33}O_5N$	C, H, N	163.5–164.5	EtOH	1.96
19		$C_{26}H_{31}O_5N$	C, H[j,k]	191–192	EtOAc	0.46
20		$C_{26}H_{33}O_5N$	C, H[j,l]	146–146.5	EtOH	1.68

[a]Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. [b]All compounds gave satisfactory nmr and ir data. In all cases H-6 is a sharp s in the range of 4.45–5.57 as compared to broad s at 5.66 for 1 in the nmr spectrum. [c]Half-maximal effective dose. The C_{50} value of helenalin is 0.393 μmol/l. [d]R. Adams and W. Herz, *J. Amer. Chem. Soc.*, 71, 2546 (1949), reported mp 169–172° (benzene). [e]R. Adams and W. Herz, *J. Amer. Chem. Soc.*, 71, 2546 (1949), reported mp 179.5–180.5°. [f]Freeze-dried solids. [g]This compound was shown to be tlc homogeneous and had a molecular ion peak at *m/e* 396.0574 corresponding to $C_{18}H_{21}O_5Br$. [h]Oil. [i]This compound was shown to be tlc homogeneous and had *m/e* 356 (M^+). [j]Insufficient sample for N analysis. [k]*M/e* 437.2191 ($C_{26}H_{31}O_5N$). [l]*m/e* 439.2352 ($C_{26}H_{33}O_5N$).

Table II. Results of Screening Test *vs.* the Ehrlich Ascites Carcinoma[a]

Compd	Dose, μmol/kg/day	Mortality C	Mortality T	Volume T/C, ml	Volume SDT ± ml	Ascitocrit T/C	Ascitocrit SDT ± ml	Av TPCV, T as % of C
1[b]	38.2	2/10	1/10	0.16/6.83	0.31	0/0.228	0	0
1[b]	53.5	2/10	6/10	0/6.83	0	0/0.228	0	0
1[b]	68.8	2/10	4/10	0.13/6.83	0.32	0.005/0.228	0.01	0.04
2[c]	38.2	1/9	2/10	0/4.64	0	0/0.226	0	0
7[c]	38.2	1/9	7/10	0/4.64	0	0/0.226	0	0
9[c]	38.2	1/9	4/10	0/4.64	0	0/0.226	0	0
10[c]	38.2	2/10	9/10	0/5.94	0	0/0.277	0	0
13[c]	38.2	2/10	10/10					
14[c]	38.2	2/10	8/10	0/5.94	0	0/0.277	0	0
FU[c,d]	38.2	1/10	1/10	1.8/6.62	0.71	0.145/0.254	0.056	15.5

[a]T = treated group, C = vehicle control group, TPCV = average total packed cell volume of tumor cells on final day of assay, SD = standard deviation of TPCV of treated group. The average SD of the control group was ±1.27 ml and the average ascitocrit was SD ± 0.053. [b]Vehicle was 0.9% NaCl–DMSO (90:10). [c]Vehicle was 0.9% NaCl–DMSO (20:80). [d]FU = 5-fluorouracil.

action, the solvent was removed *in vacuo* and the crude oil was chromatographed on silica gel.**

Helenalin Acrylate (6). A solution of 1 (200 mg) and acrylic anhydride (0.5 ml) in 5 ml of dry pyridine was allowed to stand 5 hr at room temperature. Excess pyridine was removed *in vacuo* to yield an oil. The product was isolated by column chromatography on Florisil.

Helenalin Dimethylamine Adducts. Compounds 17–20 were synthesized by a procedure described previously.[1]

Helenalin (1). Helenalin (1) was isolated by column chromatography on silica gel of the crude extract of plant material *Helenium autumnale* L.

Acknowledgment. We thank Dr. M. E. Wall of the Research Triangle Institute, N. C., for kindly providing us with the crude extract of the plant material of *Helenium autumnale* L.

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**Washing with cold 0.05% $NaHCO_3$ or chromatography of the crude oil on Florisil resulted in facile elimination of HBr to generate compound 6.

Syntheses of Analgesics. 34.[1] Synthesis of 3-Hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (Studies on the Syntheses of Heterocyclic Compounds. 509[2])

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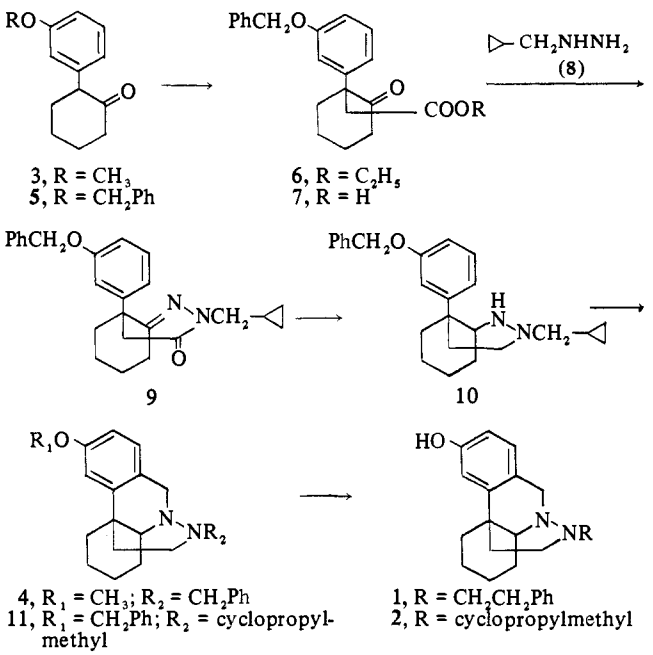
We have reported the synthesis of the 3-hydroxy-9-azamorphinan and N-substituted compounds,[3] some of which showed an analgesic activity, and especially 3-hydroxy-*N*-phenethyl- (**1**) and 3-hydroxy-*N*-cyclopropylmethyl-9-azamorphinans (**2**) were found to have a potent analgesic effect. The modified synthesis and pharmacological activity of **2** were investigated successively. Herein we wish to report these results.

9-Azamorphinan was synthesized by an eight-step procedure from 2-(3-methoxyphenyl)cyclohexanone (**3**) by

use of Pictet-Spengler type cyclization as a key reaction.[3c] In this synthesis some difficulties were encountered in removing protecting groups from the oxygen and nitrogen atoms of 9-azamorphinan.

In order to modify the above defects, the synthesis of 3-hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (**2**) from 2-(3-benzyloxyphenyl)cyclohexanone (**5**) was examined as follows. The benzyne reaction of 2-benzyloxychlorobenzene with cyclohexanone gave 2-(3-benzyloxyphenyl)cyclohexanone (**5**),[4] which was condensed with ethyl bromoacetate in the presence of sodium hydride to afford the ester **6**. The hydrolysis of ester **6** by 5% sodium hydroxide solution gave γ-ketocarboxylic acid **7**, which was condensed with cyclopropylmethylhydrazine (**8**), prepared from cyclopropylmethyl bromide[5,6] with hydrazine hydrate, in benzene to give ketocinnoline **9**. The ir spectrum of this compound showed an amidocarbonyl band at 1660 cm^{-1} and the nmr spectrum ($CDCl_3$) revealed two quartets at 3.40 and 3.80 ppm due to each proton of *N*-methylene attached to the cyclopropyl residue (Scheme I).

Scheme I



Reduction of the ketocinnoline **9** with lithium aluminum hydride in dioxane gave the decahydrocinnoline derivative **10**, easily characterized as hydrochloride, which was subjected to Pictet-Spengler type reaction in the presence of hydrogen chloride to afford a mixture of 9-azamorphinans (**2** and **11**). Both compounds were separated by silicic acid column chromatography. The latter **11** showed C_{10}-methylene protons in the nmr spectrum and was converted into the former compound **2** by debenzylation with boiling hydrochloric acid. Moreover, compound **2** was identical with the authentic sample[3c] in spectral comparison.

Pharmacology. Table I gave the results of screening for the analgesic activities of 3-hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (**2**) by the acetic acid induced stretching method.[7] Male albino mice dd strain (15.6-21.0 g) were used. After this compound was administered subcutaneously to five groups of animals consisting of ten mice per group, the effective ratio until 60 min was examined and ED_{50} was calculated by the Lichfield-Wilcoxone method.[8]

An antagonistic effect of morphine analgesia (ED_{100}, 16 mg/kg sc) was calculated by modification of the method described by Haffner[9] and the results were summarized in Table II. This compound (**2**) was found to be about twice as potent as pentazocine in the analgesic activity and the antagonistic effect of morphine analgesia.

Table I.[7] Effective Ratio and ED_{50} by Lichfield-Wilcoxone Method[8]

Method	Compd	DE_{50}, mean value, mg/kg	95% fiducial limit, mg/kg
Stretching	2	4.5	2.7-7.6
	Pentazocine	7.4	6.3-8.7
	Morphine	1.4	1.2-1.6

Table II.[9] Comparison of the Antagonistic Effect of Morphine Analgesia by Haffner Method

Compd	ED_{50}, mean value, mg/kg	95% fiducial limit, mg/kg
2	9.0	5.7-14.3
Pentazocine	19.0	11.4-31.5

Experimental Section†

Cyclopropylmethylhydrazine (8). To 138.7 g of 100% H_2NNH_2 H_2O 75 g of cyclopropylmethyl bromide[5,6] was added dropwise at 18-30° within 3 hr under stirring. The stirring was continued for 1 hr at 40-50°. The reaction mixture was extracted with 500 ml of Et_2O. Evaporation of Et_2O gave 26.9 g (56.3%) of hydrazine **8** as a colorless oil, bp 105-123° (143 mm), which was characterized as its oxalate as colorless needles: mp 178-178.5° (from MeOH); nmr (free base) (CCl_4) δ 0-1.31 (5 H, m, cyclopropane ring protons), 2.55 (2 H, d, NCH_2), 3.32 ppm (3 H, 2, $NHNH_2$). *Anal.* ($C_4H_{10}N_2 \cdot C_2H_2O_4$) C, H, N.

3,4,5,6,7,8-Hexahydro-2*H*,4a*H*-3-keto-4a-(3-benzyloxyphenyl)-2-cyclopropylmethylcinnoline (9). A solution of 7.5 g of γ-ketocarboxylic acid **7** and 2.6 g of cyclopropylmethylhydrazine in 120 ml of dried PhH was heated under reflux for 6 hr. The PhH layer was washed (saturated $NaHCO_3$ solution and H_2O), dried ($MgSO_4$), and evaporated to leave a pale yellow oil, which was triturated with EtOH to give 6.05 g (70%) of ketocinnoline **9** as colorless prisms: mp 113-114.5° (from EtOH); ir (KBr) 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.15-0.63 (5 H, m, cyclopropane ring protons), 3.40, 3.80 (2 H, each proton, a pair of d, J = 14.0, 7.5 Hz, NCH_2), 5.03 (2 H, s, $PhCH_2O$), 6.64-7.60 ppm (9 H, m, Ar H). *Anal.* ($C_{25}H_{28}N_2O_2$) C, H, N.

2-Cyclopropylmethyl-4a-(3-benzyloxyphenyl)decahydrocinnoline (10). To a stirred suspension of 2.4 g of $LiAlH_4$ in 70 ml of dioxane a solution of 4 g of ketocinnoline **9** in 20 ml of dioxane was added under reflux. After the stirring had been continued for 6 hr at the same temperature, 30% aqueous NaOH was added to the reaction mixture to decompose an excess of $LiAlH_4$ under a current of N_2. The organic layer was separated, dried (K_2CO_3), saturated with HCl gas, and evaporated to give a pale green oil, which was crystallized from MeOH to give 2.2 g (51%) of decahydrocinnoline **9** hydrochloride as colorless needles: mp 230-232° dec (from MeOH-Et_2O); ir (KBr) 3140 cm^{-1} (NH). *Anal.* ($C_{25}H_{32}N_2O \cdot HCl$) C, H, N

Pictet-Spengler Type Reaction of 2-Cyclopropylmethyl-4a-(3-benzyloxyphenyl)decahydrocinnoline (10). A mixture of 2 g of decahydrocinnoline **10** hydrochloride, 10 g of 37% aqueous HCHO, 15 ml of concentrated HCl, and MeOH was heated under reflux for 4.5 hr. The aqueous layer, obtained by removal of MeOH, was basified with aqueous NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (K_2CO_3), and evaporated to give a pale yellow oil, which was chromatographed on silicic acid using $CHCl_3$ and $CHCl_3$-EtOH (1:1) as eluents.

Evaporation of the $CHCl_3$ eluate gave 450 mg (24%) of 3-benzyloxy-*N*-cyclopropylmethyl-9-azamorphinan (**11**) as a pale yellow oil, which was converted into HCl salt as usual and recrystallized from EtOH-Et_2O to afford colorless needles: mp 175-176.5°; nmr (free base) ($CDCl_3$) δ 0-0.72 (5 H, m, cyclopropane ring protons), 0.72-1.90 (10 H, m, cyclohexane ring protons, 15-H_2),

†All melting points were measured in capillary tubes in a sulfuric acid bath and are uncorrected. Ir and nmr spectra were measured on a type Hitachi-215 and JMN-MH-60 (60 Mc) recording photometer with tetramethylsilane as internal standard, respectively.

1.90 ~ 3.32 (5 H, m, 14-H, 16-H_2, and NCH_2), 3.90 (2 H, s, 10-H_2), 4.92 (2 H, s, $PhCH_2$), 6.60–7.50 ppm (8 H, m, Ar H). *Anal.* ($C_{26}H_{32}N_2O \cdot HCl$) C, H, N.

Evaporation of the subsequent $CHCl_3$–EtOH (10:1) eluate gave 1.0 g (70%) of 3-hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (**2**) as a pale yellow oil, which was triturated with Et_2O to give a solid, which was recrystallized from EtOH to give colorless prisms, mp 172–174°. The spectral data of this compound were superimposable with that of an authentic sample.[3c]

3-Hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (2). A mixture of 200 mg of 3-benzyloxy-*N*-cyclopropylmethyl-9-azamorphinan (**11**) hydrochloride, 10 ml of EtOH, and 10 ml of concentrated HCl was heated under reflux for 2 hr. The aqueous layer, obtained by removal of EtOH, was basified with aqueous NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (K_2CO_3), and evaporated to give a pale yellow oil, which was crystallized from EtOH to give 110 ml (78.6%) of **2** as colorless prisms, mp 172–174° (from EtOH). This was identical with an authentic sample[3c] by comparison of spectroscopic data and mixture melting point test.

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Synthesis of 6-(α-Hydroxy-β-*N*,*N*-dialkylaminoethyl)phenanthridines as Potential Antimalarials†

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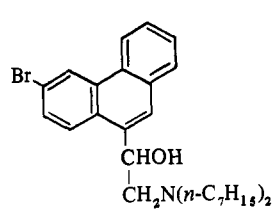
The objective of this work has been the synthesis of 6-(α-hydroxy-β-*N*,*N*-dialkylaminoethyl)phenanthridines (**2** and **3**) and water-soluble salts of these compounds for antimalarial testing. These compounds were chosen for synthesis and testing because of their similarity to the 9-phenanthrenemethanols, one of which (**1**) has been found to be curative for chicks with *Plasmodium gallinaceum* and not be phototoxic.[3,4]



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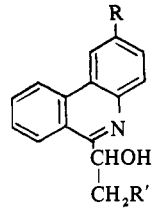
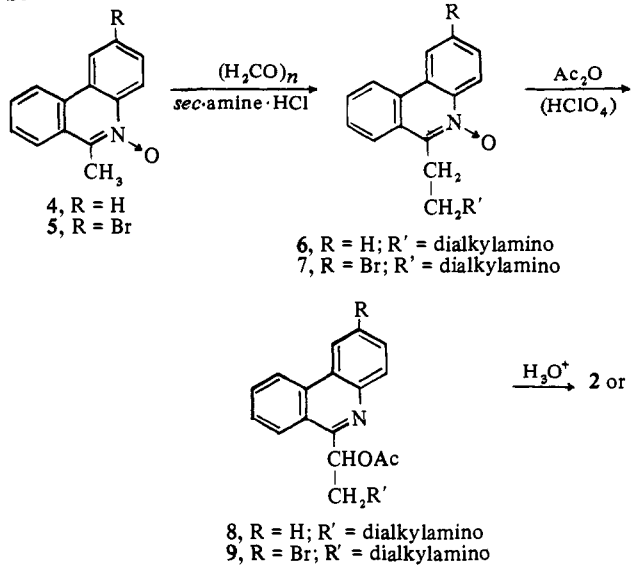


2, R = H; R' = dialkylamino
3, R = Br; R' = dialkylamino

Scheme I outlines the principal method which has been studied. Mannich bases (**6** and **7**) were made in 51–96% yields (Table I) from 6-methylphenanthridine 5-oxides (**4** and **5**) in the first successful application of the Mannich reaction (in experiments modeled after a Mannich reaction of 6-methylphenanthridine[5]) to the side chain of azine *N*-oxides. The Mannich base *N*-oxides when treated with Ac_2O and $HClO_4$ yielded acetates **8** and **9** in about 40% yields (Table II) which were hydrolyzed to 6-(α-hydroxy-β-*N*,*N*-dialkylaminoethyl)phenanthridines (**2** and **3**) (Table III).

Scheme I



4, R = H
5, R = Br

6, R = H; R' = dialkylamino
7, R = Br; R' = dialkylamino

8, R = H; R' = dialkylamino
9, R = Br; R' = dialkylamino

Of the Mannich base *N*-oxides (**6** and **7**) which were allowed to react with Ac_2O[6] alone, only 6-(β-*N*-morpholinoethyl)-phenanthridine 5-oxide (**6c**) yielded an acetate which could be purified. However, by reacting 1 mol of $HClO_4$ and 1 mol of Mannich base *N*-oxide with Ac_2O the hydrogen perchlorates of the acetates could be precipitated and in some cases purified (Table II). In comparison with the foregoing method, the addition of $HClO_4$ after the Ac_2O rearrangement reaction gave an inferior product (**8a**·$HClO_4$).

The acetates and the corresponding alcohols were readily characterized by the nmr absorptions (two doublets or an irregular triplet) of their benzylic hydrogens at τ 3.0–3.25 and 4.2–4.6, respectively.

Infrared and nmr spectral analyses indicated that acetate **8e** was produced but we were unable to purify **8e** or its hydrolysis product, alcohol **2e**.

When the acetates were hydrolyzed (Table III) by using refluxing concentrated HCl, the reaction mixtures showed more evidence of decomposition (darkening) than by using 3 *N* HCl at room temperature. With the more vigorous conditions hydramine cleavage may have occurred. The latter phenomenon is believed to have occurred during the melting point determinations of **2b**·2HCl and **3a**·HCl (Table IV)

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