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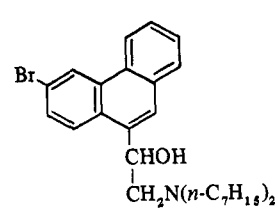
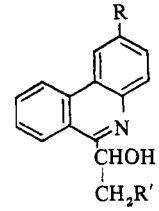
The objective of this work has been the synthesis of 6-(α-hydroxy-β-*N*,*N*-dialkylaminoethyl)phenanthridines (**2** and **3**) and water-soluble salts of these compounds for antimalarial testing. These compounds were chosen for synthesis and testing because of their similarity to the 9-phenanthrenemethanols,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



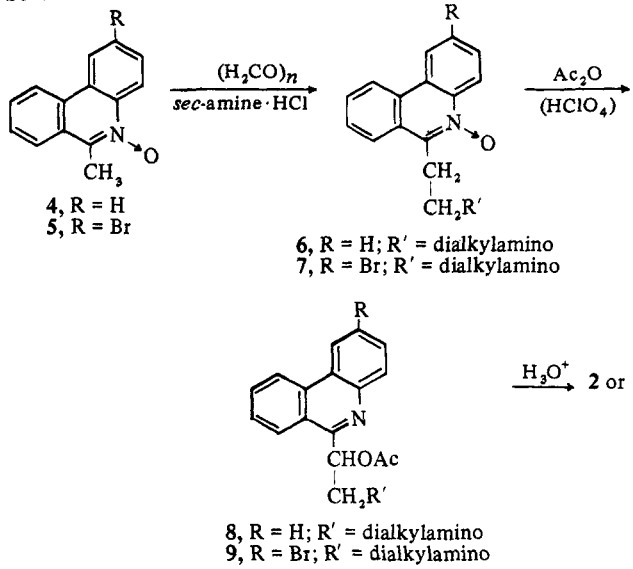
1



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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Table I. Mannich Base *N*-Oxides from Scheme I

Mannich base *N*-oxide	R	R′	Reflux time, hr	% yield	Mp, °C	Recrystn solvent	Formula	Analyses
6a·HCl	H	$N(Me)_2$	8	95	189 dec	EtOH	$C_{17}H_{18}N_2O\cdot HCl$	C, H, N, O
6a·0.5H_2O	H	$N(Me)_2$			77–77.5[a]	Petroleum ether[g]	$C_{17}H_{18}N_2O\cdot 0.5H_2O$	C, H, N, O
6b·HCl[b]	H	$N(n\text{-}Bu)_2$	12	73	294–297 dec	Me_2CO	$C_{23}H_{30}N_2O\cdot HCl$	C, H, Cl, N
6b·2HCl	H	$N(n\text{-}Bu)_2$	12	73	250–253 dec	EtOH	$C_{23}H_{30}N_2O\cdot 2HCl$	C, H, Cl, N
6b	H	$N(n\text{-}Bu)_2$			58–59[c]	Hexane		
6c·HCl	H	*N*-Morpholino	8	96	214–215 dec	80% EtOH	$C_{19}H_{20}N_2O_2\cdot HCl$	C, H, Cl, N, O
6c·H_2O	H	*N*-Morpholino			82–83	Petroleum ether[g]	$C_{19}H_{20}N_2O_2\cdot H_2O$	C, H, N, O
6d·HCl·H_2O	H	*N*-Piperidino	8	77	205 dec	EtOH	$C_{20}H_{22}N_2O\cdot HCl\cdot H_2O$	C, H, Cl, N
6d·2H_2O	H	*N*-Piperidino			76–78[d]	Petroleum ether[g]		
6e·HCl[e,f]	H	$N(n\text{-}C_7H_{15})_2$	16		195–198 dec	Me_2CO	$C_{29}H_{42}N_2O\cdot HCl$	C, H, Cl, N
7a·HCl	Br	$N(Me)_2$	2	73	216–217 dec	EtOH	$C_{17}H_{17}BrN_2O\cdot HCl$	C, H, Br, Cl, N
7a	Br	$N(Me)_2$			139–140	Heptane–C_6H_6		
7b	Br	$N(n\text{-}C_4H_9)_2$		63	119–120	Hexane	$C_{23}H_{29}BrN_2O$	C, H, Br, N
7c·HCl	Br	*N*-Morpholino	16	51	222–223 dec	EtOH		
7c	Br	*N*-Morpholino			143–144	Heptane–C_6H_6	$C_{19}H_{19}BrN_2O_2$	C, H, N

[a]Picrate from EtOH, mp 165–166°. *Anal.* ($C_{17}H_{18}N_2O\cdot C_6H_3N_3O_7$) C, H, N. [b]From **6b** and 11.7% w/v HCl. [c]Picrate from EtOH, mp 130–131°. *Anal.* ($C_{23}H_{30}N_2O\cdot C_6H_3N_3O_7$) N. [d]Picrate from EtOH, mp 159–160°. *Anal.* ($C_{20}H_{22}N_2O\cdot C_6H_3N_3O_7$) C, H, N. [e]From adding dry HCl to **6e** in absolute EtOH. [f]Picrate from EtOH, mp 81–83°. *Anal.* ($C_{29}H_{42}N_2O\cdot C_6H_3N_3O_7$) N. [g]Bp 60–80°.

Table II. Preparation of Acetates

Acetate	Method	% yield	Mp, °C	Recrystn solvent	Formula	Analyses
8a·$HClO_4$	B	54	200–201 dec	MeCN	$C_{19}H_{20}N_2O_2\cdot HClO_4$	C, H, N
8a·HCl	C	32	189 dec[a]	EtOH–Me_2CO	$C_{19}H_{20}N_2O_2\cdot HCl$	Cl, N
8b·$HClO_4$	B	43	151–152	AcOH	$C_{25}H_{32}N_2O_2\cdot HClO_4$	C, H, N
8c[b]	A	36	115–116	80% Me_2CO	$C_{21}H_{22}N_2O_3$	C, H, N
8d	A	Not purified				
8e	A, B	Not purified				
9a·$HClO_4$	C	Not purified				
9b·$HClO_4$	B	Not purified				

[a]**8a**·PcOH, mp 158–159° dec. *Anal.* ($C_{19}H_{20}N_2O_2\cdot 2C_6H_3N_3O_7$) N. [b]**8b**·PcOH, from EtOH, mp 182–183°. *Anal.* ($C_{21}H_{22}N_2O_3\cdot C_6H_3N_3O_7$) C, H, N. [c]Purified by distillation.

Table III. Preparation of Alcohols from Acetates

Alcohol	Hydrolysis time, hr	% yield	Mp, °C	Recrystn solvent	Formula	Analyses
2a[a]	5[b]	87	124–125	Et_2O	$C_{17}H_{18}N_2O$	C, H, N
2b	93[c]	64	74–76	EtOH	$C_{23}H_{30}N_2O$	C, H, N
2c[d]	4[b]	76	114–115	Me_2CO	$C_{19}H_{20}N_2O_2$	C, H, N
2d·2HCl·H_2O	4[b]	37[e]	160–162	95% EtOH–Me_2CO	$C_{20}H_{22}N_2O\cdot 2HCl\cdot H_2O$	C, H, Cl, N
2f[f]	4[b]	90	115–118	EtOH	$C_{14}H_{11}NO$	C, H, N
3a	96[c]	40[g]	127–128	MeCN	$C_{17}H_{17}BrN_2O$	C, H, Br, N
3b	48[c]	40[h]	65–66	Heptane	$C_{23}H_{29}BrN_2O$	C, H, Br, N

[a]**2a**·PcOH from Me_2CO, mp 165° dec. *Anal.* ($C_{17}H_{18}N_2O\cdot 2C_6H_3N_3O_7$) N. [b]12 *N* HCl, reflux. [c]3 *N* HCl, room temperature. [d]**2c**·PcOH from EtOH, mp 190–191° dec. *Anal.* ($C_{19}H_{20}N_2O_2\cdot C_6H_3N_3O_7$) N. [e]Based on **6d**. [f]From 6-acetoxymethylphenanthridine 5-oxide: C. W. Muth, J. C. Patton, B. Bhattacharya, D. L. Giberson, and C. A. Ferguson, *J. Heterocycl. Chem.*, in press. [g]Based on **7a**. [h]Based on **7b**.

because these compounds melted and resolidified before decomposition. This behavior parallels that reported by Lutz, *et al.*,[7] for similar compounds which were shown to have undergone hydramine cleavage as they were heated.

None of the phenanthridinemethanol hydrochlorides of Table IV, **2a**, nor any of the intermediates for these compounds have shown any significant antimalarial activity in mice (infected with *Plasmodium berghei*) or chicks (infected with *Plasmodium gallinaceum*).‡

Experimental Section

All melting points were done in a Mel-Temp apparatus and are uncorrected. The infrared spectra (ir) were recorded by using either a Beckman IR-8 or Perkin-Elmer 137 spectrometer. Nuclear magnetic resonance spectra (nmr) were recorded using either a Varian HA-60 nmr or a Varian T-60 nmr spectrometer. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The analyses for all new compounds are within 0.4% of the calculated values and the elements analyzed for are indicated. The analytical results are on file with the editor of this journal.

2-Bromo-6-methylphenanthridine 5-Oxide (5). 2-Bromo-6-methylphenanthridine[8] was treated with *m*-chloroperoxybenzoic acid[9] with the modification of extracting the reaction mixture with 5% NaOH before column chromatography. The product (**5**) after recrystallization from EtOH melted at 194–197° dec and the yield was 94%. The analytical sample, recrystallized from EtOH, melted at 197–198° dec. *Anal.* ($C_{14}H_{10}BrNO$) C, H, N.

Mannich Base *N*-Oxides and/or Hydrochlorides (6a–e, 7a–c). A mixture of 0.046 mol of *N*-oxide (**4**[10] or **5**), 0.05 mol of formaldehyde (as paraformaldehyde), and 0.051 mol of *sec*-amine·HCl was dissolved in EtOH (125 ml of 95% EtOH for **4** and 535 ml of absolute EtOH for **5**) and heated under reflux for 4 hr when an additional 0.033 mol of formaldehyde was added and refluxing was continued until the total reflux time indicated in Table I had elapsed. From subsequent experiments it was learned that all of the paraformaldehyde could be added initially without any significant change in yields. In some cases when the product precipitated during the reaction or after the reaction mixture cooled, the product was recrystallized from the solvent indicated in Table I. If the product did not precipitate, the solvent was distilled and the residue was dissolved in 10% HCl and filtered (charcoal). The filtrate, on concentration *in vacuo*, yielded a residue which was crystallized from EtOH.

The Mannich base *N*-oxides were obtained from their hydrochlorides by treatment with 10% NaOH. The solvents used for re-

‡All test results were obtained from the U. S. Army Walter Reed Institute of Research, Washington, D. C.

Table IV. Alcohol Hydrochlorides

Alcohol·HCl	Method[a]	Mp, °C	Formula	Analyses
2b·2HCl	A	93–100, resolidification, 115–165 dec	$C_{23}H_{30}N_2O \cdot 2HCl$	C, H, Cl, N, O
2c·2HCl·H_2O	B	165–166[b]	$C_{19}H_{20}N_2O_2 \cdot 2HCl \cdot H_2O$	Cl
2d·2HCl·H_2O	B	160–162[c]	*d*	
3a·HCl	A	124–130, resolidification, melts again 140–150 dec	$C_{17}H_{17}BrN_2O \cdot HCl$	Cl, N
3b·2HCl	C	142 dec	$C_{23}H_{29}BrNO \cdot 2HCl$	C, H, Cl

[a]Method A, addition of dry HCl to ethereal solution of alcohol; method B, addition of dry HCl to EtOH containing alcohol; method C, addition of ethanolic HCl to **3b** in ethanol followed by cooling to 0° and dilution with ether. [b]95% EtOH. [c]95% EtOH–Me_2CO. [d]See Table III.

crystallization and melting points of the Mannich base *N*-oxides are listed in Table I.

Acetates from Mannich Base *N*-Oxides and Acetic Anhydride. Method A. Acetic anhydride (306 g) was stirred with 37.0 g (0.113 mol) of 6-(β-*N*-morpholinoethyl)phenanthridine 5-oxide monohydrate (**6c**·H_2O) for 1 day. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Water was added to the residue and the mixture was made basic by adding $NaHCO_3$ solution. The mixture was extracted with ether and the ethereal solution was washed with saturated brine solution and concentrated to yield a dark red viscous oil. This was purified by columnar chromatography using neutral alumina with 5:1 EtOAc–C_6H_6 as the developer. The eluent was concentrated to a residue which was triturated with acetone to yield a solid which was recrystallized from 80% acetone to give 14 g (36%) of **8c** as colorless needles, mp 115–116°.

Method B. $HClO_4$ (70%, 2.15 g, 0.0150 mol) was added dropwise to 40 ml of Ac_2O at such a rate that the temperature did not rise above 25°. To this solution was added 5.05 g (0.0144 mol) of 6-(β-*N*,*N*-di-*n*-butylaminoethyl)phenanthridine 5-oxide (**6b**) with stirring at 23–25°. After 6 hr of stirring at 23–25°, 0.35 g of yellow solid, mp 213–215°, was collected by filtration and the reddish brown filtrate was diluted with a large volume of ether to yield an ether-insoluble brown oil. The ether was decanted and the oil was triturated with a small amount of AcOH to yield 3.05 g (43%) of **8b**·$HClO_4$, mp 151–153°. The analytical sample was recrystallized from AcOH as fine yellow crystals, mp 151–152°.

8a·$HClO_4$ precipitated from its reaction mixture without the addition of ether.

Method C. This was like method B except that MeCN was added to the reaction mixture to cause dissolution of the Mannich base *N*-oxide hydrogen perchlorate or hydrochloride.

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Communications to the Editor

Metabolism of Acetylmethadol. A Sensitive Assay for Noracetylmethadol and the Identification of a New Active Metabolite

Sir:

α-*l*-Acetylmethadol (**1**) is an orally effective analgesic in both laboratory animals and in man. Early pharmacology and metabolism studies led to the conclusion that **1** exerted its activity, at least in part, through an active metabolite (*cf.* Way and Adler[1] for a comprehensive review of the literature up to 1962). Metabolism studies on α-*dl*-acetylmethadol reported in 1965[2] strongly suggested that the active metabolite was noracetylmethadol (**2**). Noracetylmethadol had been synthesized in 1959 by Pohland, *et al.*,[3] and shown to be an effective analgesic in animals and man.[4]

The current interest in the use of α-*l*-acetylmethadol as an alternative to methadone in the maintenance of heroin addicts has prompted us to reinvestigate the metabolism of this drug. In this communication we report a sensitive method for the assay of the active metabolite, noracetylmethadol, in body fluids. We also wish to report the identification of a second active metabolite of acetylmethadol in the rat.

Noracetylmethadol Assay. The method is similar to that used by Änggård, *et al.*, in 1970[5] for the assay of amphetamine. It is based on formation of the trichloroacetamide derivative which is suitable for gas–liquid chromatography with the sensitive electron-capture detector.

In an initial experiment rats were dosed with α-*dl*-acetylmethadol (20 mg/kg ip). The animals were sacrified at intervals, blood was collected, and the liver, lung, and brain were removed. Plasma samples (2–3 ml) were made alkaline to pH 9.5 with 1 *N* NaOH and were extracted twice with 7 ml of butyl chloride (C_4H_9Cl). The C_4H_9Cl extracts were evaporated to dryness *in vacuo*. The residue was dissolved in 0.5 ml of dry toluene in a stoppered centrifuge tube, and 50 μl of 1% trichloroacetyl chloride in dry toluene was added. The reaction mixture was heated at 70–80° for 15 min and then evaporated to dryness *in vacuo*. The residue was taken up in hexane and 1–2 μl was injected onto the gas chromatograph (gc). Analyses were accomplished with a Hewlett-Pac-