coupling constants observed in DMSO for the free bases and their protonated forms. Evidently, on protonation, the bulk of the solvated quaternary nitrogen in \( \text{I} \cdot \text{HCl} \) is significantly increased by H bonding with DMSO. This would enhance the population of IA at the expense of IB and IC. Similarly, protonation of II should increase the population of IIA with a concomitant decrease in IIB, due to the increased steric requirements of the solvated ammonium group.

**Biological Data.** The \( \text{dl-erythro} \) and \( \text{dl-threo} \) isomers of \( \alpha-(2\text{-piperidyl})\cdot3,6\text{-bis(trifluoromethyl)}\cdot9\text{-phenanthrenemethanol} \) were tested\(^2\) for antimalarial activity as their HCl and TSOH salts and as their oxazolopyridine derivatives against *Plasmodium berghei* in mice and *P. gallinaceum* in chicks by Dr. Leo Rane at the University of Miami. The test results, furnished to us through the Walter Reed Army Institute of Research, show these materials to be highly active against *P. berghei*, giving five cures out of five infected mice at dosages of 40 mg/kg for the three epimers and five cures at 80 mg/kg for the erythro compds.\(^6\) No toxic deaths were reported up to dosages of 640 mg/kg. Against *P. gallinaceum*, the minimum dosage showing activity was 20 and 160 mg/kg for the three and erythro compds, respectively.

To attempt a general correlation of epimer conformation with antimalarial activity on the above limited data is premature.

**Experimental Section**

\( \text{dl-erythro-}\alpha-(2\text{-piperidyl})\cdot3,6\text{-bis(trifluoromethyl)}\cdot9\text{-phenanthrenemethanol Hydrochloride (I \cdot HCl).} \) \( \text{H}_2 \) was passed through a mixt of 115 g (0.27 mole) of 2-pyridyl 3,6-bis(trifluoromethyl)-9-phenanthryl ketone, 5.0 g of \( \text{PtO}_2 \) (Engelhard 85%), 4.21 of \( \text{MeOH} \), and 40 ml of conc HCl for 16 hr. Darco was added and, after filtration, the filtrate was evaporated to 10% of the original vol, pptg a mass of white crystals. The solids were dissolved in MeOH (Darco) and again concd to 10% the original vol to give 96.0 g (82.3% of \( \text{I} \cdot \text{HCl} \), mp 331-332° dec. Anal. (\( C_{21}H_{16}NO_3F_6 \) \( \cdot \) HCl) C, H, N, F.

\( \text{dl-threo-}\alpha-(2\text{-piperidyl})\cdot3,6\text{-bis(trifluoromethyl)}\cdot9\text{-phenanthrenemethanol Hydrochloride (II \cdot HCl).} \) The mother liquors from the above recryst were concd to dryness, treated with dil \( \text{K}_2\text{CO}_3 \) soln, and dried. The mixt of I and II (15.0 g, 35 mmoles) in 200 ml of MeOH was treated with 4.9 g (25 mmoles) of \( \text{TsOH} \cdot \text{H}_2\text{O} \), refluxed for 5 min, and cooled to ppt \( \text{II} \cdot \text{TsOH}. \) Recryst (2x, MeOH, Darco) gave an analytical material, mp 269-270°. Anal. (\( C_{21}H_{14}F_6NO_3 \)) C, H, N, F.

II \( \cdot \text{TsOH} \) (50 g, 0.1 mole) was neutralized by stirring overnight with dil aq \( \text{NaOH} \) soln. II was dissolved in anhyd \( \text{Et}_2\text{O} \) and satd with HCl gas to ppt II \( \cdot \text{HCl}. \) Refluxing with \( \text{CCl}_4 \) removed a yellow impurity to leave II \( \cdot \text{HCl} \) as a white powder, mp 284-285° (44.2 g, 95%). Anal. (\( C_{21}H_{16}NO_3F_6 \) \( \cdot \) HCl) C, H, N.

I \( \cdot \{3,6\text{-bis(trifluoromethyl)}\cdot9\text{-phenanthryl}\} \) hexahydro-3\text{-H-oxazolo}[3,4-\text{e}]pyridine. III. A mixt of 4.9 g (11 mmoles) of I, 2 ml of (\( \text{CH}_3\text{O}_2 \) soln, and 50 ml of MeOH was refluxed 8 hr. Addil (\( \text{CH}_3\text{O}_2 \) soln (2 ml) was added, the reflux was contd overnight. The mixt was cooled and filtered, and the product was recrystd (EtOH, Darco) to give 3.0 g (63%) of III as white flakes, mp 167-168°. Anal. (\( C_{21}H_{16}NO_3 \)) C, H, N.

IV. A similar reaction of II gave 4.5 g of crude product. The solid was dissolved in \( \text{CHCl}_3 \), poured onto a silica gel H column (75 g), and eluted with \( \text{CHCl}_3 \). Recryst (MeOH-H\( _2\text{O} \)) gave 4.0 g (84%) of IV as a white powder, mp 181-182°. Anal. (\( C_{21}H_{14}NO_3F_6 \)) C, H, N.

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**References**


**N-Demethylation of Morpine and Structurally Related Compounds with Chloroformate Esters**

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Hundreds of modifications of morphine and structurally related compounds have been performed and the compounds tested in an effort to analyze the relationship between structure and analgetic activity.\(^3,4\) The most common of these modifications is replacement of the Me group attached to the basic N with some other substituent. Thus,\(^5\)

**Notes**

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\(^{\dagger}\) All melting points (uncorr) were taken on a Büchi apparatus. Instruments employed were: Beckman IR-9 infrared spectrophotometer and Beckman DK-2 uv spectrophotometer. Elemental anal. were correct (±0.3%) and were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

\(^{\S}\) The synthesis and activity of \( \text{I} \cdot \text{HCl} \) has been previously reported by Nodiff, *et al.*\(^1\).
the secondary amine serves as an important intermediate in the synthesis of such compounds. Although there are several methods reported\(^5\) for the demethylation of tertiary amines, they suffer from the disadvantage of the toxicity of reagents employed and/or the low yields of demethylated product.

One approach to this problem which seemed worthwhile exploring involved demethylation of aminetics with a chloroformate ester\(^8\) followed by hydrolysis of the resulting carbamate to the secondary amine as outlined below.

\[
R'R'\text{NMe} \quad \text{CICO}_R \quad R'R''\text{CO}R' \quad \text{HOH} \quad R'R''\text{NH}
\]

Cleavage of tertiary amines with chloroformate esters was first reported in 1911.\(^5\) Gadamer and Knoch\(^9\) studied the effect of ethyl chloroformate on a variety of cyclic tertiary amines and observed that bulbcapnine, corydine, and laudanosine were converted to the corresponding ethyl carbamates, whereas compounds such as morphine, codeine, heroin, and tropine were not cleaved. Several examples of this reaction have been published since,\(^10\)\(^-\)\(^13\) and in this regard, phenyl chloroformate was found to be superior to both benzyl and ethyl chloroformate in the cleavage of tertiary amines.\(^14\)

We wish to describe the utilization of this reaction as a means of conveniently demethylating, in high yield, structures related to morphine.

Treatment of morphine (1) with phenyl chloroformate in the presence of KHC\(_O_3\) in boiling CHCl\(_3\) and subsequent treatment of the product with a mild base afforded, after purification, a nonbasic crystalline material which was assigned structure 2, based on its spectral properties. This assignment was confirmed further by LAH reduction of 2 to morphine and by its hydrolytic conversion to normorphine (3) with KOH. It is noteworthy that the reaction of morphine with phenyl chloroformate was unsuccessful in the absence of base, possibly because esterification of the 3- or 6-OH generates HCl which may protonate the basic N and hence diminish its reactivity.

Cocodeine (4) was demethylated with ethyl chloroformate in a two-phase system containing aq KOH and CHCl\(_3\). The spectral characteristics of the neutral intermediate appear to be in harmony with 5. The ethyl carbonate group of 5 could be hydrolyzed selectively to 6 which then was cleaved to norcodeine (7) under more vigorous conditions.

Reaction of 3-methoxy-N-methylmorphinan (8) with phenyl chloroformate at room temp afforded carbamate 9. The carbamate was obtained in crystalline form by selectively hydrolyzing the phenyl chloroformate contaminant with aq K\(_2\)CO\(_3\). Structure 9 was corroborated by its recrystallization to 8 with LAH. Hydrolysis of 9 with KOH gave the desired secondary amine (10). Demethylation of 8 also was carried out with ethyl chloroformate. Hydrolysis of this product (11) with HBrHOAc afforded 3-hydroxy-morphinan (12).

It is noteworthy that the present procedure also can be employed as a convenient and relatively inexpensive method for introducing radioactivity into a N-Me group. Thus, \([\text{H}]\text{LAH}\) reduction of the carbamate intermediate obtained from the demethylation step would afford a \([\text{H}]\)-labeled Me group.\(^\ddagger\) A \([\text{C}]\)-label may be incorporated by demethylation with \([\text{C}]\text{ClOOC}\) followed by reduction.\(^15\)

**Experimental Section**

\(^\ddagger\) Melting points were determd in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. The \([\text{C}]\)-enriched laudanosine was obtained with a Perkin-Elmer 237B spectrophotometer in CHCl\(_3\) solution or KBr disk. The nmr spectra were run with a Varian A-60D spectrometer (CDCl\(_3\), TMS). Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D mass spectrometer.
cooled, treated with EtOAc (10 ml), and refluxed for 30 min. After the addition of H₂O and 1 N NaOH alternately, the mixture was filtered and concentrated in vacuo to remove THF. The residue was acidified with 1 N HCl and extracted with Et₂O. The aq acid solution was basified and treated with Et₂O, and the dried Et₂O extract was treated with ethanolic HCl to afford 0.51 g (yield, 78%) of 4(3H)-pteridinone. The residue was suspended in 1 N HCl (50 ml) and treated with Et₂O. Removal of Et₂O afforded an oil (2.5 g) which was dissolved in a mixture of glacial AcOH (10 ml) and 48% HBr (10 ml). After refluxing for 2 hr, the reaction mixture was poured into ice water (300 ml), extracted with Et₂O, and the dried Et₂O extract was treated with ethanolic HCl to afford an oil (3.2 g) whose infrared spectrum included characteristic absorptions at 1690 cm⁻¹ (C=O of N-CO₂Et) and 1740 cm⁻¹ (C=O of O₂-CO₂Et). This was treated with a mixture of MeOH (90 ml) and 10% aq KOH (10 ml) for 2 hr, cooled in vacuo to remove MeOH, and treated with 1 N HCl. Removal of Et₂O afforded 2.5 g of an oily uncrystallizable material. A solution of 2.0 g of the oil in 95% EtOH (80 ml) was treated with ethyl chloroformate (5 ml) and 15% aq KOH (20 ml) and refluxed under N₂ for 24 hr. The solution was dillied with H₂O (20 ml) and the EtOH was removed under reduced pressure. The aq acid solution was basified and treated with Et₂O. The Et₂O was removed under reduced pressure to give 0.7 g (yield, 43%) of 7: mp 183-185° (reported mp 185°); 7·HCl, mp 309-311° (dec) (reported mp 309° dec).¹⁹

Narcodine (7). A solution of 3.8 g (0.012 mole) of codeine (4) in CHCl₃ (50 ml) was treated with ethyl chloroformate (5 ml) and 15% aq KOH (20 ml) and refluxed for 2 hr, cooled in vacuo to remove MeOH, and extracted with Et₂O. Removal of Et₂O afforded an oil (2.5 g) which was dissolved in a mixture of glacial AcOH (10 ml) and 48% HBr (10 ml). After refluxing for 2 hr, the reaction mixture was poured into ice water (300 ml), extracted with Et₂O, and basified to afford 1.1 g (31%) of 12, mp 260-262° (reported mp 309° dec). I²

**References**


**Synthesis of 4(3H)-Pteridinones**

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The sedative-hypnotic activity of some 4(3H)-quinazolones prompted us to synthesize a number of the isosteric 4(3H)-pteridinones and to investigate their hypnotic and sedative activities. The existing literature gives only a few examples of preparation of 3-alkyl or 3-aryl substituted 4(3H)-pteridinones and no data at all on their pharmacology. The synthesis of the title compounds involved the intermediate 3-aminopyrazinecarboxamides, described in Table I, which were obtained, in good yield, from 3-aminopyrazinoic acid (I), via the mixed anhydride (II) and reaction of the latter with appropriate amines (R₂NH₂).

The 3-aminopyrazinecarboxamides (III) could be cyclized to the desired 4(3H)-pteridinones (IV) by condensation with an ortho ester R₂(COC₆H₄)₃ in Ac₂O solution. The amides (III), in contrast to the 4(3H)-pteridinones (IV), reveal a characteristic fluorescence under uv light, which is helpful for their identification by chromatography.

In preliminary CNS screening the majority of the compounds were found to be without hypnotic or sedative activity. Compounds 23, 30, and 31 showed a slight sedative activity at 300 mg/kg (mouse) and with 30, 31, and 38 some analgesic activity was observed at 150-250 mg/kg (mouse; phenylbenzoquinone test) and 150-500 mg/kg (mouse; hot-plate test), but all the compounds showed too low a therapeutic index, the LD₅₀ (mg/kg; mouse; Litchfield and Wilcoxon) being 1250 (1042-1500), 575 (483-684), 1220 (1070-1391), and 1750 (1400-2187) for 23, 30, 31, and 38, respectively.

**Experimental Section**

The melting points of all but four compounds 21-47 were taken with a Mettler FP-1 apparatus, all the others with a Büchi apparatus, and are uncorrected. UV and ir spectra were measured for some typical compounds and were as expected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

3-Aminopyrazinecarboxamides (1-20). A mixture of 5.56 g (0.04 mole) of 3-aminopyrazinoic acid, 7.4 g (0.04 mole) of Bu₂N, and 50 ml of dioxane was stirred at room temperature until a clear solution resulted. This solution was cooled to 7-8° and 4 ml (0.04 mole) of EtOCOCI was added dropwise, keeping the temperature at 11-12°. After cooling again to 7-8°, 0.04 mole of the appropriate amine hydrochloride was added, and the reaction was allowed to proceed at room temperature for 3 hr. The solvent was removed on a rotary evaporator under reduced pressure and the residue was triturated for 30 min with 50 ml of H₂O, filtered, dried, and recrystallized. Recrystallized solvents and physical data are given in Table I.

4(3H)-Pteridinones (21-47). A mixture of 0.01 mole of I₃, 25 ml of ortho ester, and 20-30 ml of Ac₂O was refluxed for 5 hr and then concentrated in vacuo. The residue was triturated with 20 ml of EtOH, and, after evaporation of the solvent, washed with Et₂O, filtered, dried, and recrystallized. Recrystallized solvents and physical data are given in Table II. For 23 the reaction was carried out in anhyd HCO₂H, and for 24 in 1:1 anhyd HCO₂H-Ac₂O.