

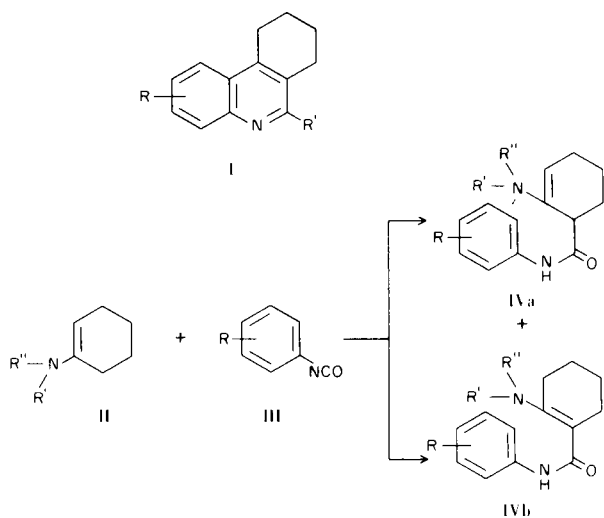
Heterocyclic Compounds IV. Synthesis of Some Mono- and Diazaphenanthrene Derivatives (1)

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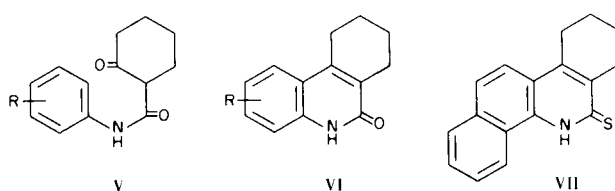
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This paper describes the preparation of compounds of the type I which were required as intermediates in connection with a project on the synthesis of potential antimalarials. Following Ried and Kaeppler's (2) procedure an enamine from cyclohexanone (II) was allowed to react with arylisocyanates (III) to give enamides (IV) in almost quantitative yield (see Table I). The nmr spectrum of IV showed it to be a mixture (3) of the isomers IVa and IVb.

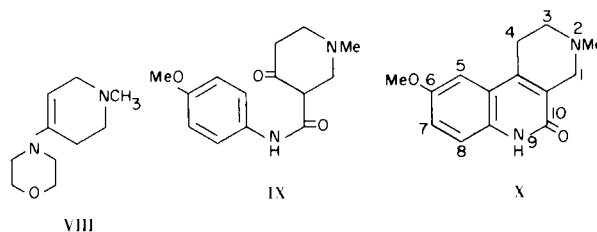


Treatment of IV with 70% sulfuric acid (2) at 0° led to the ketoamide (V) which could be cyclized to VI by further acid treatment (see Table II). One step conversion of IV to VI occurred if an acid solution of IV was allowed to stand at room temperature for about three days. Substitution of glacial acetic acid or trifluoroacetic acid for sulfuric acid gave a poorer yield.

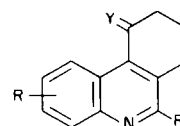
Arylthiocyanates also react the same way as arylisocyanates. The tetracyclic compound (VII) was obtained in good yield from morpholinocyclohexene and α -naphthylisothiocyanate.



To obtain a diazaphenanthrene derivative, the morpholine enamine of *N*-methyl-4-piperidone (VIII) was allowed to react with *p*-methoxyphenylisocyanate. The resulting ketoamide (IX) is sensitive to light and develops color on standing. Cyclization of IX to X was best accomplished by treatment with polyphosphoric acid.



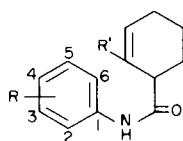
Attempts to oxidize VI were unsuccessful under a variety of conditions. Treatment of VI with phosphorus oxychloride (4) led to the chloro compound (XI) which could be oxidized to XII with *t*-butyl chromate but the yield was very poor.



- XI Y = H₂, R' = Cl
- XII Y = O, R' = Cl
- XIII Y = H₂, R' = H
- XIV Y = H₂, R' = Br
- XV Y = H₂, R' = CH₃

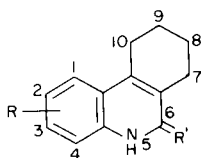
Reduction of compounds of type XI to XIII was easily achieved by treating them with hydrogen at 40 psi in

TABLE I



No.	R	R'	M.p., °C	Yield %	Molecular formula	C	Analytical Data				
							Calcd. H	N	C	Found H	N
1	4-Cl		137-138	76	C ₁₇ H ₂₁ ClN ₂ O ₂	63.65	6.55	8.78	63.95	6.27	8.78
2	4-Cl	OH	115-117	73	C ₁₃ H ₁₄ ClNO ₂	62.03	5.57	5.57	61.84	5.77	5.46
3	2-Cl		80	75	C ₁₇ H ₂₁ ClN ₂ O ₂	63.65	6.55	8.74	63.67	6.47	8.91
4	2,5-dichloro		105-106	80	C ₁₇ H ₂₀ Cl ₂ N ₂ O ₂	57.46	5.63	7.88	57.78	5.82	7.84
5	2,5-dichloro	OH	116-117	78	C ₁₃ H ₁₃ Cl ₂ NO ₂	54.54	4.54	4.89	54.88	4.56	4.90
6	4-OCH ₃		113-115	96	C ₁₈ H ₂₄ N ₂ O ₃	68.33	7.65	8.85	68.28	7.59	8.79
7	4-OCH ₃	OH	112	80	C ₁₄ H ₁₇ NO ₃	67.99	6.93	5.66	68.12	7.02	5.67

TABLE II



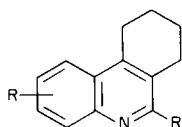
No.	R	R'	M.p., °C	Yield %	Molecular Formula	C	Analytical Data						
							Calcd. H	N	Cl/Br	C	Found H	N	Cl/Br
1	2-OCH ₃	O	260	90	C ₁₄ H ₁₅ NO ₂	73.34	6.59	6.11		73.40	6.74	6.28	
2	2-Br	O	329-330	68	C ₁₃ H ₁₂ BrNO	56.11	4.31	5.02		56.27	4.34	4.91	
3	4-OCH ₃	O	171-172	67	C ₁₄ H ₁₅ NO ₂	73.36	6.55	6.11		73.38	6.38	6.19	
4	3,4 benzo	O	340	93	C ₁₇ H ₁₅ NO	81.90	6.06	5.62		82.20	5.86	5.64	
5	3,4 benzo	S	180-182	90	C ₁₇ H ₁₅ NS	76.96	5.70	5.28		76.36	5.70	5.69	
6	2-Cl	O	325	78	C ₁₃ H ₁₂ ClNO	66.82	5.14	5.99	15.20	67.01	5.11	5.56	14.84

presence of 10% Pd/C catalyst and a small amount of sodium hydroxide.

When alkylation of XI with lithium dimethylcopper complex (6) was attempted, the 6-methyl derivatives (XV) was formed in extremely poor yield and could only be

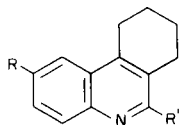
detected spectroscopically. In contrast, when the 6-bromo-compound (XIV), obtained by treating VI with phosphorus tribromide or phosphorus pentabromide, was allowed to react with lithium dimethylcopper, the 6-methyl compound (XV) was obtained in almost quantitative yield (9).

TABLE III



No.	R	R'	M.p., °C	Yield %	Molecular Formula	Analytical Data							
						Calcd. C	Calcd. H	Calcd. N	Cl/Br	Found C	Found H	Found N	Cl/Br
1	2-OCH ₃	Cl	150-152	75	C ₁₄ H ₁₄ ClNO	67.87	5.65	5.65	14.35	67.43	5.68	5.44	14.34
2	H	Cl	111-112	77	C ₁₃ H ₁₂ ClN	71.72	5.51	6.43	16.32	71.65	5.58	6.22	16.03
3	2-CH ₃	Cl	169	85	C ₁₄ H ₁₄ ClN	72.57	6.05	6.05	15.33	72.24	6.32	6.11	15.25
4	2-Cl	Cl	198-199	83	C ₁₃ H ₁₁ Cl ₂ N	61.90	4.37	5.55		62.15	4.51	5.56	
5	2-Br	Cl	201	88	C ₁₃ H ₁₁ BrClN	52.60	3.72	4.70		52.74	3.89	4.59	
6	2-CH ₃	N(CH ₃) ₂	61- 62	80	C ₁₆ H ₂₀ N ₂	79.95	8.39	11.66		79.67	8.24	11.72	
7	2-CH ₃	NHCH ₃	110	70	C ₁₅ H ₁₈ N ₂	79.60	8.02	12.38		79.45	7.9	12.46	
8	2-CH ₃	NHC ₂ H ₅	76- 78	68	C ₁₆ H ₂₀ N ₂	79.95	8.33	11.67		79.78	8.43	11.59	
9	2-CH ₃	H	131	70	C ₁₄ H ₁₅ N	85.23	7.66	7.10		85.27	7.58	7.31	

Recently Heindel and coworkers (7,8) have shown that reactive nuclear halogen in quinolines and pyridines can be replaced by dialkylamino or monoalkylamino functions by treating these compounds with suitably substituted formamides. We have found that secondary and tertiary (9) aminofunctions can be easily substituted for the C-6 halogen in our compounds. Both chlorine and bromine groups can be replaced with equal ease and the yields of the amino compounds are of the order of 60%. Thus, when tetrahydrophenanthridines (XI) were refluxed with *N,N*-dimethylformamide, methylformamide, or ethylformamide, the corresponding *N*-substituted phenanthridines (XVI-XVIII) were obtained.



XVI	R = CH ₃ , R' = N(CH ₃) ₂
XVII	R = CH ₃ , R' = NH CH ₃
XVIII	R = CH ₃ , R' = NH C ₂ H ₅

EXPERIMENTAL

Morpholinocyclohexene (II).

This compound was prepared by the method described by Hünig (10).

General methods for the syntheses of compounds of the type IV, V, VI and IX are given below:

Preparation of Enamides (IV).

Equimolar proportions of the appropriate isocyanate and morpholino-cyclohexene (II) were reacted in chloroform solution according to the method described by Ried and Kaeppler (2) and are recorded in Table I.

Preparation of Ketoamides (V).

The enamides (IV) were hydrolyzed using 70% sulfuric acid at 0° according to the method of Reid and Kaeppler (2).

Preparation of Phenanthridones (VI).

(a) The ketoamides (V) were cyclized to VI upon treating with concentrated sulfuric acid on a steam bath for 15-20 minutes by the method of Reid and Kaeppler (2).

(b) The enamides (IV) were dissolved in 70% sulfuric acid (10 ml. sulfuric acid/g.) and the solution kept at room temperature over a period of 72 hours. The reaction mixture in each case was decomposed with excess of ice when a white solid precipitated out. The product recovered after filtration was washed with ether and recrystallized from dimethylformamide to afford pure VI (Table II).

1-Methyl-4-oxo-3-(*p*-methoxyphenylcarboxamido)piperidine (IX).

A mixture of piperidone (8.8 g.), morpholine (11.3 g.) and *p*-toluene sulfonic acid (200 mg.) in benzene (500 ml.) was refluxed using a water separator. Benzene was removed after the total removal of water to afford the enamine in almost quantitative yield. This was used as such for the next operation.

The morpholine enamine of *N*-methylpiperidone on treatment with *p*-methoxy phenylisocyanate under the conditions described earlier afforded the enamide in almost quantitative yield. During crystallization with ether-methanol this adduct deposited yellow crystalline material, which on recrystallization from chloroform-hexane gave the title compound IX, m.p. 95-96°. The ir, nmr and mass spectra of this compound were consistent with its structure.

Anal. Calcd. for C₁₄H₁₈N₂O₃: C, 64.12; H, 6.87; N, 10.68. Found: C, 63.91; H, 6.96; N, 10.46.

2-Methyl-6-methoxy-10-oxo-1,2,3,4,9,10-hexahydro-2,9-diazaphenanthrene (X).

The ketone (IX, 1 g.) was added to PPA (10 g.) and the mixture heated on a steam bath for an hour. The resulting reddish-brown, viscous mass was poured into ice water when a clear solution was obtained which was basified (sodium hydroxide) and extracted thoroughly with chloroform. The organic layer was washed with water, dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue on standing produced a yellow solid which was recrystallized from chloroform, m.p. 210° dec.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60. Found: C, 68.50; H, 6.64.

6-Chlorotetrahydrophenanthridines (XI).

The tetrahydrophenanthridines (VI) and phosphorus oxychloride (1 g./5 ml.) were refluxed for ½ hour. The reaction mixture was cooled and then poured into an excess of cold water and stirred vigorously. The solid that separated was recrystallized from methanol or ethyl acetate. The chloro derivatives (XI) so obtained are listed in Table III.

2-Methoxy-6-chloro-10-oxo-7,8,9,10-tetrahydrophenanthridine (XII).

To a solution of 1 g. of 2-methoxy-6-chloro-7,8,9,10-tetrahydrophenanthridine (XI, R = 2-OCH₃, R' = Cl) in 3 ml. of glacial acetic acid and 1 ml. of acetic anhydride were added 10 ml. of a solution of *t*-butyl chromate in carbon tetrachloride with constant stirring. The contents were then heated overnight on a steam bath. After cooling the reaction mixture, a solution of 1 g. oxalic acid in 10 ml. water was added to it. The contents were then extracted with 3 x 100 ml. carbon tetrachloride. Successive washings of the organic layer with water, sodium bicarbonate solution and water followed by drying and concentration gave a yellowish gummy residue. Purification by column chromatography using neutral alumina as the adsorbent led to yellow crystals (2%) m.p. 155-156°. It showed carbonyl absorption at 5.9 μ . The nmr spectrum (deuteriochloroform) displayed singlet at τ 2.3 (1H), multiplet at τ 2.8, doublet at τ 6.12 (3H) and a multiplet at τ 7.2-8.2 (6H); mass spectrum, M⁺ at m/e 261.

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.24; H, 4.59; N, 5.75; Cl, 13.57. Found: C, 65.01; H, 4.71; N, 5.30; Cl, 14.12.

2-Methoxy-7,8,9,10-tetrahydrophenanthridine (XIII).

To a solution of 6-chloro-2-methoxy-7,8,9,10-tetrahydrophenanthridine (1 g.) in 100 ml. of ethanol were added 300 mg. of 10% palladium-charcoal and 6.2 ml. of 1N sodium hydroxide solution. The contents were shaken under hydrogen atmosphere (40 psi) over a period of 20 hours. The catalyst was removed by filtration and the alcohol removed under reduced pressure. The residue was dissolved in chloroform, washed with water and dried (magnesium sulfate). Removal of the solvent provided 750 mg. (87%) of the desired compound, m.p. 105-106° (benzene-ether); mass spectrum, M⁺ m/e 213.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.76; H, 6.95; N, 6.67.

6-Bromo-2-methyl-7,8,9,10-tetrahydrophenanthridine (XIV).

A mixture of 6-hydroxy-2-methyltetrahydrophenanthridine (3

g.) and phosphorus tribromide (30 ml.) was refluxed for 20 minutes. After cooling, the reaction mixture was poured into a large excess of cold water and the solid was recovered under suction. Recrystallization from methanol provided the title compound (50%), m.p. 172-173°. The nmr spectrum (chloroform) showed multiplets at τ 2.05-2.45 (3H), τ 6.95-7.15 (4H); singlet at τ 7.48 (3H) and multiplet at τ 8.05 (4H); mass spectrum, M⁺ m/e 275 and 277.

Anal. Calcd. for $C_{14}H_{14}BrN$: C, 60.86; H, 5.07; N, 5.07. Br, 28.98. Found: C, 60.56; H, 5.38; N, 5.21; Br, 28.71.

2,6-Dimethyl-7,8,9,10-tetrahydrophenanthridine (XV).

Lithium dimethylcopper complex was prepared according to the procedure in the literature (6). The 6-bromo compound XIV was treated with the complex at 0° for 6 hours. The usual work up (9) provided the title compound in almost quantitative yield, m.p. 85-86° (dichloromethane-hexane). The nmr spectrum showed multiplets at τ 1.9-2.5 (3H), τ 6.9 (4H), singlets at τ 7.4 (3H), τ 7.5 (3H) and a multiplet at τ 8.1 (4H); mass spectrum, M⁺ m/e 221.

Anal. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 84.98; H, 8.02; N, 6.71.

Preparation of 6-Aminotetrahydrophenanthridines (XVI)-(XVIII).

The 6-chlorotetrahydrophenanthridines (XI, 1 g.) were refluxed overnight with the appropriate formamides (15 ml.). Excess formamide in each case was removed under reduced pressure and the residue treated with saturated solution of sodium bicarbonate. The solid compound thus separated was dissolved in chloroform, washed with water and dried over magnesium sulfate. Removal of the solvent provided the amino compounds (Table III) which were purified through recrystallization.

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