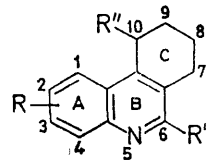
Synthesis and Reactions of 10-Bromo-7,8,9,10-tetrahydrophenanthridines

By **M. S. Manhas,* C. T. Chen, V. V. Rao, I. R. Trehan,** and **S. D. Sharma,** Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030, U.S.A.

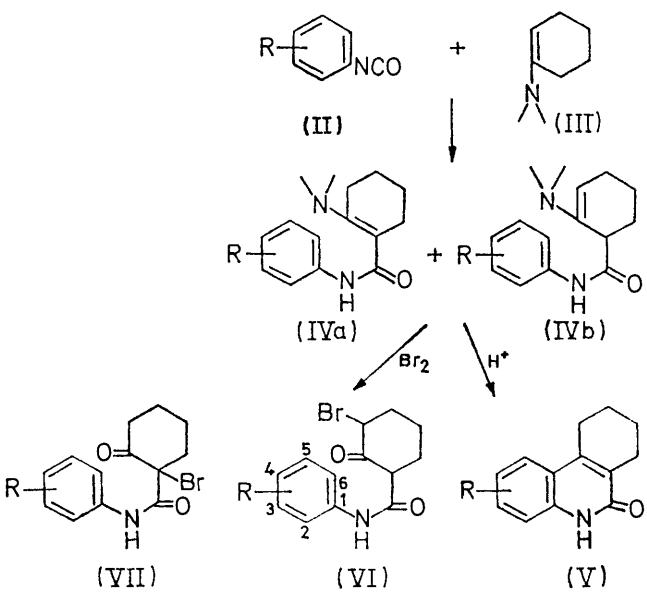
The synthesis of substituted 10-bromo-7,8,9,10-tetrahydrophenanthridines is discussed and their reactions are explored. A ready method for the dehydrohalogenation of these 10-bromophenanthridines is described.

In the course of a study on potential antimalarials it was found desirable to synthesize compounds of type (I)



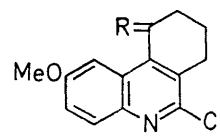
(I)

carrying such a functional group at C-10 as would permit the introduction of various substituents on ring C. In an earlier publication [1] we have reported the synthesis of various 7,8,9,10-tetrahydrophenanthridines (I; R″ = H) following the method of Ried and Kaeppler [2] which involves the formation of the enamide (IV) from an aryl isocyanate (II) and an enamine (III) from cyclohexanone and the subsequent cyclization of (IV) to a C-10 unsubstituted tetrahydrophenanthridinone (V).

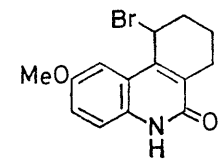


Attempts to functionalize C-10 in (V) or its derivatives were not very successful; for example, oxidation of (VIII) with t-butyl chromate [3] gave a poor yield of (IX); treatment with *N*-bromosuccinimide [4] did not brominate (VIII).

We have now developed a ready method for the synthesis of 10-bromo-7,8,9,10-tetrahydrophenanthridinones (X). Enamides (IV) formed in the reaction between (II) and (III) were treated without isolation



(VIII) R = H_2
(IX) R = O



(X)

with bromine at solid CO_2–acetone temperature; after hydrolysis of the reaction mixture the products that were obtained in 80—90% overall yield were found to be the α-bromo-ketones (VI).[5] The enamides (IV) in solution are known from their n.m.r. spectrum to be a mixture [1,6] of the isomers (IVa) and (IVb)—the vinyl proton signal in the region τ 4·96 corresponds in area to *ca.* one-half of a proton. The presence of a broad one proton signal at τ 5·32 in the n.m.r. spectrum of the bromo-ketone indicated the structure (VI; R = 2-OMe) and excluded the isomeric structure (VII).

The bromo-ketone (VI) was cyclized to (X) in excellent yield with warm polyphosphoric acid. The bromine in (X) was expected to be active but Kornblum oxidation [7,8] of (X) was unsuccessful even at elevated temperatures.

Several analogues of (X) (Table 2) were synthesized following the same method as for (X). When (XI) was heated under reflux with phosphoryl chloride, the dichloro-compound (XII) was obtained. Obviously, the bromine in (XI) was reactive enough for displacement under the reaction conditions. Treatment of (XII) with ethanolic potassium hydroxide led to the ether (XIII) as the sole product in low yield. No reaction was observed when (XII) was refluxed with 10% aqueous potassium hydroxide solution or pyridine and the starting material was recovered in each case.

Both dehydrohalogenation and substitution occurred when (XIV) was heated for 6 h with methanolic potassium acetate; the unsaturated compound (XVI) and the acetoxy-derivative (XV) were formed in the ratio of 2 : 3 as shown by the n.m.r. spectrum of the total products.

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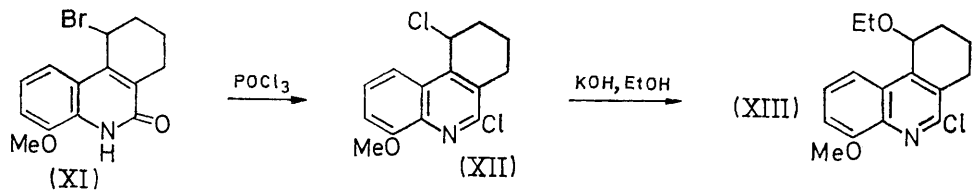
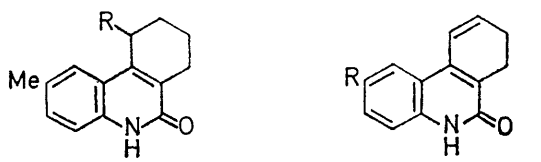
[2] W. Ried and W. Kaeppler, *Annalen*, 1964, **673**, 132; 1965, **688**, 177.
[3] R. V. Oppenauer and H. Oberrauch, *Anales Asoc. quim. argentina*, 1949, **37**, 246 (*Chem. Abs.*, 1950, **44**, 3871).
[4] C. Djerassi, *Chem. Rev.*, 1948, **43**, 271.
[5] Cp. M. E. Kuehne, *J. Amer. Chem. Soc.*, 1961, **83**, 1492.
[6] G. A. Berchtold, *J. Org. Chem.*, 1961, **26**, 3043.
[7] N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, 1959, **81**, 4113.
[8] A. P. Johnson and A. Pelter, *J. Chem. Soc.*, 1964, 520.

In an effort to favour dehydrobromination over the substitution of the bromine, (XIV) was heated with 1,4-diazabicyclo[2,2,2]octane in dimethyl sulphoxide solution. The only product was the desired compound (XVI) but the yield was poor. Efficient dehydrohalogenation by hot dimethylformamide which is a mild base has been reported by Heller and his co-workers.[9] When this method was applied to (X), the unsaturated compound (XVII) was obtained in excellent yield. The transformation of (XVII) to structures of interest to us will be described in a future publication.





EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord. The n.m.r. spectra were obtained with a Varian Associates A-60-A instrument. Mass spectra were recorded on a C.E.C.-103C mass spectrometer. Microanalyses were performed by A. Bernhardt, Mikronalytisches Laboratorium in Max Planck Institut, Mülhelm (Ruhr), West Germany.

The following is a general procedure for the bromination of the enamides (IV) to the bromo-ketones (VI) (see Table 1) and their cyclization to the 10-bromo-7,8,9,10-tetrahydrophenanthridinones (Table 2).

10-Bromo-2-methoxy-7,8,9,10-tetrahydrophenanthridin-6(5H)-one (X).—*N*-(*p*-Methoxyphenyl)-2-morpholinocyclohex-2-enecarboxamide[2] (IVb; R = OMe) (15·8 g) was dissolved in chloroform (500 ml) and a solution of bromine (6·4 g) in chloroform (200 ml) was added to it rapidly with constant stirring and cooling in an acetone–solid CO_2 bath. The reaction was stirred at this temperature for an additional hour and finally allowed to stand at room temperature for 3 h. It was then diluted with water (500 ml) and left overnight. The organic layer was separated and the aqueous phase was extracted with fresh solvent. Evaporation of the combined organic extracts provided the bromo-ketone (VI; R = *p*-OMe) (11·8 g, 78%) which was crystallized from dimethylformamide–ethanol to give an analytically pure sample, m.p. 104°; $\nu_{max.}$ (Nujol) 3450 (NH), 1710 (C=O), and 1650 cm^{-1} (amide carbonyl); τ ($CDCl_3$) 2·63 (d, 2H, *J* 9 Hz), 3·12 (d, 2H, *J* 9 Hz), 5·32 (broad, 1H), 6·2 (S, 3H), and 7·8 (m, 7H) (Found: C, 51·25; H, 4·8; N, 4·35; Br, 24·9. $C_{14}H_{16}BrNO_3$ requires C, 51·55; H, 4·9; N, 4·3; Br, 24·55%).

A mixture of the bromo-ketone (VI; R = *p*-OMe) (6 g) and polyphosphoric acid (30 ml) was heated on a steam-bath for 20 min. The resulting dark brown melt was cooled and gradually poured over crushed ice. The solid that separated out was recrystallized from dimethylformamide to yield the bromophenanthridinone (X) (5·5 g, 95%), m.p. 188—189°; $\lambda_{max.}$ (Nujol) 1660 cm^{-1} (amide carbonyl); mass spectrum, M^+ at *m/e* 307 and 309 (Found: C, 54·4; H, 4·3; N, 4·4. $C_{14}H_{14}BrNO_2$ requires C, 54·55; H, 4·55; N, 4·55%) (see Table 2).

6-Chloro-2-methoxy-7,8,9,10-tetrahydrophenanthridin-10-

[9] M. Heller, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, 1964, **86**, 2309.

TABLE 1

Bromo-ketones (VI)

R	Yield (%)	M.p. (°C) (solvent)	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
4-Cl	76	145—146 (MeOH)	$C_{13}H_{13}BrClNO_2$	47·2	3·95	4·35	47·35	3·75	4·2
2-Cl	87	108 (EtOH)	$C_{13}H_{13}BrClNO_2$	47·2	3·93	4·25	47·3	3·55	4·05
2-OMe	94	119—120 (CH_2Cl_2–hexane)	$C_{14}H_{16}BrNO_3$	51·55	4·92	4·3 Br, 24·55	51·25	4·8	4·35 Br, 24·9
4-Me	89	144 (Benzene)	$C_{14}H_{16}BrNO_2$	54·2	5·15	4·55 Br, 25·8	54·4	5·25	4·65 Br, 25·65

TABLE 2

10-Bromo-7,8,9,10-tetrahydrophenanthridinones

R	Yield (%)	M.p. (°C) (solvent)	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
2-Cl	69	189 (MeOH)	$C_{13}H_{11}BrClNO$	49·9	3·5	4·5	49·8	3·4	4·4
4-Cl	75	200 (DMF)	$C_{13}H_{11}BrClNO$	49·9	3·5	4·5	49·8	3·55	4·5
4-OMe	82	169—170 (DMF)	$C_{14}H_{14}BrNO_2$	54·55	4·55	4·55	54·85	4·65	4·25
2-Me	93	188—189 ($CHCl_3$)	$C_{14}H_{14}BrNO$	57·55	4·8	4·8	57·55	4·5	4·95

one (IX).—To a solution containing 6-chloro-2-methoxy-7,8,9,10-tetrahydrophenanthridine [2] (VIII) (4 g), acetic acid (12 ml), and acetic anhydride (4 ml) was added t-butyl chromate solution (40 ml). [Stock solution of t-butyl chromate was prepared by dissolving chromium trioxide (93 g) in t-butyl alcohol (234 ml).] The reaction mixture was stirred overnight at room temperature and then poured into water when a white solid separated out. Chromatography of this solid over acidic alumina using methylene chloride as the eluant afforded the title compound (1 g). Two crystallizations from ethyl acetate gave analytically pure (IX), m.p. 155°; $\lambda_{max.}$ 1700 cm^{-1} (CO) (Found: C, 65·0; H, 4·7; N, 5·3. $C_{14}H_{12}ClNO_2$ requires C, 64·7; H, 4·6; N, 5·75%).

6,10-*Dichloro*-4-*methoxy*-7,8,9,10-*tetrahydrophenanthridine* (XII).—A mixture of 10-bromo-4-methoxy-7,8,9,10-tetrahydrophenanthridin-6(5*H*)-one [10] (XI) (2 g) and phosphoryl chloride (15 ml) was refluxed for ½ h. The dark brown reaction mixture after cooling was poured on ice with vigorous stirring. The solid that separated gave the title compound (1·5 g, 70%), m.p. 174—175° (benzene–light petroleum) (Found: C, 59·35; H, 4·65; N, 4·75. $C_{14}H_{13}Cl_2NO$ requires C, 59·55; H, 4·6; N, 4·95%).

10-*Acetoxy*-2-*methyl*-7,8,9,10-*tetrahydro*-6-*phenanthridin*-6(5H)-*one* (XV).—10-Bromo-2-methyl-7,8,9,10-tetrahydro-6-phenanthridin-6(5*H*)-one [10] (XIV) (3 g) was dissolved in 30% methanolic potassium acetate (200 ml) and refluxed for 6 h on a steam-bath. Methanol was removed under reduced pressure and the resulting solid was stirred with water and then filtered. The white solid (XV) so obtained was crystallized from a mixture of dimethyl sulphoxide and ethanol, m.p. 242°. A recrystallized sample showed intense i.r. absorption at 1730 cm^{-1} (acetate carbonyl) and a sharp n.m.r. signal at τ 7·95 (O·CO·CH_3) (Found: C, 70·65; H, 6·65; N, 5·35. $C_{16}H_{17}NO_3$ requires C, 70·85; H, 6·3; N, 5·15%).

2-*Methoxy*-7,8-*dihydrophenanthridin*-6(5H)-*one* (XVII).—A solution of 10-bromo-2-methoxy-7,8,9,10-tetrahydrophenanthrid-in-6(5*H*)-one (X) (2·5 g) in anhydrous dimethylformamide (50 ml) was refluxed for 10 h. Excess of dimethylformamide was removed under reduced pressure and the residue was extracted with chloroform. This solution was washed with a solution of sodium hydrogen carbonate and water and then dried ($MgSO_4$). Evaporation of the solvent furnished the olefin (XVII), in almost quantitative yield, m.p. 230—231° (CH_2Cl_2); $\nu_{max.}$ 1670 cm^{-1} (amide carbonyl); τ ($CDCl_3$) 2·5—2·99 (m, 4H), 3·08 (d, 1H, *J* 10 Hz), 3·58 (m, 1H), 6·18 (s, 3H), and 6·8—7·85 (m, 4H); mass spec., M^+ at *m/e* 227 (Found: C, 73·85; H, 5·5; N, 6·3. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·75; N, 6·15%).

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[1/1553 *Received*, 26*th August*, 1971]

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