173. *The Tautomerism and Steric Properties of 9-Substituted Phenanthridines.*

By C. B. Reese.

The amino-form (IIa) of 9-aminophenanthridine has been found to predominate in aqueous-ethanolic solution. The tautomeric equilibrium of the isomeric 5-aminoacridine (I) is considered in comparison. The ultraviolet absorption spectra of the methiodides of 9-amino-, 9-methylamino-, and 9-dimethylamino-phenanthridine have been examined. Phenanthridone (VII) has been shown to adopt the lactam form in ethanol.

Albert and his colleagues[1] determined the base-strengths of 5-aminoacridine (I) and some of its *N*-alkyl derivatives. Short[2] examined its infrared spectrum in chloroform solution and concluded that the imino-form (Ib) made no contribution in this solvent. Ultraviolet absorption spectra of these compounds have also been examined.[3] As these results seemed inconclusive, it was decided to investigate the tautomerism of the related isomer, 9-aminophenanthridine (II). Morgan and Walls[4] commented on this problem when they prepared this compound, but no detailed investigation ensued.

9-Chlorophenanthridine (III), prepared by the action of phosphoryl chloride on phenanthridone[5] (VII), reacted readily with ammonia, methylamine, and dimethylamine, yielding 9-amino- (IV; $R = R' = H$), 9-methylamino-[6] (IV; $R = H$, $R' = Me$), and

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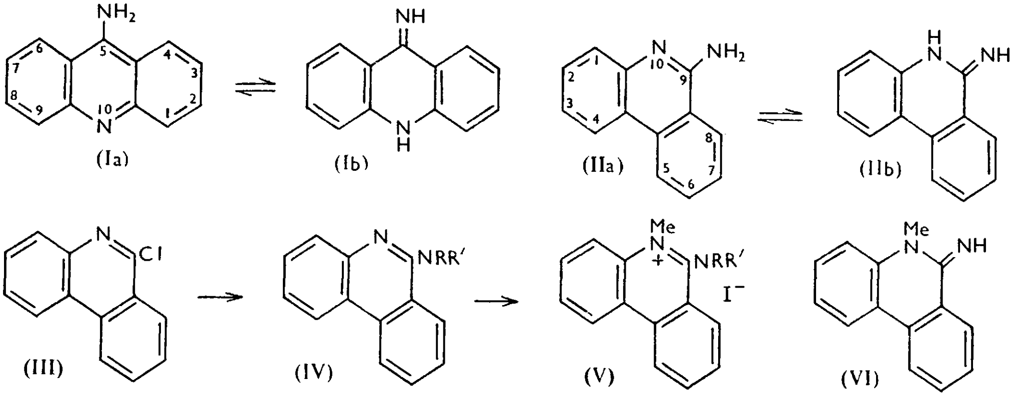
[1] Albert in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV, p. 491 *et seq.*
[2] Short, *J.*, 1952, 4584.
[3] Craig and Short, *J.*, 1945, 419; Acheson, Burstall, Jefford, and Sanson, *J.*, 1954, 3742.
[4] Morgan and Walls, *J.*, 1932, 2225.
[5] Badger, Seidler, and Thomson, *J.*, 1951, 3207.
[6] Morgan and Walls, *J.*, 1938, 389.

9-dimethylamino-phenanthridine (IV; R = R′ = Me) respectively. These three compounds reacted at position 10 with methyl iodide to yield the corresponding methiodides (V). 9 : 10-Dihydro-9-imino-10-methylphenanthridine (VI) was obtained when 9-amino-10-methylphenanthridinium iodide (V; R = R′ = H) was treated with alkali.



In order to determine the tautomerism constant of 9-aminophenanthridine, its base-strength and those of three of its *N*-methyl derivatives were measured. As these compounds were sparingly soluble in water, their pK_a's were determined, in ~M/400-concentration, in 70% ethanol at 20°. The values were: 9-amino- 6·30, 9-methylamino- 6·70, and 9-dimethylamino-phenanthridine 4·91; and compound (VI) 9·10.

The pK_a of 9-aminophenanthridine had previously been found [7] to be 7·31 in water and 6·75 in 50% ethanol. Thus our value obtained in 70% ethanol was approximately one unit less than the true value. It should be emphasized that our pK_a values are not absolute and their significance lies in the differences.

Angyal and Angyal [8] have used the pK_a values of heterocyclic bases to determine tautomeric equilibrium constants. This method has now been applied to 9-aminophenanthridine. However, owing to the possible introduction of steric hindrance, it was necessary to apply with extreme care the well-substantiated approximation [8–10] that *N*-methylation of compounds of this type changes their pK_a's only slightly. It was assumed that the pK_a of the non-tautomeric 9 : 10-dihydro-9-imino-10-methylphenanthridine (VI) did not differ appreciably from that of the imino-form of 9-aminophenanthridine (IIb). The observed similarity between the ultraviolet absorption spectra of compound (VI) and 9-aminophenanthridine in acid solution (Fig. 1) indicated that methylation at position 10 of the conjugate acid of the latter compound did not introduce steric hindrance and thus change its chromophore considerably.

As 9 : 10-dihydro-9-imino-10-methylphenanthridine (VI) was found to be a much stronger base than 9-aminophenanthridine, it was concluded that the imino-form (IIb) did not contribute greatly to the structure of the latter in 70% ethanol. From the pK_a values the tautomerism constant 6·3 × 10^2 was calculated, indicating that the amino-form had a greater stability than the imino-form by 3·9 kcal./mole.

It is noteworthy that 9-dimethylaminophenanthridine is a much weaker base than 9-amino- or 9-methylamino-phenanthridine. Steric interaction between the two *N*-methyl groups and the 8-hydrogen atom probably prevents the first compound from adopting a planar configuration and thus partially localizes the lone-pair of electrons on the exocyclic nitrogen atom. This interpretation is substantiated by the difference (see Fig. 1) between

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[7] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[8] Angyal and Angyal, *J.*, 1952, 1461.
[9] Kenner, Reese, and Todd, *J.*, 1955, 855; Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.
[10] Albert and Goldacre, *J.*, 1946, 706.

the ultraviolet absorption spectrum of the conjugate acid of 9-dimethylaminophenanthridine and those of 9-aminophenanthridine and 9 : 10-dihydro-9-imino-10-methylphenanthridine (VI). Evidently one methyl group on either the 9-amino-group or the 10-nitrogen atom is insufficient to distort the planarity of the molecule.

The structures allotted to the methiodides accord with the facts that action of alkali on the first yields compound (VI), and hydrolysis of the third [6] yields 10-methylphenanthridone (VIII). The evidence in favour of the structure of 9-methylaminophenanthridine methiodide is that its ultraviolet spectrum (Fig. 2, curve *B*) differs from that of 9-dimethylaminophenanthridine in acid solution (Fig. 1, curve *C*). If the chromophore of the conjugate acid of 9-aminophenanthridine (Fig. 1, curve *A*) is taken to be that of a planar cation, it is unlikely that 9-dimethylaminophenanthridine methiodide (Fig. 2, curve *C*) has a planar cation. This is possibly also true, to a smaller extent, for 9-methylaminophenanthridine methiodide (Fig. 2, curve *B*). The resemblance between curve *C* of Fig. 1 and curve *C* of Fig. 2 suggests that 9-dimethylamino-, as well as 9-amino- and 9-methylamino-phenanthridine, is protonated on position 10. The spectroscopic evidence confirms what is expected from models of these compounds. It is not possible to make a planar model of 9-dimethylaminophenanthridine, its methiodide, or 9-methylaminophenanthridine methiodide.

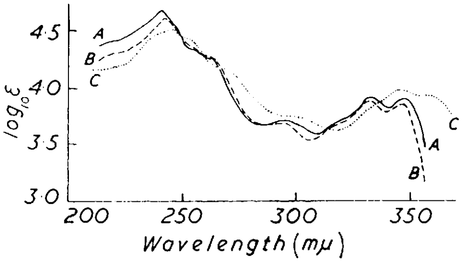


FIG. 1. *Ultraviolet absorption spectra in* 0·1N-*hydrochloric acid of* 9-*aminophenanthridine* (*A*; ——), 9 : 10-*dihydro*-9-*imino*-10-*methylphenanthridine* (*B*; – – – –), *and* 9-*dimethylaminophenanthridine* (*C*; . . . .).

FIG. 2. *Ultraviolet absorption spectra in* 95% *ethanol of* 9-*amino*- (*A*; ——), 9-*methylamino*- (*B*; – – – –) *and* 9-*dimethylamino*-10-*methylphenanthridinium iodide* (*C*; . . . .).

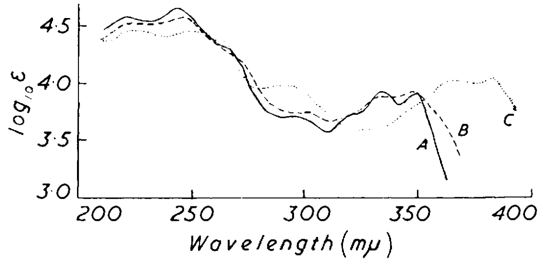
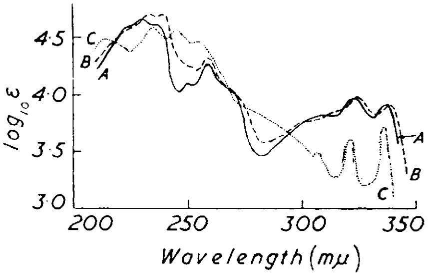


FIG. 3. *Ultraviolet absorption spectra in* 95% *ethanol of phenanthridone* (*A*; ——), 10-*methylphenanthridone* (*B*; – – – –), *and* 9-*methoxyphenanthridine* (*C*; . . . .).



The pK_a results [10,11] for derivatives of 5-aminoacridine (I) followed the same general pattern as for the corresponding derivatives of 9-aminophenanthridine (II). However, in the case of 5-aminoacridine the result was less definite and it was possible that the two tautomeric forms (Ia and Ib) had similar stabilities. Acheson *et al.*[3] recently used ultraviolet spectroscopic evidence to support the prevalence of the imino-form (Ib) in certain solutions, but their argument was invalidated by the introduction of a steric factor in a model compound.[12]

The ultraviolet absorption spectrum, in 95% ethanol, of phenanthridone (VII) (Fig. 3, curve *A*) resembles that of 10-methylphenanthridone (VIII) (curve *B*) but is quite unlike that of 9-methoxyphenanthridine (IX) (curve *C*). Therefore, it seems probable that

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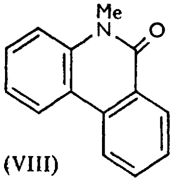
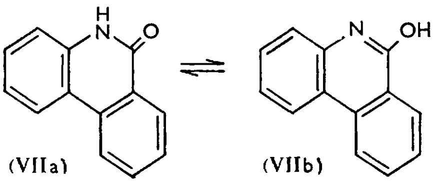
[11] Albert and Goldacre, *J.*, 1943, 454.

[12] Albert, Chem. Soc. Special Publ. No. 3, 1955, p. 130.

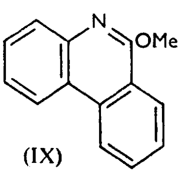
phenanthridone exists almost exclusively in the lactam (VIIa) rather than the lactim form (VIIb) in ethanol. Albert and Phillips[13] reached the same conclusion from pK_a studies. This result is expected as the energy difference of 3·9 kcal./mole between the two tautomers of 9-aminophenanthridine is much less than the difference in stability between a lactam and a lactim grouping.[14]



(VIII)



(VIIa) (VIIb)



(IX)

EXPERIMENTAL

M. p.s are corrected. pK_a's were determined by plotting pH against the volume of 0·1N-hydrochloric acid added from a micro-burette to approximately M/400-solutions of the bases and noting the pH value of the inflexion of the curve. This was checked with the pH value when 0·5 equivalent of hydrochloric acid had been added.

9-*Aminophenanthridine.*—A mixture of 9-chlorophenanthridine (3 g.) and methanol, saturated with ammonia at 0° (8 c.c.), was heated for 5 hr. at 180°. The solvent was removed and the residue was extracted with dilute sulphuric acid. Crude 9-aminophenanthridine was precipitated when this extract was neutralized with aqueous sodium hydroxide. It recrystallized from aqueous ethanol as needles (1·6 g.). A small quantity was sublimed at 140°/0·5 mm. to yield a pale yellow solid, m. p. 193—195° (Morgan and Walls[4] record m. p. 195·5°) (Found: N, 14·8. Calc. for $C_{13}H_{10}N_2$: N, 14·4%).

9-*Amino*-10-*methylphenanthridinium Iodide.*—9-Aminophenanthridine (0·31 g.) and methyl iodide (1 c.c.) were heated for 4 hr. at 125°. Crude 9-*amino*-10-*methylphenanthridinium iodide*, which was washed with ether to remove excess of methyl iodide, was obtained in quantitative yield. It recrystallized from methanol in fine yellow needles, m. p. 257° (Found, in material dried at 60°: C, 49·8; H, 3·7; N, 8·6. $C_{14}H_{13}N_2I$ requires C, 50·0; H, 3·9; N, 8·3%).

9 : 10-*Dihydro*-9-*imino*-10-*methylphenanthridine.*—9-Amino-10-methylphenanthridinium iodide (0·25 g.) was suspended in chloroform (50 c.c.). 3N-Aqueous sodium hydroxide (10 c.c.) was added and the mixture shaken vigorously until the turbidity in the aqueous layer disappeared. The chloroform layer was dried (Na_2SO_4), and the solvent removed under reduced pressure to leave a brown gum. This was further dried by azeotropic distillation with benzene, and then recrystallized from this solvent as a discoloured solid (0·065 g.). This crude 9 : 10-*dihydro*-9-*imino*-10-*methylphenanthridine* was purified by " cold-finger " distillation at 110°/0·5 mm. to give a colourless crystalline solid, m. p. 92° (Found: C, 80·7; H, 5·6; N, 13·5. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·5%).

9-*Methylaminophenanthridine.*—This was prepared by the method of Morgan and Walls. The purified material had m. p. 187—188° (Morgan and Walls[7] record m. p. 187°) (Found: N, 13·7. Calc. for $C_{14}H_{12}N_2$: N, 13·5%).

9-*Dimethylaminophenanthridine.*—9-Chlorophenanthridine (1 g.) was heated with pure anhydrous dimethylamine (about 2 g.) for 2 hr. at 100°. The excess of dimethylamine was allowed to evaporate and the residue was extracted with benzene. The solvent was removed under reduced pressure to leave a brown gum in quantitative yield. This gum, recrystallized from light petroleum (b. p. 60—80°) and finally purified by " cold-finger " distillation at 110°/0·5 mm., gave 9-dimethylaminophenanthridine, m. p. 60° (Morgan and Walls[7] record m. p. 61·5°).

10-*Methyl*-9-*methylaminophenanthridinium Iodide.* 9-Methylaminophenanthridine (0·31 g.) was quaternized with excess of methyl iodide in the same manner as above. The *methiodide hemihydrate* crystallized from methanol in pale yellow needles, m. p. 223—224° with darkening and effervescence (Found, in material before and after being dried at 100°: C, 50·1; H, 4·6; N, 8·1. $C_{15}H_{15}N_2I,\frac{1}{2}H_2O$ requires C, 50·1; H, 4·5; N, 7·8%).

9-*Dimethylamino*-10-*methylphenanthridinium Iodide.*—This was prepared from 9-dimethylaminophenanthridine in a similar manner. It had m. p. 222° (decomp.) (Morgan and Walls[7]

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[13] Albert and Phillips, *J.*, 1956, 1294.

[14] Branch and Calvin, " The Theory of Organic Chemistry," Prentice-Hall, New York, 1941, p. 289.

give m. p. 230°) (Found, in material dried at 80°: C, 52·6; H, 4·8. Calc. for $C_{16}H_{17}N_2I$: C, 52·7; H, 4·7%).

9-*Methoxyphenanthridine.*—9-Chlorophenanthridine (0·21 g.) in anhydrous methanol (30 c.c.) was treated with a solution of sodium methoxide [from sodium (0·1 g.) and methanol (8 c.c.)] and refluxed for ½ hr., after which the solvent was removed. A benzene extract of the residue was evaporated to pale yellow crystals of 9-methoxyphenanthridine in quantitative yield. A colourless crystalline solid, m. p. 52°, was obtained by a " cold-finger " distillation of the crude product at 108°/1·0 mm. (Found: C, 80·4; H, 5·2; N, 6·6. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3; N, 6·7%).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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