233. *The Conversion of Mepacrine and Similar Derivatives of 5-Aminoacridines into Thioacridones by the Action of Hydrogen Sulphide.*

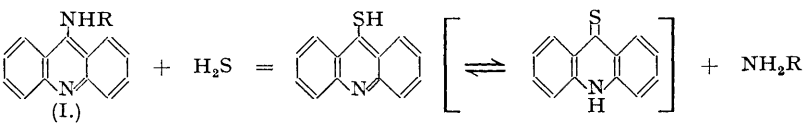
By R. S. Asquith, D. Ll. Hammick, and P. L. Williams.

Mepacrine and similar derivatives of 5-aminoacridine of the type (I) react with hydrogen sulphide in alkaline, alcoholic solution to give the corresponding thioacridones when the group R is capable of exerting a + *I* effect.

In the course of an attempt to prepare a dithiocarbamate by the action of carbon disulphide and ammonia on an alcoholic solution of mepacrine, the slow deposition of a red crystalline compound, m. p. 254° (uncorr.), was observed. This was shown to be 2-chloro-7-methoxythioacridone by analysis and by comparison (mixed m. p.) with a specimen prepared by the method used by Edinger and Ritsema (*J. pr. Chem.*, 1903, **68**, 88) for the preparation of thioacridone. 2-Chloro-7-methoxythioacridone has also been obtained by Das Gupta (*J. Indian Chem. Soc.*, 1940, 244) by the action of potassium xanthate on 2 : 5-dichloro-7-methoxyacridine in phenol at 115°; he gives m. p. 245° (uncorr.).

Further investigation has shown that the thioacridone can readily be prepared by passing hydrogen sulphide into alcoholic solutions of mepacrine containing ammonia, sodium hydroxide, or other basic substances. We have also studied the reaction with hydrogen sulphide under these conditions with other derivatives of 2-chloro-5-amino-7-methoxyacridine and of 5-aminoacridine of the general formula (I) as well as with the corresponding 5-chloroacridines.

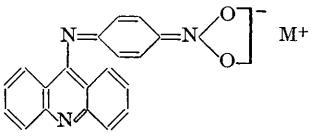
We have established the fact that the reaction is essentially :



by isolating the amine as well as the thioacridone in the case where R is *p*-C_6H_4·OMe.

We also find that, although the reaction is little influenced by the substitution of chlorine and methoxyl groups in the 2 and the 7 position in the acridine nucleus, it depends markedly on the nature of the substituent R in the 5-amino-group. Thus when R is $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$, $[CH_2]_3{\cdot}OH$, Me, or p-$C_6H_4{\cdot}OMe$, the thioacridone is produced under comparable conditions in yields of 80—90% within 3 hours at room temperature. When R is p-$C_6H_4{\cdot}NO_2$, the reaction is slower, 20% yields being obtained after 24 hours. When, however, R is H (as in 5-aminoacridine and 2-chloro-5-amino-7-methoxyacridine), COMe, Ph, or m-$C_6H_4{\cdot}NO_2$, conversion into thioacridone cannot be brought about (*e.g.*, by hydrogen sulphide in alcoholic alkalis, heating with sodium sulphide in alcohol, fusion with sodium sulphide at 180°). Both 5-chloroacridines react readily with hydrogen sulphide in alkaline alcohol.

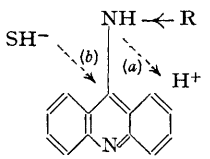
Those substituents R which render the group NHR labile are, with the exception of the p-nitrophenyl group, at once recognisable as increasing, by a $+ I$ inductive effect, the electron density on the 5-amino-nitrogen atom and thus increasing its basicity. Under alkaline conditions the 5-p-*nitroanilino*-derivative may, however, be expected to pass into the form :



That this is the case is to be inferred from its solubility in aqueous alkali and the deep red colour of the alkaline solution, properties not possessed by the m-*nitro*-isomer. Under the alkaline conditions of the reaction, therefore, it is apparent that a $+ I$ effect is present in the case of the p-nitro-derivative. The groupings which inhibit the reaction are, in contrast, $- I$ in their effect.

Bearing in mind the fact that the reaction takes place only in alkaline media, the simplest mechanism that can be postulated is an attack on the 5-carbon atom in the acridine nucleus by SH^- (process *a*) accompanied by the attachment of a proton to the amino-nitrogen atom (process *b*), though a mechanism involving $S^=$ ions cannot be excluded. In either case a $+ I$ effect by the group R will, as has been pointed out, increase the negativity of the nitrogen atom at position 5 and decrease the positivity of the 5-carbon atom. On the other hand a $- I$ effect by the group R will lower the basicity of the amino-nitrogen at 5 and increase the positivity of the 5-carbon atom.

The fact that the reaction is facilitated by increase in the negativity of the amino-nitrogen, instead of being diminished as the positivity of the 5-carbon atom is diminished, suggests that the rate-determining process is the attack on the amino-nitrogen by hydrions, process (*b*) :



Complete elucidation of the mechanism must await the results of kinetic experiments; nevertheless, support for the view put forward above has been obtained in a preliminary study of the reaction in the case of 5-p-*anisidinoacridine*. Thus we find that in aqueous alcoholic solution no reaction occurs in concentrated alkali (5 c.c. of 5N-sodium hydroxide + 20 c.c. of alcohol), where the hydrion concentration is very small. The rate is highest in the presence of solutions such as sodium carbonate and acetate, in which there is both sufficient alkalinity to provide an adequate concentration of SH^- and also a reservoir of the essential H^+ ion. Our results are summarised in the Table, which shows the yields of thioacridone obtained under different conditions of alkalinity. In each case 0·5 g. of 5-*p*-anisidinoacridine was dissolved in 20 c.c. of absolute alcohol, and 5 c.c. of a molar solution of the material shown were added; hydrogen sulphide was bubbled into the solution for 50 minutes at room temperature.

M-Solution added (5 c.c.).	Thioacridone precipitated after 50 mins. (%).	M-Solution added (5 c.c.).	Thioacridone precipitated after 50 mins. (%).
Ammonium chloride ...	0	Ammonium acetate ...	33
Ammonia	6	Sodium carbonate	40
Sodium hydroxide	12	Sodium acetate	40
Ammonium carbonate	13·7		

Experimental.

All but three of the acridine derivatives investigated are known substances and were prepared as described in the literature or supplied by Messrs. I.C.I., Blackley. Specimens of 5-(2-hydroxyethyl)-amino- and 5-(3-hydroxypropyl)amino-acridine were given by Dr. F. E. King.

5-p-*Anisidinoacridine.*—5-Chloroacridine (5 g.) was dissolved in phenol (30 g.) at 70°. *p*-Anisidine (4 g.) was added and the temperature maintained at 100°, with mechanical stirring, for 45 minutes. The mixture was cooled to 30° and poured into acetone at 0°. The solution was allowed to stand for 90 minutes, by which time the bright scarlet hydrochloride of 5-*p*-anisidinoacridine had been precipitated. The precipitate was collected and washed with acetone to free it from phenol. The hydrochloride was dissolved in water, the free *base* precipitated with N-sodium hydroxide, dried over calcium chloride, and recrystallised from light petroleum (b. p. 100—120°). Yield, 62%; m. p. 149° (uncorr.) (Found: C, 79·5; H, 5·34. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·33%).

5-(m-*Nitroanilino*)*acridine.*—This *base* was prepared as above using 5-chloroacridine (10 g.) and *m*-nitroaniline (8 g.) in phenol (65 g.). Yield, 60%. Recrystallised from aqueous alcohol it had m. p. 177° (uncorr.) (Found: C, 72·8; H, 4·4. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·2%).

5-(p-*Nitroanilino*)*acridine.*—This was prepared as above, using 5-chloroacridine (10 g.) and *p*-nitroaniline (8 g.) in phenol (65 g.). The hydrochloride was dissolved in water and N-sodium hydroxide added till the solution was just neutral to litmus. (Excess of alkali redissolves the base as the sodium salt.) Yield, 80%. Recrystallised from aqueous alcohol, the *base* formed yellow-orange needles, m. p. 221° (uncorr.) (Found: C, 71·9; H, 4·0; N, 13·1. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·2; N, 13·3%).

Action of Hydrogen Sulphide on the 5-*Aminoacridines.*—Each reaction was examined by dissolving the 5-aminoacridine (0·5 g.) in absolute alcohol (20 c.c.), adding ammonia (*d* 0·88; 5 c.c.), and passing hydrogen sulphide through the solution until precipitation was complete. The solution first goes dark red owing to super-saturation with thioacridone, which is then suddenly precipitated. The yields varied between 75 and 90%.

R.	Yield of thioacridone (%).	R.	Yield of thioacridone (%).
Me	75	*p*-Nitroanilino-	20 (after 24 hours)
p-Anisidino-	90	5-Chloro-	90

The thioacridone obtained from these reactions recrystallised from methyl alcohol as dark red needles, m. p. 266° (uncorr.) (Found: C, 73·5; H, 4·29; N, 6·46. Calc. for $C_{13}H_9NS$: C, 73·9; H, 4·33; N, 6·63%).

2-Chloro-7-methoxythioacridone was formed in 90% yield from 2-chloro-5-(2-hydroxyethylamino)-7-methoxyacridine, mepacrine, and 2-chloro-5-(3-hydroxypropylamino)-7-methoxyacridine. It recrystallised from absolute alcohol as red-gold plates, m. p. 254° (uncorr.) (Found: C, 60·73; H, 3·87; N, 5·15; Cl, 13·1; S, 12·1. Calc. for $C_{14}H_{10}ONClS$: C, 61·0; H, 3·63; N, 5·08; Cl, 12·9; S, 11·61%).

Preparation of Thioacridone and p-*Anisidine from* 5-p-*Anisidinoacridine.*—*p*-Anisidinoacridine (15 g.) was dissolved in absolute alcohol (200 c.c.), and ammonia (*d* 0·88; 10 c.c.) added. Hydrogen sulphide was passed through the solution for 3 hours. Excess of alcohol was distilled off on a water-bath and the residue shaken with 5% sodium hydroxide solution (200 c.c.) to dissolve the thioacridone. This solution was extracted with ether (200 c.c.). The ether layer was dried ($CaCl_2$) and then the ether was evaporated off on a water-bath. The impure *p*-anisidine in the residue was not isolated but converted directly into the acetyl derivative, m. p. 127°. Yield, 23%. Thioacridone was obtained in 90% yield from the sodium hydroxide solution by acidifying and collecting the precipitate.

Dyson Perrins Laboratory, University of Oxford. [*Received, August 28th,* 1947.]