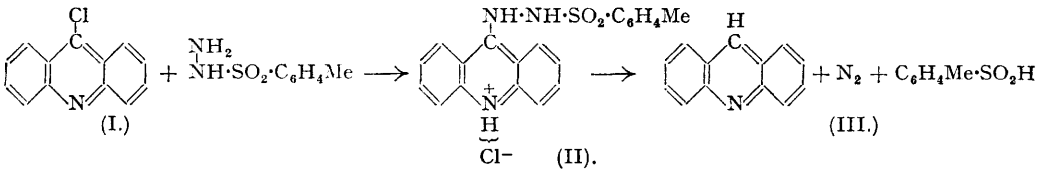
245. *Acridine Syntheses and Reactions. Part V. A New Dehalogenation of 5-Chloroacridine and its Derivatives.*

By Adrien Albert and Richard Royer.

5-Chloroacridine and its derivatives have been dehalogenated by condensing them with toluene-*p*-sulphonylhydrazide and heating the resulting adducts with dilute alkalis. This reaction makes possible for the first time the transformation of those 5-chloroacridines (and hence acridones), which have easily reducible groups (*e.g.*, ·CN and ·NO_2), into the corresponding acridines.

The formerly difficult steps of chlorinating an aminoacridone to an amino-5-chloroacridine, followed by replacement of the chlorine atom, have been satisfactorily accomplished for 3-aminoacridone by first converting it into the carbethoxy-derivative.

It would be valuable to have a standard method for replacing an active chlorine atom in heterocyclic compounds by hydrogen without the use of hydrogenation or reducing agents. In this way, the hydrogenation of the nucleus could be avoided and the integrity of such easily reducible groups as ·NO_2 and ·CN preserved.



(I.) (II). (III.)

The reductive dehalogenation of 4-chloro-3-nitro-6 : 7-benzquinoline, recently accomplished by means of toluene-*p*-sulphonylhydrazide (Albert, Brown, and Duewell, *J.*, 1948, 1284), seems to be such a general method, and the present work describes its successful application in the acridine series. As 5-chloroacridines can be prepared quantitatively from the corresponding acridones by the action of phosphorus oxychloride, it can also be used to transform acridones into acridines. The only other recorded attempt to perform a reaction similar to (II ⟶ III) in a heterocyclic system was made by Dewar (*J.*, 1944, 619) on 4-chloro-8-nitro-6-methoxyquinazoline. The yield was only 8%, but the conditions used were different from those worked out here.

5-Chloroacridine (I) was mixed with toluene-*p*-sulphonylhydrazide in chloroform solution. Next day, the adduct, 5-N′-(*toluene*-p-*sulphonyl*)*hydrazinoacridine hydrochloride* (II) was filtered off and heated with alkali, in aqueous ethylene glycol, at 97° for 2 hours. The products (III) of this reaction are acridine, nitrogen, and toluene-*p*-sulphinic acid. The sulphinic acid was identified by conversion into 2 : 4-dinitrophenyl *p*-tolyl sulphone (m. p. and mixed m. p. confirmed). The yields of dehalogenated acridines from 5-chloroacridine and also from six substituted 5-chloroacridines are shown in the annexed table. The maximal yields range from 40 to 73% calculated on the chloroacridine taken. The ratio of alkali (about a tenfold excess) to adduct was not varied, but the volume of solvent was changed, thus maintaining different concentrations of hydroxyl ion. Sodium hydroxide is too destructive for the cyano- and nitro-derivatives, and in these cases the best yields were obtained with very dilute sodium carbonate.

Results with other alkalis (including glycine-, *cyclo*hexylamine- and piperidine-buffers) and solvents (including water) were far inferior.

2-*Chloroacridine* was obtained in two interconvertible modifications, m. p. 129° and 134°, respectively, thus resembling 1-chloroacridine (forms, m. p. 79° and 90°; Clemo, Perkin, and Robinson, *J.*, 1924, **125**, 1751). The differences in m. p. of about 10° between the 1-, 2-, 3- and

4-chloro-5-aminoacridines prepared by Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169) and by Wilkinson and Finar (*J.*, 1946, 115) are due to the same effect.

This reaction makes it possible for the first time to prepare acridines with cyano-substituents in the benzene rings; 3-*cyanoacridine* was thus obtained. Use of stronger alkali led also to *acridine-3-carboxyamide*, identified by hydrolysis to acridine-3-carboxylic acid (Albert and Goldacre, *J.*, 1946, 710). The present reaction is also of special value for the preparation of nitroacridines. These have been made previously by nitrating acridine or by the ring-closure of nitrodiphenylamine-2-aldehydes, but neither method can be recommended for preparative purposes.

Transformation of 5-chloroacridines into the corresponding acridines through the N'-toluenesulphonylhydrazide adducts (*for conditions see p.* 1148).

5-Chloro-acridine derivative.	Yield of adduct, %.	Acridine derivative.	Yield, % (calc. on adduct), and m. p. NaOH. 0·25N.	NaOH. 0·5N.	NaOH. N.	NaOH. 2N.	Na_2CO_3. 0·125N.	Na_2CO_3. 0·25N.	Na_2CO_3. N.	Highest recorded m. p.
(Unsubstituted)	92 (crude)	(Unsubstituted)	58 105—107°	70 106—108°	70 105—106°	79 104—106°	—	—	—	110—111°
(Unsubstituted)	48 (pure)	(Unsubstituted)	61+20[a] 105—110°	85 108—110°	93 108—110°	78 100—102°	—	—	—	110—111
2-Chloro-	92 (crude)	2-chloro-[e]	75 128—129°	76 128—129°	77 128—129°	76 128—129°	—	—	—	129
3-Cyano-	100 (crude)	3-cyano-	—	0	—	—	65 206—207°	53 203—205°	15[c] 201—203°	209 —
2-Nitro-	97 (crude)	2-nitro-	—	0	—	—	54 175—177°	28 174—177°	0	— 183
3-Nitro-	99 (pure)	3-nitro-	—	0	—	—	52 209—211°	37 204—207°	0	— 215
3-Urethano-	78 (crude)	3-amino-	—	—	51[b] 211—212°	51[b] 209—211°	—	—	25[d] 201—204°	— 213—214
1 : 3-Dimethyl-	80 (crude)	1 : 3-dimethyl-	67 67—68°	84 68—69°	87 65—67°	84 64—66°	—	—	—	— 71

[a] The extra 20% was obtained by a further acid treatment as described in the text.
[b] Complete removal of the carbethoxy-group occurred during the reaction.
[c] Acridine-3-carboxyamide was also obtained in 42% yield.
[d] A subsequent hydrolysis with N-sodium hydroxide was performed to remove the carbethoxy-group.
[e] The crude preparations were converted without loss into a higher-melting form (cf. p. 1151).

When easily reducible groups are absent, an alternative method for dehalogenating 5-chloroacridines is known, viz., catalytic hydrogenation over Raney nickel, followed by oxidation with chromic acid (Albert and Willis, *J. Soc. Chem. Ind.*, 1946, **65**, 26). For the purposes of comparison, 5-chloroacridine and 5-chloro-1 : 3-dimethylacridine were converted by this process into acridine and 1 : 3-dimethylacridine, respectively. The yields were approximately the same as those obtained by the new method.

The present reaction has a formal similarity to the McFadyen and Stevens reaction for converting acids into aldehydes (*J.*, 1936, 584), but the mechanism of the latter reaction is not known and the yields are nil when a nitro-group is situated *para* to the carbon which is to receive the hydrogen atom (Niemann and Hays, *J. Amer. Chem. Soc.*, 1943, **65**, 482). However, this ban did not operate in the present case (cf. 2-nitroacridine). Because the present reaction requires alkali and does not occur in acid solution, the necessity for the formation of an anion can be assumed. Those examples with electron-attracting substituents (·Cl, ·NO_2, ·CN) would be able to retain their anion at a higher hydrogen-ion concentration than the other examples; this explains why the dimethyl and the unsubstituted adducts were more sensitive to a fall in pH (see Table). The reaction cannot be described as a reduction, because easily reducible groups (·NO_2, ·CN) survive it. It may be regarded essentially as the thermal decomposition of an anion of (II).

The unsubstituted adduct (II) formed a small amount (*ca.* 20%) of an acid- and alkali-soluble

by-product in 0·25N-sodium hydroxide. This could be transformed into acridine by acidifying with hydrochloric acid and evaporating to dryness in a vacuum at 120° (see Table). No such by-product was obtained in 0·5N-sodium hydroxide, but at a higher temperature (120°) a solution of sodium hydroxide (0·5N. or 2N.) in ethylene glycol produced traces of 5-aminoacridine (identified by mixed m. p. with an authentic specimen) as well as acridine.

An old problem in acridine chemistry, the chlorination of aminoacridones to 5-chloro-*x*-aminoacridines has usually been attacked after first protecting the amino-group by acetylation. This is not very successful, and it was found that 5-chloro-3-acetamidoacridine is highly unstable and gives only a 35% yield of 3 : 5-diaminoacridine even when dissolved in dry phenol and treated with a stream of dry ammonia for an hour at 120°. On the other hand, *5-chloro-3-urethanoacridine*, readily prepared by the action of ethyl chloroformate on 3-aminoacridone, was much more stable; it gave a 60% yield of 3 : 5-diaminoacridine even when no special drying precautions were taken and, when treated with toluene-*p*-sulphonylhydrazide, it was readily converted into 3-aminoacridine.

Experimental.

(Microanalyses are by The Wellcome Chemical Works, Dartford, The Wellcome Chemical Research Laboratories, Beckenham, and Messrs. Weiler and Strauss.)

Toluene-p-*sulphonylhydrazide*.—To toluene-*p*-sulphonyl chloride (9·52 g.; 0·05 mol.) in benzene (25 ml.) hydrazine hydrate (10 g. of 50%; 0·1 mol.) was added and the whole was shaken by hand until heat was no longer evolved (15 minutes) and then mechanically for 2 hours. The product was filtered off, washed with cold water (25 ml.) and then with light petroleum (15 ml.), and dried to constant weight at 75°. The crude product (95%, m. p. 105—108°) was recrystallised from 15 parts of water (73% recovery) or 5 parts of chloroform (67% recovery) and then melted at 112°. This substance has previously been prepared by Freudenberg and Blümmel (*Annalen*, 1924, **440**, 45), who did not give sufficiently detailed directions.

Adducts [5-N′-(*toluene*-p-*sulphonyl*)*hydrazinoacridine hydrochlorides*, e.g., II]. Cold saturated chloroform solutions of toluene-*p*-sulphonylhydrazide and the relevant 5-chloroacridine were mixed and set aside for 1—2 days. When electron-attracting substituents were present (·CN, ·NO_2, ·Cl), a precipitate was formed almost quantitatively; this was filtered off and air-dried. In the other cases, a fast stream of dry hydrogen chloride was bubbled through the solution for about 10 seconds and the precipitate was filtered off a day later. The adducts are yellow, infusible substances and attempts to liberate the base always resulted in decomposition. The following examples were analysed. 5-N′-(*Toluene*-p-*sulphonyl*)-*hydrazinoacridine hydrochloride* was recrystallized three times from methanol containing hydrogen chloride (0·01N.) and dried in a vacuum at 20° (Found: C, 59·1; H, 4·8; N, 10·7; Cl, 8·9. $C_{20}H_{18}O_2N_3ClS$ requires C, 60·0; H, 4·5; N, 10·5; Cl, 8·9%). 3-*Nitro*-5-N′-(*toluene*-p-*sulphonyl*)*hydrazinoacridine hydrochloride* was analysed as first precipitated (Found: C, 53·95; H, 3·85; Cl, 8·2. $C_{20}H_{17}O_4N_4ClS$ requires C, 54·0; H, 3·85; Cl, 8·0%). 5-N′-(*Toluene*-p-*sulphonyl*)*hydrazino*-1 : 3-*dimethylacridine hydrochloride* was recrystallized from methanolic hydrogen chloride as above (Found: N, 9·7. $C_{22}H_{22}O_2N_3ClS$ requires N, 9·8%).

Decomposition of the Adducts.—N-Sodium hydroxide solution was made by dissolving sodium hydroxide (4 g.) in water (30 ml.) and ethylene glycol (70 ml.), the 2N- and 0·5N-solutions by using half and double these amounts of fluids, respectively. The finely powdered adducts (0·005 mol.) were added to these solutions and the mixtures were heated in a boiling water-bath for 2 hours (3 hours if evolution of gas was incomplete). Any undissolved lumps were broken up from time to time. The reaction mixture was poured into twice its volume of water and refrigerated. The precipitate was filtered off and extracted with N-hydrochloric acid. The extract was poured into an excess of aqueous ammonia and the required acridine was filtered off. Except for the example referred to above, no further material was recoverable by removing the water and glycol in a vacuum after acidification.

5-*Chloro*-1 : 3-*dimethylacridine*.—This was obtained by the action of phosphorus oxychloride on 2′ : 4′-dimethyldiphenylamine-2-carboxylic acid according to the general method described by Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169). It formed pale yellow crystals from benzene, m. p. 114° (Kaufmann, *Annalen*, 1894, **279**, 281, gave m. p. 108°) (Found: C, 74·5; H, 5·1. Calc. for $C_{15}H_{12}NCl$: C, 74·5; H, 5·0%).

5-*Chloro*-3-*urethanoacridine*.—To 3-aminoacridone (3·3 g.) and diethylaniline (2·4 g.) in boiling absolute alcohol (240 ml.), was added freshly distilled ethyl chloroformate (1·7 g.). After being heated under reflux for 30 minutes, the solution was concentrated to one-third of its volume and poured into N-hydrochloric acid (50 ml.). 3-Urethanoacridone was obtained (in 95% yield) as a greenish-yellow solid, decomposing at *ca.* 355° and only slightly soluble in the usual organic solvents. This acridone (1·5 g.) and phosphorus oxychloride (7·5 ml.) were heated under reflux for 1 hour and then refrigerated; the orange solid was filtered off and decomposed by ice and ammonia, giving *5-chloro-3-urethanoacridine* in 87% yield. It formed yellow crystals, m. p. 183°, from benzene (Found: C, 63·5; H, 4·25. $C_{16}H_{13}O_2N_2Cl$ requires C, 63·9; H, 4·35%).

3 : 5-*Diaminoacridine*.—The last-mentioned chloro-compound was aminated in phenol, by the general method of Albert and Gledhill (*loc. cit.*), in 87% yield. The amino-compound (0·3 g.) and hydrogen bromide (47% w/w; 5 ml.) were heated under reflux for 2½ hours and then evaporated to dryness. The resulting solid was dissolved in water, and the solution was made neutral to litmus, filtered from weakly basic material, and poured into an excess of 2·5N-sodium hydroxide. The precipitate of 3 : 5-diaminoacridine was crystallized from chlorobenzene, forming orange crystals, m. p. 245° (decomp., sealed tube); yield, 68% (Found: C, 74·5; H, 5·3; N, 19·6. Calc. for $C_{13}H_{11}N_3$: C, 74·6; H, 5·3; N, 20·1%). Reduction of 3-nitro-5-aminoacridine by the method of Albert and Ritchie (*J.*, 1943, 458) gave the same

substance (m. p. and mixed m. p.). The previous workers gave a lower m. p. (229—230°, from dilute alcohol).

2-*Chloroacridine* was obtained as pale yellow crystals, m. p. 129° or 134° from benzene (by supersaturation) (Found: C, 73·0; H, 3·8; N, 6·6; Cl, 16·7. $C_{13}H_8NCl$ requires C, 73·1; H, 3·8; N, 6·6; Cl, 16·6%). This substance could not be prepared by hydrogenating 2 : 5-dichloroacridine over Raney nickel at 20°, as both chlorine atoms tended to be replaced.

3-*Cyanoacridine* was obtained as pale yellow crystals, m. p. 209°, from chlorobenzene (by supersaturation) (Found: C, 82·2; H, 3·95; N, 13·7. $C_{14}H_8N_2$ requires C, 82·3; H, 3·95; N, 13·7%).

Acridine-3-carboxyamide was obtained as cream-coloured crystals, m. p. 243° (from chlorobenzene) (Found: C, 75·6; H, 4·3. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5%).

This work was supported by the Wellcome Trustees.

WELLCOME RESEARCH INSTITUTION, LONDON, N.W.1. [*Received, October 29th*, 1948.]