295. *Quinoline Compounds containing Arsenic. Part IV. Synthesis of Derivatives of Quinoline-5- and -8-arsonic Acids.*

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8-BROMO-5-NITROQUINOLINE (J., 1931, 1940) condensed readily with hot piperidine, and the *5-nitro-8-piperidinoquinoline* gave *5-amino-8-piperidinoquinoline* on reduction. All attempts to replace the amino- by the arsono-group, however, failed.

When 8-bromo-5-nitroquinoline was reduced by West's method (J., 1925, **127**, 494) a practically quantitative yield of a base, m. p. 156—157°, was obtained which was almost certainly *8-bromo-5-aminoquinoline*; on acetylation it yielded *8-bromo-5-acetamido-*

quinoline, m. p. 179—180° (compare Claus and Howitz, *J. pr. Chem.*, 1893, **48**, 154; Claus and Setzer, *ibid.*, 1896, **53**, 411).

8-Chloro- or -bromo-5-aminoquinoline was readily converted into 8-*chloro-* or *-bromo-quinoline-5-arsonic acid* by means of the Bart reaction, but the halogen atom in the acids was unreactive towards boiling piperidine. Attempts to activate it by introducing a nitro-group failed because the acids were unchanged or oxidised by heating with (*a*) a mixture of sulphuric and nitric acids at 140° for 4 hours, (*b*) sulphuric acid containing potassium nitrate at 140° for 4 hours, (*c*) fuming sulphuric acid (10% SO_3) containing potassium nitrate at 95—100° for 10 hours.

When 5-nitro-8-aminoquinoline (J., 1931, 1940) was diazotised in presence of hydrochloric acid and treated with sodium arsenite, the only pure product isolated was 5-*chloroquinoline*-8-*arsonic acid*: this acid (m. p. 284—285°) depressed the m. p. (226—227°) of 8-chloroquinoline-5-arsonic acid and, unlike it, was slowly nitrated by fuming sulphuric acid (10% SO_3) and potassium nitrate at 95—100°. Since the chlorine atom in the nitro-derivative is very reactive, the nitro-group is without doubt in position 6 and the nitro-compound is therefore 5-*chloro*-6-*nitroquinoline*-8-*arsonic acid*.

Dikshoorn (*Rec. trav. chim.*, 1929, **48**, 553, 556) found that, whereas 8-bromoquinoline was nitrated to give only 8-bromo-5-nitroquinoline, 5-bromoquinoline gave a mixture of 12 parts of 5-bromo-8-nitroquinoline and 1 part of 5-bromo-6-nitroquinoline. It is therefore not surprising that no nitration takes place in 8-bromo- and 8-chloroquinoline-5-arsonic acids, since the reactive 5-position is blocked. In 5-chloroquinoline-8-arsonic acid, on the other hand, the nitro-group may with difficulty be introduced into the 6-position, on the assumption that the arsono-group exerts at most a general damping effect on the molecule.

When 5-chloro-6-nitroquinoline-8-arsonic acid was heated with piperidine and with potassium hydroxide solution, 6-*nitro*-5-*piperidinoquinoline*-8-*arsonic acid* and 6-*nitro*-5-*hydroxyquinoline*-8-*arsonic acid* respectively were readily obtained. The accessibility of the latter compound opens up a way for the synthesis of stovarsol and salvarsan analogues of quinoline, which is being investigated.

The above quinoline compounds of arsenic are being tested by the Joint Committee on Chemotherapy (formed by the Medical Research Council and the Department of Scientific and Industrial Research) in respect of their chemotherapeutic actions in malaria and trypanosomiasis.

EXPERIMENTAL.

5-*Nitro*-8-*piperidinoquinoline*.—8-Bromo-5-nitroquinoline (7·5 g.) and piperidine (15 g.) were heated to 80°, and then at 95—100° for 30 mins. The product

pptd. by excess of H_2O crystallised from EtOH in long, yellow, rectangular prismatic needles (7·1 g.), m. p. 95—96° (Found : C, 65·4; H, 5·7; N, 16·1. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·9; N, 16·3%).

5-*Amino*-8-*piperidinoquinoline*.—Iron filings (17 g.) were added slowly to 5-nitro-8-piperidinoquinoline (26 g.) in boiling EtOH (200 c.c.) containing HCl aq. (25 c.c.; *d* 1·19), after 2 hrs.' boiling NaOEt (6 g. Na in 150 c.c. EtOH) was added, and the whole refluxed for a few mins. The solid was extracted with boiling EtOH and the combined liquids were acidified with HCl aq., steam-distilled to remove EtOH, filtered, and rendered alkaline with NH_3 aq. The *base* crystallised from C_6H_6–light petroleum (b. p. 60—80°) in stellate clusters of long, yellow, silky needles (12 g.), m. p. 182—183° (Found : C, 73·8; H, 7·5; N, 18·1. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%). A dil. alc. solution gave with *N*/1000-iodine a red coloration which changed to green on warming. The *acetyl* derivative crystallised from C_6H_6 in long, pale yellow, prismatic needles, m. p. 210—211° (Found : C, 71·2; H, 7·2; N, 15·5. $C_{16}H_{19}ON_3$ requires C, 71·3; H, 7·1; N, 15·6%).

8-*Bromo*-5-*aminoquinoline*.—Prepared from 8-bromo-5-nitroquinoline (25·3 g.) by West's method (see 5-amino-8-piperidinoquinoline) and liberated by means of excess of conc. NaOH aq., the *base* crystallised from aq. alcohol (20% EtOH) in brownish-yellow, feathery needles (19 g.), m. p. 156—157° (Found : C, 48·3; H, 2·9; N, 12·2. $C_9H_7N_2Br$ requires C, 48·4; H, 3·2; N, 12·6%). Its AcOH solution has an intense red colour, and the yellow solutions in HCl aq., HNO_3, and H_2SO_4 become intense orange-red on dilution with H_2O.

The *acetyl* derivative crystallised from C_6H_6 in sheaves of light brown, rectangular prismatic needles, m. p. 179—180° (Found : C, 49·8; H, 3·5; N, 10·3. $C_{11}H_9ON_2Br$ requires C, 49·8; H, 3·4; N, 10·6%).

The preceding compounds are soluble in the usual solvents (slightly in light petroleum) and in HCl aq., HNO_3, and H_2SO_4.

8-*Bromoquinoline*-5-*arsonic Acid*.—8-Bromo-5-aminoquinoline (5·6 g.) in HCl aq. (30 c.c., *d* 1·12; H_2O, 12 c.c.) was diazotised at 0° ($NaNO_2$, 2 g., in H_2O, 5 c.c.) and after 1 hr. the mixture was poured into a solution of sodium arsenite (10·5 g.) in H_2O (25 c.c.) and saturated $CuSO_4$ aq. (2·5 c.c.). After 12 hrs., the whole was warmed gently, the liquid filtered, and the bulky residue extracted thrice with 5% NaOH aq. The reaction of the combined filtrates was adjusted with HCl aq. to p_H 3—4. The pptd. *arsonic acid* was redissolved in hot Na_2CO_3 aq. (charcoal) and repptd. at p_H 3—4 with HCl aq. It then crystallised from dil. AcOH in stellate clusters of flat colourless needles (5·3 g.), m. p. 234—235° (decomp.) (Found : N, 4·3; Br, 23·8; As, 22·4. $C_9H_7O_3NBrAs$ requires N, 4·2; Br, 24·1; As, 22·6%).

The yield of arsonic acid was only 0·8 g. when the Bart reaction was carried out in alkaline solution.

The arsonic acid is slightly sol. in hot H_2O, readily in AcOH, dil. NaOH aq. and NH_3 aq. and conc. HCl aq. and H_2SO_4, moderately easily in EtOH, but almost insol. in C_6H_6, $CHCl_3$, and light petroleum.

A gelatinous sodium salt is pptd. by conc. NaOH aq. from a solution of the arsonic acid in dil. alkali; it dissolves on boiling and crystallises in needles on cooling.

Gelatinous silver, lead, mercuric, cupric, and calcium salts are precipitable from an aq. solution of the ammonium salt, the last only on boiling; it redissolves on cooling.

8-*Chloro*-5-*aminoquinoline*.—8-Chloro-5-nitroquinoline (Fourneau, Tréfouel,

and Wancolle, *Bull. Soc. chim.*, 1930, **47**, 740) (16 g.) was reduced in the same way as the 8-bromo-compound. The base (12 g.) crystallised from aq. alcohol (10% EtOH) in long, light brown needles, m. p. 154—155° (Found : C, 60·6; H, 4·1; N, 15·4. Calc. for $C_9H_7N_2Cl$: C, 60·5; H, 4·0; N, 15·7%) (Claus and Schöller, *J. pr. Chem.*, 1893, **48**, 146, give m. p. 152°), and formed an *acetyl* derivative, hydrated needles from hot H_2O; m. p. after 3 hrs.' heating at 100°, 172—173° (Found : C, 59·8; H, 4·1; N, 12·6. $C_{11}H_9ON_2Cl$ requires C, 59·9; H, 4·1; N, 12·7%).

8-*Chloroquinoline*-5-*arsonic acid* (4·1 g.) prepared (from 8-chloro-5-aminoquinoline, 4·5 g.) in the same way as the 8-bromo-acid, was pptd. in a crystalline condition from its solution in Na_2CO_3 aq. on acidification with HCl aq. to p_H 3—4. Recrystallised from dil. AcOH, it formed needles, m. p. 226—227° (decomp.) (Found : As, 26·3. $C_9H_7O_3NClAs$ requires As, 26·1%).

5-*Chloroquinoline*-8-*arsonic Acid.*—5-Nitro-8-aminoquinoline (5·5 g.) was suspended in HCl aq. (55 c.c., *d* 1·12) and H_2O (16 c.c.) and diazotised at 15° ($NaNO_2$, 2·5 g., in H_2O, 7 c.c.). After 2 hrs. the solution was poured into a solution of sodium arsenite (21 g.) in H_2O (50 c.c.) and saturated $CuSO_4$ aq. (5 c.c.) and heated at 90—100° for 1 hr., small quantities of 40% $NaNO_2$ aq. being added to ensure that there was always a slight excess of HNO_2 present. The mixture was then made slightly alkaline with NaOH aq., and the *arsonic acid* isolated and purified in the same way as the 8-bromo-acid; it formed colourless needles (4·9 g.), m. p. 284—285° (decomp.) (Found : N, 4·7; Cl, 12·2; As, 26·4. $C_9H_7O_3NClAs$ requires N, 4·9; Cl, 12·3; As, 26·1%), and resembled this acid in solubility and in most of its salts. The pale yellow, gelatinous sodium salt dissolved in its mother-liquor on boiling and set to a firm gel on cooling. The barium and magnesium salts were pptd. in needles and in a gelatinous condition, respectively, from their boiling solutions.

5-*Chloro*-6-*nitroquinoline*-8-*arsonic Acid.*—A solution of 5-chloroquinoline-8-arsonic acid (4 g.) in oleum (20 c.c. containing 10% SO_3) was heated with KNO_3 (8 g.) on the water-bath for 21 hrs. The mixture was then poured into H_2O (100 c.c.), and the reaction adjusted to p_H 4 with NaOH aq.; yellow needles (2·2 g.), m. p. 233—234° (decomp.), of the *chloronitroquinolinearsonic acid* were pptd. (Found : N, 8·1; Cl, 10·9; As, 22·7. $C_9H_6O_5N_2ClAs$ requires N, 8·4; Cl, 10·7; As, 22·55%). The acid is slightly sol. in hot H_2O, readily in AcOH, but practically insol. in the usual neutral organic solvents. It dissolves in dil. NaOH aq. and NH_3 aq. and in moderately conc. mineral acids.

6-*Nitro*-5-*piperidinoquinoline*-8-*arsonic Acid.*—5-Chloro-6-nitroquinoline-8-arsonic acid (1 g.) was heated at 100° with piperidine (5 c.c.) for 4 hrs., the mixture added to H_2O (10 c.c.), the reaction adjusted to p_H 5—6 with HCl aq., and the amorph. ppt. crystallised from dil. AcOH; long, orange-yellow, rectangular prismatic needles (0·8 g.), m. p. 259—260° (decomp.) (Found : As, 19·9. $C_{14}H_{16}O_5N_3As$ requires As, 19·7%). The arsonic acid resembles the preceding acid in solubility. Salts : sodium, calcium, magnesium, and silver, yellow gelatinous; barium, yellow needles, sol. in hot H_2O; mercuric, yellow needles; lead, yellow amorphous; cupric, greenish-yellow gelatinous.

6-*Nitro*-5-*hydroxyquinoline*-8-*arsonic Acid.*—A solution of 5-chloro-6-nitroquinoline-8-arsonic acid (1 g.) in KOH aq. (10 c.c., *d* 1·3) was heated at 100° for 3 hrs. and poured into H_2O (10 c.c.). The cryst. *arsonic acid* pptd. at p_H 4 was redissolved in Na_2CO_3 aq. and repptd. at p_H 4; reddish-orange needles (0·7 g.), m. p. 226—227° (vigorous decomp.) (Found : As, 24·0. $C_9H_7O_6N_2As$ requires As, 23·9%). It resembles the preceding acid in solubility. Salts :

sodium, yellow needles; barium and calcium, orange-yellow gelatinous; silver and mercuric, orange gelatinous; lead, orange-brown gelatinous; cupric, greenish-yellow gelatinous, slightly sol. in hot H_2O and crystallises in needles on cooling; magnesium, orange-yellow gelatinous (only on boiling).

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