Thiazolopyridinium Salts. Part II.[1] Approaches to Thiazolo[3,4-*a*]-pyridinium Salts and Isothiazolo[2,3-*a*]pyridinium Salts

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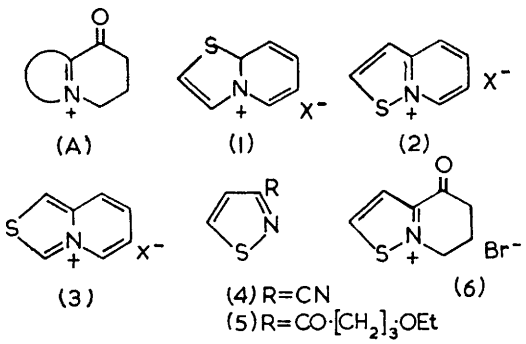
Attempts to synthesise thiazolo[3,4-*a*]pyridinium salts (3) and isothiazolo[2,3-*a*]pyridinium salts (2) by dehydration with boiling acetic anhydride of the 5,6,7,8-tetrahydro-8-oxothiazolo[3,4-*a*]pyridinium salts (11) and (12) and of the 4,5,6,7-tetrahydro-4-oxoisothiazolo[2,3-*a*]pyridinium salt (6) respectively are reported. The reasons for the failure of the aromatisation are discussed. 7-Bromo-8-hydroxy-3-methylthiazolo[3,4-*a*]pyridinium bromide (17) has been prepared by an alternative route.

We have reported a novel aromatisation reaction in which a cyclic ketone of general type (A) is converted by boiling acetic anhydride into the corresponding aromatic compound in high yield.[1-3] The aromatisation, already successfully applied to the production of thiazolo[3,2-*a*]-pyridinium salts (1),[1] appeared to offer a satisfactory route to the isomeric systems (2) and (3), and we now describe attempts to synthesise salts of types (2) and (3) which have led to a more detailed investigation of the aromatisation reaction itself.

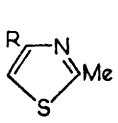
First attempts were directed at the isothiazolopyridinium salts (2). 3-Methylisothiazole was oxidised to the carboxylic acid[4] and thence converted into the nitrile (4).[5] The nitrile (4) reacted with 3-ethoxypropylmagnesium bromide to give a poor (30%) yield of the ethoxybutyrylisothiazole (5). Cleavage of the ether with hydrobromic acid, followed by evaporation to dryness of the acid solution, gave a virtually quantitative yield of the cyclic ketone bromide (6). However, treatment of the ketone (6) with boiling acetic anhydride



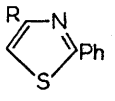
gave initially little reaction, but prolonged boiling produced a black amorphous solid apparently polymeric. In view of the length and poor yields of the synthesis and

[1] Part I, D. G. Jones and Gurnos Jones, *J. Chem. Soc.* (*C*), 1967, 515.
[2] E. E. Glover and Gurnos Jones, *J. Chem. Soc.*, 1958, 3021.
[3] A. Fozard and Gurnos Jones, *J. Chem. Soc.*, 1963, 2203.
[4] A. Holland, R. Slack, T. F. Warren, and D. Bultimore, *J. Chem. Soc.*, 1965, 7277.
[5] D. H. Jones, R. Slack, and K. R. H. Woolridge, *J. Chem. Soc.*, 1964, 3114.

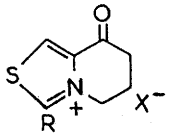
of the known instability of isothiazolium salts toward nucleophiles [6] [we feel that the ketone (6) probably easily opens in the five-membered ring to a diene], no further attempts were made to prepare the isothiazolopyridinium system (2).



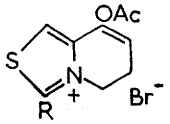
(7) R = CN
(8) R = CO·[CH$_2$]$_3$·OEt



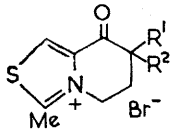
(9) R = CN
(10) R = CO·[CH$_2$]$_3$·OEt



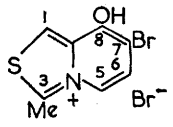
(11) R = Me
(12) R = Ph



(13) R = Me
(14) R = Ph

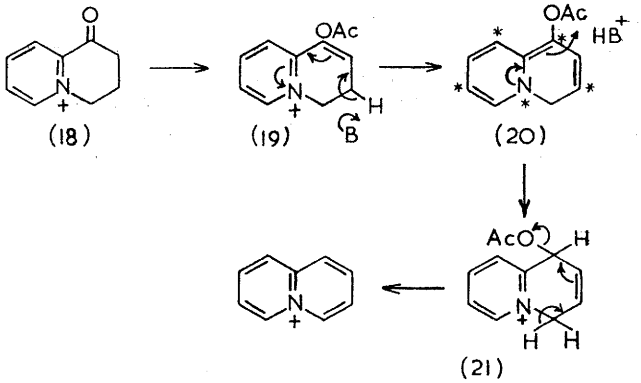


(15) R^1 = H, R^2 = Br
(16) R^1 = R^2 = Br



(17)

As the failure to obtain the isothiazolopyridinium system (2) could be attributed to instability of the isothiazole ring rather than to the failure of an aromatisation–dehydration reaction, we applied the same sequence to the isomeric thiazolo[3,4-*a*]pyridinium series (3). 4-Cyano-2-methylthiazole (7) was obtained by dehydration of the known amide [7] and converted by reaction with 3-ethoxypropylmagnesium bromide into the 4-butyrylthiazole (8) in reasonable yield. A similar reaction from the known 4-cyano-2-phenylthiazole [8] (9) gave a poor yield of the butyryl ketone (10). Both ketones (8) and (10) were cyclised by treatment with hydrobromic acid and heating of the intermediate bromobutyrylthiazoles to give the bicyclic ketones (11) and (12) respectively. However, treatment of the bicyclic ketones (11) and (12) with boiling acetic anhydride gave in high yield the enol acetates (13) and (14) respectively. The structures were clearly established by the infrared absorption at 1760 cm.$^{-1}$ (enol acetate) and by the n.m.r. spectrum; * the phenyl compound (14) showed singlets at 2·45 p.p.m. (3H, CH_3CO), 7·9 p.p.m. (5H, C_6H_5), and 8·2 p.p.m. (1H, thiazole 1-position), triplets at 6·45 p.p.m. (1H, C=C*H*CH$_2$) and 4·65 (2H, $^+NCH_2$), and a multiplet at 2·9 p.p.m. (2H, CH_2CH_2CH=C). The spectrum of the methyl compound (13) was similar. Prolonged boiling of the ketones (11) and (12) with acetic anhydride with or without added sulphuric acid led to decomposition. That derivatives of the thiazolo[3,4-*a*]pyridinium system (3) are stable enough to be isolated was shown by an alternative synthesis. The methyl ketone (11) was brominated with 1 or 2 mol. of bromine to give the monobromo-ketone (15) or the dibromo-ketone (16) respectively. As in the quinolizinium series [3] attempts to convert the monobromo-ketone into the hydroxythiazolopyridinium salt by dehydrobromination failed to give characterisable materials; however heating of the dibromo-ketone (16) dry, in a nitrogen stream led to the evolution of hydrogen bromide. The residue was the 7-bromo-8-hydroxythiazolo[3,4-*a*]pyridinium bromide (17); the n.m.r. spectrum in trifluoroacetic acid showed a methyl group (3H singlet, 2·3 p.p.m.), a singlet aromatic hydrogen (position 1) at 8·12 p.p.m., and two doublets (J 6 c./sec.) centred at 8·15 p.p.m. (position 5) and 7·7 p.p.m. (position 6). The successful synthesis of a derivative of the thiazolo[3,4-*a*]pyridinium system led to a reconsideration of the reasons for the failure of the acetic anhydride aromatisation of ketones (11) and (12).



(18) (19) (20) (21)

We have previously suggested [2] that the intermediate in the aromatisation is the enol acetate, and in fact brief boiling of the quinolizinium ketone (18) with acetic anhydride gives a product with infrared carbonyl absorption at 1765 cm.$^{-1}$ indicative of such an intermediate. This seems further confirmed by the preparation of the stable enol acetates (13) and (14) above. If we assume that the nitrogen atom is essential for the double-bond isomerisation, we can consider as a likely second stage the intermediate (20), a quinolizine. Protonation of the neutral species (20) could take place at any starred position; of these the two most likely positions are 1 and 3, and of these protonation at position 3 would regenerate intermediate (19). Protonation at position 1 would give the salt (21) which is ideally set up for 1,4-elimination, giving the quinolizinium salt. In this scheme we are equating 'aromatisation capability' with acidity of the proton at position 3 in the enol acetate (19) or with the possibility of formation of a likely neutral intermediate of type (20). We can appreciate this by a consideration of the isomeric thiazolopyridinium systems (13) and (22); while the enol acetate (22) presents an exact analogy with the quinolizinium salt (19), the enol (13) cannot lose a proton to give a similarly likely neutral intermediate. The

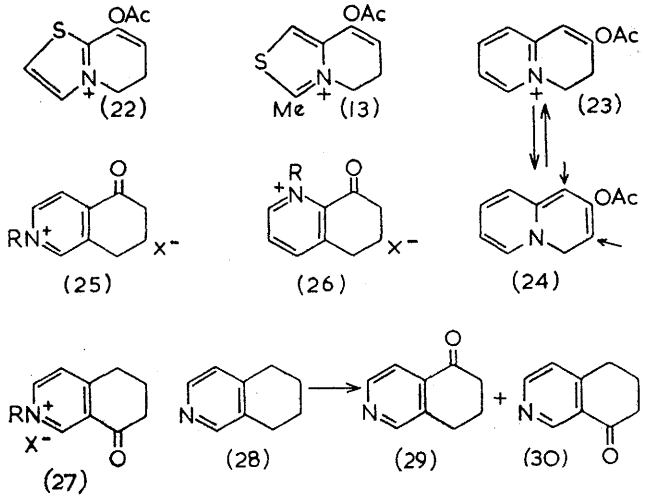
* All n.m.r. shifts are given in p.p.m. from internal SiMe$_4$; for doublets and triplets the centre of the absorption is quoted.

[6] J. M. Landesberg and R. A. Olofson, *Tetrahedron*, 1966, **22**, 2135.

[7] E. R. H. Jones, F. A. Robinson, and M. N. Strachan, *J. Chem. Soc.*, 1946, 87.

[8] T. P. Sycheva, T. Kh. Dymshits, and M. N. Shchukina, *Zhur. obshchei Khim.*, 1963, **33**, 3659; G. E. Hall and J. Walker, *J. Chem. Soc.* (*C*), 1966, 1358.

protons at position 6 in enol (13) are vinylogous with those in a 4-methylthiazole which are known to be non-acidic.[9]



The enol acetate (23) isomeric with the quinolizinium salt (19) represents a different case. Here the neutral quinolizine intermediate (24) can be postulated, but protonation either at position 1 or at position 3 gives an unsaturated acetate which cannot eliminate acetic acid; in this case in practice the acetic anhydride reaction stops at the intermediate enol acetate (23). Finally, if the above mechanistic suggestions are correct, compounds suitable for aromatisation should be the isoquinolinium ketone (25) or the quinolinium ketone (26) but *not* the isoquinolinium ketone (27). We have prepared the *N*-methylisoquinolinium ketones (25) and (27) (R = Me) by oxidation of 5,6,7,8-tetrahydroisoquinoline (28), separation of the isomeric ketones (29) and (30), and methylation of both with methyl iodide. As expected, treatment of ketone (25) with boiling acetic anhydride gave an *N*-methylisoquinolinium salt; similar treatment of ketone (27) did not.

EXPERIMENTAL

All m.p.s were done on a Kofler hot stage. Infrared spectra were determined on a Perkin-Elmer 257, n.m.r. spectra on Perkin-Elmer R10 60 Mc. instrument. All n.m.r. shifts are δ values in p.p.m. from $SiMe_4$.

3-(4-*Ethoxybutanoyl*)*isothiazole* (5).—The Grignard reagent from 3-ethoxypropyl bromide (22 g.) and magnesium (3·5 g.) in dry ether (250 ml.) was added slowly with vigorous stirring to a cold (0—5°) solution of 3-cyanoisothiazole [4,5] (12·8 g.) in dry ether (100 ml.), and stirring was continued for 1 hr. after addition. The cold solution was treated with concentrated hydrochloric acid (120 ml.), and the ether separated and again extracted with concentrated acid. The combined acid extracts were diluted, set aside for 1 hr. at room temperature, and basified with cold ammonia (*d* 0·880) with external ice-cooling. The mixture was extracted with ether, and the ether dried (Na_2SO_4) and distilled. Early fractions contained some isothiazole-3-carboxamide. The *ethoxybutyrylisothiazole* (5) had b.p. 156—159°/18 mm. (6·62 g., 29%) (Found: C, 54·6; H, 6·55; N, 7·1. $C_9H_{13}NO_2S$ requires C, 54·3; H, 6·6; N, 7·05%), $\nu_{max.}$ (film) 1690, 1110 cm.$^{-1}$; n.m.r. (CCl_4) 8·68, 7·76 (1H doublets, $J_{4,5}$ 5 c./sec., isothiazole ring) 3·1—3·6 (6H multiplet, CH_2O and $COCH_2$), 1·75—2·2, (2H multiplet), 1·15 (Me triplet) p.p.m.

4,5,6,7-*Tetrahydro*-4-*oxoisothiazolo*[2,3-a]*pyridinium Bromide* (6).—A solution of the ethoxybutanoylisothiazole (5) (0·98 g.) in 50% hydrobromic acid (20 ml.) was boiled for 1 hr. (ethyl bromide was allowed to escape from the system). The solution was evaporated under reduced pressure, and absolute ethanol added and again distilled off. The residue (1·11 g., 97%) was almost pure. Recrystallised from absolute ethanol as buff coloured needles, the *cyclic ketone bromide* (6) had m.p. 220° (decomp.) (Found: C, 36·4; H, 3·25; N, 5·6. C_7H_8BrNOS requires C, 35·9; H, 3·45; N, 6·0%), $\nu_{max.}$ (mull) 1710 cm.$^{-1}$; n.m.r. (CF_3CO_2H) 9·55, 8·06 (aromatic protons, doublets, *J* 6 c./sec.), 5·0 (triplet, CH_2N^+), 2·5—3·4 (4H multiplet) p.p.m.

Attempted Aromatisation of Compound (6).—A solution of the cyclic ketone (6) in acetic anhydride was boiled for 1 hr. Evaporation of the acetic anhydride gave a black residue, showing an absorption maximum at 1760 cm.$^{-1}$. Further boiling in acetic anhydride produced a black amorphous solid with no recognisable infrared or n.m.r. maximum.

4-*Cyano*-2-*methylthiazole* (7).—2-Methylthiazole-4-carboxamide (30 g.) was dehydrated by boiling $POCl_3$ (125 ml.) for 5 hr. The residue after removal of $POCl_3$ was basified, extracted with chloroform, dried, and distilled. The *nitrile* (7) had b.p. 137°/25 mm., m.p. 60—61° (14 g., 53%) (Found: C, 48·5; H, 2·9; N, 22·1. $C_5H_4N_2S$ requires C, 48·4; H, 3·2; N, 22·6%), $\nu_{max.}$ (CCl_4) 2220 cm.$^{-1}$.

4-(4-*Ethoxybutanoyl*)-2-*methythiazole* (8).—A solution of the nitrile (7) (14 g.) in ether (200 ml.) was added slowly with stirring to the Grignard reagent from 3-ethoxypropyl bromide (20 g.) and magnesium (2·6 g.) in ether (200 ml.). The mixture was stirred overnight, then treated with ice-cold hydrochloric acid (100 ml.). The separated acid layer was basified with ammonia (*d* 0·880), extracted with ether, and the ether extracts were dried and distilled. The *ethoxybutanoylthiazole* (8) had b.p. 174—176°/20 mm. (12·8 g., 53%) (Found: C, 56·3; H, 6·9; N, 6·3. $C_{10}H_{15}NO_2S$ requires C, 56·35; H, 7·05; N, 6·55%), $\nu_{max.}$ (film) 1685, 1155, 1110 cm.$^{-1}$; n.m.r. (CCl_4) 8·0 (singlet, thiazole 5-proton) 3·25—3·65 (OCH_2, 4H overlapping quartets), 7·1 (2H triplet, CH_2CO), 2·8 (Me singlet), 1·8—2·2 (2H multiplet), 1·15 (Me triplet).

4-(4-*Ethoxybutanoyl*)-2-*phenylthiazole* (10).—The Grignard reagent from 3-ethoxypropyl bromide (33 g.) and magnesium (4·6 g.) in ether (250 ml.) was added with cooling and stirring to the nitrile (9) [8] (33 g.) in ether (1 l.). Working-up as in the previous experiment gave the *ethoxybutanoylthiazole* (10) (8 g., 16·4%), b.p. 160—162°/0·2 mm., m.p. 62° (from petroleum ether) (Found: C, 66·5; H, 6·3; N, 5·1;. $C_{15}H_{17}NO_2S$ requires C, 66·5; H, 6·2; N, 5·1%); n.m.r. (CCl_4) 8·15 (singlet, thiazole CH), partly overlying multiplet at 8·00—8·25 (2H), 7·45—7·65 (3H multiplet), 3·1—3·7 (multiplet, 6H, OCH_2 and $COCH_2$), 1·85—2·25 (2H multiplet), 1·15 (3H triplet).

5,6,7,8-*Tetrahydro*-3-*methyl*-8-*oxothiazolo*[3,4-a]*pyridinium Salts* (11).—A solution of the ketone (8) (2 g.) in 50%

[9] H. J. M. Dou and J. Metzger, *Bull. Soc. chim. France*, 1966, 3273.

hydrobromic acid (25 ml.) was boiled for 1 hr., then evaporated to dryness. The residue was treated with absolute ethanol, again evaporated, and the residue triturated with ethyl acetate to give the cyclic ketone bromide (11, X = Br) (2·23 g., 94%), m.p. 212—214°; n.m.r. (D_2O) 9·05 (thiazolium H), 3·15 (Me singlet), multiplets at 4·7, 3·0, and 2·6 p.p.m. The *picrate* (11; X = picrate) had m.p. 138—140° (from ethanol) (Found: C, 42·3; H, 2·85. $C_{14}H_{12}N_4O_8S$ requires C, 42·4; H, 3·13%), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$.

5,6,7,8-*Tetrahydro*-8-*oxo*-3-*phenylthiazolo*[3,4-a]*pyridinium Salts* (12).—A solution of the ketone (10) (7·8 g.) in 50% hydrobromic acid (120 ml.) was boiled for 1·5 hr. then evaporated under reduced pressure. The residue was dissolved in absolute ethanol and the solution boiled for 1 hr. then evaporated. The residue on trituration with acetone gave almost pure *cyclic ketone bromide* (6 g.) (12; X = Br) (70%), m.p. 254—255° (decomp.) (from ethyl acetate–ethanol) (Found: C, 50·3; H, 3·75,; N, 4·15. $C_{13}H_{12}BrNOS$ requires C, 50·3; H, 3·9; N, 4·5%), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$.

8-*Acetoxy*-5,6-*dihydro*-3-*methylthiazolo*[3,4-a]*pyridinium Bromide* (13).—A solution of the cyclic ketone (11) (2 g.) in acetic anhydride (50 ml.) was boiled for 3 hr., then evaporated under reduced pressure. The residue, after treatment with acetone, was filtered, giving almost pure *enol acetate* (13) (95%), m.p. >220° (decomp.) (Found: C, 42·2; H, 4·04. $C_{10}H_{12}BrNO_2S$ requires C, 41·4; H, 4·15%), $\nu_{max.}$ (Nujol) 1760, 1210, 1180 cm.$^{-1}$; n.m.r. given in the text.

8-*Acetoxy*-5,6-*dihydro*-3-*phenylthiazolo*[3,4-a]*pyridinium Bromide* (14).—A solution of the cyclic ketone (12) (1 g.) in acetic anhydride (40 ml.) was boiled for 3 hr. then worked up as for compound (13), giving the *enol acetate* (14), m.p. 247—249° (Found: C, 51·3; H, 3·95; N, 4·0. $C_{15}H_{14}BrNO_2S$ requires C, 51·2; H, 4·0; N, 4·0%), $\nu_{max.}$ (Nujol) 1765, 1215, 1190 cm.$^{-1}$; n.m.r. given in the text.

7-*Bromo*-5,6,7,8-*tetrahydro*-3-*methyl*-8-*oxothiazolo*[3,4-a]-*pyridinium Bromide* (15).—To a solution of the cyclic ketone (11) (2·4 g.) in 50% hydrobromic acid was added dropwise bromine (1·6 g.). The mixture was heated on a water-bath, then evaporated under reduced pressure. The residue was recrystallised from ethanol to give the *monobromo-ketone bromide* (15), m.p. >330° (Found: C, 29·2; H, 2·9; N, 4·1. $C_8H_9Br_2NOS$ requires C, 29·3; H, 3·05; N, 4·25%), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$.

7,7-*Dibromo*-5,6,7,8-*tetrahydro*-3-*methyl*-8-*oxothiazolo*-[3,4-a]*pyridinium Bromide*. (16).—A solution of the cyclic ketone (11) (2·13 g.) in 50% hydrobromic acid was brominated as described above, but using 3·14 g. of bromine. Recrystallised from methanol the *dibromo-ketone bromide* (16) had m.p. >320° (3·1 g., 88%) (Found: C, 23·6; H, 1·9; N, 3·4. $C_8H_8Br_3NOS$ requires C, 23·65; H, 2·0; N, 3·45%), $\nu_{max.}$ (Nujol) 1695 cm.$^{-1}$; n.m.r. (CF_3CO_2H) 9·1 (thiazolium singlet), 4·9 (CH_2N^+, triplet), 3·55 (CH_2CBr_2, triplet), 3·25 (Me singlet).

7-*Bromo*-8-*hydroxy*-3-*methylthiazolo*[3,4-a]*pyridinium Bromide* (17).—The dibromo-ketone was heated in a dry tube under a current of nitrogen to 135°; the effluent gas was titrated against standard alkali until hydrogen bromide evolution ceased. The residue was the *bromo-hydroxy-bromide* (17), m.p. >320° (Found: C, 27·8; H, 2·23; N, 4·0. $C_8H_9Br_2NOS,H_2O$ requires C, 28·0; H, 2·6; N, 4·1%); n.m.r. spectrum given in the text; $\lambda_{max.}$ (H_2O or base) 308, 318, 405 mμ, $\lambda_{max.}$ (HCl) 282sh, 292, 304, 354 mμ.

5,6,7,8-*Tetrahydro*-5-*oxoisoquinoline* (29) *and* 5,6,7,8-*Tetrahydro*-8-*oxoisoquinoline* (30).—5,6,7,8-Tetrahydroisoquinoline was oxidised as previously described;[10] it was found necessary to chromatograph the oxidation product on Woelm alumina in order to obtain pure samples of the 5-oxo-derivative (29) and the 8-oxo-derivative (30) which could be clearly distinguished because of the downfield shift of the 4-proton in compound (29) [doublet at 7·9 p.p.m. compared with 7·35 p.p.m. in compound (30)]; a similar downfield shift of the broadened singlet due to the proton at position 1 was observed in compound (30), both due to the deshielding effect of the *peri*-carbonyl group. The *methiodide* (25; R = Me) had m.p. 130° (Found: C, 42·0; H, 3·95; N, 4·7. $C_{10}H_{12}INO$ requires C, 41·5; H, 4·15; N, 4·85%). The methiodide (27; R = Me) had m.p. 161—162° (Found: C, 41·9; H, 3·9; N, 4·5%).

Aromatisation of Compound (25).—The methiodide (25) was dissolved in hot acetic anhydride and the solution boiled for 2 hr. Evaporation to dryness under reduced pressure and treatment of the residue with aqueous sodium picrate gave N-*methylisoquinolinium picrate* identical with a sample prepared from *N*-methylisoquinolinium iodide. Similar treatment of compound (26) gave no trace of *N*-methylisoquinolinium salt which could be detected by u.v. examination of the reaction mixture.

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[10] N. Sugimoto, H. Kugita, and T. Tanaka, *J. Pharm. Soc. Japan*, 1956, **76**, 1308.