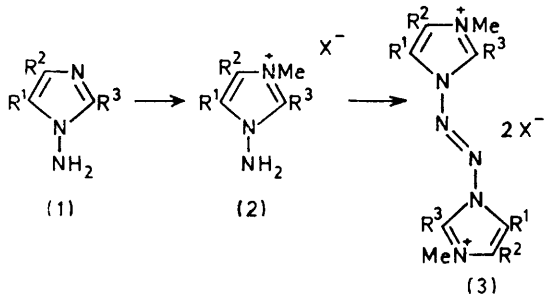
# Synthesis and Oxidation of Quaternary Salts of 1-Aminoimidazoles

By **E. E. Glover** * and **K. T. Rowbottom**, Department of Chemistry, Teesside Polytechnic, Middlesbrough Teesside
**D. C. Bishop**, Allen and Hanburys Ltd., Ware, Hertfordshire

The synthesis of some 1-aminoimidazoles from *N*-acetylamidrazones and phenacyl bromide is reported. Quaternisation and subsequent oxidation of the 1-aminoimidazolium salts gave 1,1'-azoimidazolium salts.

THE synthesis of 1-aminoimidazo[1,2-*a*]pyridinium salts and their oxidation to the corresponding 1,1'-azo-compounds has previously been reported.[1] These last compounds are potential neuromuscular blocking agents; we now report the synthesis of other diquaternary salts of 1,1'-azoimidazoles (3) from 1-aminoimidazoles (1). Although the syntheses of some 1,2-diaminoimidazoles,[2] 1,5-diaminoimidazoles,[3] and 1-amino-2-mercaptoimidazoles[4] have been described, no general route to 1-aminoimidazoles has so far been reported.



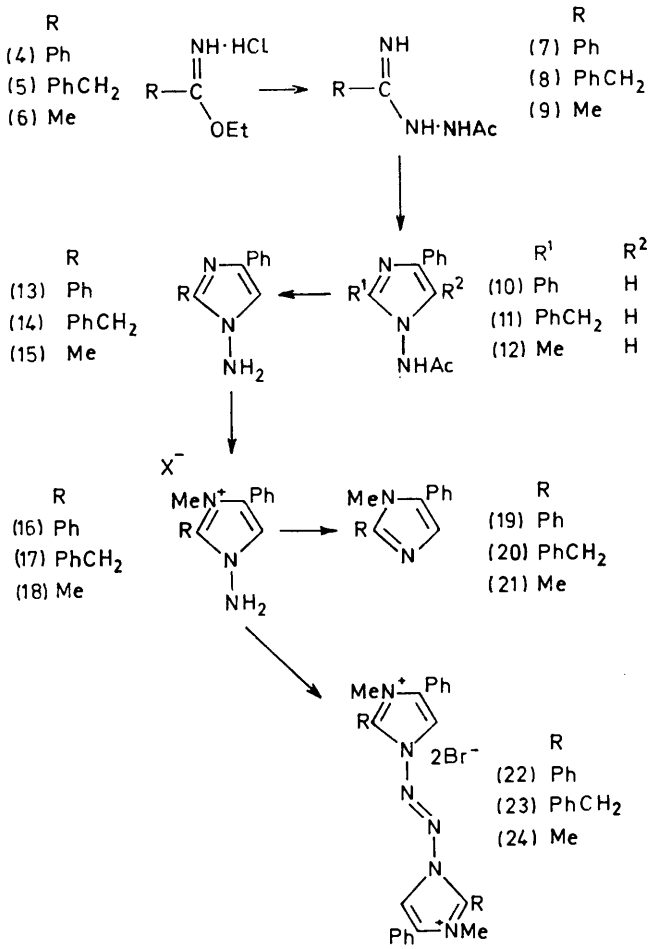
(1) (2) (3)

Attempts to *N*-aminate 1-methylimidazole by the general procedure described[5] for the *N*-amination of tertiary amines, or the more recent procedure[6] for the *N*-amination of pyridine, were unsuccessful. We therefore studied the reaction between *N*-acetylamidrazones and α-halogeno-ketones.

The *N*-acetylacetamidrazones (8) and (9) were prepared from the hydrochlorides of the corresponding imidic acid ethyl esters by use of the procedure of Postovskii and Vereshagina,[7] but an adaptation of the procedure of Doyle *et al.*[8] for the preparation of *N*-phenylindole-2-carboxamidrazone, was preferred for *N*-acetylbenzamidrazone (7).

Treatment of the acetyl amidrazones (7)—(9) with phenacyl bromide in boiling acetonitrile gave the 1-acetamidoimidazoles (10)—(12) but in each case part of the starting acetyl amidrazone was precipitated from the reaction mixture as the hydrobromide. Hydrolysis and subsequent basification of the acetamidoimidazoles gave the 1-aminoimidazoles (13)—(15), quaternization of which with methyl iodide gave the corresponding quaternary salts (16)—(18).

The position of the phenyl groups in the 1-amino-3-methylimidazolium salts (16) and (18) was established by deamination to the corresponding trisubstituted imidazoles (19) and (21), respectively and comparison of these bases with authentic samples.[9,10] Deamination



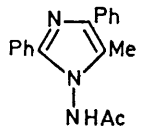
of the benzyl-1-aminoimidazole (17) likewise gave the free base (20), but this was previously unknown. However, by analogy with the imidazoles (19) and (21) it was assumed that the ring phenyl group was attached to C-5.

Oxidation of the quaternary bromides (16)—(18) with aqueous bromine gave the required tetrazenes (22)—(24).

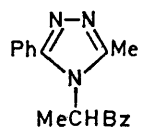
Attempts to use other α-halogeno-ketones for the

[1] E. E. Glover and M. Yorke, *J. Chem. Soc.* (*C*), 1971, 3280.
[2] A. Hetzheim, O. Peters, and H. Beyer, *Chem. Ber.*, 1967, **100**, 3418.
[3] C. L. Leese and G. H. Timmis, *J. Chem. Soc.*, 1961, 3816.
[4] T. Pyl, F. Waschk, and H. Beyer, *Annalen*, 1963, **663**, 113.
[5] R. Gösl and A. Meusen, *Chem. Ber.*, 1959, **92**, 2521.
[6] Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 130.
[7] Ya. Postovskii and N. N. Vereshchagina, *J. Gen. Chem.* (*U.S.S.R.*), 1959, **29**, 2105.
[8] F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 1956, 2853.
[9] P. G. Haines and E. C. Wagner, *J. Amer. Chem. Soc.*, 1949, **71**, 2793.
[10] F. Asinger, H. Offermanns, and P. Krings, *Annalen*, 1968, **719**, 145.

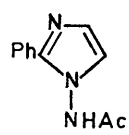
preparation of 1-aminoimidazoles were unsuccessful. Treatment of *N*-acetylbenzamidrazone (7) with 2-bromopropiophenone at 140° gave, instead of the expected acetamidoimidazole (25), the hydrobromide of the



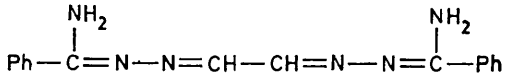
(25)



(26)



(27)



(28)

trisubstituted triazole (26), the structure of which followed from its preparation by the treatment of 3-methyl-5-phenyltriazole with 2-bromopropiophenone. hydrobromic acid gave the dihydrobromide of 1,8-diamino-1,8-diphenyl-2,3,6,7-tetra-azaocta-1,3,5,7-tetraene (28); the derived free base was identical with an authentic sample.[11]

The u.v. absorption spectra of the quaternary tetrazenes (22)—(24) showed characteristic broad bands in the region 330—360 nm.

## EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. spectra were determined with a Perkin-Elmer model 137 spectrophotometer.

*N-Acetylbenzamidrazone* (7).—Acetohydrazide (0·36 g) was added during 5 min to a stirred solution of ethyl benzimidate hydrochloride (0·9 g) in absolute ethanol (7·5 ml) and dry triethylamine (0·7 ml). The solution was stirred overnight and cooled in ice, and the deposited solid was filtered off and washed with light petroleum (b.p. 40—60°) (yield 0·54 g, 63%). Recrystallization from methanol–ether gave prisms, m.p. 168° (lit.,[7] 172°) (Found: C, 60·8; H, 6·2; N, 24·0.

TABLE 1

1-Acetamidoimidazoles *

| Acetyl amidrazone | Phenacyl bromide (g) | Reflux time (h) | Product | Cryst. solvent † | Yield [a] (%) | M.p. (°C) | Found (%) C | H | N | Rqd. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (7) 2·25 g | 1·26 | 2 | (10) [b] | EtOH–$C_6H_6$–LP | 64 | 183 | 73·1 | 5·5 | 15·0 | 73·6 | 5·45 | 15·15 |
| (8) [7] 0·48 g | 0·25 | 1·5 | (11) [c,d] | $Pr^nOH$–LP | 54 | 228—232 | 54·5 | 5·2 | 10·5 | 54·1 | 5·3 | 10·5 [e] |
| | | | (11) picrate | EtOH–$H_2O$ | | 183—184 | 55·3 | 4·1 | 16·2 | 55·4 | 3·9 | 16·15 |
| (9) [7] 1·15 g | 1·0 | 1·5 | (12) [f] | MeCN | 46 | 218—220 | 66·9 | 6·1 | 19·3 | 67·0 | 6·1 | 19·5 |
| (7) 0·2 g | Bromo-acetalde-hyde 0·077 g | 2 | (27) picrate [g,h] | $MeNO_2$–$Et_2O$ | | 227—231 | 47·3 | 3·6 | 19·4 | 47·45 | 3·3 | 19·5 |

* *Procedure.*—A solution of the amidrazone and phenacyl bromide in the minimum quantity of boiling acetonitrile was boiled under reflux for the time indicated. The solution was cooled and the solid *N*-acetylamidrazone hydrobromide filtered off and recrystallized. Evaporation of the filtrate and recrystallization of the residue gave the acetamido-compound. † LP = Light petroleum (b.p. 60—80°).

[a] Based on unrecovered acetyl amidrazone. [b] The N-*acetylbenzamidrazone hydrobromide* by-product (31%) had m.p. 204° (from ethanol–ether) (Found: C, 42·0, H, 5·0; N, 16·1. $C_9H_{11}N_3O$,HBr requires C, 41·9; H, 4·7; N, 16·3%). [c] The crude product obtained after evaporation of the solvent was treated with 48% hydrobromic acid and the resulting hydrobromide was recrystallized. [d] The N-*acetylphenylacetamidrazone hydrobromide* by-product (41%) had m.p. 192—194° (from methanol–ethyl acetate–ether) (Found: C, 42·7; H, 5·0; N, 14·9. $C_{10}H_{13}N_3O$,HBr,0·5$H_2O$ requires C, 42·7; H, 5·4; N, 14·9%). [e] For $C_{18}H_{17}N_3O$,HBr,1·5$H_2O$. [f] The N-*acetylacetamidrazone hydrobromide* by-product (29%) had m.p. 183° (from ethanol–ether) (Found: C, 25·0; H, 5·2; N, 21·3. $C_4H_9N_3O$,HBr requires C, 24·5; H, 5·1; N, 21·4%). [g] After evaporation of the solvent the crude product was treated with alcoholic picric acid and the precipitated picrate was recrystallized. [h] *N*-Acetylbenzamidrazone hydrobromide obtained as by product (31%).

TABLE 2

1-Aminoimidazoles *

| Precursor | Product | Yield | Cryst. solvent | M.p. (°C) | Found (%) C | H | N | Rqd. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| (10) 0·62 g | (13) | 0·4 g, 76% | EtOH–$H_2O$ | 163 | 76·6 | 5·7 | 18·0 | 76·6 | 5·6 | 17·9 |
| (11) 0·2 g | (14) | 0·11 g, 64% | MeOH–$H_2O$ | 137—138 | 77·2 | 6·0 | 16·8 | 77·1 | 6·1 | 16·85 |
| (12) 1·58 g | (15) | 0·77 g, 61% | $H_2O$ | 140—141 | 69·35 | 6·6 | 24·4 | 69·3 | 6·4 | 24·3 |

* *Procedure.*—A solution of the 1-acetamidoimidazole in 24% hydrobromic acid was boiled under reflux for 1—1·5 h; the acid was evaporated off and the residue dissolved in water. Basification precipitated the *N*-amino-compounds.

Treatment of *N*-acetylbenzamidrazone (7) with bromoacetone or 2-bromo-2-phenylacetophenone gave only mixtures of 3-methyl-5-phenyltriazole and the hydrobromide of the starting acetylbenzamidrazone. With bromoacetaldehyde the acetamido-compound (27) was obtained and isolated as the picrate but only in low yield. The action of bromoacetaldehyde oxime on *N*-acetylbenzamidrazone yielded a gum which when boiled in

Calc. for $C_9H_{11}N_3O$: C, 61·0; N, 6·3; N, 23·7%). The *picrate* formed yellow prisms, m.p. 156—158° (from nitromethane) (Found: C, 43·95; H, 3·7; N, 20·55. $C_9H_{11}N_3O$,-$C_6H_3N_3O_7$ requires C, 44·3; H, 3·5; N, 20·7%).

4-(1-*Benzoylethyl*)-3-*methyl*-5-*phenyl*-1,2,4-*triazole Hydrobromide* (26).—(*a*) *N*-Acetylbenzamidrazone (0·2 g) and 2-bromopropiophenone (0·24 g) were dissolved in ethanol;

[11] A. Pinner, *Annalen*, 1897, **297**, 221.

TABLE 3

1-Amino-3-methylimidazolium salts *

| Precursor | Product | X | Yield (%) | Cryst. solvent | M.p. (°C) | Found (%) C | H | N | Rqd. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (13) | (16) | I | 85 | EtOH–$Et_2O$ | 188—189 | 51·1 | 4·4 | 11·1 | 50·9 | 4·3 | 11·1 |
| | (16) | Br [a] | | MeOH–$Et_2O$ | 162—163 | 56·5 | 5·2 | 12·0 | 56·6 | 5·1 | 12·4 [b] |
| (14) | (17) | I | 74 | MeOH–$Et_2O$ | 182—183 | 52·5 | 4·7 | 10·7 | 52·2 | 4·6 | 10·7 |
| | (17) | Br [a] | | MeOH–$Et_2O$ | 184—185 | 59·4 | 5·25 | 12·2 | 59·3 | 5·3 | 12·2 |
| (15) | (18) | I | 61 | MeOH–$Et_2O$ | 96—98 | 40·9 | 4·8 | 12·9 | 40·8 | 4·7 | 13·0 |
| | (18) | $C_6H_2N_3O_7$ | | $H_2O$ | 152—153 | 48·6 | 3·9 | 20·1 | 49·0 | 3·9 | 20·2 |
| | (18) | Br [a] | | MeOH–$Et_2O$ | 133 | 47·1 | 5·4 | 15·1 | 47·6 | 5·5 | 15·2 [b] |

* *Procedure.*—The base was boiled under reflux in MeI–MeOH for 16—24 h, then the mixture was evaporated to dryness. The residue was triturated with ether until solid and then recrystallized.

[a] Prepared from the iodide by ion-exchange of an ethanolic solution on Amberlite IRA–400($Br^-$). [b] For the hemihydrate.

TABLE 4

1,2,5-Trisubstituted imidazoles *

| Precursor | Base | Purification | M.p. (°C) | Found (%) C | H | N | Rqd. (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (16) | (19) | Cryst. from EtOH–$H_2O$ | 197 | 82·2 | 6·0 | 11·7 | 82·0 | 6·0 | 12·0 |
| (17) | (20) | Bulb-tube distillation | *a* | 81·5 | 6·7 | 10·9 | 82·2 | 6·5 | 11·3 |
| | (20) picrate) | Cryst. from $MeNO_2$–$Et_2O$ | 134—136 | 57·8 | 3·9 | 14·4 | 57·9 | 4·0 | 14·7 |
| (18) | (21) | Evaporation on to a cold finger at 98° and 0·1 mmHg | 76—77·5 [b] | 76·7 | 6·8 | 16·1 | 76·7 | 7·0 | 16·3 |

* *Procedure.*—An ice-cold solution of the 1-aminoimidazolium salt in 9N-sulphuric acid was treated with an excess of saturated ice-cold aqueous sodium nitrite. After 5 min the solution was neutralized with 4N-sodium hydroxide and the base extracted into ether. After evaporation of the dried extract the residue was purified as indicated.

[a] B.p. 180° (bath temp.) at 5 mmHg. [b] Lit.,[10] 76°.

TABLE 5

1,1′-Azoimidazolium salts *

| Starting bromide | Sat. aq. bromine (ml) | Product) | Yield (%) | Cryst. solvent | M.p. (°C) | Found (%) C | H | N | Rqd. (%) C | H | N | $\lambda_{max}$ ($H_2O$)/nm (log ε) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (16) 0·66 g | 110 | (22) | 61 | MeOH–$Et_2O$ | 199—201 | 53·9 | 4·6 | 11·4 | 54·0 | 4·8 | 11·8 [a] | 199(4·90), 253(4·70), 358(3·98) |
| | | (22) dipicrate) | | $MeNO_2$–$Et_2O$ | 215—216 | 55·5 | 3·6 | 17·4 | 55·5 | 3·4 | 17·6 | |
| (17) 0·2 g | 33 | (23) | 78 | EtOH–$Et_2O$ | 143—144 | 56·4 | 5·0 | 11·2 | 56·7 | 5·0 | 11·7 [b] | 194(4·93), 241(4·52), 343(3·89) |
| | | (23) dipicrate) | | $MeNO_2$–$Et_2O$ | 156—158 | 56·2 | 3·8 | 16·5 | 56·3 | 3·7 | 17·1 | |
| (18) 0·55 g | 68 | (24) | 60 | MeOH–$Et_2O$ | 243 | 45·1 | 4·8 | 14·4 | 45·0 | 5·2 | 14·3 [a] | 200(4·79), 239(4·46), 333(3·98) |
| | | (24) dipicrate | | $MeNO_2$–$Et_2O$ | 213—215 [c] | 49·2 | 3·45 | 20·3 | 49·3 | 3·4 | 20·3 | |

* *Procedure.*—Saturated aqueous bromine was rapidly added to a saturated aqueous solution of the base. The precipitated perbromides were filtered off and boiled in absolute acetone, and the resulting tetrazenes were filtered off.

[a] For the trihydrate. [b] For the dihydrate. [c] Decomp.

the ethanol was boiled off and the resulting melt was heated at 140° for 1 h. The cooled mixture was dissolved in methanol; the solution was concentrated and decolourized with charcoal. Addition of ether precipitated the *hydrobromide* (0·116 g, 28%), m.p. 182—184° (from ethanol–ether) (Found: C, 58·3; H, 4·9; N, 11·3. $C_{18}H_{17}N_3O$,HBr requires C, 58·1; H, 4·9; N, 11·3%).

(*b*) 3-Methyl-5-phenyl-1,2,4-triazole [7] (0·2 g) and 2-bromopropiophenone (0·24 g) were heated together at 140° for 1 h. The cooled mixture was dissolved in methanol and ether was added. The precipitated *hydrobromide* (0·31 g, 68%) crystallized from methanol–ether as prisms, m.p. 182—184°, identical with sample described in (*a*).

1-(2,4-*Dinitrophenyl*)-3-*methylimidazolium Chloride*.—A solution of 1-methylimidazole (2·5 g) and 2,4-dinitrochlorobenzene (5 g) in acetone (10 ml) was boiled under reflux for 5 min. Ether was added to the cooled mixture and the *chloride* was filtered off; buff prisms (2·02 g, 23%), m.p. 244—247° (decomp.) (from ethanol–ether) (Found: C, 42·2; H, 3·3; N, 19·5. $C_{10}H_9ClN_4O_4$ requires C, 42·2; H, 3·2; N, 19·7%). The only product isolated when the chloride was treated with hydrazine hydrate by the procedure of ref. 6 was 2,4-dinitrophenylhydrazine.

1,8-*Diamino*-1,8-*diphenyl*-2,3,6,7-*tetra-azaocta*-1,3,5,7-*tetraene* (28).—A solution of *N*-acetylbenzamidrazone (1·0 g) and bromoacetaldehyde oxime (2·0 g) in chloroform (30 ml) and methanol (10 ml) was boiled under reflux for 4 h, then evaporated under reduced pressure. The residual oil was dissolved in 24% hydrobromic acid (30 ml) and boiled under reflux for 0·5 h. The *dihydrobromide* which crystallized on cooling was filtered off and gave yellow prisms, m.p. 229—239° (from methanol–ether) (Found: C, 42·1; H, 4·2; N, 18·1. $C_{16}H_{16}N_6$,2HBr requires C, 42·3; H, 4·0; N, 18·5%). The free base (0·18 g, 11·0%) crystallized from ethanol as yellow plates, m.p. 257° (lit.,[11] 220°) (Found: C, 65·45; H, 5·6; N, 28·4. Calc. for $C_{16}H_{16}N_6$: C, 65·7; H, 5·5; N, 28·75%), identical with a sample prepared by the procedure of Pinner.[11]

We thank Allen and Hanburys for a maintenance grant (to K. T. R.).

[2/1369 *Received*, 14*th June*, 1972]