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BENZO- AND INDOLOQUINOLIZINE DERIVATIVES—V[a]

A NOVEL ROUTE TO 6,7-DIHYDRODIBENZO[a,f]QUINOLIZINIUM SALTS AND TO 1,2,3,4,10,11-HEXAHYDROTRIBENZO[a,c,h]QUINOLIZINIUM SALTS

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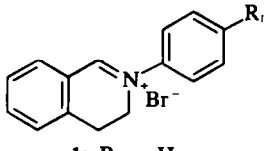
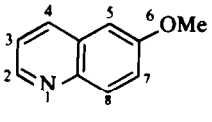
Abstract—The reaction between paraldehyde, acetone or cyclohexanone, and 2 - phenyl - 3,4 - dihydroisoquinolinium salts gives rise to 6,7 - dihydrodibenzo[a,f]quinolizinium salts and 1,2,3,4,10,11 - hexahydrotribenzo[a,c,h]quinolizinium salts.

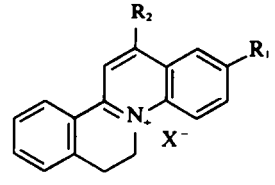
An attempt to crystallize 2 - phenyl - 3,4 - dihydroisoquinoliniumbromide (**1**) from acetone and a few drops of 48% HBr, resulted in the conversion of (**1**) into a new compound, characterized as 6,7 - dihydro - 13 - methyldibenzo[a,f]quinolizinium-bromide (**3**) from spectral data.

The peak at the highest *m/e* ratio (*m/e* 245, $C_{18}H_{15}N$, 100% rel. int.) in the mass spectrum of **3** corresponds to the molecular ion of the compound formed thermally by Hofmann elimination of HBr from the salt. This thermal decomposition before ionisation is a characteristic of salts having an aliphatic H atom β to the nitrogen.[2]



1: $R_1 = -H$
2: $R_1 = -OMe$





3: $R_1 = -H$, $R_2 = -Me$; $X^- = Br^-$
4: $R_1 = -OMe$, $R_2 = -Me$; $X^- = Br^-$
5: $R_1 = -H$, $R_2 = -H$; $X^- = ClO_4^-$
6: $R_1 = -OMe$, $R_2 = -H$; $X^- = Br^-$

The only important fragmentation observed, is the loss of a Me radical from the molecular ion, giving rise to a peak at a mass 230 ($C_{17}H_{12}N$, 11% rel. int.). The NMR spectrum shows the presence of a Me group at an aromatic C atom, at δ 4·2 ppm (3H, s), of the $-CH_2CH_2-$group as two triplets centered at δ 3·5 ppm (2H, J = 7·0 Hz) and δ 5·15 ppm (2H, J = 7·0 Hz) respectively and of 9 aromatic protons. The position of the Me group can be deduced from the comparison of the high resolution NMR spectra in CF_3COOH of 6-methoxy-quinoline (**7**)[3] with the spectra of **4** and **6** in the same solvent, as shown in Table 1.

Structure **3** agrees well with the data discussed. Nevertheless, additional confirmation is given by the results of the reduction of the quaternary salt **5**, as will be discussed later.

The course of the crystallization prompted us to investigate the possibility that other ketones or aldehydes might react in the same way as acetone with the salts **1** and **2**. The reaction of **1** and **2** with acetone in the presence of 48% HBr gave 6,7 - dihydro - 13 - methyldibenzo[a,f]quinolizinium-bromide (**2**) and its 2-methoxy analogue (**3**) in yields of 46% and 45% respectively.

Experiments, performed in the absence of any acid, led to the same results. From the reaction of **1**

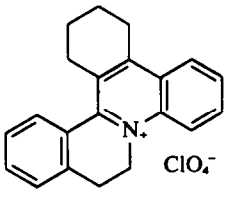
*Part IV: see Ref 1.

Table 1

	H_2^*	H_3^*	H_4^*	H_5^*	H_6^*	H_7^*	H_8^*
7[3]	8·92	8·09	9·08	7·65	—	7·95	8·29
4	—	8·29	—	7·67	—	7·85	8·41
6	—	8·42	8·88	7·60	—	7·87	8·42

*Relative to the numbering of quinoline.

and 2 with paraldehyde in ethanol, the 6,7 - dihydrodibenzo[a,f]quinolizinium salt, isolated as the perchlorate (5), and its 2-methoxy analogue (6) were obtained in yields of 35% and 44%, respectively, whereas the reaction of cyclohexanone and 1 gave 1,2,3,4,10,11 - hexahydrotribenzo[a,c,h]quinoliziniumperchlorate (8) in a yield of 41%.



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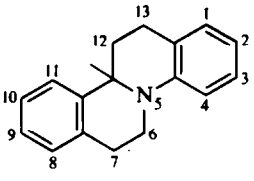

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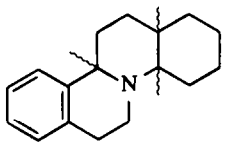

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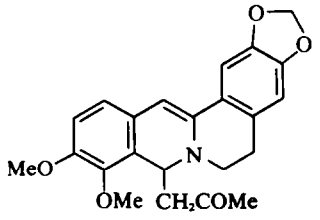
Hydrogenation of the quinolizinium salt (5) over Adams' catalyst in ethanol for 7 hr gave 6,7,12,13 - tetrahydro - 11bH - dibenzo[a,f]quinolizine (9). The PMR spectrum of 9 at 270 MHz shows a characteristic pattern for the C_6, C_7, C_{11b}, C_{12} and C_{13}-protons of the dibenzo[a,f]quinolizine system, which is identical with the pattern of the same protons in 6,7,12,13 - tetrahydro - 15bH - 9,10 - dimethoxydibenzo[a,f]quinolizine, obtained by a known synthetic route.[4] A longer reaction time (40 hr) resulted in the absorption of 5 mole H_2 with complete reduction of the quinolinium system, giving rise to a decahydro compound, the D - homo - 8 - azasteroid (10), as shown by mass spectrometry ($M^+ = 241$, 4% rel. int.; *m/e* 198, 100% rel. int., by a classic[5] propyl elimination from the D-ring of the molecular ion of 10, as proven by an appropriate metastable at *m/e* 162·5).

The results of the reduction agree well with structure 5 and also, by analogy, with the structure assignment of 3, 4, 6 and 8.

It has been known for some time[6] that 3,4-dihydroisoquinolinium salts and isoquinolinium salts will react at position 1 with acetone in the presence of alkali. When berberine is treated with the nucleophilic anion of acetone, crystalline berberine-acetone (11) is obtained.[7] Treatment, however, of an acetone adduct with acid, results in the almost quantitative recovery of the quaternary salt.[8]



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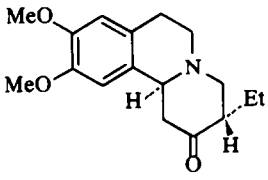

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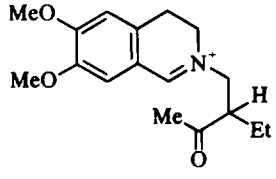

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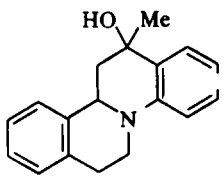
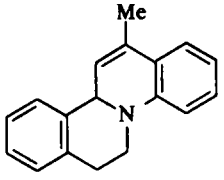
Openshaw *et al.*[9] attributed the racemisation in acidic conditions of the ketone (12) to an interconversion of the benzo[a]quinolizine (12) and the 3,4-dihydroisoquinolinium structure (13). This is believed to be the first example of the reaction of a methylketone at position 1 of the 3,4-dihydroisoquinolinium system in the presence of acid.

Actually, the enolic form of the aldehyde or ketone can initiate the reaction by attacking the position 1 of the isoquinolinium system (1). The possibility of further intramolecular electrophilic reaction of the carbonium ion on the activated *ortho* position of the N-arylsubstituent, with formation of a 6-membered ring is likely to be the driving force of the reaction. This would give rise, after elimination of HBr, to the compound (14), which easily eliminates water in the presence of acid to give 15. The presence of 3, instead of 15 as the final product of the reaction can be explained by a hydride transfer, as is frequently encountered with 1,2-dihydroquinolines,[10] between the starting material (1) and the intermediate (15). The fact that the reduced compounds (16 and 17) were isolated from the mixtures agrees well with the presented mechanism. Thus, the theoretical yield in 6,7 - dihydrodibenzo[a,f]quinolizinium salt cannot exceed 50%. Nevertheless, the question whether the principal reaction, giving rise to the intermediate (14), must be regarded as proceeding in two distinct steps, as described above, or as a 1,4-polar cycloaddition,[11] involving a concerted mechanism, still remains. Work is in progress to elucidate the mechanism concerned.

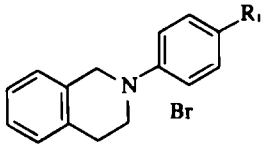
Although the dibenzo[a,f]quinolizinium cation



14: (not isolated)



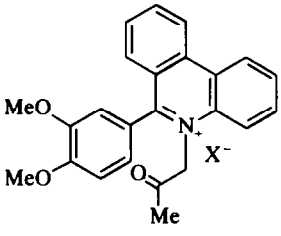
15: (not isolated)



16: $R_1 = -H$
17: $R_1 = -OMe$

and its 6,7-dihydro derivative are accessible by other synthetic routes,[12] some of them require specific substituents, activating the position where ring closure occurs, while our synthesis uses an activating group built into the cyclic system.

Remarkably few syntheses of the tribenzo[a,c,h]quinolizine skeleton have appeared in the literature, although Bradsher *et al.*[13] have developed a successful route from 5 - acetonyl - 6 - arylphenanthridinium salts such as **18**. We ourselves reported a route to 10,11 - dihydro - 15bH - tribenzo[a,c,h]quinolizines[14] (**19**) and to the different stereoisomeric 4a,5,6,7,8,8a,10,11 - octahydro - 15bH - tribenzo[a,c,h]quinolizines[15] (**20**).



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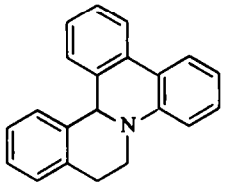

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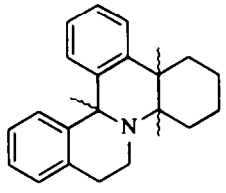

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EXPERIMENTAL

M.ps were determined on a Mettler FP 5 apparatus. IR spectra were determined on a Perkin-Elmer 237 spectrometer. NMR-spectra were obtained either with a Varian T60, or a Bruker HFX 90 or a Bruker HDX 270 spectrometer; chemical shifts were expressed in ppm downfield from TMS as an internal standard. Mass spectra were obtained with an AEI-MS 902S mass spectrometer operating at 70 eV, samples were introduced via the direct insertion lock with a source temperature of 190 to 240°C.

2-Phenyl-3,4-dihydroisoquinoliniumbromide (**1**) was prepared as described by Beke *et al.*,[16] yield: 95%. The crude product was employed, without further purification. The perchlorate of **1** ($X^- = ClO_4^-$) was prepared by treating the pseudocyanide of **1** [m.p. 97° from EtOH (Lit.[16] m.p. 96–96·5°)] in benzene with 70% $HClO_4$, m.p. 184° from EtOH. (Found: C, 58·5; H, 4·61; N, 4·51. $C_{15}H_{14}NO_4Cl$ requires: C, 58·6; H, 4·59; N, 4·55%).

2 - (4 - *Methoxyphenyl*) - 3,4 - *dihydroisoquinoliniumbromide* (**2**) was obtained as a solid by adding slowly *p*-anisidine (8·61 g) in dioxane (25 ml) to 2 - (β - bromoethyl) - benzaldehyde[17] (14·92 g) in dioxane (50 ml). Two recrystallizations from MeOH/EtOAc (1/4) yielded the pure quaternary bromide (82% yield) m.p. 151° as yellow leaflets; ν_{max} cm^{-1}, 1630, 1600, 1250, 1185, 1025, 1020, 770, 755; NMR (CF_3COOH, 90 MHz) ppm, 3·53 (2H, t, J = 8·0 Hz), ($-C^4H_2$); 3·99 (3H, s), ($-OCH_3$); 4·62 (2H, t, J = 8·0 Hz), ($-C^3H_2$); 7·14–7·97 (8H, m), ($-C^5H$, $-C^6H$, $-C^7H$, $-C^8H$, C_6H_4=); 9·01 (1H, s), ($-C^1H$). (Found: C, 59·8; H, 5·38; N, 4·49. $C_{16}H_{16}NOBr$ requires: C, 60·4; H, 5·07; N, 4·40%). The perchlorate salt of **2** ($X^- = ClO_4^-$) was obtained by treating an aqueous soln of **2** ($X^- = Br^-$) with 70% $HClO_4$, m.p. 157° from EtOH. (Found: C, 56·9; H, 4·80; N, 4·16. $C_{16}H_{16}NO_4Cl$ requires: C, 56·9; H, 4·78; N, 4·15%).

6,7 - *Dihydro* - 13 - *methyldibenzo[a,f]quinoliziniumbromide* (**3**) was obtained by heating, at 60°, for 45 min, a mixture of **1** (5·77 g) and acetone (100 ml). After cooling overnight, the yellow salt **3** (3·01 g, 46%) was collected, m.p. 201°; ν_{max} (KBr) cm^{-1}, 1615, 1600, 1565, 1380, 900, 785, 765, 755, 740; NMR (CF_3COOH – 60 MHz) ppm, 3·1 (3H, s), (CH_3–); 3·5 (2H, t, J = 7·0 Hz), ($-C^7H_2$); 5·0 (2H, t, J = 7·0 Hz), ($-C^6H_2$); 7·5–8·7 (9H, m), (C^1, C^2, C^3, C^4, C^8, C^9, C^{10}, C^{11} and C^{12} H's); *m/e* = 245·1185, $C_{18}H_{15}N$ requires 245·1204; MS, *m/e* (rel. int.): 80 (8), 82 (8), 108·5 (7), 115 (5), 120·5 (5), 121·5 (4), 122·5 (5), 217 (5), 230 (11), 241 (7), 242 (8), 243 (11), 244 (33), 245 (100), 246 (19). Evaporation of the mother liquor yielded **16** as an oil (3·6 g) which crystallized from a minimum acetone. 2 - Phenyl - 1,2,3,4 - tetrahydroisoquinoline was characterized as the free base, m.p. 45° from EtOH (Lit.[18] m.p. 44·5–45·5°).

6,7 - *Dihydro* - 2 - *methoxy* - 13 - *methyldibenzo[a,f]quinoliziniumbromide* (**4**) was similarly prepared from the corresponding salt **2** (3·18 g) in acetone (50 ml), by heating for 3½ hr, as yellow needles (1·59 g, 45%) from EtOH/acetone (2/1) m.p. 275°; ν_{max} (KBr) cm^{-1}, 1615, 1570, 1380, 1230, 815, 790; NMR (CF_3COOH, 60 MHz) ppm, 3·1 (3H, s), (CH_3–); 3·4 (2H, t, J = 7·0 Hz), ($-C^7H_2$); 4·2 (3H, s), ($-OCH_3$); 5·1 (2H, t, J = 7·0 Hz), ($-C^6H_2$); 7·4–8·5 (8H, m), (C^1, C^3, C^4, C^8, C^9, C^{10}, C^{11} and C^{12} H's); *m/e* 275·1297, $C_{19}H_{17}NO$ requires 275·1309; MS, *m/e* (rel. int.): 80 (13), 82 (13), 108·5 (11), 137·5 (9), 217 (13), 230 (10), 231 (13), 232 (10), 244 (9), 245 (21), 246 (11), 260 (18), 274 (82), 275 (100), 276 (20). (Found: C, 64·1; H, 5·11; N, 3·92; Br, 22·5. $C_{19}H_{18}NOBr$ requires C, 64·1; H, 5·09; N, 3·93; Br, 22·4%). By partial evaporation of the mother liquor, **17** (1·09 g, 34%) was collected as a yellow solid. The base was liberated and crystallized from EtOH, m.p. 94° (Lit.[18] m.p. 93–95°); ν_{max} (KBr) cm^{-1}, 3000, 2920, 2805, 1510, 1270, 1240, 1035, 825,

755; NMR ($CDCl_3$, 90 MHz) ppm, 2·91 (2H, t, J = 5·5 Hz), ($-C^5H_2$ or $-C^6H_2$); 3·38 (2H, t, J = 5·5 Hz), ($-C^6H_2$ or $-C^5H_2$); 3·71 (3H, s), ($-OCH_3$); 4·22 (2H, s), ($-C^1H_2$); 6·72–7·18 (8H, m), ($-C^5H$, $-C^6H$, $-C^7H$, $-C^8H$, $=C_6H_4$); M^+ = 239 (100% rel. int.).

6,7 - *Dihydro[a,f]quinoliziniumperchlorate* (**5**) was obtained by heating, at 80°, for 1½ hr, a mixture of the salt **1** (5·76 g), paraldehyde (30 ml) and EtOH (30 ml). The EtOH and the aldehyde were evaporated, the oily solid poured into water and extracted with ether. Addition of 70% perchloric acid to the inorganic phase precipitated **5** (2·34 g, 35%), m.p. (EtOH): 240°; ν_{max} (KBr) cm^{-1}, 3070, 1620, 1605, 1570, 1530, 1355, 1305, 1080, 770, 740; NMR (CF_3COOH, 60 MHz) ppm, 3·6 (2H, t, J = 7·0 Hz), ($-C^7H_2$); 5·3 (2H, t, J = 7·0 Hz), ($-C^6H_2$); 7·6–8·7 (9H, m), (C^1, C^2, C^3, C^4, C^8, C^9, C^{10}, C^{11} and C^{12} H's); 9·05 (1H, d, J = 9·0 Hz), ($-C^{13}H$); *m/e* = 245·0863, $C_{17}H_{11}NO$* requires 245·0840; *m/e* = 230·0974, $C_{17}H_{12}N$ requires 230·0969; MS, *m/e* (rel. int.): 36 (67), 38 (21), 44 (67), 107·5 (15), 108·5 (25), 215 (17), 216 (47), 217 (70), 228 (12), 230 (80), 231 (24), 232 (11), 244 (33), 245 (100), 246 (20).

When the mixture was allowed to stand for several days, **5** ($X^- = Br^-$) was obtained as a microcrystalline solid in poor yield (13%), m.p. 232°; MS, *m/e* (rel. int.): 80 (20), 82 (20), 108·5 (10), 114 (14), 115 (19), 115·5 (13), 217 (19), 228 (15), 229 (12), 230 (100), 231 (38), 232 (76), 233 (32), 234 (7).

6,7 - *Dihydro* - 2 - *methoxydibenzo[a,f]quinoliziniumbromide* (**6**) was prepared by heating, at 80°, for 3½ hr, a mixture of the salt **2** (6·36 g), paraldehyde (30 ml), and EtOH (40 ml). The yellow solid **6** was collected and recrystallized from EtOH, m.p. 239° (2·97 g, 44%); ν_{max} (KBr) cm^{-1}, 1620, 1605, 1570, 1385, 1265, 870, 820, 780, 755; NMR (CF_3COOH, 60 MHz) ppm, 3·5 (2H, t, J = 7·0 Hz), ($-C^7H_2$); 4·2 (3H, s), ($-OCH_3$); 5·15 (2H, t, J = 7·0 Hz), ($-C^6H_2$); 7·7–8·5 (8H, m), (C^1, C^3, C^4, C^8, C^9, C^{10}, C^{11} and C^{12} H's); 8·9 (1H, d, J = 9·0 Hz), ($-C^{13}H$); *m/e* = 261·1148, $C_{18}H_{15}NO$ requires 261·1153; MS, *m/e* (rel. int.): 94 (13), 96 (12), 108·5 (10), 217 (45), 218 (12), 246 (24), 247 (10), 260 (100), 261 (45), 262 (41), 263 (16). (Found: C, 63·2; H, 4·75; N, 4·00; Br, 23·4. $C_{18}H_{16}NOBr$ requires: C, 63·2; H, 4·71; N, 4·09; Br, 23·4%).

1,2,3,4,10,11 - *Hexahydrotribenzo[a,c,h]chinoliziniumperchlorate* (**8**) was prepared as described for **5** by heating for 6 hr, at 80°, a mixture of the bromide **1** (5·76 g), cyclohexanone (30 ml) and EtOH (40 ml). The perchlorate **8** (3·13 g, 41%), was obtained as a white solid, which recrystallized from EtOH or $EtOH/CH_3CN$ (4/1) as white needles, m.p. 216°; ν_{max} (KBr) cm^{-1}, 2950, 1610, 1580, 1565, 1510, 1265, 1080 (br), 780, 770, 765, 740; NMR (CF_3COOH, 60 MHz) ppm, 1·8–2·5 (4H, m), ($-C^2H_2$, $-C^3H_2$); 3·2–3·7 (6H, m), ($-C^1H_2$, $-C^4H_2$, $-C^{11}H_2$); 5·0 (2H, t, J = 6·5 Hz), ($-C^{10}H_2$); 7·7–8·6 (8H, m), (C^5, C^6, C^7, C^8, C^{12}, C^{13}, C^{14} and C^{15} H's); *m/e* = 295·0999, $C_{21}H_{13}NO$* requires 295·0996; *m/e* = 280·1125, $C_{21}H_{14}N$ requires 280·1125; MS, *m/e* (rel. int.): 44 (77), 139 (15), 139·5 (12), 254 (11), 266 (18), 267 (20), 278 (20), 280 (100), 281 (58), 282 (19), 294 (17), 295 (34), 296 (12). (Found: C, 65·4; H, 5·26; N, 3·67; Cl, 9·22. $C_{21}H_{20}NO_4Cl$ requires: C, 65·4; H, 5·23; N, 3·63; Cl, 9·19%).

*Fragment originating from a thermal oxidation product of the organic cation by ClO_4^- before ionisation in the source of the mass spectrometer.[2,19]

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REFERENCES

[1]G. Van Binst and D. Tourwé, *Heterocycles* in press
[2]G. Van Binst and R. Salsmans, in preparation
[3]E. Diaz and P. J. Nathan, *Spectrochim. Acta* **25**, 1547 (1969)
[4]D. Tourwé, results Ph.D. thesis (1974)
[5]H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds* p. 307, Holden-Day, San Francisco (1967)
[6]R. C. Elderfield, *Heterocyclic Compounds*, Vol. 4, p. 462, Wiley, New York (1952)
[7]M. Shamma, *The Isoquinoline Alkaloids* p. 286. Academic Press, New York (1972)
[8]T.-K. Chen and C. K. Bradsher, *Tetrahedron* **29**, 2951 (1973)
[9]H. T. Openshaw and N. Whittaker, *J. Chem. Soc.* 1461 (1963)
[10]B. D. Tilak, T. Ravindranathan and K. N. Subbaswani, *Tetrahedron Letters* 1959 (1966)
[11]R. R. Schmidt, *Ibid.* 3443 (1968)
[12]D. W. Brown, S. F. Dyke, M. Sainsbury and W. E. D. Lugton, *Tetrahedron* **26**, 4985 (1970); A. Fozard and C. K. Bradsher, *J. Org. Chem.* **31**, 3683 (1966); L. Amoros-Marin and C. K. Bradsher, *J. Heterocyclic Chem.* **7**, 1421 (1970); T. Kametani, T. Terui and K. Fukumoto, *Yakugaku Zasshi* **88**, 1388 (1968); *Chem Abstr.* **70**, 77754 (6), (1968)
[13]C. K. Bradsher and K. B. Moser, *J. Org. Chem.* **24**, 592 (1959)
[14]G. Van Binst, R. B. Baert and R. Salsmans, *Synthetic Commun.* **3**, 59 (1973)
[15]G. Van Binst and R. B. Baert, *J. Heterocyclic Chem.* in press
[16]D. Beke, M. Barczai-Beke and L. Föcze, *Chem. Ber.* **95**, 1054 (1962)
[17]A. Rieche and E. Schmitz, *Ibid.* **89**, 1254 (1956)
[18]A. Rieche and E. Höft, *J. Prakt. Chem.* **288**, 295 (1962)
[19]R. Salsmans and G. Van Binst, *Org. Mass Spectrom.* **8**, 357 (1974)