Bromination of Certain Aryl Substituted Pyrrolidines

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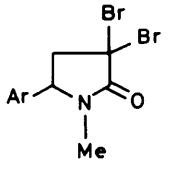
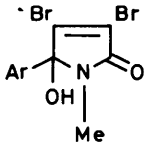
The structures of the bromination products of a number of aryl substituted pyrrolidines have been determined.

In the pioneering work of Pinner[1] on the structure of nicotine it was found that bromination of the latter gave two compounds which were named dibromocotinine and dibromoticonine. The structures originally given to these compounds have since been corrected to (**1**)[2] and (**2**)[3] respectively. Since there have been few studies on the bromination of pyrrolidines we report the results of the bromination of a number of such alkyl- and aryl-substituted compounds.[4]



(**1**) Ar = 3-pyridyl
(**3**) Ar = Ph
(**5**) Ar = C_6H_4F-*m*

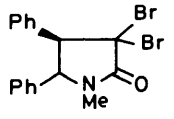


(**2**) Ar = 3-pyridyl
(**4**) Ar = Ph
(**6**) Ar = C_6H_4F-*m*

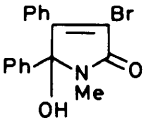
The bromination of 1-methyl 2-alkyl (methyl, isopropyl, cyclohexyl and benzyl) pyrrolidines gave complex mixtures of products. However 1-methyl-2-phenylpyrrolidine on bromination in hot aqueous hydrobromic acid gave as the sole product the dibromoticonine analogue (**3**) (46%). In order to obtain the dibromocotinine analogue (**4**) the bromination was conducted in aqueous acetic acid. In the case of 2-(3-fluorophenyl)-1-methyl pyrrolidine, bromination in hot aqueous hydrobromic acid gave a mixture of the dibromocotinine analogue (**5**), (46%) and the dibromoticonine analogue (**6**), (50%). The structures of these products were evident from their i.r. and ^{1}H n.m.r. spectra when compared with those of dibromocotinine (**1**) and dibromoticonine (**2**). The ^{13}C n.m.r. data for dibromocotinine and dibromoticonine and their analogues are given in Tables 1 and 2 respectively.

1-Methyl-2,3-diphenylpyrrolidine (*cis*/*trans* mixture) gave two major products. These were shown, by spectroscopic and elemental analysis to be the dibromocotinine analogue (**7**) and the hydroxypyrrolone (**8**). The ^{13}C n.m.r. spectra for these two compounds are given in Table 3. 1,2-Dimethyl-3-phenylpyrrolidine (*cis*/*trans* mixture) gave two major products which were shown to be the pyrrolidone (**9**) and the maleimide (**10**). The ^{13}C n.m.r. data for these two compounds are given in Table 4.

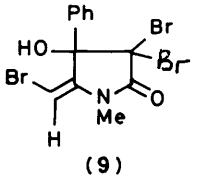
The stereochemistry of the exocyclic bromomethylene group in (**9**) was deduced to be (*E*) from a comparison of the ^{1}H n.m.r. spectra of (**9**) and its derived acetate. That there was no significant difference in the chemical shift for the olefinic proton in these two compounds suggests that it must be too remote for anistropic interaction with the acetate carbonyl group.



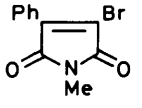
(**7**)



(**8**)



(**9**)



(**10**)

Finally both *cis*- and *trans*-1-methyl-2,5-diphenylpyrrolidine gave *cis*-1,2-dibenzoyl-1,2-dibromoethene, the yield of the *cis* product being substantially higher with the former (51%) than with the latter (11%). This may be a result of steric hindrance to attack by bromine in the *trans*-pyrrolidine relative to the *cis*-pyrrolidine.

It has been suggested[5] that dibromocotinine (**1**) is an intermediate in the formation of dibromoticonine (**2**) from nicotine. We have demonstrated that this is not the case; (**1**) is recovered unchanged when subjected to the bromination conditions which convert nicotine into (**2**).

Experimental

M.p.s were taken on an Electrothermal melting-point apparatus. ^{1}H N.m.r. spectra were taken on a Varian EM-360 spectrometer. I.r. spectra were taken on a Perkin-Elmer 157G instrument. ^{13}C N.m.r. spectra were taken on a Bruker WM-360 instrument.

1-Methyl-2-phenylpyrrolidine and 2-(3-fluorophenyl)-1-methylpyrrolidine were prepared as previously described.[6] 1,2-Dimethyl-3-phenylpyrrolidine and 1-methyl-2,3-diphenylpyrrolidine were prepared in the same manner from the appropriately substituted cyclopropyl ketones. 1-Methyl-2,5-diphenylpyrrolidine was prepared from *trans*-1-benzoyl-2-phenyl cyclopropane[7] and the pyrrolidine isomers were separated by chromatography. Dibromocotinine (**1**) (m.p. 124—125 °C) and dibromoticonine (**2**) (m.p. 199—200 °C) were prepared according to the literature.[2,3]

Bromination of 1-Methyl-2-phenylpyrrolidine.—In aqueous hydrobromic acid. Bromine (55.8 g, 0.35 mol) was added slowly with stirring to a solution of 1-methyl-2-phenylpyrrolidine (14 g, 85 mmol) in a mixture of 48% hydrobromic acid (14.6 ml, 0.085 mol) and water (100 ml) at 130 °C. On cooling, a solid was precipitated, and this was collected, stirred with methanol–

Table 1. ^{13}C N.m.r. data* for dibromocotinines

Carbon no.	(1)	(3)	(5)
2	167.3	167.1	167.3
3	54.8	55.1	55.0
4	51.7	52.4	52.0
5	58.6	60.8	60.4
Me	29.1	28.9	29.1

* Spectra recorded in $(CD_3)_2SO$, p.p.m. relative to $SiMe_4$

Table 2. ^{13}C N.m.r. data* for dibromoticonines

Carbon no.	(2)	(4)	(6)
2	162.5	162.5	162.6
3	120.8	119.8	120.3
4	132.6	145.2	144.6
5	90.9	92.6	91.5
Me	24.8	24.8	24.8

* Spectra recorded in $(CD_3)_2SO$, p.p.m. relative to $SiMe_4$

water (1:2), filtered off, and dried to yield 3,4-*dibromo*-5-*hydroxy*-1-*methyl*-5-*phenylpyrrol*-2(5H)-*one* (**4**) (13.8 g, 46%) which was crystallised from benzene, m.p. 190—191 °C; $\nu_{max.}$(Nujol) 1 690 (C=O) and 3 300 cm^{-1} (OH); δ [$CDCl_3$—$(CD_3)_2SO$] 7.5 (5 H, s, ArH), 5.8—6.8 (1 H, br, exchangeable D_2O, OH) and 2.8 (3 H, s, NMe); $\lambda_{max.}$(EtOH) 224 nm (log ε 4.05). A sample was further purified by sublimation (140 °C/0.05 mmHg), m.p. 193—194 °C. (Found: C, 38.1; H, 2.8; Br, 44.8, N, 4.1. $C_{11}H_9Br_2NO_2$ requires C, 38.0; H, 2.6; Br, 46.1; N, 4.0%).

(ii) *In aqueous acetic acid.* Bromine (12.4 g) was added to a solution of 1-methyl-2-phenylpyrrolidine (5 g, 0.31 mol) in 80% aqueous acetic acid (20 ml) and the mixture heated at *ca.* 80 °C for 2 h. The resulting precipitate was extracted with dichloromethane and the extract dried and concentrated to give a gum, column chromatography (silica/$CHCl_3$) of which gave 3,3-dibromo-1-methyl-5-phenyl-2-pyrrolidone (**3**), m.p. 84—85 °C (cyclohexane); $\nu_{max.}$(Nujol) 1 715 cm^{-1} (C=O); δ($CDCl_3$), 6.95—7.45 (5 H, complex, ArH), 4.55 (1 H, dd, *J* 6 and 8 Hz, 2-H), 3.52 (1 H, dd, *J* 8 and 15 Hz, *trans* 3-H), 2.95 (1 H, dd, *J* 6 and 15 Hz, *cis* 3-H), and 2.27 (3 H, S, NMe). (Found: C, 39.85; H, 3.3; N, 4.2; Br, 48.4. $C_{11}H_{11}Br_2NO$ requires C, 39.67; H, 3.33; N, 4.2; Br, 47.99%).

Bromination of 2-(3-*Fluorophenyl*)-1-*methylpyrrolidine.*—A solution of the above pyrrolidine (4.0 g, 23 mmol) in a mixture of 48% hydrobromic acid (3.8 ml, 20 mmol) and water (50 ml) was heated to 130 °C and bromine (21.5 g, 0.135 mol) was gradually added with stirring. After being cooled, the solid precipitate was extracted with chloroform and the extract dried and concentrated under reduced pressure. Column chromatography (silica gel/$CHCl_3$) gave first 3,3-*dibromo*-5-(3-*fluorophenyl*)-1-*methyl*-2-*pyrrolidone* (**5**) (3.4 g), m.p. 83—84 °C $\nu_{max.}$(Nujol) 1 725 cm^{-1} (C=O) δ ([$^2H_6$]DMSO) 6.9—7.7 (4 H, complex, ArH), 4.80 (1 H, dd, *J* 6 and 8 Hz, 2-H), 3.70 (1 H, dd, *J* 8 and 14 Hz, *cis*-3-H), 3.02 (1 H, dd, *J* 6 and 14 Hz, *trans*-3-H), and 2.87 (3 H, s, NMe) (Found: C, 37.7; H, 2.8; Br, 45.0; N, 3.9. $C_{11}H_{10}Br_2FNO$ requires C, 37.6; H, 2.9; Br, 45.5%; N, 4.0), followed by 3,4-*dibromo*-5-(3-*fluorophenyl*)-5-*hydroxy*-1-*methyl*-*pyrrol*-2(5H)-*one* (**6**) (4.09 g), m.p. 193—194 °C, (ether–benzene) $\nu_{max.}$(Nujol) 1 680 cm^{-1} (C=O) and 3 440 cm^{-1} (OH); δ[$(CD_3)_2SO$], 7.70 (1 H, s, exchangeable D_2O, OH), 6.9—7.7 (4 H, complex, ArH), and 2.77 (3 H, s, NMe); $\lambda_{max.}$(EtOH) 224 (log ε 4.00), 263 (3.26), and 271 (3.14) (Found: C, 36.1; H, 2.2; Br, 43.4; N, 3.8. $C_{11}H_8Br_2FNO_2$ requires C, 36.2; H, 2.2; N, 3.8; Br, 43.8%).

Table 3. ^{13}C n.m.r. data*

Carbon no.	(7)	(8)
2	—	163.7
3	—	115.6
4	64.1	136.9
5	64.5	92.4
Me	28.8	22.2

* Spectra recorded in $(CD_3)_2SO$, p.p.m. relative to $SiMe_4$

Table 4. ^{13}C n.m.r. data*

Carbon no.	(9)	(10)
2	164.1	165.3
3	47.0	122.5
4	91.8	139.2
5	152.2	168.3
=CHBr	118.6	—
Me	25.4	24.4

* Spectra recorded in $(CD_3)_2SO$, p.p.m. relative to $SiMe_4$

Bromination of 1-*Methyl*-2,3-*diphenylpyrrolidine.*—Bromine (6.75 g, 42 mmol) was added slowly with stirring to a solution of the above pyrrolidine (2 g, 0.84 mmol) in 48% hydrobromic acid (1.4 ml, 8.4 mmol) and water (25 ml) at 110 °C. The mixture was cooled and the precipitate was extracted with chloroform, and the extract dried and concentrated under reduced pressure to give a solid. This was crystallised from ethanol to give 3,3-*dibromo*-1-*methyl*-4,5-*diphenyl*-2-*pyrrolidone* (**7**) (0.08 g), m.p. 214—215 °C $\nu_{max.}$ 1 715 cm^{-1} (C=O); δ[$(CD_3)_2SO$], 7.3—7.7 (10 H, ArH), 4.99 (1 H, d, *J* 9 Hz, 4-H), 3.94 (1 H, d, 5-H, *J* 9 Hz), and 2.65 (3 H, s, NMe) (Found: C, 50.2; H, 3.5; Br, 39.2; N, 3.2. $C_{17}H_{15}Br_2NO$ requires C, 49.88; H, 3.67; Br, 39.09; N, 3.42%). The filtrate from the above crystallisation was evaporated under reduced pressure to leave a solid which was triturated with chloroform and crystallised from acetone to give 3-*bromo*-5-*hydroxy*-1-*methyl*-4,5-*diphenylpyrrol*-2(5H)-*one* (**8**) (0.5 g), m.p. 223—224 °C, $\nu_{max.}$ 1 695 (C=O) and 3 285 cm^{-1} (OH); δ[$(CD_3)_2CO$—$(CD_3)_2SO$] 7.1—7.7 (10 H, complex, ArH), 3.1 (1 H, s, OH), 2.7 (3 H, s, NMe); $\lambda_{max.}$(ethanol) 252 nm, (log ε 4.39) and 291 (4.26) (Found: C, 59.3; H, 4.1; Br, 23.4; N, 4.0. $C_{17}H_{14}BrNO_2$ requires C, 59.24; H, 4.06; Br, 23.2; N, 4.06%).

Bromination of 1,2-*Dimethyl*-3-*phenylpyrrolidine.*—Bromine (13.7 g, 75 mmol) was added slowly with stirring to the above pyrrolidine (3 g, 17 mmol) dissolved in 48% hydrobromic acid (3.0 ml, 17 mmol) and water (25 ml) at *ca.* 120 °C. After the mixture had been cooled the solid precipitate was extracted with ether and the extract dried and concentrated under reduced pressure. Column chromatography (silica/$CHCl_3$) gave first a yellow solid (0.61 g) identified as 3-*bromo*-1-*methyl*-4-*phenylmaleimide* (**10**), m.p. 84—85 °C, (hexane), $\nu_{max.}$ 1 775 (C=O) minor and 1 710 cm^{-1} (C=O) major; δ[$(CD_3)_2SO$], 7.75—7.8 (2 H, complex, ArH), 7.5—7.6 (3 H, complex, ArH), and 7.0 (3 H, NMe); *m/z* {mass, (intensity), [isotope pattern associated with mass]} 267 (61.83), 265 (61.83) [1:1], 209 (4.13), 207 (4.32) [1:1], 182 (7.13), 180 (7.16) [1:1], 130 (18.32), 129 (100), and 101 (17.5) (Found: C, 49.7; H, 3.05; N, 5.2; Br, 29.95. $C_{11}H_8BrNO_2$ requires C, 49.62; H, 3.03; N, 5.26; Br, 30.0%), followed by 3,3-*dibromo*-5-*bromomethylene*-4-*hydroxy*-1-*methyl*-4-*phenyl*-2-*pyrrolidone* (**9**) (0.88 g), m.p. 179—180 °C, (light petroleum–benzene), $\nu_{max.}$ 1 705 (C=O) and 3 060—3 460 cm^{-1} (OH); δ[$CDCl_3$–$(CD_3)_2SO$], 8.02 (1 H, s, OH), 7.65—7.95 (2 H, complex ArH), 7.35—7.65 (3 H, complex, ArH), 5.5 (1 H, s, =CHBr), and 7.0 (3 H, s, NMe) (Found: C, 32.8; H, 2.3; Br, 54.6;

N, 3.05. $C_{12}H_{10}Br_3NO_2$ requires C, 32.68; H, 2.51; Br, 54.37; N, 3.17%). Acetylation with acetic anhydride (2 equiv.) pyridine (2 equiv.) and 4-dimethylaminopyridine (0.01 equiv.) in methylene dichloride at room temperature gave the acetate (96%), m.p. 169—170 °C; $\nu_{max.}$ 1 715 (C=O) and 1 755 cm^{-1} (C=O). $\delta(CDCl_3)$, 7.15—7.6 (5 H, s, ArH), 5.5 (1 H, s, =CHBr), 3.1 (3 H, s, NMe), 2.25 (3 H, s, OAc) (Found: C, 34.85; H, 2.5; N, 2.8. $C_{14}H_{12}Br_3NO_3$ requires C, 34.87; H, 2.5; N, 2.9%).

Bromination of cis-1-*Methyl*-2,5-*diphenylpyrrolidine*.—Bromine (6.75 g) was slowly added to the above pyrrolidone (2 g, 8.4 mmol) dissolved in 48% hydrobromic acid (1.42 ml, 8.4 mmol) and water (25 ml) at 125 °C. The mixture was cooled and the solid precipitate was extracted with dichloromethane and the extract dried and concentrated under reduced pressure. Column Chromatography (silica-gel; $CHCl_3$–MeOH 10%) of the residue gave cis-1,2-*dibenzoyl*-1,2-*dibromoethene* (1.7 g). A sample crystallised twice from ethanol gave amber coloured plates, m.p. 110—111 °C (lit.,[8] m.p. 108 °C), $\nu_{max.}$ 1 670 cm^{-1} (C=O); $\delta(CDCl_3)$, 7.6—8.0 (4 H, complex, ArH) and 7.1—7.6 (6 H, complex, ArH) (Found: C, 48.55; H, 2.6; Br, 40.95. $C_{16}H_{10}Br_2O_2$ requires C, 48.74; H, 2.56; Br, 40.58%).

Bromination of *trans*-1-methyl-2,5-diphenylpyrrolidine in similar manner also gave *cis*-1,2-dibenzoyl-1,2-dibromoethene (0.35 g, 11%), m.p. 109—111 °C.

Acknowledgements

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