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NITRATION STUDIES IN SOME β-CARBOLNIE BASES

Part II. Mononitro Derivatives of Ajmalicine and Serpentine*

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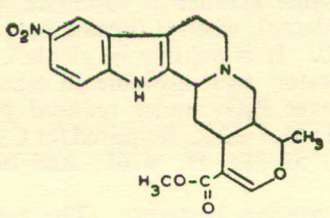
Abstract. The extension of nitration studies to ajmalicine and serpentine has revealed that in contrast to the other alkaloids of this series only one mononitro derivative instead of three position isomers is formed with threse two bases, the substitution taking place at C-10, according to spectral data. Furthermore, the reaction has to be carried out under comparatively more drastic conditions.

In continuation of the nitration studies in the ajmaline series of alkaloids[1,2] the reaction has been extended to two other Rauwolfia bases namely ajmalicine and serpentine. The nitration of ajmalicine had to be carried out in glacial acetic acid medium, with twice the molar quantity of the mixture used for reserpine. Altogether over 30 experiments had to be undertaken with 0.1–10 g quantities to establish the optimum conditions of this reaction. It was found that when a solution of ajmalicine in glacial acetic acid was treated with a mixture of (1 : 1) concd nitric acid and glacial acetic acid, and the reaction mixture was left over a period of 15 min, the initial yellow colour of the reaction mixture did not change much and nitrate of the nitro derivative started crystallising out.

Various procedures were tried out for working up the reaction products. One of these consisted in basifying the diluted reaction mixture with strong ammonia and then extracting it out with ethyl acetate and chloroform. As this apparently simple procedure adversely affected the yields of the pure nitro- base, the procedure described in experimental was ultimately adopted. The nitro- base thereby obtained formed bright yellow needles (yield 63%) m.p. 176–78°C and analysed for $C_{21}H_{23}O_5N_3$. Its hydrochloride, picrate and chloroplatinate were also prepared and analysed.

The location of the nitro group was ascertained by NMR spectrum. There is a signal at 2.8 τ due to H-12 (*J* 9, c/s, *ortho* coupling with H-11). It does not show any *meta* coupling. The signal of H-11 is at 1.74 and shows, in addition to the *ortho* coupling with H-12, a *meta* coupling with H-9 (*J* 2.3 c/s.)



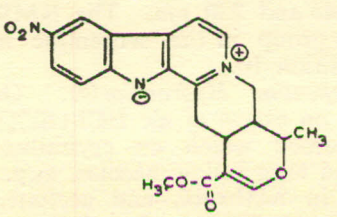
I

10-Nitroajmalicine (I) when reduced with zinc and acetic acid in the hot did not yield the free amino base in a crystalline state, but it formed a crystalline hydrochloride, which melted at 138–40°C, and analysed for $C_{21}H_{23}O_3N_2 . NH_2HCl$.

Employing the general procedure used for the nitration of reserpine, with twice the molar quantity of nitric acid used for it, the reaction mixture gave through its crystalline hydroiodide salt the unreacted base without any loss. As this procedure proved ineffective with even the use of concd HNO_3 (1.4 d) without any dilution with glacial acetic acid, it was evident that much more drastic conditions are required for the nitration of serpentine. After a considerable amount of work the nitration conditions arrived at consisted in treating the base with a 2 : 1 mixture of nitric acid and sulphuric acid at 5°C, using magnetic stirrer. The reaction product was worked up as described in the experimental. The mononitroserpentine was ultimately obtained on repeated crystallisations from a mixture of alcohol and benzene (1 : 1) in 57% yield, m.p. 256–58°C, and analysed for $C_{21}H_{19}O_5N_3 . H_2O$. Its NMR studies in $CDCl_3$ revealed that the nitro group is located at C-10 (II).

In the aromatic region of the spectrum there is a signal at 2.6 τ of H-12 which is split into a doublet (*J* 8.8 c/s having an *ortho* coupling with H-11) and showing no *meta* coupling. The signal of H-11 is a quartet centred at 1.75. It has *ortho* coupling with H-12, and a *meta* coupling with H-9 (*J* 2.3 c/s). It is clearly revealed in the spectrum that H-9 is showing a doublet at 1.8 indicatiing a *meta* coupling with H-11 of 3 c/s.

The nitro base was further characterised through



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its crystalline hydrochloride, picrate, chloroplatinate, hydroiodide, succinate, oxalate and citrate. In contrast, however, to ajmalicine it failed to yield any crystalline product in the form of a base or hydrochloride on reduction with Zn–HCl. A number of other reduction procedures were tried out but did not provide any positive result.

Experimental

Nitration of Serpentine. Serpentine (2 g) was treated with 20 ml of 2: 1 mixture of nitric acid (d 1.4) and concd H_2SO_4 cooled to 5°C with vigorous shaking, using magnetic stirrer, keeping the temperature at about 15°C. The reaction was quenched by pouring the mixture into crushed ice after a probe of the solution did not show any trace of violet fluorescence in UV. This stage was reached in about 7 min. The resulting precipitate of the semi-crystalline nitrate was filtered, washed repeatedly with water, sucked and then brought on the porous plate. The still moist product was taken up in alcohol alongwith acetic acid (10%) and kept in cold, when the nitrate of the nitro derivative came out in the form of yellow spindle shaped needles. The crystallisate was filtered, washed with water and dried over a porous plate (yield 1.5 g).

The nitrate was then rubbed well with alcoholic ammonium hydroxide and the liberated base was filtered, repeatedly washed with small quantities of cold dilute alcohol and dried. On recrystallisation from 1 : 1 mixture of alcohol and benzene, nitroserpentine was obtained in the form of bright yellow silky needles, which melted at 256–58°C (dec) and analysed for $C_{21}H_{19}O_5N_3.H_2O$ (yield 0.9 g).

The alcoholic mother liquor was concentrated under reduced pressure and kept in cold whereby a second crop of 10-nitroserpentine was obtained (yield 0.25 g). Total yield 57%.

Characterisation of 10-*Nitroserpentine*

10-Nitroserpentine is readily soluble in mixture of benzene and methanol, sparingly soluble in these solvents individually, and nearly insoluble in ether and ethyl acetate. It crystallises from these solvents in bright yellow silky needles, melting at 256–58°C (dec) and analysed for $C_{21}H_{19}O_5N_3.H_2O$. (Found: C, 62.26; H, 4.98; N, 10.18%. Calcd for $C_{21}H_{19}O_5N_3.H_2O$: C, 61.70; H, 5.10; N, 10.21%. The IR spectrum of the base in nujol indicated peaks at 1510 (—NO_2), 1730 (CO) and 3570 cm^{-1} (NH). Its UV spectrumi n chloroform indicate λ_{max} 267 nm, 326, 394 nm, and λ_{min} 295, 358 nm, with showed shoulders at 245 and 250 nm. The NMR spectrum that the nitro group in the serpentine molecule is located at position 10.

10-*Nitroserpentine Hydrochloride.* On treating the base with an excess of alc HCl (10%), a yellow paste was formed which on crystallisation from alcohol formed long yellow needles, m.p. 272–75°C. It is soluble in methanol, and acetone, sparingly soluble in water. (Found after drying over P_2O_5 under reduced pressure: Cl, 8.3%. $C_{21}H_{19}O_5N_3.HCl$: requires: Cl, 8.2%).

10-*Nitroserpentine Hydroiodide.* On treating a solution of the base in acetic acid (5%) with a concentrated solution of KI a yellow semicrystalline precipitate was obtained, which when sucked, washed with water, and crystallised from alcohol, formed brownish yellow rods melting at 290–92°C. (Found after drying over P_2O_5 under reduced pressure: I, 22.42%. $C_{21}H_{19}O_5N_3.HI$ required: I, 22.36%).

10-*Nitroserpentine Chloroplatinate.* 10-Nitroserpentine hydrochloride was dissolved in water and a 3%-solution of platinic chloride was added to it with good ice cooling. The resulting buff coloured precipitate was sucked, washed with water and dried. The chloroplatinate was insoluble in nearly all the organic solvents and failed to crystallise. After drying at 100°C, it shrinks at 256°C and charrs at 280°C. (Found after drying over P_2O_5 under reduced pressure: Pt, 13.75%. $(C_{21}H_{19}O_5N_3)_3.H_2PtCl_6$ requires: Pt, 13.09%).

10-*Nitroserpentive Picrate.* To a methanol–benzene solution of the base a solution of picric acid in methanol was added. On concentration the picrate crystallised out as yellow stout rods, m.p. 240–42°C. It is soluble in methanol, acetone and insoluble in ether. (Found after drying over P_2O_5 under reduced pressure: C, 51.74; H, 3.80; N, 13.32%. $C_{21}H_{19}O_5N_3.C_6H_3O_7N_3$ requires: C, 51.58; H, 3.50 and N, 13.34%).

10-*Nitroserpentine Succinate.* 10-Nitroserpentine was dissolved in a fairly concentrated aqueous solution of succinic acid, filtered and kept at room temperature when the succinate slowly crystallised out as aggregates of needles. On recrystallisation from methanol and few drops of acetone it melted at 156–58°C. It is readily soluble in alcohol, methanol and acetone and insoluble in ether. (Found after drying over P_2O_5 under reduced pressure: C, 58.19; H, 5.12; N, 8.12%. $C_{21}H_{19}O_5N_3.C_4H_6O_4$ requires: C, 58.70; H, 4.89 and N, 8.2%).

10-*Nitroserpentine Oxalate.* The oxalate was prepared by bringing together the components in ethyl acetate solution. On keeping at room temperature colourless needles of 10-nitroserpentine oxalate were obtained, m.p. 252–55°C. It is sparingly soluble in alcohol, acetone, water and insoluble in ether. (Found after drying over P_2O_5 under reduced pressure: C, 54.58; H, 4.31; N, 8.09%. $C_{21}H_{19}O_5N_3.C_2H_2O_4$ requires: C, 55.08; H, 4.57; N, 8.38%).

10-*Nitroserpentine Citrate.* The citrate was prepared in the same manner as succinate and crystallised from methanol, when it formed colourless rods, m.p. 208–10°C. It is soluble in alcohol, methanol, acetone and water and insoluble in ether. (Found after drying over P_2O_5 under reduced pressure: C, 55.25; H, 4.41; N, 7.52%. Required for $C_{21}H_{19}O_5N_3.C_{66}H_8O_7$: C, 55.38; H, 4.61 and N, 7.17%).

10-*Nitroserpentine Tartarate.* The tartarate was prepared following the procedure described above. It crystallised from methanol in the form of colourless needles melting at 210–12°C, soluble in methanol, acetone, partly soluble in water and insoluble in

ether. (Found after drying over P_2O_5 under reduced pressure. C, 56.61; H, 4.46; N, 7.32%. Required for $C_{21}H_{19}O_5N_3$. $(CHOH)_2$. $(COOH)_2$. C, 57.09, H, 4.76; and N, 7.71%).

Nitration of Ajmalicine

Ajmalicine (5 g) was dissolved in glacial acetic acid (75 ml) and a 1 : 1 mixture of nitric acid (d 1.4) and glacial acetic acid (1.6 ml) was added to the solution with shaking. The temperature of the reaction mixture was kept below 30°C. The initial yellow colour of the reaction mixture did not change much and the nitrate of the nitro derivative started crystallising out. At this stage, which was reached in about 5 min the reaction mixture was kept for further 10 min and then poured into crushed ice. The resulting orange yellow precipitate was sucked, washed with glacial acetic acid and finally with cold water. It was dried over a porous plate, stirred up in alcohol, and treated with a little alcoholic ammonia (10%), when the suspension went into solution. On keeping the solution in cold, 10-nitroajmalicine was obtained in the form of yellowish needles, which after recrystallisation from methanol melted at 176–78°C (yield 3.15 g). It was analysed for $C_{21}H_{23}O_5N_3$.

Characterisation of the Base

10-Nitroajmalicine is readily soluble in mixtures of methanol–acetone, methanol–benzene, partly soluble in chloroform and nearly insoluble in ethyl acetate. (Found after drying over P_2O_5 at 60°C: C, 63.47; H, 6.60; N, 9.89%. Calcd for $C_{21}H_{23}O_5N_3$: C, 63.47; H, 5.79; N, 10.57%.) The IR spectrum of the base in nujol indicated peaks at 870 (C—N), 1510 (NO_2), 1608 (aromatic ring), 1680 and 3580 cm^{-1} (NH). Its UV spectrum in chloroform indicated λ_{max} 249, 388 nm and λ_{max} 303 nm with shoulders at 292 and 340 nm. Its NMR spectrum studies showed that the nitration has occurred at the position 10 of the ajmalicine molecule.

Its various salts were prepared by generally following the procedure described in the case of the salts of serpentine. The solubility of these salts were also of a similar character in each case.

10-*Nitroajmalicine Hydrochloride*. M.p. 256–58°C. (Found: Cl. 8.44%. Calcd for $C_{21}H_{23}O_5N_3$.HCl: Cl, 8.18%).

10-*Nitroajmalicine Picrate*. M.p. 210–12°C. (Found: C, 52.10; H, 4.21; N, 15.84%. Calcd for $C_{21}H_{23}O_5N_3.C_6H_3O_7N_3$. C_2H_5OH: C, 52.21; H, 4.71; N, 12.24%).

10-*Nitroajmalicine Oxalate*. M.p. 230–32°C. (Found: C, 56.20; H, 5.92; N, 9.53%. Calcd for $(C_{21}H_{23}O_5N_3)_2$. $C_2H_2O_4.3H_2O$; C, 56.27; H, 5.35; N, 8.95%).

10-*Nitroajmalicine Chloroplatinate*. M.p. 230–33°C. (Found: Pt, 15.81%. Calcd for $(C_{21}H_{23}O_5N_3)_2$. H_2PtCl_6.Pt, 16.17%).

Reduction of 10-*Nitroajmalicine to Aminoajmalicine Hydrochloride*

10-Nitroajmalicine (0.2 g) was dissolved in 10 ml 50% acetic acid, and zinc dust was gradually added with constant striring and heating on the water bath till the yellow colour of the reaction mixture disappeared. Unreacted zinc was filtered off, and the solution strongly ammoniated. The resulting brownish grey precipitate which consisted of the reduced base and $Zn(OH)_2$ was sucked and washed with water. The reduced base was extracted out with ethyl acetate, the ethyl acetate solution was washed with water, dried (Na_2SO_4), filtered and freed of the solvent under reduced pressure. On crystallisation of the residue from alc HCl, 10-aminoajmalicine hydrochloride was obtained in cream-coloured needles (0.06 g), which melted at 208–10°C. (Found after drying over P_2O_5 at 100°C under reduced pressure: C, 62.21; H, 6.52; N, 9.60; Cl, 8.26%. $C_{21}H_{25}O_3N_3$.HCl requires: C, 62.45; H, 6.44; N, 10.40; Cl, 8.79%).

Summary. The nitration of ajmalicine and serpentine yielded a mononitro derivative in each case the nitro group being located at position 10. Nitroajmalicine gave on reduction with Zinc–HCl an amino base which was amorphous in character, but could be characterised through its crystalline HCl. As against this, the reduction of nitroserpentine failed to furnish any uniform crystallisable product.

In contrast to reserpine and rescinnamine, much more drastic nitration conditions have had to be employed for the more stable structures of ajmalicine and serpentine, and each of them provides only a single mononitro product, as against three position isomers obtained from weaker bases, rescinnamine and reserpine, none of which occupy the *para* position to the indole nitrogen atom, as in the case of ajmaline.

References

1. S. Siddiqui and V.U. Ahmed, Proc. Pakistan Acad. Sci., **5**, 1 (1968).
2. S. Siddiqui, V.U. Ahmed, M. Ataullah Khan and Saira Ismail, Z. Naturforsch., **28b**, 486 (1973).