Pakistan J. Sci. Ind. Res., Vol. 27, No. 5, October 1984

NITRATION STUDIES IN IMIPRAMINE MONONITRO AND DINITRO DERIVATIVES OF IMIPRAMINE (10-11 DIHYDRO–N–N–DIMETHYL 5H –DIBENZ (b,f) AZEPINE –5–PROPANAMINE)

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(Received October 14, 1984)

Nitration studies in imipramine have yielded 2-nitroimipramine and 2,8-dinitroimipramine. The chemical and spectral data have shown that electrophilic substitution has taken place at C-2 and C-8.

INTRODUCTION

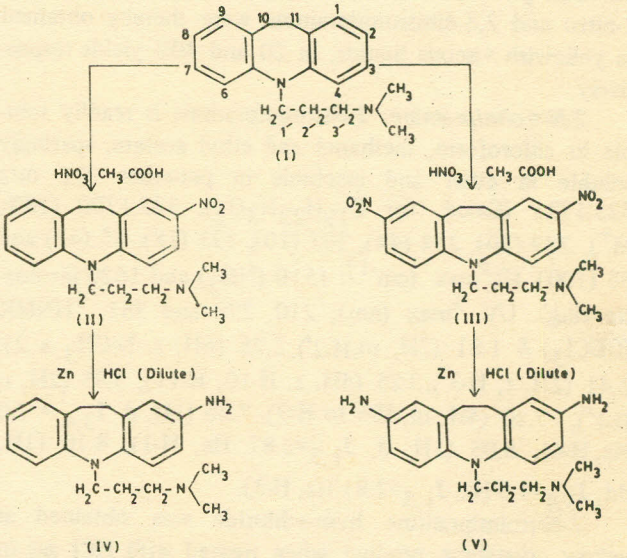
Reserpine has long been used in the treatment of hypertension on the one hand and a variety of mental ailments on the other [1]. As a result of clinical studies Moyer *et al.* noted that its extended use results in heavy depression leading to suicidal tendencies in about 50% of patient [2]. On account of this complication, a large number of derivatives were prepared by different workers [3] with the object of eliminating or reducing either one or the other of these two actions. Nitration studies under taken in this context by Siddiqui *et al.* resulted in three isomers of reserpine, namely 1–, 12– and 9–nitroreserpine, in 50, 12 and 3% yield, respectively. Pharmacological studies showed that 1 – and 12 nitro derivatives have the same order of hypotensive activity as that of reserpine but are free from its side effects.

In the light of these results as well as the finding that mononitro ajmaline is more than twice as active as the mother base in its anti-arrythmic activity [4], it was considered of interest to extend nitration studies to the potent pschychomotor stimulant drug [5] imipramine (I), as a result of which 2-nitroimipramine (II) and 2,8-dinitroimipramine (III) have been obtained in 20 and 40% yields respectively.

The nitration of the base was carried out in glacial acetic acid medium, and it was found that the optimum conditions of the reaction were highly critical, in respect of temperature, time and the proportion of reactants, as described in the experimental.

Mononitroimipramine (II) has molecular formula $C_{19}H_{23}N_3O_2$, $M^+ = 325$, ^{1}HNMR indicated that the NO_2 group is substituted at C-2 thus it showed one proton doublet at δ 8.05 ($J_{1,3} = 2.8$ Hz) which has been attributed to H-1. Similarly H-3 showed doublet of doublet at δ 8.10 ($J_{3,4} = 7.0$ Hz, $J_{1,3} = 2.8$ Hz), a doublet at δ 7.26 ($J_{3,4} = 7.0$ Hz) has been assigned to H-4 and a multiplet at δ 7.10 to the aromatic protons H-6 to H-9. Chemical evidence of the mononitro derivative has been provided through reduction of II to 2-amino imipramine (IV).

Dinitroderivative (III) showed M^+ at 370, corresponding to $C_{19}H_{22}N_4O_4$. The location of two nitro groups at C-2 and C-8 has been arrived at through chemical shifts



and coupling constants of the aromatic protons in the ^{1}HNMR spectrum. Thus it showed two-protons doublet at δ 8.01 ($J_{1,3} = J_{7,9} = 2.8$ Hz) which has been assigned to H-1 and H-9. Similarly a two-protons doublet of doublet at δ 8.05 ($J_{3,4} = J_{6,7} = 7.0$ Hz, $J_{1,3} = J_{7,9} = 2.8$ Hz) is due to H-3 and H-7. Finally, a two-protons doublet at δ 7.21 ($J_{3,4} = J_{6,7} = 7.0$ Hz) has been attributed to H-4 and H-6. Chemical evidence of the formation of dinitro derivative has been provided through its reduction to 2,8 diamino imipramine (V).

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EXPERIMENTAL

Melting points were recorded in glass capillary tubes and are uncorrected. IR were recorded in chloroform solution on a Unicam SP-200G spectrometer and UV spectra were taken on Shimadzu UV 240 spectrometer in methanol, while mass spectra were taken on Finnigan MAT 112 connected to PDP 11/34 computer system. ^{1}HNMR spectra were recorded in $CDCl_3$ solution on Bruker WP-100 SY FT-NMR spectrometer with TMS as internal reference.

Imipramine (1g = 0.00357 mole) was dissolved in glacial acetic acid (10 ml), and 1:1 mixture of concd. HNO_3 (1.4d, 0.8 ml = 0.01780 mole), and glacial acetic acid was added slowly in two minutes with occasional shaking at 10-15°C. The initial green coloured solution turned to dark green, finally changing to dark yellow. This stage was reached in about 15 minutes, when the reaction was quenched by pouring the mixture into crushed ice and strong ammonia was added with vigorous shaking till pH-6 was reached. The resulting viscous material was then shaken out repeatedly with ethyl acetate. On working up the combined ethyl acetate extract in the usual way 0.9 g of a light yellow viscous liquid was obtained which was subjected to thick layer chromatography on silica gel in chloroform-methanol (7:3) solvent system. 2-nitro and 2,8-dinitroimipramine were thereby obtained as yellowish viscous liquids, in 20 and 40% yields respectively.

2-Nitroimipramine: 2-Nitroimipramine is readily soluble in chloroform, methanol and ethyl acetate, sparingly soluble in ether and insoluble in pet-ether. E.I m/z 325.1721 (Calcd. for $C_{19}H_{23}N_3O_2$), 325.1790 (18%, M^+), 279 (20), 234 (44), 207 (10), 193 (18), 85 (42) and 58 (100), IR $\bar{\nu}$max (cm^{-1}): 1510 (NO_2) and 1620 (aromatic ring). UV λmax (nm); 210, 270 and 385. ^{1}HNMR ($CDCl_3$) δ 1.81 (2H, m,H-2′), 2.25 (6H, s, N-CH_3 x 2), 2.41 (2H, t, H-3′), 3.25 (4H, s, H-10, H-11), 3.95 (2H, t, H-1′), 7.10 (4H, m, H-6 to H-9), 7.26 (1H, d. $J_{3,4}$ = 7.0 Hz, H-4), 8.05 (1H, d, $J_{1,3}$=2.81 Hz, H-1), 8.10 (1H, dd, $J_{3,4}$=7.0 Hz, $J_{1,3}$=2.81 Hz, H-3).

2-Nitroimipramine hydrochloride was obtained as yellow crystalline product when treated with HCI gas in chloroform solution. On recrystallization from methanol it formed needles m.p. 180-1°C. The hydrochloride is insoluble in ether, sparingly soluble in benzene and chloroform and readily soluble in methanol. (Found after drying at room temperature over P_2O_5 under reduced pressure: CI,9.67%; Calcd. for $C_{19}H_{23}N_3O_2$. HCI, 9.82%).

2-Aminoimipramine: 2-Nitroimipramine (0.25 g) was taken in (5 ml) 10% aqueous hydrochloric acid and zinc dust was added to the solution with constant stirring on boiling water bath till the greenish colour of the reaction mixture disappeared. Unreacted zinc was filtered off and the colourless filtrate ammoniated with prior addition of ammonium chloride. It was extracted out with ethyl acetate which on usual working yielded 2-aminoimipramine as light yellow liquid (yield 38%). It is soluble in alcohol, methanol and ethyl acetate. El m/z 295.2031 (Calcd. for $C_{19}H_{25}N_3$ 295.2048) (100%, M^+), 265 (20), 249 (74), 210 (76), 85 (44) and 58 (82). IR νmax. (cm^{-1}): 3400, 3350 (NH - stretching), 1545 (NH-bending) and band at 1620 due to aromatic ring.

2,8-Dinitroimipramine: 2,8-Dinitroimipramine is soluble in usual organic solvents, sparingly soluble in ether and insoluble in pet.ether. El m/z 370. 1643 (Calcd. for $C_{19}H_{22}N_4O_4$ 370. 1640) (60%, M^+), 324 (44), 278 (23), 233 (18), 192 (48), 191 (76) and 83 (70). IR νmax (cm^{-1}): 1520 (NO_2) and 1630 (aromatic ring). UV λmax. (nm): 210, 270 and 385. ^{1}HNMR $CDCl_3$), δ 1.81 (2H, m, H-2′), 2.25 (6H, s, N-CH_3x2), 2.41 (2H, t, H-3′), 3.25 (4H, s, H-10, H-11), 3.95 (2H, t, H-1′), 7.21 (2H, d, $J_{3,4}$= 7.0Hz. H-4, H-6), 8.01 (2H, d, $J_{1,3}$=$J_{7,9}$=2.80 Hz, H-1, H-9), 8.05 (2H, dd, $J_{3,4}$=$J_{6,7}$=7.0 Hz, $J_{1,3}$=$J_{7,9}$=2.8 Hz, H-3, H-7).

2.8-Dinitroimipramine hydrochloride was obtained as yellow crystalline precipitate following the procedure recorded in the case of mononitroderivative. On recrystallization from methanol it formed elongated rods m.p. 212-3°C. (Found after drying at room temperature over P_2O_5 under reduced pressure: Cl, 8.64; Calcd. for $C_{19}H_{22}N_4O_4$. (HCl, 8.73%).

2,8-Diaminoimipramine: On reduction of III with Zn/HCI as described for II, 2,8-diaminoimipramine (IV) was obtained as chromatographically pure viscous liquid (yield 31%). It is soluble in chloroform, methanol and ethyl acetate. EI m/z 310.2148 (Calcd. for $C_{19}H_{26}N_4$ 310.2157) (32%, M^+), 265 (21), 225 (30), 191 (10), 85 (46) and 58 (100%). IR νmax (cm^{-1}): 3400, 3330 and 1540.

Acknowledgement: The authors are thankful to Ciba-Giegy Pakistan Ltd., Karachi-2, for the generous supply of imipramine hydrochloride.

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