Some new derivatives of Imipramine[10,11-Dihydro-N, N-dimethyl(-5H-dibenz (b,f) azepine-5-Propanamine)] and Chloroquine [7-chloro-4-(4-diethylamino-1-methyl butyl amino quinoline)]

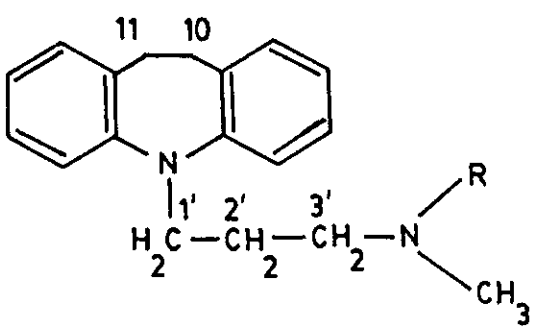
SALIMUZZAMAN SIDDIQUI*, S.SALMAN AHMAD
S.IMTIAZ HAIDER AND BINA SHAHEEN SIDDIQUI,
H.E.J.Research Institute of Chemistry,
University of Karachi, Karachi-32, Pakistan

(Received 9th June, 1985)

Summary: von Braun (BrCN) reaction and its extension carried out on imipramine resulted in the formation of N-cyano, N-amido and N-dimethyl amino-(diamine) derivatives. On the other hand, chloroquine on reaction with BrCN yielded three cyano derivatives. All these derivatives have been characterized through spectral studies.

Introduction

In continuation of studies in the structure and activity relationship, some extensions of von Braun BrCN reaction on a number of alkaloids and simpler bases (3-7) leading to a whole series of new derivatives have been reported earlier. The present paper deals with the studies in the preparation of synthetic analogues of imipramine and chloroquine through cyanogen bromide reaction. These studies have led to the following new derivatives in good yields.



1) Imipramine R= CH_3

2) N-Cyanoimipramine R= CN

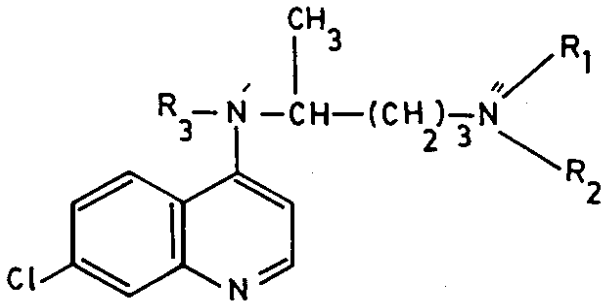
3) N-Amidoimipramine R= $CO-NH_2$

4) N-Methylaminoimipramine R= CH_2-NH_2.

On reaction of imipramine with freshly prepared cyanogen bromide, as described in the experimental, N-cyanoimipramine was obtained as yellowish viscous liquid b.p. 163°C (yield theoretical) which on hydrolysis with 10% aq HCl at 70-80°C and on usual work up gave, white irregular plates of the amido derivative m.p. 135°C (yield 88%). Reduction of the cyanamide with 10% aqueous HCl and zinc dust yielded the diamine as a brownish viscous liquid in 71% yield. On treatment with ethereal HCl, the diamine formed white elongated rods of the hydrochloride m.p. 123 °C. All the derivatives of imipramine have been characterized through their I.R., U.V., ^{1}HNMR spectral studies.

Through the same procedure of cyanogen bromide reaction when carried out on chloroquine, which is

an antimalarial and anti-amoebic drug, following cyano derivatives have been obtained and characterized through their mass, I.R. and U.V. spectral data.



5) Chloroquine; $R_1 = R_2 = C_2H_5$, R_3=H

6) N''-Cyano chloroquine, R_1=CN, R_2= C_2H_5 R_3=H

7) N',N''-Dicyano chloroqine; R_1=R_3= CN, R_2=C_2H_5

8) N',N''-Dicyano chloroquine; R_1=R_2= CN; R_3=H.

Attempts to obtain the amido derivatives and diamines of these cyanamides through their partial hydrolysis and reduction under the reaction conditions employed in the previous studies have so far failed to yield any uniform product.

Experimental

Melting and boiling points were recorded in glass capillary tubes and are uncorrected. I.R. were recorded in chloroform solution on Unicam SP-200 G spectrometer and U.V. spectra were measured in methanol on Shimadzu U.V. 240 spectrometer. The mass spectra were taken on Finnigan MAT 312 and MAT 112 double focussing mass spectrometer connected to PDP 11/34 computer system. ^1H NMR spectra were obtained in $CDCl_3$ solution on Bruker WP-100 SYFT NMR spectrometer with TMS as internal reference.

Cyanoimipramine

To a solution of imipramine (5 gm) in dry ether (100 ml), an ethereal solution of freshly prepared cyanogen bromide was added (1.2 mole) with good cooling and mechanical stirring for fifteen minutes. The white crystalline hydrobromide of the base, which separated out, was filtered and the ethereal filtrate was extracted with dilute acetic acid to remove any unreacted base. The ethereal layer was neutralized with a little dilute ammonia, washed with water, dried over anhydrous Na_2SO_4 and freed of the solvent. The cyanamide thereby obtained, in theoretical yield, as a yellowish viscous liquid b.p. 163°C is soluble in chloroform, ethyl acetate and ether while insoluble in petroleum ether. EIMS m/z 291.17321 (calcd for $C_{19}H_{21}N_3$ 291.17353) (26% M^+) 265 (4), 235 (2), 208 (100), 193 (56), 167 (12), 83 (64) and 57 (66). I.R. ν_{max} (cm^{-1}): 2210 (C≡N), 3060, 1610, and 1480 (aromatic ring). U.V. λ_{max} (n.m): 215,255 and 280. ^1H NMR δ :7.40-6.86 (8H m, aromatic proton) 3.69 (2H, t, H-1'), 3.31 (4H, s, H-10, H-11), 2.82 (2H, t, H-3'), 2.54 (3H, s, N-CH_3) and 1.81 (2H, m, H-2').

Amidoimipramine:

Cyanoimipramine (1g) was taken in 10 ml of aqueous hydrochloric acid (10%) and mechnically stirred for about an hour at 70°C, till a clear solution was obtained. It was cooled, basified with ammonia and extracted out with ethyl acetate. The crystalline residue left on usual work up and removal of

the solvent formed irregular plates from methanol water (9.5:0.5) m.p. 135 °C (yield 88%). It is soluble in chloroform and methanol insoluble in ether, benzene and pet.ether EIMS m/z 309.1839 (calcd. for $C_{19}H_{23}N_3O$ 309.1841) (M^+ 18%), 234 (20), 208 (100), 193 (52), 167 (12), 83 (50) and 57 (38). I.R. ν_{max} (cm^{-1}): 3400 and 3520 (N-H stretching), 1640 (amide C=O stretching) and 1570 (N-H bending). U.V. λ_{max} (n.m): 215, 256 and 262. ^{1}HNMR δ : 7.44-6.91 (8H, m, aromatic protons), 4.74 (2H, s, NH_2), 3.69 (2H, t, H-1), 3.26 (4H, s, H-10, H-11), 2.81 (2H, t, H-3), 2.60 (3H,s, $N-CH_3$) and 1.79 (2H, m, H-2).

Imipramine diamine

Cyano imipramine (1g) was taken in 10% aqueous hydrochloric acid and heated with Zn dust on water bath, till it went into solution. Heating was continued for fifteen minutes. The unreacted zinc was filtered off, the filtrate basified with ammonia after prior addition of ammonium chloride and the liberated base was extracted out with ethyl acetate. The darkish ethyl acetate solution on purification with petroleum ether and removal of the solvent afforded the diamine as a brownish liquid in 71% yield which is soluble in common organic solvents. The hydrochloride obtained on treatment of the diamine with ethereal hydrochloric acid formed elongated rods m.p. 123°C. EIMS m/z 295.2041 (calcd. for $C_{19}H_{25}N_3$ 295.2048) (M^+ 24 %), 234 (20), 208 (100), 193 (46), 167 (6), 83 (10) and 57 (12). I.R. ν_{max} (cm^{-1}): 3420, 3390 (N-H stretching) and 1590 (N-H bending) U.V. $_{max}$ (n.m): 215, 250 and 278. ^{1}HNMR δ :7.25-6.88 (8H, m, aromatic protons), 3.32 (2H, s, NH_2) 3.81 (2H, s, $N-CH_2-N$), 3.70 (2H, t, H-1), 3.28 (4H, s, H-10, H-11) 2.79 (2H, t, H-3), 2.49 (3H, s, $N-CH_3$) and 1.80 (2H, m, H-2).

Cyano chloroquinine

To a solution of chloroquine (5g) in dry chloroform (100 ml) was gradually added freshly prepared cyanogen bromide (1.2 mole). It was stirred at O°C for 20 minutes and the white hydrobromide of the unconverted chloroquine which settled down was filtered off. The filterate worked up according to the procedure described for cyano imipramine afforded a yellowish liquid showing three spots on t.l.c. which was subjected to prep. thick layer chromatography (silica gel; benzene-chloroform 6:4). As a result N-cyano, (Rf=0.8), N',N''-dicyano (Rf=0.6) and N',N'' dicyanochloroquine (Rf=0.9) were obtained as colourless liquids in 60, 18 and 7% yields, respectively

N'' cyanochloroquine

EIMS m/z 316.6318 (calcd. for $C_{17}H_{21}N_4Cl$ 316.6288) (M^+, 20%), 290 (5), 287 (6), 246 (14), 231 (34), 205 (64), 177 (20) 94(100) and 57 (98). I.R. ν_{max} (cm^{-1}): 2200 (C=N) and 3400 (N-H stretching). U.V. λ_{max} (nm): 215, 265 and 335.

N',N'' dicyanochloroquine

EIMS m/z 341.6145 (calcd. for $C_{18}H_{20}N_5Cl$ 341.6140) (M^+, 6%), 315 (6), 289 (7), 245 (14), 230 (38), 205 (100), 177 (20), 83 (78) and 57 (98). I.R. ν_{max} (cm^{-1}): 2205 (C=N), U.V. λ_{max} (nm):215, 262 and 333.

N,N-dicyano chloroquine

EIMS m/z 313.5913 (calcd. for $C_{16}H_{16}N_5Cl$ 313.5928) (M^+, 12%), 246 (34), 231 (100), 205 (80), 177 (5), 83 (30) and 57 (68). I.R. ν_{max} (cm^{-1}): 2200 (C=N). U.V. λ_{max} (nm): 215, 260 and 330.

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