POLYHALOGENOAROMATIC COMPOUNDS. PART 51.[1] SYNTHESIS OF NEW HETEROCYCLES FROM PENTACHLOROPYRIDINE AND 2,3,5,6-TETRACHLOROPYRIDINE WITH ALIPHATIC DIAMINES

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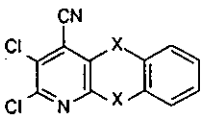
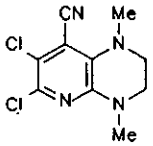
Abstract- The reaction of pentachloropyridine or 2,3,5,6-tetrachloropyridine with *N,N,N',N'*-tetramethylethanediamine (TMEDA) or *N,N'*-dimethylethanediamine (DMEDA) in dimethylformamide gave dihydropyridopyrazines (**5,9**) and (**6**) respectively by replacement of the 2,3- or 3,4-chlorine atoms.

Pentachloropyridine readily undergoes nucleophilic substitution at the 2- and/or 4-positions.[2] Large nucleophiles attack preferentially the less hindered α-position while small nucleophiles may react exclusively at the more activited 4-position.[2] Attempts at preparing fused heterocyclic systems from pentachloropyridine with aliphatic primary diamines not only in ethanol but also in dimethylformamide, dimethylaniline or neat were unsuccessful,[3] as the N-monosubstituted compounds did not undergo intramolecular cyclisation at the 3-position. Even tetrachloro-4-nitro- and tetrachloro-4-sulphonylpyridine in which the 3-chlorine is expected to be activated react with nucleophiles mainly by displacement of the 4-substituent.[4,5] Only in the case of the not readily available tetrachloro-4-cyanopyridine,[6] nucleophiles replace the chlorines rather than the cyano group. In the case of the bidentate reagents o-phenylenediamine, o-dihydroxybenzene and *N,N,N',N'*-tetramethylethanediamine (TMEDA) the heterocycles (1; X = NH or O) and (2)[7] respectively are obtained.

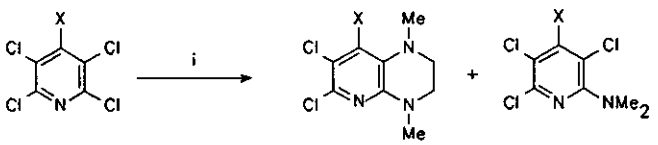


(1)



(2)

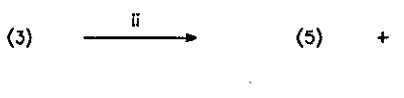
We now report that reaction of the readily available pentachloropyridine (**3**) with TMEDA in dimethylformamide (DMF) under reflux gave the fused heterocycles 6,7,8-trichloro-1,4-dimethyl-2,3-dihydropyrido[2,3-*b*]pyrazine (**5**) (41.3%) together with the known tetrachloro-6-dimethylaminopyridine[8] (**7**) (34.7%). The structure of **5** was confirmed by an X-ray analysis (cf. Figure). When the pyridine (**3**) was made to react with DMEDA in the same solvent under similar conditions a mixture of the isomeric heterocycles (**5**) and (**9**) were obtained in yields of 19.7% and 26.0% respectively. The presence of the 4-chlorine atom in the pyridine (**3**) is not essential for activation under the above conditions, as the tetrachloropyridine (**4**) was made to react successfully with TMEDA or DMEDA to give in both cases 6,7-dichloro-1,4-dimethyl-2,3-dihydropyrido[2,3-*b*]pyrazine (**6**) in yields of 46.8% and 29.0%, respectively. In the reaction with TMEDA, 2,3,5-trichloro-6-dimethylaminopyridine[9](**8**) was also formed (37.8%).

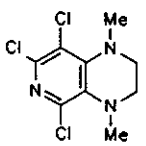


(3) : X=Cl
(4) : X=H

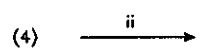
(5) : X=Cl
(6) · X=H

(7) : X=Cl
(8) : X=H

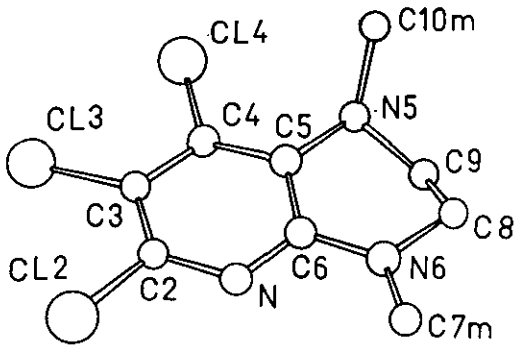




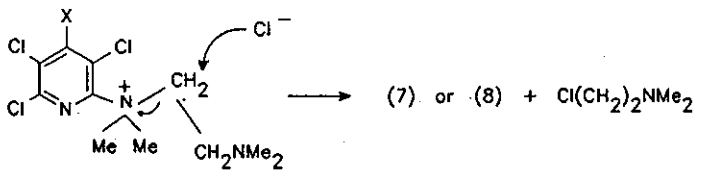
(9)



Reagents: i, *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) in DMF
ii, *N,N'*-dimethylethane-1,2-diamine (DMEDA) in DMF

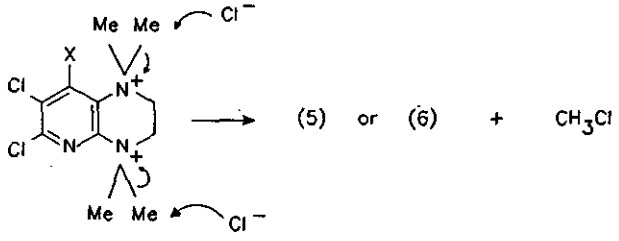


The initial attack of DMEDA on pentachloropyridine (**3**) occurs by analogy with other sec. amines [8,10] on the 2 and the 4 positions. This is followed by substitution of the 3-position to yield the isomeric mixture of the pyridopyrazines (**5** and **9**). As we found no evidence of the presence of the isomer (**9**) in the case of TMEDA, the less hindered 2-chlorine in pentachloropyridine (**3**) is replaced exclusively followed by ring-closure involving the 3-position to give the pyridopyrazine (**5**). In the 2,3,5,6-tetrachloropyridine (**4**) the initial attack by the diamines also occurs in the 2-position followed by intramolecular cyclisation. The isolation of the α-dimethylaminopyridines (**7** and **8**) from the reactions of TMEDA with both pyridines (**3** and **4**) lend further support to the mode of cyclisation. These by-products (**7** and **8**) are tentatively formed by attack of a chloride ion on the 2'-methylene group in the intermediaete (**10**) followed by elimination of (2-chloroethyl)dimethylamine as shown (**10** → **7** or **8**).



(10)

The loss of a methyl group from the expected reaction product (**11**) of TMEDA with the chlorinated pyridines (**3** or **4**) can be explained in an analogous way, namely by attack of a chloride ion on one of the methyl group followed by loss of MeCl (**11** → **5** or **6**).



(11)

EXPERIMENTAL

Melting points were determined on a Kofler block. Ir and uv spectra were recorded with a Perkin Elmer 682 and a Beckmann Acta M-VI spectrophotometers, respectively. A Bruker WP80SY was used for ^{1}H nmr spectroscopy. Pentachloropyridine and 2,3,5,6-tetrachloropyridine were provided by Montecinca, S.A.

Reactions of pentachloropyridine,- (i) With NN'-dimethylethane-1,2-diamine (DMEDA). A solution of DMEDA (1.450 g, 16.4 mmol) and pentachloropyridine (2.01 g, 8.0 mmol) in DMF (20 ml) was stirred in Argon under reflux for 7 h. The mixture was cooled and poured into water and then extracted with ether. The ethereal solution was washed with H_2O, dried over Na_2SO_4 and evaporated to give a residue which was chromatographed on silica gel and eluted with a mixed solvent of CCl_4 and $CHCl_3$ (1:1). Two fractions were collected which were further purified (tlc, silica gel). Developing the first fraction with a mixed solvent of CCl_4 and $CHCl_3$ (1:1) gave 6,7,8-trichloro-1,4-dimethyl-2,3-dihydropyrido[2,3-*b*]pyrazine **(5)** (0.419 g; 19.7%), mp 114-115°C (from hexane); ir (KBr) ν: 3000 w, 2950 m, 2860 m, 1565 s, 1520 s, 1470 m, 1445 s, 1420 w, 1395 s, 1355 s, 1300 s, 1270 m, 1240 m, 1222 m, 1200 s, 1175 m, 1130 w, 1115 m, 1095 w, 1050 m, 1025 w, 985 s, 935 w, 915 s, 810 s, 750 m, 708 s, 685 w, 590 m, 580 m, 550 m cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.74 (s, 3H), 2.9-3.2 (m, 2H), 3.16 (s, 3H) and 3.3-3.5 (m, 2H); uv $\lambda_{max}(\epsilon)$ (cyclohexane) 339 nm (8180), 270 (shoulder) (6930), 252 (10 800). Anal. Calcd for $C_9H_{10}N_3Cl_3$: C, 40.55; H, 3.8; Cl, 39.9; N, 15.8. Found: C, 40.2; H, 3.7; Cl, 40.0; N, 15.4; eluting the second fraction with $CHCl_3$ gave the isomeric 5,7,8-trichloro-1,4-dimethyl-2,3-dihydropyrido[3,4-*b*]pyrazine (9) (0.555 g; 26.0%), mp 91-93°C (from hexane); ir (KBr) ν: 2990 w, 2950 m, 2890 w, 2870 w, 2820 w, 1555 s, 1510 s, 1460 m, 1445 m, 1415 s, 1370 s, 1345 m, 1260 m, 1245 m, 1225 s, 1192 m, 1165 m, 1100 s, 1060 s, 1030 m, 1000 m, 942 m, 942 m, 895 s, 850 m, 800 s, 745 m, 730 s, 635 w, 620 w, 565 w cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.82 (s, 3H), 2.9-3.1 (m,

2H), 3.18 (s, 3H), 3.18-3.32 (m, 2H); uv $\lambda_{max}(\epsilon)$ (cyclohexane) 300 (shoulder) nm (2740), 251 (20 330). Anal. Calcd for $C_9H_{10}N_3Cl_3$: C, 40.55; H, 3.8; Cl, 39.9; N, 15.8. Found: C, 40.2; H, 3.8; Cl, 40.3; N, 15.7.

(ii) *With N,N,N',N'-tetramethylethane-1,2-diamine (TMEDA).* A solution of TMEDA (11.07 g; 95.3 mmol) and pentachloropyridine (8.02 g; 31.9 mmol) in DMF (100 ml) was stirred in Argon under reflux for 7 h. The reaction mixture was worked up as above and the residue was recrystallized twice from n-hexane to give **5** (2.75 g), identical with the product from (i). The combined mother liquors were chromatographed on silica gel and eluted with n-hexane and then with $CHCl_3$. The first hexane fraction was evaporated to give tetrachloro-6-dimethylaminopyridine (**7**) (2.88 g; 34.7%), mp 45-48°C (lit.,[8] 44 °C); the chloroform fraction was evaporated to leave a residue on which recrystallization gave an additional amount of **5** (0.784 g): the total yied 41.3%.

Reactions of 2,3,5,6-tetrachloropyridine.- (i) *With DMEDA.* A mixture of DMEDA (0.827 g, 9.38 mmol), 2,3,5,6-tetrachloropyridine (2.00 g, 9.22 mmol), sodium hydrogen carbonate (2.09 g), and DMF (20 ml) was stirred in Argon under reflux for 7 h. The mixture was cooled and poured into water and then extracted with ether. The ethereal solution was washed with H_2O, dried over Na_2SO_4 and evaporated to give a residue which was chromatographed (SiO_2) and eluted first with CCl_4 and then with $CHCl_3$. The chloroform fraction was evaporated and the residue was recrystallized from n-hexane to give 6,7-dichloro-1,4-dimethyl-2,3-dihydropyrido[2,3-*b*]pyrazine **(6)** (0.621 g; 29.0%), mp 69-70.5 °C; ir (KBr) ν_{max} 3065 w, 2990 w, 2940 m, 2860 m, 1590 s, 1550 s, 1520 s, 1475 s, 1455 s, 1400 s, 1370 s, 1300 s, 1285 s, 1250 s, 1200 s, 1160 s, 1115 s, 1075 w, 1015 m, 920 m, 850 m, 830 m, 695 m, 650 s, 620 w, 570 m, 530 w cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.8 (s, 3H), 3.0 (s, 3H), 3.1-3.3 (m, 2H), 3.4-3.6 (m, 2H) and 6.5 (s, 1H); uv $\lambda(\epsilon)$ (cyclohexane) 337 nm (10 150), 282 (8590). Anal. Calcd for $C_9H_{11}N_3Cl_2$: C, 46.6; H, 4.8; Cl, 30.5; N, 18.1. Found: C, 47.0; H, 4.8; Cl, 30.6; N, 18.0.

(ii) *with TMEDA.* A solution of TMEDA (17.29 g; 148.8 mmol) and 2,3,5,6-tetrachloropyridine (8.013 g; 37.0 mmol) in DMF (100 ml) was stirred in Argon under reflux for 7 h. The reaction mixture was treated as before, and the crude product was chromatographed (SiO_2) and eluted first with CCl_4 and then with $CHCl_3$. The CCl_4 fraction (3.417 g) was rechromatographed on silica gel with n-hexane to give 2,3,5-trichloro-6-dimethylaminopyridine[9] **(8)** (2.97 g; 37.8%), mp 33-34°C (from n-pentane); ir ν_{max} 3070 w, 2950 m, 2910 m, 2870 m, 2800 w, 1575 s, 1525 s, 1490 s, 1400 s, 1355 m, 1315 w, 1245 w, 1200 m, 1150

s, 1055 s, 970 m, 890 m, 865 m, 730 w, 675 m, 655 m cm^{-1}; ^1H-nmr ($CDCl_3$) δ: 3.2 (s, 6H), 7.55 (s, 1H). The chloroform fraction was evaporated and recristallized from n-hexane to give **6** (4.015 g; 46.8%), identical with product obtained from DMEDA.

Table 1. Atomic fractional co-ordinates ($x10^4$) with esds in parentheses.

Atom	x	y	z
CL2	2060(2)	1664(2)	4190(1)
CL3	-1071(2)	992(1)	3991(1)
CL4	-2096(1)	-2056(2)	4240(1)
N	2337(4)	-898(4)	4523(1)
C2	1409(5)	27(5)	4323(2)
C3	40(5)	-269(6)	4231(2)
C4	-385(5)	-1623(6)	4341(2)
N5	118(4)	-3972(4)	4659(2)
C5	521(5)	-2615(5)	4529(2)
N6	2872(5)	-3102(5)	4824(2)
C6	1918(5)	-2183(5)	4620(2)
C7	4333(6)	-2814(7)	4811(3)
C8	2508(7)	-4499(6)	4958(3)
C9	963(7)	-4568(6)	5090(2)
C10	-64(8)	-4838(7)	4150(3)

Crystallographic Analysis of **5**.- *Crystal and intensity data:* $C_9H_{10}N_3Cl_3$, M_r=266.7, tetragonal unit cell, a=9.675(2), c=23.810 (7)Å, V=2229Å^3, space group $P4_12_12$, z=8, D_x=1.59 g/cm^3, μ=7.94 cm^{-1}, F(000) = 1088, 293°K, crystal size: 0.16 x 0.14 x 0.13 mm, 2263 reflections measured in the range $0 \le h \le 11$, $0 \le 1 \le 28$ on an automated ENRAF-NONIUS four-circle diffractometer with graphitemonochromatized Mo-Kα radiation (λ=0.71069Å, θ_{max}=25°), 1228 unique reflections (R_{int}=5.4), from which 1103 were observed ($I>2.5\sigma(I)$). 3 standard reflections monitored every 100 measurements. Intensities were corrected for Lorentz and polarization effects.

Structure solution and refinement.- The structure was solved by multisolution direct methods using the (Ω-tangent formula)[11] and refined by full-matrix least-squares procedure (SHELX-76).[12] The hydrogen-atom positions were found from the difference Fourier map but were not refined. The final R- and R_w-factors with the weighting scheme $w=1/\sigma_F^2+0.0104F^2$, were 0.049 and 0.063, respectively. Maximum and minimum height in final difference Fourier: 0.25 and -0.40 eÅ^{-3}. Ratio of maximum least-squares shift to error in final refinement cycle=0.37, S=1,18. The atomic scattering factors were taken from the International Tables for Crystallography and all calculations were performed on a VAX4000 computer. The refined fractional atomic co-ordinates are shown in Table 1.

AKNOWLEDGEMENTS

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