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Synthesis of 2-Methylindole Analogues and Skatole Dimers Under Friedel-Crafts Reaction Conditions

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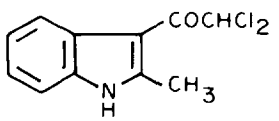
Abstract : A one pot synthesis of 2-methylindole analogues and skatole dimers of biological interest using excess amounts of the substrates and the catalyst and higher temperature under Friedel-Crafts acylation conditions is reported. The products were defined by spectroscopic and single crystal X-ray analysis. Rationalization for the formation of the products has also been attempted.

In the previous communication[1] we reported the synthesis of some novel indolylquinoline analogues of biological interest using indole or its 5-substituted derivatives under Friedel-Crafts reaction conditions. Our recent findings[2-5] as well of others[6,7] that the employment of excess amounts of arenes and sometimes elevated temperature under these reaction conditions leads to the formation of polynuclear compounds, as secondary reaction products, have enlarged the scope of the reaction. The substrates chosen in the present study are 2-methylindole and skatole (3-methylindole). Considerable attention had been given to the study of acid-catalysed polymerisation of indole and skatole and different structures of their dimers were proposed[8] on the basis of theoretical consideration and systematic degradative studies. This paper reports the synthesis of novel 2-methylindole analogues and skatole dimers under Friedel-Crafts reaction conditions and rationalisation of their formation.

RESULTS AND DISCUSSION

When the reaction was carried out either at room temperature (27°C) or at 55-60°C in nitrobenzene for 16h with stoichiometric amounts of 2-methylindole, dichloroacetyl chloride and anhydrous $AlCl_3$, the 3-acylated product **I** was obtained as the only isolable product and the result is in accord with those reported in

literature.[9,10] However, when two molar proportions of each of 2-methylindole and anhydrous $AlCl_3$ and one molar proportion of dichloroacetyl chloride were used in carrying out the reaction for the same period of time two abnormal products 2 and 3 besides the normal 3-acylated product 1 were obtained. The presence of a p-substituted benzene ring in 2 was evident from its IR and NMR spectra indicating the



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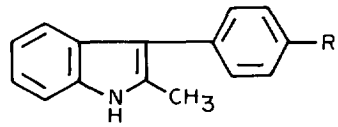
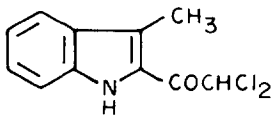


2. R = NO_2
3. R = $NHCOCHCl_2$



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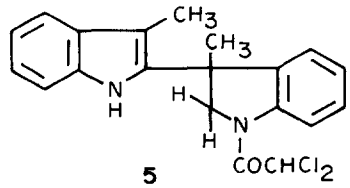

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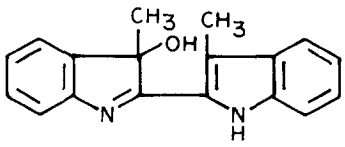

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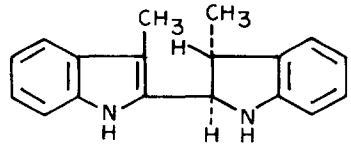

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involvement of the solvent, nitrobenzene in its formation. The structure of the product 2 was confirmed as 2-methyl-3-(4-nitrophenyl)indole by single crystal X-ray analysis. The product was synthesized earlier by Settimo and Saettone[11] from 2-methyl-3-phenylindole by nitration.

The structure of compound 3 was deduced to be 2-methyl-3-(4-dichloroacetamidophenyl) indole by comparison of its MS, IR, ^1H and ^{13}C NMR data with those of the nitro derivative 2.

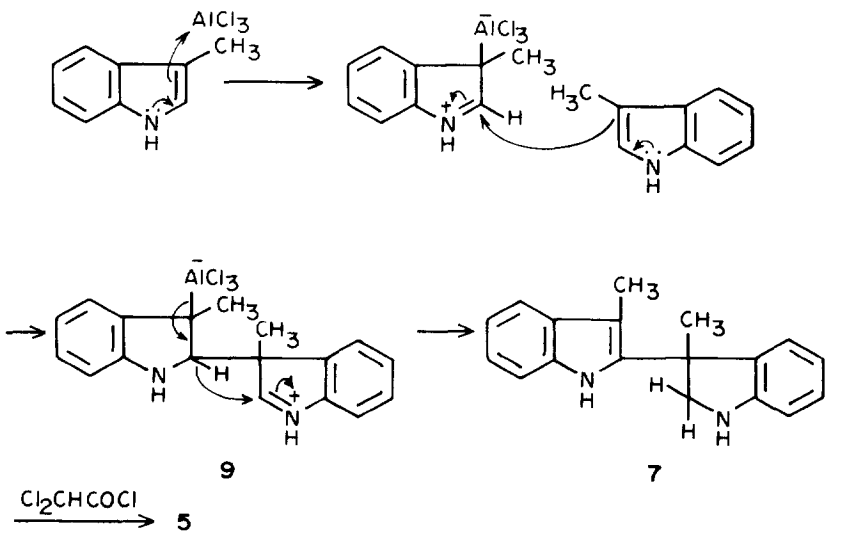
It is well known that $AlCl_3$ coordinates strongly with meta directing groups such as NO_2 group. Thus, when excess of the catalyst is used, it also coordinates with the nitro group of the solvent rendering it an electrophile which attacks 2-methylindole at 3-position. Apparently there is no role of dichloroacetyl chloride in the formation of product 2. In fact, the compound 2 was formed although in lower yield and in a longer period when 2-methylindole was treated with anhydrous $AlCl_3$ in

nitrobenzene at 55-60°C for 32h.

The formation of product **3** may be envisaged to have occurred by reduction of the nitro group of compound **2** initially formed and subsequent acylation of the resulting amino moiety. In fact when one molar proportion of dichloroacetyl chloride was treated with more than two molar proportion of anhydrous $AlCl_3$ in nitrobenzene at 55-60°C, the product dichloroacetamidobenzene **10** was, indeed, formed. In the long history of Friedel-Crafts acylation in nitrobenzene involving acyl chloride and anhydrous $AlCl_3$, the role of nitrobenzene acting as an electrophile and reduction of nitro group are, to our knowledge, unprecedented.

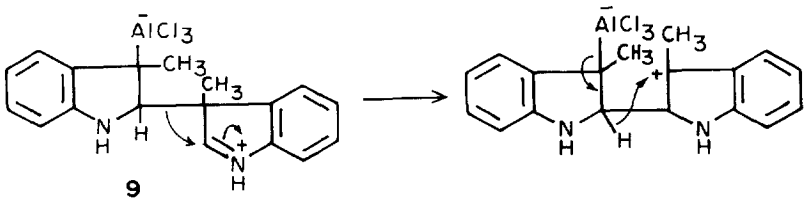
When skatole was used as the substrate and the reaction was carried out employing it in two molar proportion with two mols of anhydrous $AlCl_3$ and one mole of dichloroacetyl chloride in nitrobenzene at 55-60°C for 16h, three products **4**, **5** and **6** were obtained. The product **4** was characterised as 2-dichloroacetyl-3-methylindole by spectroscopic methods and single crystal X-ray analysis. The spectroscopic data of product **5** indicated it to be a dichloroacetyl derivative of a skatole dimer. However, these data appeared to be inadequate for unambiguous determination of the structure which was elucidated by single crystal X-ray crystallography.

A mechanism for the formation of compound **5** has been rationalized (see Scheme-I). Evidently the acylation step necessarily follows the formation of skatole dimer **7**.



Scheme - I

It may be mentioned that Schmitz-DuMont proposed structure **7** for the skatole dimer formed by acid-catalysed polymerisation of skatole mainly based on the failure of 2-methylindole to form a dimer.[12,13] However, structure **8** of the dimer was shown to be the correct one.[14-16] In the present study the structure of the skatole dimer has been proved to be **7**. Thus, it appears that the structure of skatole dimer may be either **7** or **8** depending on the conditions under which it is formed. The structure **8** may be visualised to be generated as shown in Scheme-2 from the intermediate **9** in Scheme-1.



⟶ **8** Scheme-2

The molecular formula of product **6**, $C_{18}H_{16}N_2O$ as determined by MS and elemental analysis indicated it to be a derivative of a skatole dimer. The spectroscopic data, particularly the ^{13}C values strongly suggested the presence of a sp^3 quaternary carbon bearing a hydroxy group in compound **6**. The complete structure of product **6** was unequivocally established as 2-(3'-hydroxy-3'-methylindoleninyl)-3-methylindole. To our knowledge, this is the first report of this hydroxy derivative of skatole dimer. The formation of hydroxy derivative **6** may be visualised to have arisen by oxidation of skatole at the 3-position followed by acid-catalysed dimerisation. The reaction could also very well involve initial acid-catalysed dimerisation followed by oxidation of the intermediate.

The molecular structures of compounds **2**, **4**, **5** and **6** determined by single crystal X-ray crystallography are shown in the corresponding SCHAKAL[17] drawings (see Figure 1). For comparison a graphical superimposition of the four molecules was generated in a further SCHAKAL drawing (supplementary materials). The intermolecular interactions of the four structures are quite different in the crystal. For compound **2** no short contacts indicating an intermolecular interaction were found, although the N-H group of the indole fragment would be a potential hydrogen bond donor.

Intermolecular bond pairs via a crystallographic inversion center exist for compounds **4** and **6**, so that, in both cases, pairs of centrosymmetrically related molecules form dimers in the crystal. For compound **5** an N-H ..... O (carbonyl) hydrogen bond generates infinite chains in the direction of the monoclinic b-axis.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr pellets on a Shimadzu IR-435 instrument, ^1H and ^{13}C NMR spectra were recorded either in $CDCl_3$

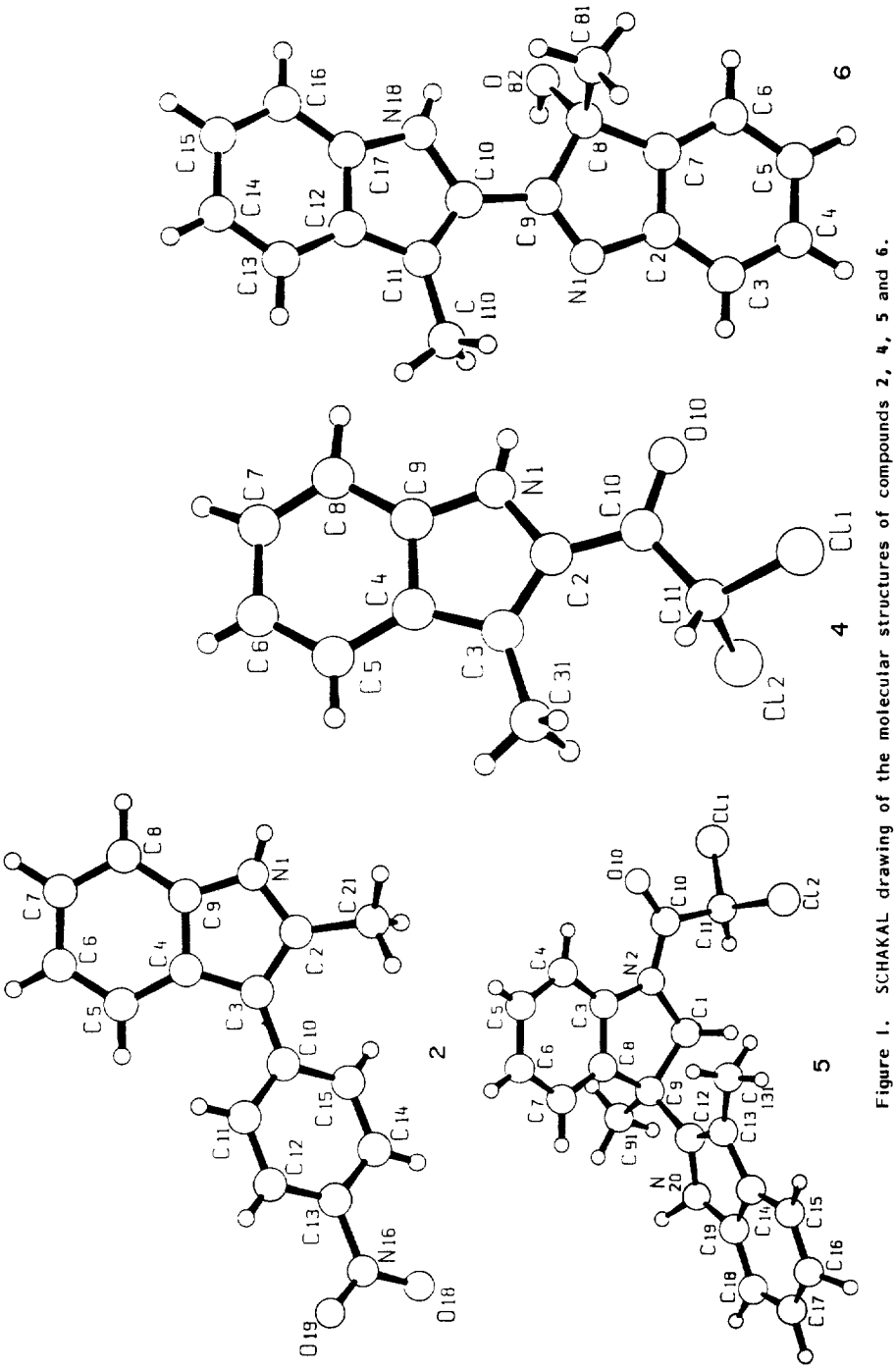


Figure 1. SCHAKAL drawing of the molecular structures of compounds 2, 4, 5 and 6.

or DMSO-d_6 with tetramethylsilane as internal standard on a JEOL FX-100 Fourier transform spectrometer operating at 99.6 and 25.5 MHz respectively. The mass spectra were taken on a MS-50 A.E.I. mass spectrometer operating at 70 eV by the direct insertion method.

General Procedure for the Reaction. In the modified method the reaction was carried out with 2-3 mols of substrate, 1 mol of dichloroacetyl chloride and 2-2.5 mol of anhydrous $AlCl_3$. The substrate was dissolved in nitrobenzene, cooled to 15-20°C followed by gradual addition of the catalyst. Dichloroacetyl chloride was then added slowly with constant stirring. The reaction mixture was kept at ambient temperature (27°C) for 1 h, warmed to 55-60°C for 4 h and then kept overnight at ambient temperature (total period 16 h). The product was decomposed with ice-HCl mixture, extracted with ether or n-butanol, the solvent removed under reduced pressure, and the residue was subjected to column chromatography over silica gel. The products were further purified by crystallisation.

In the normal procedure the substrate, the acylating agent, dichloroacetyl chloride and the catalyst, anhydrous $AlCl_3$ were used in the molar ratio 1:1:1 and the reaction was carried out in the same manner as described above for the modified method.

3-Dichloroacetyl-2-methylindole (1). The product was obtained using 2-methyl indole, dichloroacetyl chloride and anhydrous $AlCl_3$ and eluted with $CHCl_3$ and crystallised from EtOAc.

Compound 1 (yield 55% when 1 molar proportions used), mp 193-194°C; IR (KBr) 3208, 1611, 1527, 1456, 1428, 1358, 1320, 1254, 1167, 1104, 1011, 987, 935, 862, 804, 738 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.76 (3H,s,CH_3), 7.24 (2H,dd,J=2,8Hz), 7.36 (1H,s, $COCHCl_2$), 7.40 (1H,d,J=8Hz), 8.06 (1H,dd,J=2,8Hz), 12.36 (1H,brs,indole NH); ^{13}C NMR (DMSO-d_6) δ 15.0 (CH_3), 70.0 ($CHCl_2$), 108.0 (C3), 111.6, 120.7, 122.0, 122.4 (C4,C5,C6, C7), 126.0 (C3a), 135.0 (C2), 137.4 (C7a), 180.0 (CO); MS (EI) m/z 245 (M^++4,10), 243 (M^++2,65), 241 (M^+,96), 212 (5), 178 (63), 159 (100), 158 (100), 142 (30), 130 (88), 115 (30), 103 (65), 77 (73). Anal. Calcd. for $C_{11}H_9NOCl_2$: C, 54.57; H, 3.75; N, 5.79. Found C, 54.50; H, 3.72; N, 5.71.

2-Methyl-3-(4'-nitrophenyl)indole (2). The product was obtained by the modified method using 2-methylindole as substrate and eluted with benzene and crystallised from CH_2Cl_2-hexane. Compound 2 (yield 21%), mp 211-212°C, (lit.[11] 214-216°C). The product 2 was also obtained in 8% yield when 2-methylindole was treated with anhydrous $AlCl_3$ in nitrobenzene for 32h at 55-60°C in the absence of the acylating agent. IR (KBr) 3376, 2338, 1593, 1549, 1498, 1458, 1431, 1393, 1337, 1257, 1179, 1106, 1024, 986, 852, 749 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.60 (3H,s,CH_3), 7.12-7.20 (2H,m), 7.40-7.52 (1H,m), 7.68 (1H,dd,J=1.5,8Hz), 7.82 (2H,dd,J=2,8Hz,3'-H,5'-H), 8.40 (2H,dd,J=1.5,8Hz,2'-H, 6'-H), 11.40 (1H,brs,indole NH); ^{13}C NMR (DMSO-d_6) δ 12.6 (CH_3), 110.8 (C3), 111.9, 117.5, 119.9, 121.2 (C4,C5,C6,C7), 132.7 (C3',C5'), 126.3 (C3a), 128.6 (C2',C6'),

134.9, 135.2 (C7a,C2), 143.2, 144.2 (C1',C4'); MS (EI) m/z 252 (M^+,100), 243 (10), 206 (21), 191 (18), 165 (7), 130 (13), 115 (7), 102 (8), 78 (6). Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found : C, 71.36; H, 4.73; N, 11.14.

2-Methyl-3-(4'-dichloroacetamidophenyl)indole (3). The product was eluted with C_6H_6-$CHCl_3$ (1:1) and crystallised from CH_3OH. Compound 3 (yield 18%), mp 150-151°C; IR (KBr) 3383, 3114, 1677, 1608, 1514, 1459, 1431, 1406, 1336, 1309, 1242, 1186, 1114, 1029, 985, 866, 834, 804, 741 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.46 (3H,s,CH_3), 6.64 (1H,s, $COCHCl_2$), 7.0-7.4 (4H,m), 7.48 (2H,d,J=8Hz,3'-H,5'-H), 7.72 (2H,d,J=8Hz,2'-H,6'-H), 10.70 (1H,brs, amido NH), 11.16 (1H,brs, indole NH); ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 66.9 ($CHCl_2$), 110.4 (C7), 112.9 (C3), 118.6, 119.5, 121.0 (C4,C5,C6), 120.4 (C3',C5'), 127.4 (C3a), 129.5 (C2',C6'), 131.8, 132.7 (C1',C4'), 134.3, 135.1 (C2,C7a), 162.0 (-NHCO); MS (EI) m/z 334 (M^++2,31), 332 (M^+,44), 307 (20), 289 (16), 220 (11), 219 (7), 154 (100), 136 (72), 89 (34), 77 (38). Anal. Calcd. for $C_{17}H_{14}N_2OCl_2$: C, 61.28; H, 4.23; N, 8.41. Found : C, 61.32; H, 4.25; N, 8.44.

2-Dichloroacetyl-3-methylindole (4). The product was obtained using 3-methylindole as the substrate and eluted with $CHCl_3$ and was crystallised from EtOAc. Compound 4 (yield 66% when 1 molar proportions used), mp 175°C; IR (KBr) 3308, 1644, 1571, 1518, 1452, 1424, 1389, 1341, 1273, 1218, 1161, 1056, 802, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.66 (3H,s,CH_3), 7.12 (1H,dd,J=2,8Hz), 7.28 (1H,dd,J=2,8Hz), 7.40-7.60 (1H,m), 7.48 ($COCHCl_2$), 7.80 (1H,d,J=8Hz), 11.80 (1H,brs,indole NH); ^{13}C NMR (DMSO-d_6) δ 10.4 (CH_3), 69.0 ($CHCl_2$), 118.6, 120.0, 121.0, 126.9 (C4,C5,C6,C7), 122.0, 126.6 (C2,C3), 127.6 (C3a), 137.4 (C7a), 178.6 (CO); MS (EI) m/z 243 (M^++2,64), 241 (M^+,83), 206 (40), 178 (26), 158 (100), 143 (30), 130 (100), 115 (25), 103 (45), 77 (58). Anal. Calcd. for $C_{11}H_9NOCl_2$: C, 54.57; H, 3.75; N, 5.79. Found : C, 54.52; H, 3.72; N, 5.75.

2-(1'-Dichloroacetyl-3'-methylindolinyl)-3-methylindole (5). The product 5 was obtained by the modified method using 3-methylindole as the substrate, eluted with C_6H_6-$CHCl_3$ (1:1) and crystallised from EtOAc. Compound 5 (yield 42%), mp 222-224°C; IR (KBr) 3385, 3020, 1670, 1480, 1420, 1340, 1310, 1270, 1245, 1210, 1180, 1110, 1030, 950, 810, 760 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.80 (3H,s,CH_3), 1.84 (3H,s,CH_3), 4.4 (2H,brs, CH_2), 7.18 (1H,s,$COCHCl_2$), 6.96-7.44 (7H,m), 8.20 (1H,d,J=8Hz); ^{13}C NMR (DMSO-d_6) δ 8.90 (CH_3), 27.2 (CH_3), 44.7 (C3'), 62.1 (C2'), 67.0 ($CHCl_2$), 105.7 (C3), 110.8 (C7), 116.5 (C7'), 117.5 (C4), 118.3 (C6), 120.5 (C5), 123.9 (C5'), 125.3 (C4'), 128.0 (C6'), 129.4 (C3a), 134.6 (C3'a), 137.3 (C7a), 139.2 (C2), 140.6 (C7'a), 160.8 (NHCO); MS (EI) m/z 374 (M^++2,65), 372 (100), 357 (76), 301 (20), 261 (38), 246 (65), 217 (23), 144 (27), 130 (88), 103 (20), 77 (28). Anal. Calcd. for $C_{20}H_{18}N_2OCl_2$: C, 64.35; H, 4.86; N, 7.50. Found : C, 64.30; H, 4.82; N, 7.54.

2-(3'-hydroxy-3'methylindoleninyl)-3-methylindole (6). The product was eluted with benzene and crystallised from CH_2Cl_2-hexane. Compound 6 (yield 33%), mp 182°C; IR (KBr) 3400, 3240, 3050, 2920, 1580, 1560, 1450, 1365, 1340, 1245, 1180, 1095, 990,

740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (3H,s,CH_3), 2.66 (3H,s,CH_3), 7.04-7.62 (8H,m), 9.20 (1H,brs,NH); ^{13}C NMR ($CDCl_3$) δ 10.5 (CH_3), 24.2 (CH_3), 83.9 (C3'), 111.3, 119.5, 119.8, 121.3 (C4,C5,C6,C7), 119.7, 124.9, 125.4, 129.4 (C4',C5',C6',C7'), 126.6, 128.4 (C3'a,C3a), 136.9, 140.0 (C7a,C7'a), 152.2 (C2), 175.0 (C2'); MS (EI) m/z 276 (M^+,90), 258 (100), 233 (50), 216 (21), 155 (45), 130 (52), 105 (25), 91 (25), 77 (72). Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found : C, 78.20; H, 5.80; N, 10.18.

Dichloroacetamidobenzene (10). Dichloroacetyl chloride (1 mol) was treated with anhydrous $AlCl_3$ (2.5 mol) in nitrobenzene at 55-60°C. Worked up as usual and the residue was chromatographed on silica gel. The petroleum ether-benzene (1:1) eluate on crystallization from petroleum ether furnished compound **10** (yield 23%), mp 110-112°C; ^1H NMR ($CDCl_3$) δ 6.04 (1H,s,$COCHCl_2$), 7.12-7.56 (5H,m,ArH), 8.10 (1H,brs, amide NH); MS (EI) m/z 205 (M^++2), 203 (M^+). Anal. Calcd. for $C_8H_7NOCl_2$: C, 47.09; H, 3.46; N, 6.86. Found : C, 47.01; H, 3.41; N, 6.90.

X-Ray Experiments, Structure Determination and Refinements. X-ray work was performed almost the same way for all four compounds as follows : in a first step crystal quality, preliminary cell constants and space groups were estimated from rotation and Weissenberg photographs.

Precise lattice constants from centering of high order reflections and three dimensional intensity data were measured on a STOE four-circle diffractometer with Ni-filtered CuK_α radiation. Reflection intensities were recorded by the ω-2θ-scan technique with variable scan range and variable scan speed. Standard reflections measured routinely every 90 minutes showed in no case any significant variations during the data collections.

Phase determination was carried out successfully with Direct Methods using SHELXS[18], fielding unambiguously all non-hydrogen atoms for all four structures. Least square refinements (with the corresponding programs of the XTAL[19] system) proceeded straightforward. First isotropic, later anisotropic thermal parameters were assigned to all non hydrogen atoms. The hydrogens, which could all be located from different syntheses, were included with isotropic temperature factors. The anomalous dispersion for chlorine was correctd. An absorption correction was applied for **4** and **5**, but not for **2** and **6**. A $1/\sigma^2$ (F_o) weighting scheme was used in all the refinements. Unobserved reflections were included in the refinement only if $|F_c| > |F_o|$. After convergence of all parameters no significant peaks or holes were seen in final difference syntheses.

Crystal Data of 2. $C_{15}H_{12}O_2N$, M_r=252.27, space group orthorhombic Pbca. Crystals were obtained from solution in CH_2Cl_2-hexane. The specimen used for X-ray experiments had dimensions of 0.5x0.5x0.2mm. Lattice constants (Å, degrees), a=7.646(1), b=12.865(1), c=25.186(2), $\alpha=\beta=\gamma=90$, cell volume V=2477.4Å^3, formula

units/cell Z=8, X-ray density ρ_x=1.351g.cm^{-3}, number of independent reflections 2057, unobserved ($F_o < 2\sigma(F_o)$) 210, linear absorption coefficient $\mu(CuK_\alpha)$=7.57cm^{-1}, R-value= 0.043, $R_w=[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$=0.049.

Crystal Data of 4. $C_{11}H_9O_1N_1Cl_2$, M_r=242.10, space group monoclinic $P2_1/n$. Crystals were obtained from solution in ethyl acetate. The specimen used for X-ray experiments had dimensions of 0.75x0.38x0.15mm. Lattice constants (Å, degrees) a=11.643(4), b=7.254(2), c=14.039(5), β=111.54(3), cell volume V=1102.9Å^3, formula units/cell Z=4, X-ray density ρ_x=1.451g.cm^{-3}, number of independent reflections 1919, unobserved ($F_o < 2\sigma(F_o)$) 319, linear eabsorption coefficient $\mu(CuK_\alpha)$=50.47cm^{-1}, R-value-0.053, $R_w=[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$=0.047.

Crystal Data of 5. $C_{20}H_{18}O_1N_2Cl_2$, M_r=373.28, space group monoclinic $P2_1/c$. Crystals were obtained from solution in ethylacetate. The specimen used for X-ray experiments had dimensions of 0.43x0.38x0.38mm. Lattice constants (Å, degrees) a=8.353(1), b= 18.364(2), c=11.924(1), β=97.50(1), cell volume V=1813.4Å^3, formula units/cell Z=4, X-ray density ρ_x=1.363g.cm^{-3}, number of independent reflections 2903, unobserved ($F_o < 2\sigma(F_o)$) 211, linear absorption coefficient $\mu(CuK_\alpha)$=32.92cm^{-1}, R-value=0.059, $R_w=[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$=0.067.

Crystal Data of 6. $C_{18}H_{16}O_1N_2$, M_r=276.34, space group triclinic $P\bar{1}$. Crystals were obtained from solution in CH_2Cl_2-hexane. The specimen used for X-ray experiments had dimensions of 0.5x0.28x0.1mm. Lattice constants (Å, degrees) a=7.250(1), b=8.301(1), c=11.900(1), α=90.11(1), β=95.86(1), α=86.84(1), cell volume V=711.3Å^3, formula units/cell Z=2, X-ray density ρ_x=1.289g.cm^{-3}, number of independent reflections 2573, unobserved ($F_o < 2\sigma(F_o)$) 253, linear absorption coefficient $\mu(CuK_\alpha)$ =6.52cm^{-1}, R-value=0.044, $R_w=[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$=0.044.

Supplementary Material. Hydrogen bonding table, atomic coordinates, bond lengths, anisotropic displacement parameters, torsion angles, observed and calculated structure factors of compounds **2**, **4**, **5** and **6** and graphical superimposition of the four molecules (Figure 2) (36 pages) are deposited in the Cambridge Crystallographic Data Centre.

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