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Synthesis of Indolylquinolines Under Friedel-Crafts Reaction Conditions

Shashi B. Mahato*[a], Nirup B. Mandal[a], Sukanya Chattopadhyay[a], Gopa Nandi[a], Peter Luger[b], and Manuela Weber[b]

[a] Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Jadavpur, Calcutta -700 032, India

[b] Institut für Kristallographie, Freie Universität Berlin,Takustr.6, D - 14195, Germany.

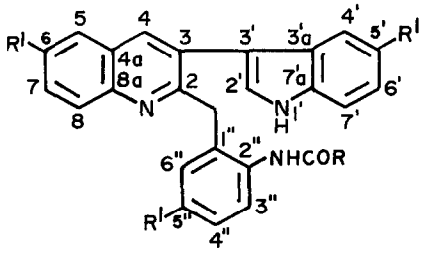
Abstract : A one-pot synthesis of some novel indolylquinoline analogues of biological interest using indole or its 5-substituted derivatives as substrates under Friedel-Crafts acylation conditions is reported. The synthesis of the compounds was accomplished by the employment of excess amounts of the substrates and higher temperature. The complete structure of the derivative obtained by using indole as substrate and dichloroacetyl chloride as acylating agent was unequivocally established as 2-(2"-dichloroacetamidobenzyl)-3-(3'-indolyl)-quinoline **2a** by single crystal X-ray analysis. The structures of other similar indolylquinolines **2b-2e** and **3** were defined by spectroscopic analysis. The mechanism of formation of the analogues has also been rationalised.

The indole and quinoline nuclei are prevalent in a wide variety of biologically active compounds. Some quinoline derivatives have been shown to possess promising antileishmanial activity.[1-3] Our successful synthesis of polynuclear compounds using arenes of varying nucleophilicity under Friedel-Crafts acylation conditions[4-7] prompted us to explore the possibility of preparing indolylquinoline analogues by this method using indole or its 5-substituted derivatives as substrates. Acid-catalysed polymerisation of indole[8] and conversion of indole derivatives to quinolines by pyrolysis[9] and reaction with halogenocarbenes[10] are known. However, synthesis of indolylquinoline derivatives from indole does not appear to have been reported. This paper reports a single-step preparation of potential indolylquinoline analogues. We believe this approach to the synthesis of these analogues is notable for its preparative simplicity, general applicability and conceptual novelty.

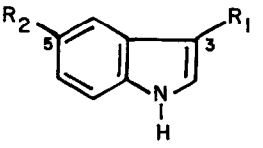
RESULTS AND DISCUSSION

When the reaction was carried out at ambient temperature with stoichiometric amounts of indole, dichloroacetyl chloride and anhydrous $AlCl_3$, the 3-acylated derivative **8** was obtained as the major product along with minor amounts of the 3,5-diacylated compound **9**. The formation of these products is in accord with the results reported in the literature.[11,12]

The indolylquinoline analogues **2a-2e** were synthesised in moderate yields (43-48%) using indole **1**, its 5-methoxy- or 5-bromo- derivatives as substrates, dichloroacetyl-chloride as the acylating agent and anhydrous $AlCl_3$ as the catalyst. Chloroacetylchloride and acetyl chloride were also used for the substrate, indole. The reactions were conducted in nitrobenzene as solvent. The molecular formula of the product **2a** obtained by the use of indole and dichloroacetyl chloride as the substrate and acylating agent respectively was deduced to be $C_{26}H_{19}N_3OCl_2$ by elemental and mass spectral analysis. The molecular composition strongly indicated the involvement of three moles of indole in the formation of the product. The ^1H NMR spectrum of the compound **2a** displayed discernible



2a : R = $CHCl_2$, R^1 = H
2b : R = CH_2Cl, R^1 = H
2c : R = CH_3, R^1 = H
2d : R = $CHCl_2$, R^1 = OCH_3
2e : R = $CHCl_2$, R^1 = Br



8 : R_1 = $COCHCl_2$. R_2 = H
9 : R_1 = R_2 = $COCHCl_2$

signals corresponding to a methylene and a $COCHCl_2$ group at δ 4.4 and 6.92 respectively. The ^{13}C NMR spectrum displayed signals assigned to one sp^3 methylene, one sp^3 methine, nine tetrasubstituted and fourteen protonated aromatic carbons and one amide carbonylcarbon (Table 1). However, the spectroscopic data appeared to be inadequate for unambiguous determination of the structure which was eventually elucidated by single-crystal X-ray analysis. The molecular structures of the compound is shown in a SCHAKAL[13] drawing in Fig.1 which also gives the X-ray crystallographic atom numbering scheme. An intermolecular hydrogen bond N(18)-H(18) ..... O(28) is found via the inversion center at (0.5, 1, 0.5), so that pairs of centrosymmetrically related molecules form dimers in the crystal (Fig.2). Thus, the complete structure of the compound **2a** was unequivocally established as 2-(2"-dichloroacetamidobenzyl)-3-(3'-indolyl)-quinoline.

The structures of the other indolylquinoline analogues **2b-2e**, which are very similar to that of **2a** were determined by elemental analysis and on the basis of the mass, ^{1}H and ^{13}C NMR data. The crystallographic data for compound **2a** are given in the supplementary material.

The dramatic difference in the results using excess of the indoles and higher temperture is remarkable and this one-pot synthesis provided an easy access to the interesting products.

A mechanism for the formation of the indolylquinoline compounds has been rationalised for the substrate indole and acylating agent dichloroacetyl chloride (see scheme 1). This is based on that reported in the literature regarding oligomerisation of indole in acidic media.[14] Electrophilic attack by the indole-$AlCl_3$ complex produces a 2-(3-indolyl)-indoline intermediate **4** which is further attacked by another indole-$AlCl_3$ complex at the more basic indoline nitrogen atom with ring opening. Oligomerisation is interrupted by N-acylation with further ring-opening to generate **5** which can tautomerise to **6**. Cyclisation of **6** conceivably yields a dihydroquinoline derivative **7** which may undergo aerial oxidation to give the final product **2a**. A minor ketonic product **3** was obtained which evidently formed by aerial oxidation of the benzyl methylene group of **2a**.

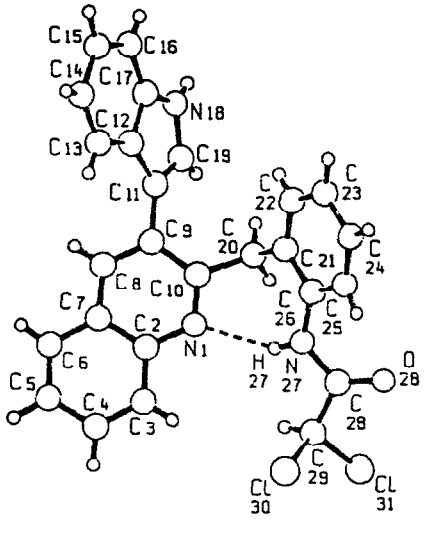


Fig. 1. SCHAKAL drawing of the molecular structure of compound **2a**.

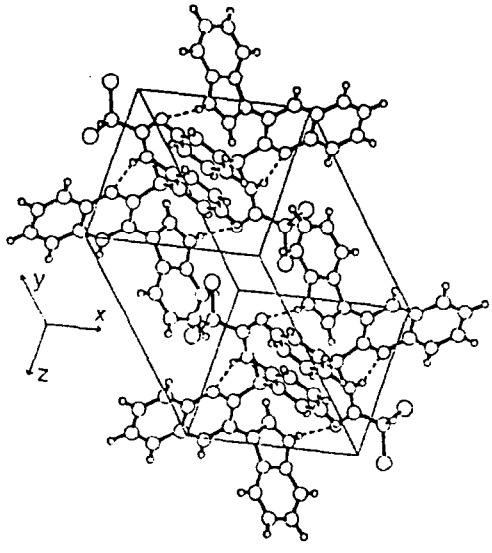
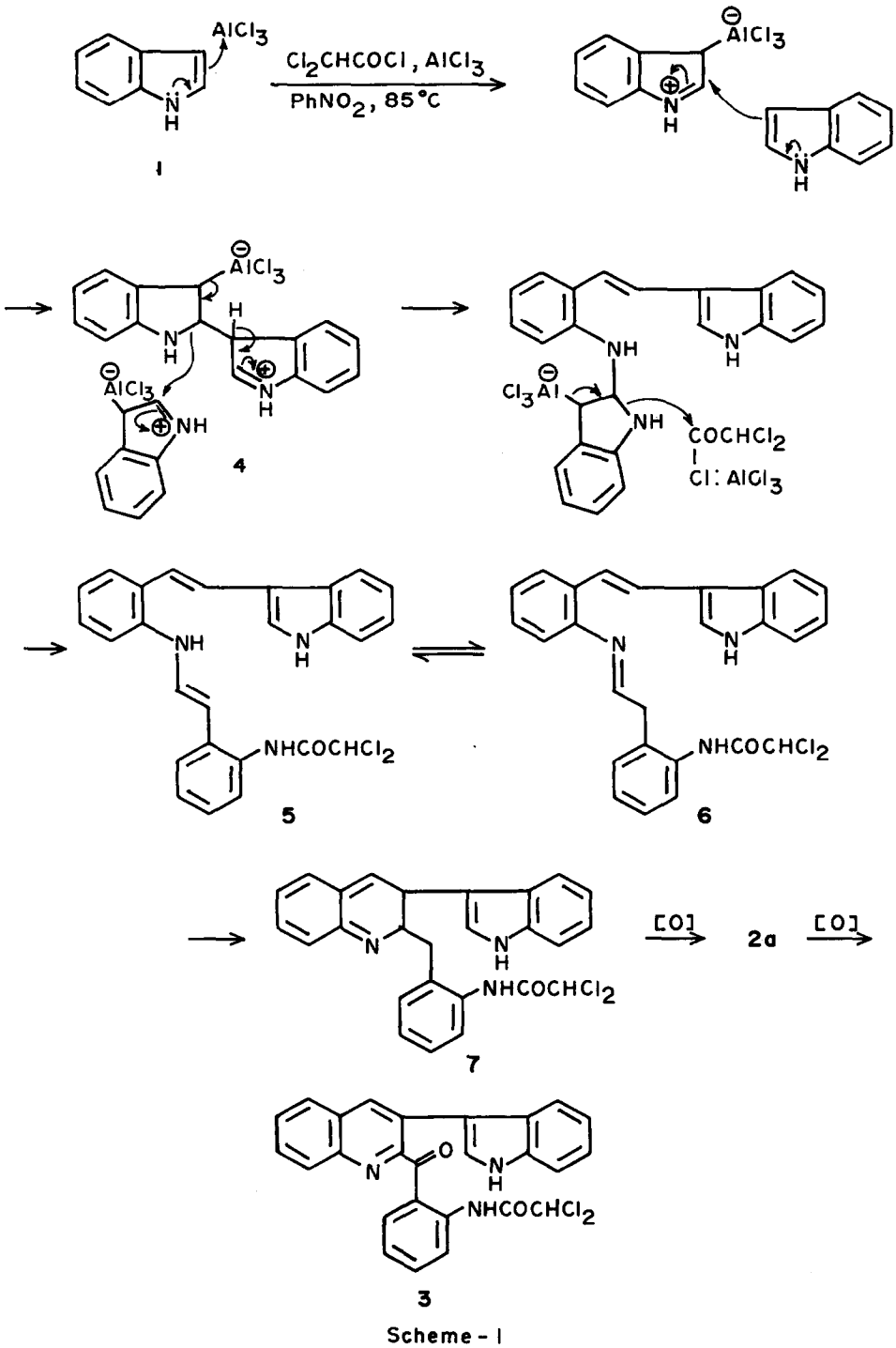


Fig. 2. Dimerisation of compound **2a** by a pair of hydrogen bonds via a crystallographic inversion centre.

Table 1. ^{13}C NMR chemical shifts δc (±0.1) of **2a–2e** and **3** (DMSO-d_6)

Carbon atom	2a	2b	2c	2d	2e	3
2	160.1	160.2	160.2	158.4[a]	159.7	156.0
3	133.2	132.6	131.1	133.9	132.6	134.2
4	137.9	137.8	137.8	138.1	137.0	136.1
4a	129.3[c]	129.3	129.4[c]	131.1	128.8	128.1
5	125.5[a]	125.1[a]	125.0	112.4[b]	128.5	125.9[a]
6	125.0[a]	124.9[a]	123.8[a]	157.9[a]	119.3	124.9[a]
7	126.7	126.7	126.7	112.9[b]	130.0	126.1
8	127.6	127.7	127.6	128.7	129.5	128.7
8a	145.6	145.6	145.5	136.4	144.3	144.6
2'	124.5	124.4	123.5[a]	124.4	126.7	124.2
3'	112.5	112.6	112.6	113.2	112.5	110.9
3'a	128.5[c]	128.5	128.8[c]	129.3	128.8	128.1
4'	119.6[b]	119.6	119.6[b]	104.9	124.3	120.5
5'	121.7	121.7	121.6	156.8	118.0	121.9
6'	118.5[b]	118.6	118.5[b]	100.9	120.6	119.8
7'	111.9	111.9	111.9	113.0	113.9	111.9
7'a	136.2	136.2	136.9	128.3	135.5	136.2
1"	126.7	126.7	126.7	127.9	128.0	135.4
2"	135.2	135.9	136.0	127.9	134.7	139.0
3"	118.5	118.6	118.5	122.5	119.6	118.5
4"	126.3	126.3	126.3	112.4	129.5	126.1
5"	121.7	121.7	121.6	154.9	117.9	122.7
6"	129.7	129.7	127.6	115.6	132.3	129.9
-NHCO	162.4	164.9	167.9	163.4	162.3	162.6
$-CH_2-$	37.5	37.8	38.2	37.9	37.8	
$-CHCl_2$	67.7			67.2	67.2	67.5
OCH_3				55.8		
				55.5		
				55.0		
$-CH_2Cl$		43.5				
$-CH_3$			23.9			
C=O						198.9

[a,b,c] Assignments within a column may be interchanged.


AlCl3
Cl2CHCOCl, AlCl3
PhNO2, 85°C
1
4
NH
COCHCl2
Cl: AlCl3
5
6
NHCOCHCl2
[O]
2a
7
3

Scheme - I

In vitro biological screening of the indolylquinoline derivatives using a pathogenic *Leishmania donovani* AG83 strain revealed that these compounds possess significant anti-leishmanial activity, the details of which will be published elsewhere.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu IR-435 instrument. ^{1}H and ^{13}C NMR spectra were recorded either in $CDCl_3$, CD_3OD 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 either on a Hitachi Model RMU-6L mass spectrometer or on a MS-50 A.E.I. mass spectrometer operating at 70 eV by the direct insertion method.

3-Dichloroacetyl indole (8) and 3,5-di-dichloroacetyl indole (9). The synthesis of normal products **8** and **9** were accomplished using the substrate indole, acylating agent, dichloroacetyl chloride and the catalyst, anhydrous $AlCl_3$ in the molar ratio 1:1:1. The substrate was dissolved in nitrobenzene, cooled to 15-20°C followed by gradual addition of the catalyst. The acylating agent was then added in portions with constant stirring. The stirred reaction mixture was kept at ambient temperature (25°C) for 1 h, warmed upto 45°C and then kept overnight at ambient temperature. The product was decomposed with an ice-HCl mixture and then taken up with ether. The ether solution was washed free from acid and dried. The residue was subjected to chromatography on silica gel. The products **8** and **9** thus obtained were further purified by crystallisation from EtOAc.

Product **8** (yield 67%), mp 240°C, IR (KBr) 3220, 3050, 2920, 1680, 1515, 1505, 1453, 1425, 1316, 1260, 1238, 1150, 800, 748 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.25-7.40 (2H,m), 7.56 (1H,s,COC*H*Cl_2), 7.52-7.66 (1H,m), 8.23 (1H,m), 8.62 (1H,s on D_2O shake), 12.4 (1H,s,-N*H*); ^{13}C NMR (DMSO-d_6) δ 68.8 ($CHCl_2$), 110.5 (C3), 112.7 (C7), 122.6 (C6), 123.7 (C5), 125.2 (C3a), 135.7 (C2), 136.9 (C7a), 180.8 (CO); MS (EI) *m/z* 229 (M^++2,13), 227 (M^+,25), 144 (100), 116 (28) and 88 (18). Anal. Calcd. for $C_{10}H_7NOCl_2$: C, 52.66; H, 3.09; N, 6.14. Found : C, 52.60; H, 3.10; N, 6.15.

Product **9** (yield 7%), mp 108°C, IR (KBr) 3240, 3050, 3005, 1678, 1642, 1590, 1538, 1505, 1470, 1338, 1280, 1182, 1060, 980, 870, 810, 760 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.20, 7.50 (s each, 2 X COC*H*Cl_2), 7.66 (1H,d, *J*=8Hz), 8.06 (1H,dd, *J*=2,8Hz), 8.56 (1H,s), 9.10 (1H,d, *J*=2Hz), 12.4 (1H,brs,-N*H*); ^{13}C NMR (CD_3OD) δ 69.6, 69.5 (2 X $COCHCl_2$), 113.2 (C3), 113.9(C7),125.9, 126.2 (C4,C6), 127.9 (C5), 138.8 (C2,C7a), 187.9 (CO); MS (EI) *m/z* 341 (M^++4,3), 339 (M^++2,7), 337 (M^+,5), 254 (100), 143 (27). Anal. Calcd. for $C_{12}H_7NO_2Cl_4$; C, 42.52; H, 2.08; N, 4.13. Found : C, 42.55; H, 2.10; N, 4.10.

General Procedure for the Abnormal Reaction. In the modified method the reaction was carried out with 3.5-4 mols of substrate, 1 mol of acyl chloride and 1.5-2 mols of anhydrous $AlCl_3$. The substrate was dissolved in nitrobenzene, cooled to 15-20°C followed by gradual addition of the catalyst. The acylating agent was then added slowly with

constant stirring. The reaction mixture was kept at ambient temperature (25°C) for 1 h, warmed to 85°C for 4 h and then kept overnight at ambient temperature. 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.

2-(2"-Dichloroacetamidobenzyl)-3-(3'-indolyl)-quinoline (2a) and 2-(2"-dichloroacetamidobenzoyl)-2-(3'-indolyl)-quinoline (3). The product **2a** and **3** were eluted with C_6H_6-$CHCl_3$ (1:1) and crystallised from CH_2Cl_2-hexane.

Compound **2a** (yield45%), mp 194°C; IR (KBr) 3300, 3185, 3079, 1690, 1610, 1530, 1480, 1449, 1410, 1335, 1280, 1239, 1177, 1131, 1014, 939, 839, 754 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.4 (2H,s,CH_2), 6.64 (1H,d, J=8Hz, 3"-H), 6.92 (2H,s, 2'-H and $COCHCl_2$), 7.00-8.16 (11H,m,Ar*H*), 8.40 (1H,s,4-H), 11.3 (1H,s, amide N*H*), 11.6 (1H,s, indole N*H*); MS (EI) *m/z* 461 (M^++2,40), 459 (M^+,70), 425 (15), 423 (12), 377 (36), 376 (100). Anal. Calcd. for $C_{26}H_{19}N_3OCl_2$: C, 67.83; H, 4.16; N, 9.12. Found : C, 67.78; H, 4.11; N, 9.10.

Compound **3** (yield 9%), mp 215°C; IR (KBr) 3402, 3254, 2996, 1703, 1643, 1584, 1447, 1278, 1159, 1100, 947, 922, 858, 796, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.08 (1H,s, $COCHCl_2$), 6.86 (1H,dd, J =2,8Hz, 3"-H), 6.98 (1H,d, J =2Hz, 2'-H), 7.16-8.48 (10H,m,Ar*H*), 8.58 (1H,s, 4'-H), 8.60 (1H,d, J =8Hz, 6"-H), 12.60 (2H,brs, 2 X N*H*); MS (EI) *m/z* 475 (M^++2,12), 473 (M^+,16), 390 (100), 334 (9), 271 (8), 243 (52), 216 (30). Anal. Calcd. for $C_{26}H_{17}N_3O_2Cl_2$: C, 65.83; H, 3.61; N, 8.86. Found : C, 65.77; H, 3.58; N, 8.80.

2-(2"-Chloroacetamidobenzyl)-3-(3'-indolyl)-quinoline (2b). The product **2b** was eluted with C_6H_6-$CHCl_3$ (1:1) and was crystallised from CH_2Cl_2-hexane, yield 47%, mp 186°C; IR (KBr) 3228, 1668, 1617, 1587, 1529, 1480, 1407, 1333, 1238, 1139, 1008, 957, 923, 861 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 (2H,s,CH_2Cl), 4.40 (2h,s,CH_2), 6.56 (1H,d, J=8Hz), 6.84 (1H,t-like, $W_{\frac{1}{2}}$=8Hz), 7.20-8.0 (10H,m,Ar*H*), 8.16 (1H,s,4'-H), 8.20 (1H,d, J=8Hz , 6"-H), 8.64 (1H,brs,N*H*CO), 11.8 (1H,s,indole N*H*); MS (EI) *m/z* 425 (M^+,50), 376 (100), 256 (22). Anal. Calcd. for $C_{26}H_{20}N_3OCl$: C, 73.32; H, 4.73; N, 9.87. Found : C, 73.28; H, 4.81; N, 9.81.

2-(2"-Acetamidobenzyl)-3-(3'-indolyl)-quinoline (2c). The product **2c** was eluted with C_6H_6-$CHCl_3$ (1:1) and crystallised from CH_2Cl_2-hexane, yield 45%; mp 246°C; IR (KBr) 3212, 3046, 2914, 1678, 1613, 1587, 1548, 1481, 1406, 1366, 1310, 1271, 1239, 1211, 1140, 1046, 1007, 962, 883, 862, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (3H,s, CH_3), 4.3 (2H,s,CH_2), 6.36 (1H,dd,J=2,8Hz), 6.70 (1H,t-like,$W_{\frac{1}{2}}$=8Hz), 7.00-8.20 (12H,m,Ar*H*), 8.64 (1H,brs, amide N*H*), 11.3 (1H,brs, indole N*H*); MS (EI) *m/z* 391 (M^+,100), 376 (36), 255 (34). Anal. Calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41; N, 10.73. Found : C, 79.81; H, 5.37; N, 10.70.

2-(2"-Dichloroacetamido-5"-methoxybenzyl)-3-[3'-(5'-methoxyindolyl)]-6-methoxyquinoline (2d). The product **2d** was eluted with C_6H_6-$CHCl_3$ (1:1) and was crystallised from CH_2Cl_2-

hexane, yield 37%; mp 182°C; IR (KBr) 3318, 3110, 2980, 2920, 2855, 1685, 1586, 1540, 1480, 1410, 1338, 1280, 1240, 1128, 1010, 948, 900, 850, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.44, 3.72, 3.86 (9H,s each, 3 X OCH_3), 4.24 (2H,s,CH_2), 5.83 (s), 6.06 (d, *J*=2Hz), 6.52-7.48 (7H,m,Ar*H*), 7.68 (1H,d, *J*=8Hz), 8.08 (1H,d, *J*=8Hz), 8.20 (1H,s), 8.48 (1H,brs, amide N*H*), 11.96 (1H,s, indole N*H*); MS (EI) *m/z* 551 (M^++2,8), 549 (M^+,12), 466 (100), 450 (5), 423 (4), 315 (2). Anal. Calcd. for $C_{29}H_{25}N_3O_4Cl_2$: C, 63.28; H, 4.58; N, 7.63. Found : C, 63.23; H, 4.55; N, 7.58.

2-(2"-Dichloroacetamido-5"-bromobenzyl)-3-[3'-(5'-bromoindolyl)]-6-bromoquinoline (2e). The product **2e** was eluted with $CHCl_3$ and crystallised from ethyl acetate, yield 46%, mp 232°C; IR (KBr) 3420, 3005, 2920, 1685, 1580, 1522, 1475, 1402, 1370, 1310, 1273, 1242, 1210, 1180, 1100, 1060, 948, 920, 885, 820, 800, 750, 692 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.4 (2H,s,CH_2), 6.72 (1H,s,$COCHCl_2$), 6.88 (1H,s,2'-H), 7.36-7.72 (6H,m,Ar*H*), 7.92 (2H, d, *J*=2Hz,4'-H, 5-H), 8.38 (1H,d, *J* =2Hz,6"-H), 8.40 (1H,s,4-H), 10.6 (1H,brs, N*H*CO), 11.8 (1H,brs, indole N*H*); MS (EI) *m/z* 699 (M^++2,7), 697 (M^+,10), 661 (2), 614 (100), 612 (100), 610 (33), 571 (2), 569 (2), 533 (3), 419 (3), 413 (3), 410 (3), 335 (8), 255 (5), 212 (8), 164 (5). Anal. Calcd. for $C_{26}H_{16}N_3OCl_2Br_3$: C, 44.80; H, 2.31; N, 6.02. Found : C, 44.74; H, 2.35; N, 6.05.

Crystallisation and X-ray Experiments. Suitable single crystals of **2a** were obtained from solution in CH_2Cl_2-hexane. A prismatic specimen with dimensions 0.50 x 0.48 x 0.25 mm was selected for the X-ray measurements. From preliminary rotation and Weissenberg photographs, the space group was determined to be triclinic, $P\bar{1}$.

The precise lattice constants and intensity data of hemisphere with $\sin\theta/\lambda \leqslant 0.58 Å^{-1}$ were measured on a STOE four-circle diffractometer with Ni-filtered Cu Kα-radiation. Orientatiion matrix and lattice constants were refined from 174 high order reflections. Reflection intensities were recorded by the θ-2θ-scan technique with variable scan range and variable scan speed. Three standard reflections which were measured every 90 minutes showed no significant variations during the whole data collection.

Structure Determination and Refinement. Phase determination was carried out successfully with Direct Methods (SHELXS[15]). All non-hydrogen atoms of the **2a** molecule could be identified unambiguously.

Least squares refinements (with the corresponding programs of the XTAL[16] system) proceeded straightforward. First isotropic, later anisotropic thermal parameters were assigned to all carbon, nitrogen, oxygen, and cholorine atoms. The hydrogens, which could all be be located from difference syntheses, were included with isotropic temperature factors. The anomalous dispersion for cholorine was corrected. No absorption correction was applied.

Unit weights were used throughout the refinements. Unobserved reflections were included in the refinement only if $|F_c| > |F_o|$. After convergence of all parameters a

final R-value of 6.4% was obtained. The maximum and average shift/error ratios at the end of the refinement were 0.32 and 0.01. A final electron density map showed all residual density below 0.59eÅ^{-3}.

The molecule consists mainly of three planar fragments : the indole group (average deviation of contributing atoms from a least squares plane is σ = 0.013Å), the quinoline ring system (σ = 0.024Å) and the phenyl ring C(21)-C(26) (σ = 0.008Å) with the dichloro substituted amide group bonded to this ring. Interplanar angles are : indole/quinoline 54.1(2)°, indole/phenyl 107.1(2)° and quinoline/phenyl 58.1(3)°. The plane through the amide atoms N(27), C(28), O(28), C(29) has an angle of 36.3(2)° with the phenyl ring and an angle of 34.9(2)° with the quinoline system. This arrangement allows an intramolecular hydrogen bond N(27)-H(27) ..... N(1) with an N ..... N-contact of 2.856(4)Å and H(27) ... N(1) = 2.18(4)Å.

Crystal Data of (2a). $C_{26}H_{19}ON_3Cl_2$, M_r = 406.36, lattice constants (Å, degrees) a = 9.717(1), b = 10.307(1), c = 12.997(4), α = 76.24(1), β = 68.92(8), γ = 68.89(7), cell volume (Å^3) V = 1124.3, formula units/cell Z=2, X-ray density (g.cm^{-3}) ρ_x = 1.360, space group triclinic, $P\bar{1}$, number of independent reflections 3635, unobserved ($I < 2\sigma$)60, linear absorption coefficient μ (Cu K α) = 27.84 cm^{-1}, no absorption correctiion. R-value =0.064, $R_w = [\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$ = 0.068.

Supplementary Material. X-ray data for compound **2a**, bond lengths, Fig.3, the final atomic parameters with Ueq values as well as listing of complete atomic parameters with Uij values, valence angles and dihedral angles, Tables II-V (9 pages) are deposited in the Cambridge Crystallographic Data Centre.

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