REACTIONS OF AMIDINES WITH DIPHENYLAMINE-2,2'-DICARBONYL CHLORIDE

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Abstract - Amidines react with diphenylamine-2,2'-dicarbonyl chloride to yield polyheterocycles. Reactions of some of the latter with reducing agents are also reported.

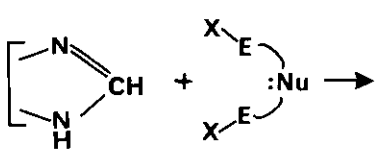
The reactions of compounds containing the amidine group (I) with a multifunctional reagent (II) containing two electrophilic terminal centers spaced from a central nucleophilic center, to give derivatives of the type (III) have been reported earlier by Katritzky et al[1]. The reactions of diphenylamine-2,2'-dicarbonyl chloride (IV) were investigated in this connection with benzimidazole, 5,6-dimethylbenzimidazole, 4-quinazolone and N,N'-diphenylbenzamidine.

We have now extended the scope of this reaction to other amidine derivatives[2]. In each case, the reaction proceeded to give polyheterocycles having the common structural unit (III, E ≡ >C = O). The action of reducing agents on some of these and related[1] polyheterocycles have also been investigated.

Reaction with 6-bromo-, 2-methyl-, and 6-nitro-4-quinazolone

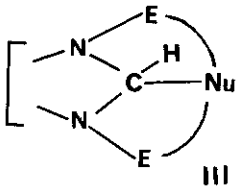
The reagent, diphenylamine-2,2'-dicarbonyl chloride (IV) was prepared according to the method of Hanning and Brummer[3] as modified by Katritzky et al[1]. 6-Bromo-4-quinazolone[4] reacted with a molar proportion of IV in the presence of excess triethylamine in refluxing diglyme to yield 12-bromo-4b,9a,14b-triazatribenzo[a,e,j]phenalene-9,10,15-trione (VI), $C_{22}H_{12}N_3O_3Br$, as an amorphous solid. The compound showed the expected twin M^+ at 445 and 447 corresponding to ^{79}Br and ^{81}Br. Intense M^+-1 peaks at m/e 444, m/e 446 characteristic of compounds containing the grouping (III, E ≡ >C = O)[1] were observed. The MS fragmentation was similar to that observed for the unsubstituted hexacycle (V)[1]. Characteristic peaks were obtained at M^+-HCO (418, 416), M^+-HCO_2 (402, 400) and m/e 322. Peaks at m/e 224 and 226 could be ascribed to bromoquinazolone while those at m/e 222 and 221 were due to the loss of quinazolinyl and quinazolone respectively from M^+. The m/e 222 successively loses CO, CO and C_2H_2 to give peaks at m/e 194, 166 and 140. Doubly charged peaks were observed at m/e 223.5 and 222.5 (M^{++}), and 209.5 and 208.5 $(M-CO)^{++}$. The IR spectrum showed bands at 1742, 1680 (C=O), 1602 (C=C) cm^{-1}. The NMR spectrum of this compound could not be recorded due to its extreme insolubility.

6-Nitro-4-quinazolone[5] on reflux in tetrahydrofuran with IV and excess triethylamine furnished 12-nitro-4b,9a,14b-triazatribenzo[a,e,j]phenalene-9,10,15-trione (VII), $C_{22}H_{12}N_4O_5$, m.p. 225-227°C. The compound showed the expected spectroscopical properties (C=O at 1745, 1670 and C=C at 1610 cm^{-1}). The 200 MHz ^1H-NMR indicated the presence of two conformers of the compound in the ratio 7:3. In the less predominant conformer the C_{11}-H doublet (J = 3Hz)

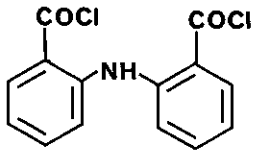


I

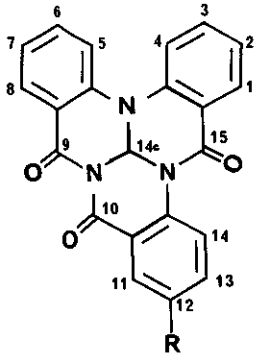
II



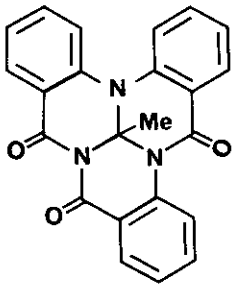
III



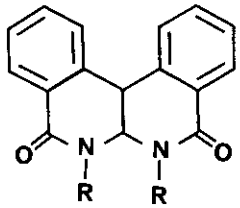
IV



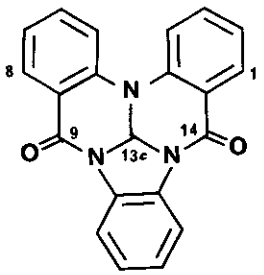
V; R = H
VI; R = Br
VII; R = NO_2



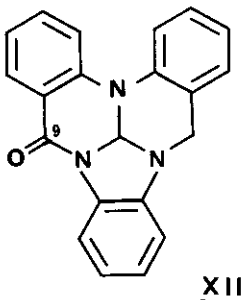
VIII



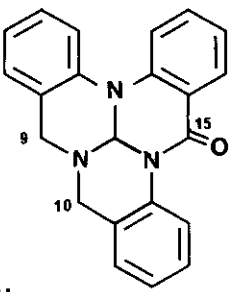
IX; R = CH_2Ph
X; R = $CH_2CH_2CH_2CH_3$



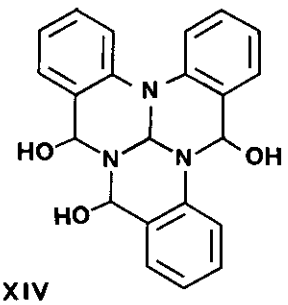
XI



XII



XIII



XIV

was deshielded slightly from δ 8.99 to δ 9.15. A similar but smaller deshielding was observed for the C_{13}-proton (dd, J = 3 and 8.5 Hz) from δ 8.55 to δ 8.59. The C_{14}-proton appeared as a broadened doublet (J = 8.5 Hz) around δ 6.78. The sharp 1H singlet at δ 7.03 could be assigned to the C_{14c}-proton. An examination of the Dreiding model of VII showed that two relatively unstrained conformers are possible. In only one of these, there is coplanarity between the C_{10}-carbonyl and the C-ring which would lead to larger deshielding of the ortho-(C_{11}-H) and para-(C_{13}-H) protons. From the ^{1}H-NMR this appears to be the less abundant conformer.

The 2-methyl-4-quinazolone[6] under conditions similar to those described above furnished 14c-methyl-4b,9a,14b-triazatribenzo[a,e,j]phenalene-9,10,15-trione (VIII), $C_{23}H_{15}N_3O_3$ (C=O at 1740 and C=C at 1600 cm^{-1}). The methyl attached to C_{14c} appeared somewhat downfield at δ 1.74.

Acyclic Amidines

It was observed that the two acyclic amidines, viz., N,N'-dibenzylformamidine[7] and N,N'-dibutylformamidine[7], smoothly furnished the tetracyclic products, $C_{29}H_{23}N_3O_2$ (M^+ 445) (IX) and $C_{25}H_{27}N_3O_2$ (M^+ 377) (X) respectively, on reflux with a molar proportion of the acid chloride (IV). Thus the reaction took place more smoothly than for N,N'-diphenylbenzamidine where a bis-amide is obtained as the initial product, which had to be pyrolyzed at 170°C to yield the desired product. The reasons for the lack of reactivity of the latter compound is obviously due to steric hindrance around the central carbon which bears a bulky phenyl group, as well as by the reduced nucleophilicity of the nitrogens which bear phenyl substituents. Both compounds exhibited characteristic IR bands for the amide carbonyls (1735, 1665 cm^{-1} for IX; 1740, 1675 cm^{-1} for X). The central proton resonated downfield at δ 6.53 for X. In the 200 MHz ^{1}H-NMR of compound IX, however, this proton gave two signals of approximately equal intensity at δ 6.76 and δ 6.92 indicating the presence of two non-equivalent conformers. The benzylic protons were sharply differentiated in IX appearing as broadened doublets (J ≈ 14 Hz) at δ 4.34 and δ 5.76. The MS fragmentation pattern of IX and X was very characteristic. The base peak was generated by the loss of the R-NHCO (R = benzyl or n-butyl) moiety. Characteristic fragments were also obtained at m/e 221 (M^+-RNCO-R), 195 (M^+-CN), 194 (M^+-HCN), 167 (195-CO), 166 (194-CO).

Reduction studies

Compound XI[1] on treatment with BH_3 (generated in situ from $NaBH_4$-BF_3.Et_2O) in THF gave compound XII, $C_{21}H_{15}N_3O$ (M^+ 325), m.p. 180-182°C, which still retained one of the amide carbonyls. Reduction of the other to a methylene was evident from a 2H singlet at δ 4.38 in the 80 MHz ^{1}H-NMR ($CDCl_3$) spectrum. Similarly, compound V on reduction with BH_3.THF gave a product, $C_{22}H_{17}N_3O$, m.p. 193-195°C, in which an amide carbonyl had been retained, the other two being reduced to methylenes. The IR spectrum showed bands at 1750, 1685 (C=O) cm^{-1}. The almost identical ^{13}C-chemical shifts of the two methylene carbons (δ 51.2 and δ 51.3) indicated that these were in very similar environments. Thus the reduction product should be XIII rather than one of the other two possibilities (reduction of 9-CO and 15-CO, or 10-CO and 15-CO to methylene groups). Use of $NaBH_4$ in THF at 30°C, however, led to a different result. The hexahydro-derivative (XIV), m.p. 75°C, formed lacked any carbonyl band but instead showed a very broad hydroxyl band (3000-3500 cm^{-1}). The MS fragmentation pattern was quite different from that of the parent compound showing the successive loss of hydroxyl groups.

EXPERIMENTAL

IR and UV spectra were recorded on a Beckman IR-20 and Varian 634 S spectrometers respectively, ^{1}H-NMR spectra on Varian CFT-20 and XL-200 instruments. The ^{13}C-NMR spectrum was recorded on a 50 MHz Bruker instrument. Analytical samples were routinely dried over P_2O_5 at 2 mm Hg for 24 h.

M.p.s were determined on a Kofler block apparatus and are uncorrected. Solutions were dried over anhydrous Na_2SO_4.

Preparation of starting materials — Diphenylamine-2,2'-dicarbonyl chloride[3], 6-bromo-4-quinazolone[4], 5-nitro-4-quinazolone[5], 2-methyl-4-quinazolone[6], N,N'-dibenzylformamidine[7] and N,N'-dibutylformamidine[7] were prepared according to literature methods.

12-Bromo-4b,9a,14b-triazatribenzo[a,e,j]phenalene-9,10,15-trione (VI) — The acid chloride (IV) (2.94 g, 10 mmol), 6-bromo-4-quinazolone (2.25 g, 10 mmol) and Et_3N (3.05 g, 30 mmol) were refluxed in diglyme (150 ml) for 4 h and then filtered. The filtrate was concentrated, diluted with benzene and chromatographed over silica gel. The benzene eluates furnished a mixture of VI and unreacted quinazolone. The latter was removed by extraction with DMSO, to yield amorphous VI (0.67 g, 15%), which could not be crystallised on account of its insolubility. (Found: C,59.11; H,2.31; N,9.32. $C_{22}H_{12}N_3O_3Br$ requires C,59.20; H,2.69; N,9.42%).

12-Nitro-4b,9a,14b-triazatribenzo[a,e,j]phenalene-9,10,15-trione (VII) — The acid chloride (IV) (2.94 g, 10 mmol), 6-nitro-4-quinazolone (1.91 g, 10 mmol) and Et_3N (3.05 g, 30 mmol) were refluxed in THF (150 ml) for 4 h. The precipitated $Et_3N^+HCl^-$ was filtered off. The filtrate was concentrated to 20 ml and diluted with cyclohexane-petroleum ether (b.p. 60-80°C) (1:1) (100 ml). The precipitated VII was filtered and crystallised from benzene as granules, m.p. 225-227°C (0.69 g, 15%). (Found: C,63.95; H,3.00; N,13.73. $C_{22}H_{12}N_4O_5$ requires C,64.08; H,2.91; N,13.59%). MS m/e 412 (M^+), 312, 294, 257, 222, 221 (M^+ - nitroquinazolone), 195, 192, 191, 181, 145.

14c-Methyl-4b,9a,14b-triazatribenzo[a,e,j]phenalene-9,10,15-trione (VIII) — A procedure similar to that for VII gave VIII (in 15% yield) as an amorphous solid. (Found: C,72.28; H,3.86; N,10.89. $C_{23}H_{15}N_3O_3$ requires C,72.44; H,3.94; N,11.03%). UV λ_{max}^{EtOH} 324, 217 nm; $\lambda_{max}^{50\%\ HClO_4}$ 286, 209 nm.

Tetracycles (IX) and (X) — These compounds were obtained by procedures similar to that for VII.

IX: m.p. 187°C (benzene) (yield, 28%), was purified by column chromatography (silica gel, petrol-benzene 1:9 eluates). (Found: C,78.36; H,5.31; N,9.62. $C_{29}H_{23}N_3O_2$ requires C,78.20; H,5.17; N,9.44%). UV λ_{max}^{EtOH} 340, 211 nm (log ε : 3.05, 4.45); $\lambda_{max}^{50\%\ HClO_4}$ 295, 285, 207 nm (log ε : 3.36, 3.37, 4.48). MS m/e 445 (M^+), 311, 239, 221, 195, 194, 167, 166, 141, 140, 139, 135, 106, 91.

X: m.p. 113-116°C (benzene-ethyl acetate 4:1) (yield, 32%), was purified by column chromatography (silica gel, benzene-ethyl acetate 4:1 eluates). (Found: C,73.06; H,7.28; N,11.32. $C_{23}H_{27}N_3O_2$ requires C,73.21; H,7.16; N,11.14%). UV λ_{max}^{EtOH} 333, 223 nm (log ε : 3.73, 4.67); $\lambda_{max}^{50\%\ HClO_4}$ 296, 284, 272, 229, 203 (log ε : 4.00, 4.00, 3.94, 4.65, 4.63). MS m/e 377 (M^+), 339, 323, 278, 277, 222, 221, 195, 194, 167, 166, 140, 139.

$NaBH_4$-BF_3.Et_2O reduction of XI — BF_3-etherate (0.6 ml) in dry THF (6 ml) was added during 0.5 h to a well-stirred mixture of XI (200 mg, 0.58 mmol) and $NaBH_4$ (120 mg, 3.17 mmol) which

was maintained at 0°C under N_2 atmosphere. The solution was then allowed to warm up for 1.5 h to room temperature, and then refluxed for 2.5 h. 6M HCl (5 ml) was then added and THF removed. The aq. phase was saturated with $NaHCO_3$ and then extracted with ether (3 x 30 ml). The dried and concentrated extract on chromatography over silica gel yielded XII, m.p. 180-182°C (150 mg, 81%) in the petroleum ether-benzene (1:1) eluates. (Found: C,77.69; H,4.57; N,12.78. $C_{21}H_{15}N_3O$ requires C,77.54; H,4.61, N,12.92%). UV λ_{max}^{EtOH} 333, 235, 211 nm (log ε : 3.81, 4.30, 4.46); $\lambda_{max}^{50\%\ HClO_4}$ 301, 256, 230, 207 (log ε : 4.01, 4.27, 4.31, 4.46). ^{1}H-NMR (80 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 7 Hz; C_1-H), 6.50-7.40 (12H,m; Ar-H and C_{13c}-H), 4.38 (2H, s; $-CH_2-$). MS m/e 325(M^+), 296 (M^+-CHO), 294, 279, 180, 167, 162.5 (M^{++}), 152, 149, 131.

BH_3.THF reduction of V — A 1M solution of BH_3 in THF (2 ml) was slowly added (20 min) to a cooled solution of V (100 mg, 0.272 mmol) in THF (20 ml) at 0°C under N_2 atmosphere. The solution was maintained at 0°C for 1 h, and then allowed to warm up to room temperature, at which temperature it was kept for a further 1 h. The reaction mixture was then refluxed for 1.5 h, cooled and the excess borane destroyed with 2 ml concentrated HCl. Water (10 ml) was added and the reaction mixture extracted with CH_2Cl_2-ether (1:1, 3 x 20 ml). A pale brown solid, m.p.> 300°C, (38 mg) was filtered off at this point. The organic extract dried over Na_2SO_4 and concentrated. The concentrate on chromatography over silica gel afforded XIII as a pale yellow solid, m.p. 193-195°C (45 mg, 49%) in the benzene eluates. (Found: C,77.56; H,5.09; N,12.50. $C_{22}H_{17}N_3O$ requires C,77.87; H,5.01; N,12.39%). UV λ_{max}^{EtOH} 357, 356, 280, 211 nm; $\lambda_{max}^{HClO_4}$ 357, 356, 280, 212 nm. ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.95-8.47 (12H,m; Ar-H), 5.95 (C_{14c}-H), δ 4.10 and δ 3.92 (each d, J = 14.6 Hz), δ 3.71-4.12 (4-methylene protons of C_9 and C_{10}; occur as two AB patterns - δ 4.10 and δ 3.92, J = 14.6 Hz; δ 3.73 and δ 3.86, J = 14.0 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 84.3 (C-14c), 51.3 and 51.2 (C-9,C-10), 163.0 (C-15), 142.7, 136.7, 134.9 (C-4a,4c,14a). MS m/e 339 (M^+), 338(M^+-1), 310(M^+-HCO), 209, 180, 152.

$NaBH_4$ reduction of V — $NaBH_4$ (300 mg, 7.93 mmol) in THF (100 ml) was added to a solution of V (565 mg, 1.54 mmol) in THF (100 ml), and kept for 48 h at room temperature. After the usual work-up, column chromatography over neutral alumina afforded XIV, m.p. 75°C (200 mg, 35%) in the benzene-ethyl acetate (2:1) eluates. (Found: C,70.58; H,5.18; N,11.03. $C_{22}H_{19}N_3O_3$ requires C,70.77; H,5.09; N,11.26%). UV λ_{max}^{EtOH} 340, 272, 223, 208 nm (log ε : 3.62, 3.91, 4.50, 4.52); $\lambda_{max}^{50\%\ HClO_4}$ 374, 271, 251, 203 nm (log ε : 3.55, 3.91, 4.42, 4.53). ^{1}H-NMR (80 MHz, $CDCl_3$) δ 6.50-8.00 (13H, m; Ar-H and C_{14c}-H), 4.75 (2H, br) and 4.35 (1H,br) { C_9-, C_{10}- and C_{15}-H}, 1.65 (3H,br,-OH). MS m/e 373(M^+), 356(M^+-OH), 327(M^+-CHO-OH), 310(M^+-CHO-OH-OH), 253, 221, 196, 166, 147, 140.

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