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Synthesis of hydro-bispyrazolo[3,4-*a*; 4′,3′-*j*] acridines

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Bispyrazolo[3,4-*a*;4′,3′-*j*]acridines **4a-g** have been prepared from the 2,7-di(hydroxymethylene) - 3,4,5,6-tetrahydro-1,8 (2*H*, 7*H*)-acridinediones **3** by reaction with hydrazine/phenylhydrazine. Reaction of **3** with DAMN or *o*-phenylenediamine gives the respective Schiff base **6** or **7**.

In continuation of our interest in acridine system, we have synthesised several hexahydroacridinedione derivatives **1** which showed laser properties[1,2]. As an extension of such a study, we have synthesised[3] hydrobisbenzo[1,2-*a*; 1′2′-*j*]acridines in view of the importance of benzoacridine derivatives[4]. The interest in fused ring alkaloids having acridine skeleton has increased rapidly in the last several years[5] which triggered the synthesis of pyridoacridines[6] and thiazoloacridines[7,8]. Hence we focussed our attention on the synthesis of pyrazoloacridines.

It is well known that 1,3-diketones give rise to pyrazole rings on reaction with hydrazine hydrate and phenylhydrazines[9-12]. In the present work, 2,7-di(hydroxymethylene)- 3,4,5,6-tetrahydro-1,8(2*H*,7*H*)-acridinedione **3** was treated with hydrazine hydrate in the presence of a few drops of dil. HCl, which furnished 4,5,7,8-tetrahydrobispyrazolo[3,4-*a*; 4′-3′-*j*] acridine **4a** in 85% yield. Its structure was established by IR, NMR and mass spectral data and elemental analysis. Likewise, the reaction with phenylhydrazine afforded 1,11-diphenyl-4,5,7,8-tetrahydrobis-pyrazolo[3,4-*a*; 4′,3′-*j*]acridine **4b**. Condensation of phenylhydrazine with **3d** afforded only the monopyrazole derivative **5**, probably due to the steric hindrance of the phenyl group with the 9-methyl group, along with the *gem*-dimethyl groups (Scheme I).

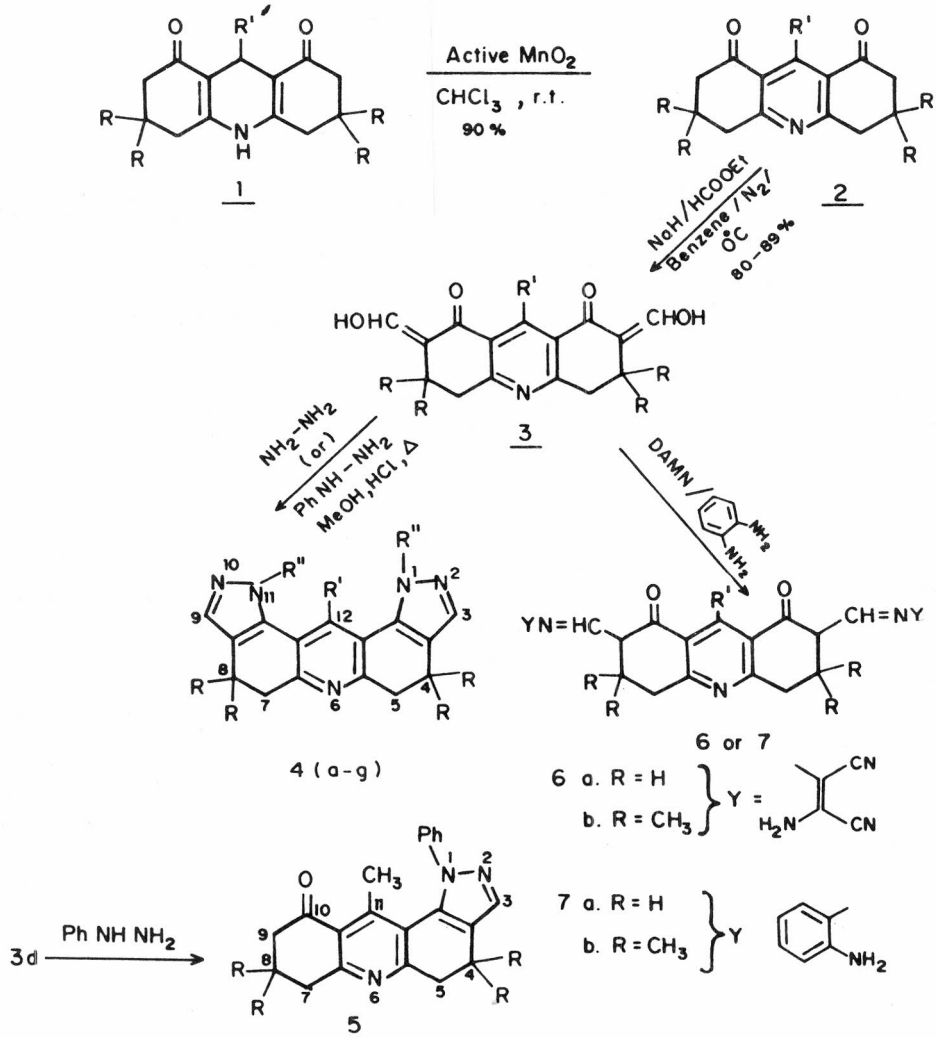
The pyrazoles **4b, d, f** may have the phenyl groups at positions-1,11 or 2,10. ^{1}H NMR spectrum revealed that the protons at position-12 in **4b** and **4f** shifted upfield by 1.55 ppm and 1.65 ppm when compared with **4a** and **4e** respectively. The C-12 methyl in **4d** shifted upfield by 1.9 ppm when compared with **4c**; whereas, less upfield shift (1.25 ppm) of the methyl protons was observed for **5** (compared with **4g**) due to the effect of one phenyl group. This suggests that the phenyl groups are at positions 1 and 11 in the bispyrazoles and at 1 instead of at 2 in the pyrazole **5**. The ^{13}C NMR data for **4b** is depicted in the structure.

In view of the interest in diazepine system[13,14], the diformyl acridinedione **3a** was reacted with diaminomaleonitrile (DAMN) with a view to get the bis-diazepinoacridine system. The reaction, however, furnished only the Schiff base **6a**. The reaction of **3a** with *o*-phenylenediamine, likewise, furnished the Schiff base **7a**. Reaction of **6a** and **6b** with hydrazine hydrate furnished the bis-pyrazoloacridines **4d** and **4e**, respectively. Attempted cyclization of the Schiff bases **6a,b** and **7a,b** to get the respective bisdiazepines, under different conditions, was however unsuccessful.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 258 spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM 390 (90 MHz); Varian-Gemini 300 (300 MHz) and JEOL GSX 400 (400 MHz) spectrometers. ^{13}C NMR spectra were recorded on a JEOL GSX 400 (100 MHz) spectrometer and mass spectra were measured on Shimatzu QP 1000 and Hewlett Packard 5985 GC/MS instruments. Column chromatography was performed on silica gel (100-200 mesh).

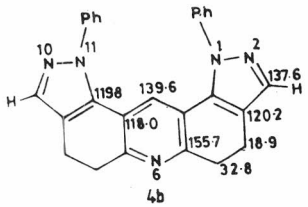
Condensation of 2,7-di(hydroxymethylene)acridines 3a-d with hydrazine hydrate and phenylhydrazine: General procedure for 4a-g and 5. To a solution of 2,7 -di(hydroxymethylene)acridine **3a-d** (5 mmoles) in methanol (25 mL), hydrazine hydrate or phenylhydrazine (1 mmole) and a few drops of dil. HCl were added and the reaction mixture refluxed for 1-2 hr. The solvent was removed, the residue cooled and water (50 mL) added to it. The solid obtained was



1-3:	R	R′
a	H	H
b	H	CH_3
c	CH_3	H
d	CH_3	CH_3

4	a	b	c	d	e	f	g
R	H	H	H	H	CH_3	CH_3	CH_3
R′	H	H	CH_3	CH_3	H	H	CH_3
R″	H	C_6H_5	H	C_6H_5	H	C_6H_5	H

Scheme I



filtered and purified by chromatography and eluted with MeOH-$CHCl_3$ (1:9) to yield the respective product.

4,5,7,8-Tetrahydrobispyrazolo[3,4-*a*; 4′,3′-*j*]-acridine 4a: Yield 85%, m.p. > 300°; IR(KBr): 3150, 1610 cm^{-1}; ^1H NMR ($CDCl_3$ - DMSO-d_6): δ 2.80-3.10 (m,8H), 7.40 (s,2H), 8.25 (s,1H); MS (%): m/z 263 (M^+, 100), 262 (55), 235 (15), 219(1), 205(9), 191(4), 179(4), 152(2), 132(4), 117(9), 103(9), (Found: C, 68.40; H, 4.69; N, 26.39. $C_{15}H_{13}N_5$ requires C; 68.42; H 4.97; N, 26.59%).

1,11-Diphenyl-4,5,7,8-tetrahydro-bispyrazolo-[3,4-*a*; 4′,3′-*j*]acridine 4b: Yield 88%, m.p. 260-62°; IR (KBr): 1590 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.75-3.00 (m, 4H), 3.05-3.30 (m, 4H), 6.70 (s,1H), 7.0-7.60 (m, 12H); ^{13}C NMR ($CDCl_3$): δ

18.9, 32.8, 118.0, 119.8, 120.2, 122.7, 124.4, 129.2, 135.7, 137.6, 139.6, 155.7; MS (%) m/z 415 (M^+ 100), 414(39) 387(5), 77(20) (Found : C, 77.95; H, 4.91; N, 16.56. $C_{27}H_{21}N_5$ requires C, 78.05; H, 5.09; N, 16.85%).

12-Methyl-4, 5, 7, 8-tetrahydro-bispyrazolo-[3,4-*a*; 4′,3′-*j*]acridine 4c: Yield 68%, m.p. > 300°; IR (KBr): 3150, 1610 cm^{-1}, ^1H NMR (DMSO-d_6): δ 2.60-2.95 (m, 8H), 3.05 (s, 3H), 7.40 (s, 2H), 11.25-11.75 (bs, 2H); MS (%): m/z 277 (M^+, 100), 276(45), 249(8), 225(3), 205(2) (Found: C, 69.16; H, 5.40; N, 25.16. $C_{16}H_{15}N_5$ requires C, 69.29; H, 5.45; N, 25.25%).

12-Methyl-1, 11-diphenyl-4, 5, 7, 8-tetrahydro-bispyrazolo[3,4-*a*; 4′,3′-*j*]acridine 4d: Yield 66%, m.p. > 300°; IR (KBr): 1590, 1490 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (s,3H), 2.55-2.80 (m,4H), 3.0-3.20 (m,4H), 7.0-7.30 (m,10H), 7.50 (s,2H); MS (%): m/z 429 (M^+, 100), 401(4), 352(2), 329(3), 215(10) (Found: C, 78.11; H, 5.21; N, 16.1. $C_{28}H_{23}N_5$ requires C, 78.29; H, 5.39; N, 16.30%).

4, 4, 8, 8-Tetramethyl-4, 5, 7, 8-tetrahydro-bispyrazolo[3,4-*a*;4′,3′-*j*] acridine 4e: Yield 89%, m.p. > 300°; IR (KBr): 3150, 1580 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (s,12H), 2.85 (s,4H), 7.40 (s,2H),8.30 (s,1H); MS: (%): m/z 319 (M^+, 32), 304(100), 274(6), 260(4), 246(2), 145(12) (Found: C, 71.19; H, 6.49; N, 21.76. $C_{19}H_{21}N_5$ requires C, 71.44; H, 6.62; N, 21.92%).

1,11-Diphenyl-4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-bispyrazolo [3,4-*a*; 4′,3′-*j*]acridine 4f: Yield 81%, m.p. 118-20°; IR (KBr): 1590 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (s,12H), 3.05 (s,4H), 6.65 (s,1H), 7.0-7.60 (m,12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.07, 28.26, 30.70, 48.20, 118.10, 119.7, 122.3, 122.6, 124.6, 129.2, 134.3, 135.8, 139.8, 155.5; MS (%): m/z 471 (M^+, 40), 456 (100), 440(5), 371(9), 356(52), 236(10), 221(30) (Found: C, 78.68; H, 6.02; N, 14.89. $C_{31}H_{29}N_5$ requires C, 78.95; H, 6.19; N, 14.84%).

4,4,8,8,12-Pentamethyl-4,5,7,8-tetrahydrobis-pyrazolo [3,4-*a*; 4′,3′-*j*]acridine 4g: Yield 76%, m.p. > 300°C; IR (KBr): 3200, 1570 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.20 (s,12H), 2.90 (s,4H), 3.20 (s,3H), 7.50 (s,2H), 10.25 (bs,2H); MS (%): m/z 333 (M^+, 53), 318(100), 294(7), 216(1), 152(27) (Found: C, 71.96; H, 6.86; N, 21.06. $C_{20}H_{23}N_5$ requires C, 72.04; H, 6.95; N, 21.00%).

1-Phenyl-4,4,8,8,11-pentamethyl-4,5,8,9-tetrahydropyrazolo [3, 4*a*]acridin-10 (9*H*)-one (5): Yield 61%, m.p. 256-258°; IR (KBr): 1670, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.05 (s, 6H), 1.30 (s,6H), 1.95 (s,3H), 2.50 (s,2H), 2.95 and 3.05 (2s,4H), 7.20-7.40 (m,5H), 7.60 (s,1H); MS (%): m/z 385 (M^+,15), 370(100), 354(2), 312(4), 273(94), 217(14) (Found: C, 77.68; H, 7.10; N, 10.69. $C_{25}H_{27}N_3O$ requires C, 77.89; H, 7.05; N, 10.89%).

Condensation of 3a and 3c with DAMN/*o*-phenylenediamine: General procedure. To the diformylacridinedione **3a,c** (2 mmoles) in methanol (25 mL) were added the respective diamine (4.2 mmoles) and a few drops of dil. HCl and the reaction mixture was refluxed for 1-2 hr. The solvent was removed and the contents poured on to crushed ice to yield a solid which was filtered, dried and crystallised from $CHCl_3$-MeOH.

2,7-Di-(maleonitril-formalidino)- 3,4,5,6-tetrahydro-1,8(2*H*,7*H*)-acridinedione 6a: Dark red solid, yield 84%, m.p. > 300°; IR (KBr): 3400, 3300, 3140, 2150, 1625 & 1570 cm^{-1}, MS (%): m/z 333 (M^+ − 188, 1%), 331(1), 215(44) 199(2), 187(38), 159(7), 131(17), 118(100), 91(8), (Found: C, 61.01; H, 3.56; N, 27.62. $C_{23}H_{17}N_9O_2$ requires C, 61.19; H, 3.79; N, 27.92%).

2, 7-Di-(maleonitril formalidino)-3, 3, 6, 6-tetramethyl-3, 4, 5, 6- tetrahydro-1, 8 (2*H*, 7*H*)-acridinedione 6b: Bright red solid, yield 86%, m.p. 296-98°; IR (KBr): 3340, 3200, 2220, 1630 and 1590 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.20 (s,12H, *gem*-dimethyl), 3.10 (s,4H), 4.0-4.5 (bs,4H), 7.30 (d,2H) (turned singlet on D_2O addition), 8.50 (s,1H,Ar-H), 11.10 (d,2H, disappeared on D_2O addition); MS (%): m/z 389 (M^+ − 118,5%), 374(1), 271(29), 256(29), 243(14), 215(100), 159(7), 131(11), 118(90), 91(61) (Found: C, 63.69; H, 4.73; N, 24.81. $C_{27}H_{25}N_9O_2$ requires C, 63.89; H, 4.96; N, 24.83%).

2,7-Di (*o*-aminoanilino-formylidene)-3,4,5,6-tetrahydro-1,8 (2*H*, 7*H*)-acridinedione 7a: Bright red solid, yield 82%, m.p. 204-6°; IR (KBr): 3360, 3300, 1620, 1610 and 1570cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.8-3.2 (CH_2), 6.7-7.2 (Ar.H), 7.6 (d,2H), 8.6 (s,Ar-H), 11.8 (2H, enolic OH); MS (%): m/z 333 (M^+ − 118,1%), 215(5), 187(7), 159(1), 131(3), 118(100), 91(40) (Found: C, 71.68; H, 5.39; N, 15.36; $C_{27}H_{25}N_5O_2$ requires C, 71.82; H, 5.58; N, 15.51%).

2,7-Di-(*o*-aminoanilino-formylidene)-3,3,6,6-tetramethyl-3,4,5,6-tetrahydro-1,8(2*H*, 7*H*)-acridinedione 7b: Bright yellow solid, yield 68%, m.p. 240-42°; IR (KBr): 3400, 3340, 1620 and 1590 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3 (s,12H), 3.0 (s,4H), 4.5(bs,NH), 6.8-7.2 (m,Ar-H), 7.6 (d,2H), 8.6(s,1H,Ar-H), 12.30 (d, enolic OH); MS (%): m/z 507 ($M^+ - 118$, 25%), 374(80), 271(10), 256(80), 243(60), 241(10), 226(22), 215(22), 131(80), 119(100), 91(10) (Found: C, 73.13; H, 6.39; N, 13.59. $C_{31}H_{33}N_5O_2$ requires C, 73.34; H, 6.55; N, 13.79%).

Trans-condensation of 6a/6b into 4a/4e. The Schiff base **6a** was refluxed with 40% hydrazine hydrate in methanol for 2 hr and poured into water. The solid obtained was filtered, dried and purified by passing through a column of silica gel and identified as **4a** by superimposable IR spectrum. Compound **6b**, likewise, gave compound **4e**.

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