Reaction of Hydrazinobenzoquinolines with 1,3-Diketones: A Structural Reinvestigation

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Reaction of several hydrazinobenzoquinolines with 1,3-diketones affords pyrazolylbenzoquinolines rather than the reported benzodiazepinoquinolines. The structural assignment is based upon NMR (^{1}H and ^{13}C) spectral data and an unambiguous synthesis.

Reaction of hydrazines with 1,3-diketones constitutes a standard synthesis of pyrazoles.[1] However, heterocycle-substituted hydrazines with 1,3-diketones have been reported to generate products having different structures.[2—4] Whereas we found the products to have pyrazole structure,[2] there are many reports in the literature indicating the formation of isomeric structures — diazepines[3] or triazepines.[4] Structures of many of these reported seven-membered heterocycles have recently been reinvestigated by us[5] and Peet et al.[6] It was conclusively established that all such structures are in error and products are indeed pyrazole derivatives. While scanning the literature, we came across a paper in this journal by Tyagi and Joshi reporting the formation of a large number of diazepines by treating 2-hydrazino-4-methyl-, 4-hydrazino-2-methylbenzo[*h*]quinolines and 1-hydrazino-3-methyl-, 3-hydrazino-1-methylbenzo[*f*]quinolines with 1,3-dicarbonyl compounds.[7] Such a structure appeared untenable as the products obtained by the reaction of 2- and 4-hydrazinoquinolines with 1, 3-dicarbonyl compounds have been shown to be pyrazole derivatives rather than the reported diazepines.[5] It was, therefore, thought of interest to reinvestigate this reaction.

In a typical experiment, 2-hydrazino-4-methylbenzo[*h*]quinoline on treatment with 2,4-pentanedione in glycerol-fused sodium acetate (conditions specified by Tyagi and Joshi), afforded a crystalline compound, mp 142 °C (lit,[7] mp 103—104 °C) in 51% yield. The same product was obtained by refluxing the reactants in ethanol containing a few drops of hydrochloric acid (61% yield). Although there was discrepancy in the mp's of our sample and that of the reported compound, the agreement in the elemental analysis and ^{1}H NMR values left us in no doubt about the identicality the two samples. Absence of NH in this compound was indicated by the lack of absorption in the region 3600—3200 cm^{-1} in its IR spectrum. Further, repeated shaking with D_2O did not alter the integration of ^{1}H NMR spectrum. The signal at δ=9.32 which was ascribed to the NH proton by the earlier workers[7] was actually found to be C_{10}–H of the benzo[*h*]quinoline. The reason for the deshielding of this proton has been delineated.[8] These observations clearly indicated that the product does not have the postulated structure.

^{1}H NMR spectrum of the compound displayed three sharp singlets of three proton intensity each at δ=2.30, 2.75, and 2.95. The last signal is due to the methyl group located on the benzoquinoline ring (as it was present in the ^{1}H NMR spectrum of the hydrazine itself) thus leaving the two signals to be assigned to the methyl groups located on the newly generated ring. A noteworthy feature of the spectrum was the presence of a sharp singlet of one proton intensity at δ=6.16 which is characteristically close to the value reported for C_4–H of pyrazole.

While analyzing the ^{1}H NMR spectrum of a large number of 2-pyrazolylheterocycles, we have shown that the two methyl groups and C_4–H of pyrazole precisely resonate at these positions observed for the above compound.[5] Furthermore, the two methyl groups display, "upfield-downfield phenomenon" as was noted and rationalized by us.[9] Besides these signals, the aromatic region displayed a singlet of one proton intensity at δ=8.20 which could be assigned to C_3–H. No such signal was reported by earlier workers as it would not show up in a presumed diazepine structure.[7] Thus, ^{1}H NMR spectral data fully supported a pyrazole structure **1a** than a diazepine **2**.

An analysis of the ^{13}C NMR spectrum of the product provided further support for the pyrazole structure **1a**. There were eight tertiary and an equal number of quaternary carbons as required for structure **1a**. Had the structure been **2**, there would have been seven tertiary and nine quaternary carbons. In accordance with our earlier observations,[5] there were signals at δ=149.72, 109.37, and 141.74 which are assigned to carbons C-3, C-4, and C-5 of the pyrazole moiety, respectively. The complete assignment of other carbons has been made on the basis of literature values[10] and DEPT technique. The data are gathered in Table 1.

Mass spectral data further supported structure **1a**. There were ions at m/z 192 and 95 which correspond to the ions generated by simple cleavage of the heterocyclic moieties through the C–N bond. Obviously such ions could not arise from a diazepine structure **2** unless the molecular ion undergoes an extensive rearrangement.

The pyrazole structure was finally established by an alternate synthesis of **1a**. Treatment of 2-chloro-4-methylbenzo[*h*]quinoline with sodium salt of 3,5-dimethyl-

Table 1. ^{13}C NMR Data of Pyrazolylbenzoquinolines (**1**, **3**, **5**)[a)]

Carbon atom	**1a**	**1b**	**3a**	**3b**	**5**
Benzoquinoline					
1(q)	—	—	—	—	147.25
2(q)	151.47	148.55	158.38	157.96	116.60
3(t)	114.92	111.96	120.27	117.02	150.72
4(q)	144.27	144.04	143.75	144.30	—
4a(q)	123.58	124.00	n.o.	118.35	147.15
5(t)	127.60	127.34	128.05	128.44	130.97
6(t)	124.81	124.32	124.35	124.91	128.67
6a(q)	131.56	130.71	130.35	130.97	130.09
7(t)	121.02	120.75	120.56	120.14	125.78
8(t)	126.59	126.37	127.63	127.60	126.62
9(t)	126.14	126.07	127.40	127.08	126.33
10(t)	127.76	127.79	128.80	n.o.	127.99
10a(q)	133.63	133.34	133.27	133.40	132.01
10b(q)	146.67	147.09	146.67	147.81	122.73
CH_3	19.14	19.01	25.07	25.30	26.37
Pyrazole					
3(q)	149.72	141.64	149.04	141.90	149.07
4(t)	109.37	107.55	106.81	107.62	109.08
5(q)	141.74	126.85	141.19	131.33	141.35
3-CH_3	13.69	—	13.49	—	13.30
5-CH_3	15.67	—	11.38	—	14.63

a) Solvent: **1a**, **1b**, **3b**; $CDCl_3$. **3a**; DMSO-d_6. **5**; $CDCl_3$+DMSO-d_6.

1*H*-pyrazole in *N,N*-dimethylformamide provided **1a**, which was found to be identical in all respects with the product obtained through the hydrazine route.

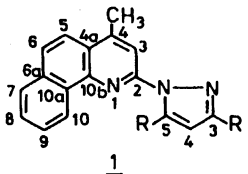
Similar treatment of 4-hydrazino-2-methylbenzo[*h*]-quinoline with 2,4-pentanedione in either glycerol-fused sodium acetate or ethanol-hydrochloric acid provided a pyrazole **3a** rather than the reported diazepine **4**.[7)] The structure revision is based on IR (absence of NH) and ^{1}H NMR (absence of NH and characteristic signal at δ=6.05) data. ^{1}H NMR spectrum of **3a** displays the three methyl signals at δ=2.05, 2.30, and 2.82 which are assigned to C_5–CH_3, C_3–CH_3 (pyrazole), and C_2–CH_3 (benzo[*h*]quinoline), respectively. A noteworthy feature of the spectrum is the values for C_3– and C_5–CH_3 (pyrazole) which are different from those displayed by **1a**. In an earlier report[5b)] we have demonstrated that in case of 2-methyl-4-(3,5-dimethyl-1-pyrazolyl)quinoline, C_5–CH_3 (5-position on the pyrazole ring) goes upfield as compared to C_3–CH_3 which is in contrast to 4-methyl-2-(3,5-dimethyl-1-pyrazolyl)quinoline where C_5–CH_3 appears downfield as compared to C_3–CH_3. We fail to understand as to how the authors could get the same values for methyl protons in both the cases!

As expected, ^{13}C NMR spectrum of **3a** displayed eight tertiary and eight quaternary carbons. The pyrazole carbons C-3, C-4, and C-5 appeared at δ=149.04, 106.81, and 141.19, respectively.

To generalize the formation of pyrazole derivatives in such reactions, 2,4-pentanedione was replaced by 1,1,3,3-tetramethoxypropane. Treatment of 2-hydrazino-4-methylbenzo[*h*]quinoline with 1,1,3,3-tetramethoxypropane in ethanol–hydrochloric acid afforded **1b**. ^{1}H NMR spectrum of **1b** displayed signals at δ=6.56 (dd, J=2.5 and 1.5 Hz, 1H) and 8.96 (d, J=2.5 Hz, 1H) which are readily assigned to C_4–H and C_5–H of pyrazole, respectively, while C_3–H merged with the aromatic protons. The observed values of coupling constants are in complete agreement with the reported values for pyrazole protons.[11)] On irradiating the signal at δ=6.56, the signal at δ=8.96 assigned to C_5–H of pyrazole was reduced to a singlet and the irradiation of signal at δ=8.96 simplified the signal at δ=6.56 into a doublet (J=1.5 Hz). Similarly, treatment of 4-hydrazino-2-methylbenzo[*h*]quinoline with 1,1,3,3-tetramethoxypropane yielded **3b**, which showed similar IR and ^{1}H NMR spectral characteristics, except for the fact that the C_5–H of pyrazole got merged into the aromatic region due to its shielding (Chart 1).

Tyagi and Joshi[7)] have further reported the formation of a diazepine derivative **6** by treating 1-methyl-3-hydrazinobenzo[*f*]quinoline with 2,4-pentanedione. We repeated the experiment and found the product (mp 112—113 °C, lit,[7)] mp 114—115 °C, 65% yield) to be 1-methyl-3-(3,5-dimethyl-1-pyrazolyl)benzo[*f*]quinoline (**5**). The structure assignment is based upon the IR (absence of NH). ^{1}H NMR [sharp singlets at δ=2.30 (3H), 2.78 (3H), 3.09 (3H), and 5.97 (1H)] and ^{13}C NMR (characteristic signals for pyrazole carbons at δ=149.07, 109.08, and 141.35) spectral data.

The reported formation of diazepine by the treatment of 1-hydrazino-3-methylbenzo[*f*]quinoline (**7**) and 2,4-pentanedione did not merit reinvestigation as the struc-



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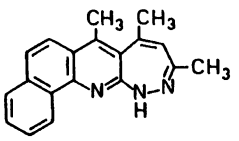
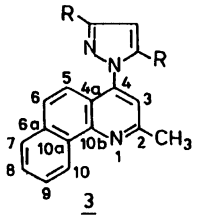


2

1; a, R = CH_3
b, R = H



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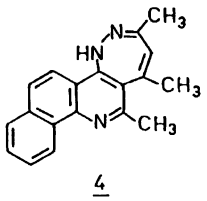

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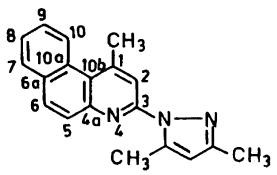
3; a, R = CH_3
b, R = H

Chart 1.

ture of the hydrazine **7** itself was shown to be in error by Rees et al.[12] The hydrazine **7** was reported to have been synthesized by refluxing 1-chloro-3-methylbenzo[*f*]-quinoline with hydrazine hydrate in glycerol (Chart 2). However, it was found that the product in this reaction is indeed 5-(2-amino-1-naphthyl)-3-methylpyrazole (**8**).[12] The unexpected behavior of 1-chloro-3-methylbenzo[*f*]quinoline on treatment with hydrazine hydrate may be traced to the greater steric interaction across the 1 and 10 position in hydrazine **7**. Interestingly the "hydrazine **7**" was further treated with nitrous acid by Tyagi and Joshi[13] who claimed the formation of 1,2,3-triazepine. In fact, the actual product that is 5-(2-amino-1-naphthyl)-3-methylpyrazole (**8**) [not the hydrazine **7**] yields pyrazolotriazine which rearranges to pyrazolopyridazine.

Experimental

Melting points are uncorrected. The IR spectra (Nujol) were recorded on a Beckman IR-20 spectrophotometer. The



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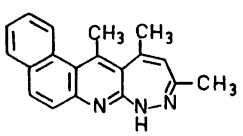

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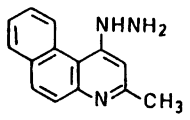

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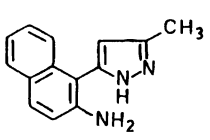

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Chart 2.

^{1}H and ^{13}C NMR spectra were recorded on R-32 Perkin–Elmer (90 MHz) and JEOL GX-270 (67 MHz) instruments, respectively using TMS as internal standard. Mass spectra were recorded on MS-50 Kratos mass spectrometer operating at 70 eV.

4-Methyl-2-(3,5-dimethyl-1-pyrazolyl)benzo[*h*]-quinoline (1a). a) A mixture of 2-hydrazino-4-methylbenzo[*h*]quinoline[13] (446 mg, 2 mmol) and 2,4-pentanedione (0.2 cm^3, 2 mmol) was refluxed in glycerol in the presence of fused sodium acetate for 4—5 h with occasional shaking. It was poured into ice-cold water, kept overnight at 0 °C. The solid was washed well with water and crystallized from ethanol to give **1a**, 300 mg (51%), mp 142 °C (lit,[7] mp 103—104 °C). ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ=2.30 (s, 3H, C_3–CH_3 pyrazole), 2.75 (s, 3H, C_5–CH_3 pyrazole), 2.95 (s, 3H, C_4–CH_3), 6.16 (s, 1H, C_4–H pyrazole), 7.72—8.15 (m, 5H, ArH), 8.20 (s, 1H, C_3–H), 9.32 (m, 1H, C_{10}–H). MS *m/z* (%): 287 (M^+, 15), 286 (100), 271 (10), 245 (4), 244 (8), 193 (8), 192 (4), 165 (8), 95 (2). Found: C, 79.54; H, 5.75; N, 14.43%. Calcd for $C_{19}H_{17}N_3$: C, 79.44; H, 5.92; N, 14.63%.

The above compound **1a** was also obtained by refluxing 2-hydrazino-4-methylbenzo[*h*]quinoline and 2,4-pentanedione in ethanol–hydrochloric acid in 61% yield.

b) 3,5-Dimethyl-1*H*-pyrazole (192 mg, 2 mmol) was added slowly to a suspension of dry sodium hydride (60%) (72 mg, 3 mmol) in 20 cm^3 of *N,N*-dimethylformamide. After a few min of stirring, 2-chloro-4-methylbenzo[*h*]quinoline (455 mg, 2 mmol) was added and the mixture was heated in an oil bath at 140—150 °C for 20 h. The mixture was cooled, diluted with water and extracted with chloroform to give **1a** which was crystallized from ethanol, 210 mg (36%), mp 142 °C. The physical and spectral data were identical to those of **1a** obtained by procedure of Tyagi and Joshi.[7]

Similarly 4-hydrazino-2-methylbenzo[*h*]quinoline[13] (446 mg, 2 mmol) on treatment with 2,4-pentanedione (0.2 cm^3, 2 mmol) yielded 2-methyl-4-(3,5-dimethyl-1-pyrazolyl)benzo-[*h*]quinoline **3a**, 355 mg (62%), mp 119—120 °C (lit,[7] mp 78—79 °C). ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ=2.05 (s, 3H, C_5–CH_3 pyrazole), 2.30 (s, 3H, C_3–CH_3 pyrazole), 2.82 (s, 3H, C_2–CH_3), 6.05 (s, 1H, C_4–H pyrazole), 7.23—7.85 (m, 6H, ArH), 9.32 (m, 1H, C_{10}–H). MS *m/z* (%): 287 (M^+, 24), 286 (100), 272 (22), 246 (5), 245 (7), 192 (3), 151 (10), 150 (6), 95 (3). Found: C, 79.64; H, 5.79; N, 14.86%. Calcd for $C_{19}H_{17}N_3$: C, 79.44; H, 5.92; N, 14.63%.

In a similar manner, 3-hydrazino-1-methylbenzo[*f*]quinoline[13] (669 mg, 3 mmol) on treatment with 2,4-pentanedione (0.3 cm^3, 3 mmol) yielded 1-methyl-3-(3,5-dimethyl-1-pyrazolyl)benzo[*f*]quinoline (**5**), 560 mg (65%), mp 112—113 °C (lit,[7] mp 114—115 °C). ^{1}H NMR ($CDCl_3$) δ=2.30 (s, 3H, C_3–CH_3 pyrazole), 2.78 (s, 3H, C_5–CH_3 pyrazole), 3.09 (s, 3H, C_1–CH_3), 5.97 (s, 1H, C_4–H pyrazole), 7.47—8.00 (m, 6H, ArH), 8.72 (m, 1H, C_{10}–H). Found: C, 79.38; H, 5.89; N, 14.60%. Calcd for $C_{19}H_{17}N_3$: C, 79.44; H, 5.92; N, 14.63%.

4-Methyl-2-(1-pyrazolyl)benzo[*h*]quinoline (1b). A mixture of 2-hydrazino-4-methylbenzo[*h*]quinoline (446 mg, 2 mmol) and 1,1,3,3-tetramethoxypropane (0.33 cm^3, 2 mmol) in 20 cm^3 absolute ethanol containing hydrochloric acid was refluxed for 2.5 h. On concentrating and cooling the mixture, a crystalline solid separated out which was filtered and crystallized from ethanol to give **1b**, 310 mg (60%), mp 115—116 °C. ^{1}H NMR ($CDCl_3$) δ=2.78 (s, 3H, C_4–CH_3),

6.56 (dd, J=2.5 and 1.5 Hz,,1H C_4–H pyrazole), 7.68—8.05 (m, 6H, ArH), 8.15 (s, 1H, C_3–H), 8.96 (d, 1H, J=2.5 Hz, C_5–H pyrazole), 9.31 (m, 1H, C_{10}–H). MS m/z (%): 259 (M^+, 19), 258 (100), 231 (4), 230 (4), 208 (6), 192 (5), 191 (30), 67 (2). Found: C, 79.03; H, 4.77; N, 16.32%. Calcd for $C_{17}H_{13}N_3$: C, 78.76; H, 5.02; N, 16.22%.

Similarly 4-hydrazino-2-methylbenzo[*h*]quinoline (446 mg, 2 mmol) on treatment with 1,1,3,3-tetramethoxypropane (0.33 cm^3, 2 mmol) yielded 2-methyl-4-(1-pyrazolyl)benzo-[*h*]quinoline (**3b**), 300 mg (58%), mp 94—95 °C. ^1H NMR ($CDCl_3$) δ=2.80 (s, 3H, C_2–CH_3), 6.52 (dd, 1H, J=2.5 and 1.5 Hz, C_4–H pyrazole), 7.36 (s, 1H, C_3–H), 7.58—7.95 (m, 7H, ArH), 9.32 (m, 1H, C_{10}–H). MS m/z (%): 259 (M^+, 100), 258 (45), 192 (5), 190 (5), 165 (3), 151 (10), 150 (9), 67 (2). Found: C, 78.88; H, 4.88; N, 16.09%. Calcd for $C_{17}H_{13}N_3$: C, 78.76; H, 5.02; N, 16.22%.

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