Reactions of Hydroxybenzophenone with Hydrazines

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The reaction of 2,2',4,4'-tetrahydroxybenzophenone with hydrazines under different conditions gave the corresponding indazol-1,3-benzenediol derivatives. It is an interesting and unique approach to the synthesis of indazoles. However, the reactions of 2-hydroxybenzophenone and 2,2'-dihydroxybenzophenone under the same conditions yielded only the hydrazones.

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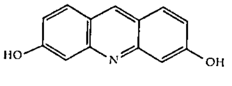
The preparation of hydroxy acridines and related hydroxy acridinones has been of interest in view of their biological activity and numerous natural products derived from such structures [2].

The 3,6-dihydroxyacridine **1** was desired as a starting material for a highly active bisether derivative [3].



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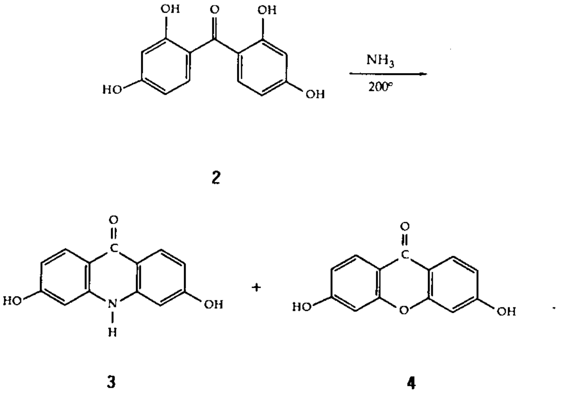
The best literature procedure [4] which involved the hydrolysis of 3,6-diaminoacridine under drastic conditions was found to be unsuitable for large scale operations or for the preparation of ring-substituted derivatives.

We envisioned, reacting commercially available 2,2',4,4'-tetrahydroxybenzophenone with an excess of aqueous ammonia in a bomb at 200° would give the corresponding dihydroxyacridinone **3** (Scheme I). This could then be converted to **1**.

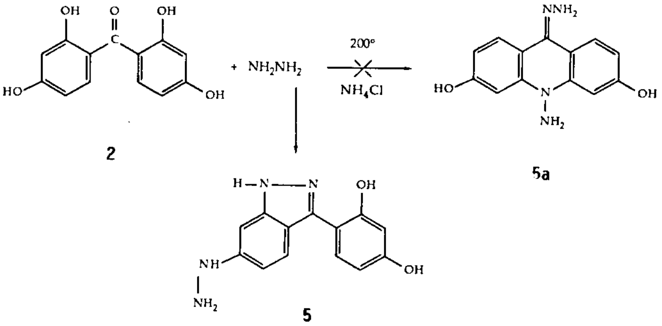
Scheme I



Under these conditions the product obtained in 29% yield was indeed the 3,6-dihydroxy-9-acridinone **3** accompanied by a 56% yield of 3,6-dihydroxy-9-xanthone **4** [5]. The reaction with methanolic ammonia in presence of ammonium chloride increased the yield of **3** to 64%, whereas the yield of **4** decreased to 22%.

It was envisaged that the replacement of ammonia by the more nucleophilic hydrazine hydrate would give a high yield of 10-amino-3,6-dihydroxy-9-acridinone hydrazone **5a** which could ultimately be converted to **1** (Scheme II).

Scheme II



However, the above reaction gave the indazole derivative **5** the structure of which was established by single crystal x-ray determination and the Ortep diagram is shown in Figure 1.

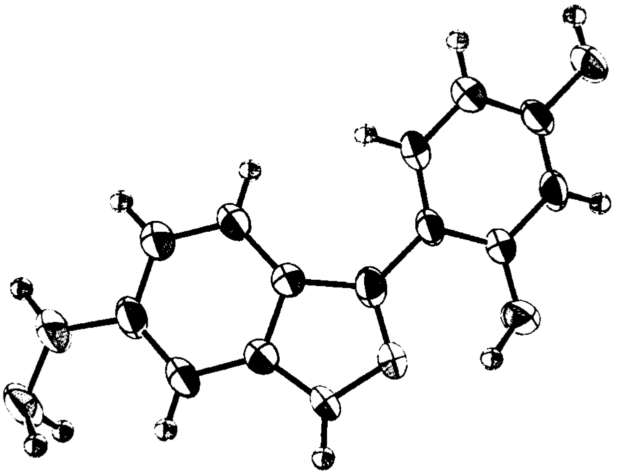
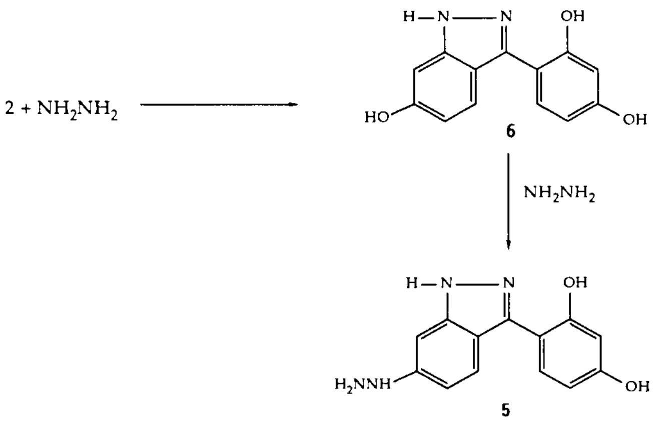


Figure 1

Variation of the above reaction conditions viz; reflux of **2** with 2.5 molar equivalents of hydrazine hydrate gave the 4-(6-hydroxy-1*H*-indazol-3-yl)-1,3-benzenediol **6** in 75% yield (Scheme III).

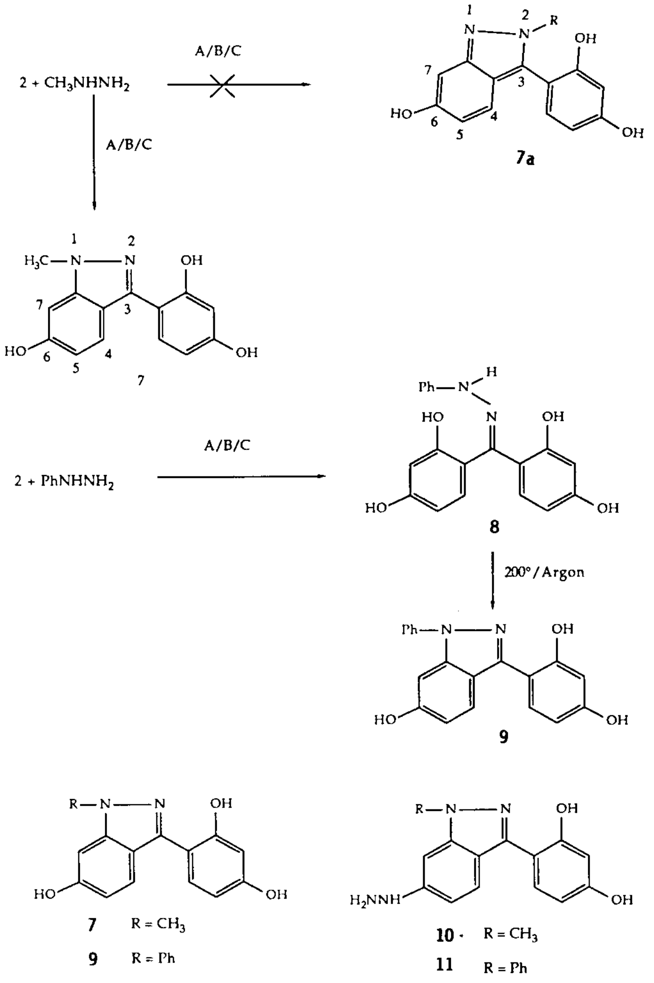
Scheme III



When **6** was heated in an autoclave with one mole equivalent of hydrazine hydrate at 200°, the product obtained was **5** (Scheme III) indicating that the cyclocondensation to the indazole nucleus most likely preceeded substitution of the second hydroxyl group by hydrazine.

The following experiments were carried out to establish the scope of this approach to indazole formation.

Scheme IV



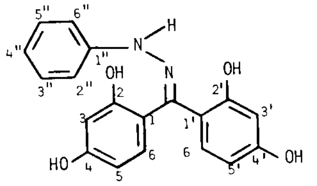
Tetrahydroxybenzophenone **2** and methylhydrazine were reacted under three sets of reaction conditions: a) 10 mole equivalents at 200° under pressure, b) 2.5 molar equivalents at 200° under pressure and c) 2.5 molar equivalents in an aqueous medium under reflux. The only product isolated from these reaction conditions was the 4-(6-hydroxy-1-methyl-*H*-indazol-3-yl)-1,3-benzenediol **7** in 60-70% yield (Scheme IV).

The assignment of structure **7** instead of **7a** was based on nmr analysis. The chemical shift of the C7 proton in **7** would be at a higher field as compared to the C7 proton in **7a**. In fact, a doublet at δ 6.7 corresponding to the C7 proton of **7** was observed.

In contrast, reaction of **2** with phenylhydrazine under analogous conditions led to the bis(2,4-dihydroxyphenyl)-methanone phenylhydrazone **8** in 80% yield (Scheme IV). The structure of **8** was confirmed from its ^{13}C nmr spectrum (Table 1).

Table 1

^{13}C NMR Data of 8



C	Chemical Shift, δ	C	Chemical Shift, δ	C	Chemical Shift, δ
C_1	113	$C_{1'}$	109	$C_{1''}$	149
C_2	160	$C_{2'}$	156	$C_{2''}$	113
C_3	103	$C_{3'}$	102	$C_{3''}$	129
C_4	158	$C_{4'}$	157	$C_{4''}$	119
C_5	107	$C_{5'}$	106	$C_{5''}$	129
C_6	131	$C_{6'}$	130	$C_{6''}$	113
-C=N	145				

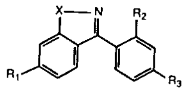
When the hydrazone **8** was heated at 200° under argon, cyclocondensation occured to 4-[(6-hydroxy-1-phenyl)-1*H*-indazol-3-yl]-1,3-benzenediol **9** in 50% yield (Scheme IV). In absence of argon, appreciable decomposition occured.

Interestingly, when **7** and **9** were heated with molar equivalent of hydrazine hydrate in a bomb at 200° neither **10** nor **11** were obtained (Scheme IV).

Removal of at least one hydroxyl group from both benzene rings of benzophenone had an appreciable effect on the reaction. Thus, the reaction of 2,2-dihydroxybenzophenone **12** (X = OH) with hydrazine hydrate, methylhydrazine and phenylhydrazine under pressure gave only the hydrazones **13** [11] (R_1 = H, CH_3, Ph) (Scheme V). Using 2.5 molar equivalents of hydrazine hydrate at 200° under

Table 2

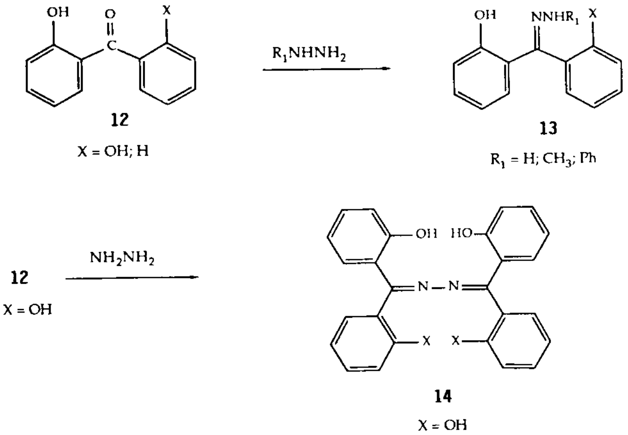
Bicyclic Compounds



No.	R_1	R_2	R_3	X	Yield %	MP°C	M.F.	1H (DMSO/d_6) δ (PPM)	m/e	Solvent of Crystallization	Method	Analysis Calcd./Found
5	$NHNH_2$	OH	OH	NH	86	245-248	$C_{13}H_{12}N_4O_2$	6.4 (d, 2H, J = 1.5 Hz) 6.5 (m, 1H), 6.56 (m, 1H) 6.7 (d, 1H, J = 1.5 Hz)	256 (M^+)	Methanol	A	C, 60.93; H, 4.72; N, 21.86 C, 60.45; H, 4.85; N, 22.03
6	OH	OH	OH	NH	75	260-265	$C_{13}H_{10}N_2O_3$	6.25 (d, 1H, J = 1.5 Hz) 6.8 (d, 1H, J = 1.6 Hz) 7.35 (m, 2H) 7.7 (m, 2H)	242 (M^+)	80% Ethanol	B, C	C, 64.5; H, 4.2; N, 11.6 C, 64.4; H, 4.11; N, 11.6
7	OH	OH	OH	NCH_3	63	242-245	$C_{14}H_{12}N_2O_3$	4.2 (s, 3H) 6.7 (d, 1H, J = 1.6 Hz) 7 (d, 1H, J = 1.6 Hz) 7.8 (m, 2H) 8 (m, 2H)	256 (M^+)	80% Ethanol	A, B, C,	C, 65.6; H, 4.7; N, 10.9 C, 65.42; H, 4.5; N, 10.8
9	OH	OH	OH	NPh	52	>300	$C_{19}N_{14}N_2O_3$	7-7.5 (m, 9H) 9.69 (1H, J = 1.2 Hz) 9.8 (d, 1H, J = 1.4 Hz)	318 (M^+)	DMF		C, 71.69; H, 4.4; N, 8.8 C, 71.56; H, 4.4; N, 8.7

pressure or under reflux conditions led to the azine **14** [12] (X = OH) (Scheme V).

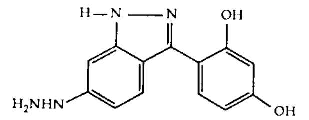
Scheme V



In contrast to the thermal cyclization of **8** to **9** (Scheme IV), attempted thermal cyclization (argon, 200°) of **13** (R_1 = CH_3, Ph) resulted in quantitative recovery of the starting product. Hydrazone formation only was observed when **12** (X = H) was treated with hydrazine hydrate under the above conditions (Scheme V).

The above reactions establish that at least two hydroxy groups are necessary in the aromatic ring destined to be the indazole ring and that a substituent on the indazole nitrogen atom prevents the displacement of the second hydroxyl group.

`Crystal Data - X-Ray Data for 5`



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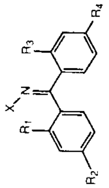
A crystal of **5** $C_{13}H_{12}N_4O_2$ was found to be triclinic space group PL-bar a = 11.447 (5), b = 13.148 (6), c = 13.757 (5)A, α = 70.15 (4), β = 65.89 (3), γ = 75.23 (4)°, V = 1761.2A^3. For Z = 6 and FW = 256.27 the calculated density is 1.45g/cm^3. Cell constants and orientation matrix data were obtained from least square refinements using setting angles of 25 reflections in the range of $7 < \theta < 16°$ measured by computer controlled diagonal slit method of centering. The colorless parallel piped crystal had approximate dimensions of 0.20 x 0.20 x 0.15 mm. Data collection and preliminary examination were performed with CuKα radiation (λ = 1.5418A) at $-109 \pm 1°$ using W-θ scan technique.

Data Collection and Processing.

The three dimensional intensity data were measured on an Enraf-Nonius AD-4 computer controlled Kappa-axis

Table 3

Linear Compounds



R_1	R_2	R_3	R_4	X	Yield %	MP°C	M.F.	1H (DMSO-d_6) δ (PPM)	m/e	Solvent of Crystallization	Method	Anaylsis Calcd./Found
OH	OH	OH	OH	NHPh	80	>300	$C_{19}H_{16}N_2O_4$	6.8-7 (m, 9H) 8.3 (d, 1H, J = 1.2 Hz) 9.3 (d, 1H, J = 1.7 Hz)	336 (M^+)	Dioxane	A, B, C	C, 67.9; H, 4.7; N, 8.3 C, 67.76; H, 4.8; N, 8.3
OH	H	OH	H	NH_2[12]	88	130-132	$C_{13}H_{12}N_2O_2$	— — —	— —	Ethanol	A	C, 68.40; H, 5.30; N, 12.28 C, 68.12; H, 5.42; N, 12.34
OH	H	OH	H	$NHCH_3$	88	145-148	$C_{14}H_{14}N_2O_2$	2.8 (s, 3H) 7-7.3 (m, 8H)	242 (M^+)	Ethanol 95%	A, B, C	C, 69.42; H, 5.8; N, 11.6 C, 69.44; H, 5.8; N, 11.42
OH	H	OH	H	NHPh	85	150-152	$C_{19}H_{16}N_2O_2$	6.8-7 (m, 13H) 7.3 (m, 2H)	304 (M^+)	Ethanol 90%	A, B, C	C, 75.08; H, 5.28; N, 9.2 C, 75.12; H, 5.31; N, 9.2
OH	H	OH	H	N=C(HOPh)$_2$	80	349-351	$C_{26}H_{20}N_2O_4$	7.1-8 (m, 16H)	424	Ethanol 95%	B, C	C, 73.58; H, 4.71; N, 6.60 C, 73.41; H, 4.62; N, 6.58

diffractometer equipped with a graphite crystal, incident beam monochromator. The data were collected at a temperature of $-109 \pm 1^\circ$ using the W-θ scan technique. The scan rate varied form 2 to 20°/minute (in omega). Data were collected to a maximum of 2θ of 110.0°. A total of 5446 reflections were collected, of which 5222 were unique.

As a check on crystal and electronic stability 3 representative reflections were measured every 41 minutes. The intensities of these standards remained constant with experimental error throughout data collection.

Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 8.6 cm^{-1} for CuKα radiation. No absorption correction was made. A secondary extinction correction was applied. The final coefficient, refined in least-squares was 0.0000017 (in absolute units).

Structure Analysis and Refinements.

The structure was solved by direct methods. Using 250 reflections (minimum E of 2.04) and 858 relationships, a total of 61 phases were obtained. A total of 40 atoms were located from an E-map prepared from the phase set with probability statistics; absolute figure of merit = 1.02, residual = 9.89 and psi zero = 0.990. The remaining non-hydrogen atoms were located in succeeding difference fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations but their positions were not refined. The structure was refined in full matrix least squares where the function minimized was $\Sigma w(|Fo| - |Fc|)^2$ and the weight w is defined as $4\ Fo^2/\sigma^2 (Fo^2)$. The standard deviation on intensities, $\sigma(Fo^2)$, is defined as follows: $\sigma^2(Fo^2) = [S^2 (C + R^2 B) + (PFo^2)^2] / Lp^2$, where S = scan rate, C = total integrated peak count, R = ratio of scan time to background counting time, B = total background counting time, Lp is the Lorentz-Polarization factor, and the parameter p is a factor introduced to downweight intense reflections. Here p was set to 0.060.

Scattering factors were taken from Cromer and Waber [6]. Anomalous dispersion effects were included in Fc [7], the values for $\triangle F'$ and $\triangle F'$ were those of Cromer [8]. Only the 2694 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 515 variable parameters and converged (largest parameter shift was 0.02 times its esd) with unweighted and weighted agreement factors of:

$$R_1 = \Sigma \mid |Fo| - \mid |Fc| / \Sigma Fo \mid = 0.065$$

$$R_2 = sQRT(\Sigma w(\mid Fo \mid - \mid Fc \mid)^2 / \Sigma WFo^2) = 0.081$$

The standard deviation of an observation of unit weight was 1.84. The highest peak in the final difference Fourier had a height of $0.38e/A^2$ with an estimated error based on $\triangle F$ [9] of 0.07. Plots of $\Sigma W(\mid Fo \mid - \mid Fc)^2$ versus $\mid Fo \mid$ reflection order in data collection, sine θ/λ, and various classes of indices showed no unusual trends.

All calculations were performed on a PDP-11/6θ based TEXRAY [10] system, a powerful laboratory computer system which includes the Enraf-Nonius SDP and proprietory crystallographic software of Molecular Structure Corporation.

EXPERIMENTAL

General Methods of Preparation.

All melting points were taken on Mel-Temp apparatus and are not corrected. Samples for elemental analysis were dried over phosphorus pentoxide under high vacuum for 1-10 hours. Infra-red specta were measured on a Perkin-Elmer model spectrophotometer (Model 21). The nmr spectra were determined with a Varian Model HA-100 spectrometer. Chemical shifts (δ) are in ppm relative to internal tetramethylsilane.

Mass spectra were recorded on A.E.I. MS902. Tables 1 and 2 list the compounds prepared.

A. A solution of 2,2',4,4'-tetrahydroxybenzophenone, (1 mole), hydrazine hydrate (10 moles) and ammonium chloride (0.3 mole) was heated in a sealed carius tube at 200-210° for 4 hours. The product usually separated on cooling.

B. A solution of tetrahydroxybenzophenone (0.01 moles) hydrazine hydrate (0.03 mole) and ammonium chloride (0.0036 mole) in 25 ml of water was heated in a sealed carius tube at 200-210° for 4 hours. The product usually separated on cooling.

C. The solution of the above reactants (B) was refluxed for 4 hours. The product usually separated on cooling.

4-(6-Hydrazino-1*H*-indazol-3-yl)-1,3-benzenediol (**5**, R = $NHNH_2$).

The tan liquid obtained after the reaction (Method A) was poured into a beaker and triturated with methanol to give yellow-tan crystals. Recrystallization from methanol gave cream crystals.

4-(6-Hydroxyl-1-methyl-*H*-indazol-3-yl)-1,3-benzenediol (**7**, R = CH_3).

The brown liquid obtained after the reaction (Method A) was poured into ice water (100 ml) and allowed to stand for 24 hours at 5-10° when a brown solid separated. Recrystallization from 80% ethanol gave brown needles.

Bis(2,4-dihydroxyphenyl)methanone Phenylhydrazone (**8**).

The reaction mixture (Method A) on cooling, dilution with water and standing at room temperature for 24 hours yielded a brown solid. Recrystallization from dioxane gave brown prisms.

4-(6-Hydroxyl-1-phenyl-1*H*-indazol-3-yl)-1,3-benzenediol (**9**, R = Ph).

Compound **8** (1.6 g, 0.048 mole) was heated in an atmosphere of argon at 200-210° for 4 hours. The dark brown solid obtained was extracted with ethanol. Repeated recrystallization from DMF yielded red needles.

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