Synthesis of Condensed Pyrazoles by Cyclization of Hydrazones with Polyphosphoric Acid

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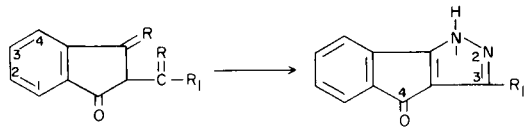
The intramolecular cyclization of the monohydrazones of 2-acyl-1,3-indandiones (**1**) to form 3-substituted indeno-[1,2-*c*]pyrazol-4(1*H*)ones (**2**) has been accomplished in only a few cases and generally with moderate yields by refluxing these hydrazones in 99% formic acid (1) or in ethanol in the presence of catalytic amounts of *p*-toluenesulfonic acid (1) or hydrochloric aicd (2).

A method of general application has been found in the use of polyphosphoric acid, a reagent previously used for cyclization of hydrazones by dehydrogenation (3), but not for cyclization of hydrazones by dehydration to form a pyrazole ring. Yields varying from 85 to 95% of compounds **2** were obtained by adding the hydrazones **1** to a large excess of polyphosphoric acid at room temperature and then heating at 90° for 10-15 minutes. If the concentration of hydrazone is too great or if the hydrazone is added to hot polyphosphoric acid high melting compounds believed to be the corresponding azines are formed.

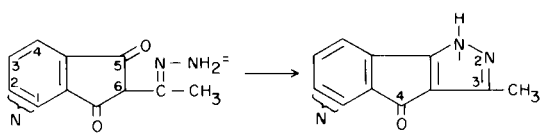
The structures of the indenopyrazolones (**2**) are supported by the elemental analyses and by the similarities of the ir infrared spectra with those of known compounds of this class (1,7).



1 **2a-d**

one R is $=N-NH_2$
and the other R is O, see Experimental
R_1, see Table I

The ring closure of the α-hydrazones at 6-acetyl-5*H*-1-pyrindine-5,7(6*H*)dione (**3**) and of 6-acetyl-5*H*-2-pyrindine-5,7-(6*H*)dione (**4**) was also achieved by this method.



3 and **4** **5** and **6**

3-Methylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]- and 3-methylpyrazolo[3′,4′:3,4]cyclopenta[2,1-*c*]pyridin-4-(1*H*)one (**5** and **6**) were respectively obtained. In the ring closure of hydrazones **3** and **4** the possibility exists for the formation of isomeric forms of compounds **5** and **6**. However, in each case only one compound was isolated by column chromatography. We assigned the above structures **5** and **6** without excluding the possibility of the other isomeric structures.

EXPERIMENTAL (4)

2-Acyl-1,3-indandione, Monohydrazones (1).

The following compounds were prepared by previously described methods (5): 2-acetyl-, 2-propionyl-, 2-phenylacetyl-1,3-indandione, α-hydrazones and 2-diphenylacetyl-1,3-indandione, 1-hydrazone.

6-Acetyl-5*H*-1-pyrindine-5,7(6*H*)dione, α-Hydrazone (**3**).

This compound was prepared as described in ref. 6.

6-Acetyl-5*H*-2-pyrindine-5,7(6*H*)dione.

A mixture of cincomeronic anhydride (95 g., 0.64 mole), acetylacetone (65 g., 0.65 mole), pyridine (105 ml.) and piperidine (1.5 ml.) was stirred at 30-40°. A deep red solution was formed in a short time and after 6 hours a yellow solid began to precipitate. After stirring for 24 hours, the very thick crystalline product was collected by filtration, washed with ether, dried, slurried in ethanol and treated with 6*N* hydrochloric acid (100 ml.) to give 93 g. (80%) of a bright yellow solid, m.p. 245-246° dec. Sublimation at 180-200° under *vacuo* gave a red-orange solid, m.p. 245-246° dec., which turned to the original yellow color (m.p. 245-246°) after standing in the air at room temperature for 24 hours. The ir shows bands at 3420 (OH, only the red-orange form) and at 2130 cm^{-1} ($\overset{+}{N}H$); nmr 2.22 (s, 3), 7.17 (d, 1), 8.23 (s, 1) and 8.50 (d, 1) ppm.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.46; H, 3.84; N, 7.43.

The hydrazone **4** was obtained in 83% yield as yellow crystals, m.p. 239-241° dec., by adding 85% hydrazine hydrate (0.5 ml.) to a refluxing solution of the above pyrindinedione (1.6 g., 0.0085 mole) in ethanol (300 ml.), refluxing for 2 hours and cooling. This hydrazone gave a positive Tollens test and formed a red solution with 10% aqueous sodium hydroxide. This behavior is characteristic of 2-acyl-1,3-indandiones hydrazones with the hydrazone group in the side chain (5). Prolonged refluxing of **4** in ethanol containing a few drops of concentrated hydrochloric acid did not cause ring closure to **6**.

TABLE I

3-Substituted indeno[1,2-c]pyrazol-4(1*H*)ones (**2a-d**)

Compound	R_1	Yield %	M.p., °C	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
2a	CH_3	90	216-217 (a)	$C_{11}H_8N_2O$	71.73	71.73	4.38	4.16	15.21	15.15
b	C_2H_5	87	159-160	$C_{12}H_{10}N_2O$	72.71	73.02	5.09	4.98	14.14	14.21
c	$CH_2C_6H_5$	96	230-231	$C_{17}H_{12}N_2O$	78.44	78.05	4.65	4.85	10.76	10.59
d	$CH(C_6H_5)_2$	95	179-180 (b)	$C_{23}H_{16}N_2O$	82.12	82.16	4.80	5.11	8.33	8.29

(a) Two isomeric compounds were isolated by column chromatography: one colorless m.p. 216-217° and one yellow brown, m.p. 213-214°. (b) Reported 180° (1).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.97; H, 4.61; N, 20.62.

3-Substituted Indeno[1,2-*c*]pyrazol-4(1*H*)ones (**2a-d**).

The following general procedure was used: Phosphorous pentoxide (18 g.) was added slowly to stirred 85% orthophosphoric acid (12 ml.). The temperature rose quickly to 135°. Stirring was continued until the temperature dropped to 25° (about 2 hours), then the appropriate hydrazone **1** (0.5 g., 0.0025 mole), finely pulverized, was added in one portion and the mixture stirred at room temperature until a uniform dispersion was achieved. A 90° oil bath was applied to the reaction flask and stirring continued for 15 minutes. The hot solution was poured into ice and neutralized with concentrated ammonium hydroxide to give the corresponding indenopyrazolones **2a-d**. The yields, m.p. and elemental analyses of these compounds are reported in Table I. The ir spectra show bands at 3130-3070 (NH), 1715-1695 (C=O) and 1615-1590 cm^{-1} (C=N, C=C). The ir spectra of the known 3-*t*-butyl- and 3-(diphenylmethyl)indeno[1,2-c]pyrazol-4(1*H*)one (1,7) show absorption at 3100-3030, 1700 and 1610 cm^{-1}.

3-Methylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4(1*H*)one (5).

This compound was obtained in 84% yield as fine needles, m.p. 262-265° dec., from 6-acetyl-5*H*-1-pyrindine-5,7(6*H*)dione, α-hydrazone (**3**) (0.5 g.) following the procedure above described for compounds **2**. The ir spectrum shows bands at 3160 (NH), 1710 (C=O) and 1610-1590 cm^{-1} (C=N, C=C).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.68; H, 3.94; N, 22.42.

3-Methylpyrazolo[3′,4′:3,4]cyclopenta[2,1-*c*]pyridin-4(1*H*)one (6).

This compound was obtained in 88% yield as fine brown needles, m.p. 255-257° dec. from 6-acetyl-5*H*-2-pyrindine-5,7-(6*H*)dione, α-hydrazone (**4**) (0.5 g.) following the procedure above described for compounds **2**. The ir spectrum shows bands at 3050, 1703 and 1615 cm^{-1}.

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.99; H, 4.02; N, 22.56.

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(4) Melting points were taken on a Fisher-Johns melting point apparatus between circular cover plates and are uncorrected. The infrared spectra were determined in potassium bromide pellets with a Perkin-Elmer Model 137 Spectrophotometer. The ultraviolet spectra were taken on a Perkin-Elmer Spectrophotometer, Model 202. The nuclear magnetic resonance spectra were obtained on a Varian Associates Spectrometer, Model A-60A. Elemental analyses were performed by Dr. A. Bernhardt; Mikroanalytisches Laboratorium Max Planck Institute fur Kohlenforschung, Mulheim (Ruhr), Germany.

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