

Some Condensations of Pyrazole-3,4-dicarboxaldehyde

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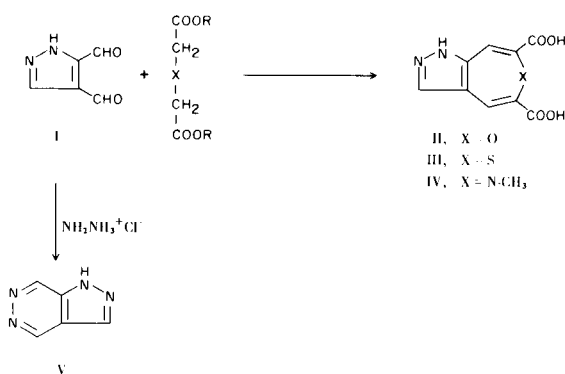
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The benzoxepin ring system has been prepared by condensation of phthalaldehyde with dimethyl diglycolate (2-4) to give 2,7-dicarboxy-4,5-benzoxepin or by a Wittig reaction with bis-(α,α -triphenylphosphonium)dimethyl ether dibromide (5) to afford the parent, 4,5-benzoxepin. This same phosphonium dibromide reacted with 2,5-dimethylthiophene-3,4-dicarboxaldehyde to produce the first heterocyclic analog, 2,8-dimethylthieno[3,4-*d*]oxepin (4).

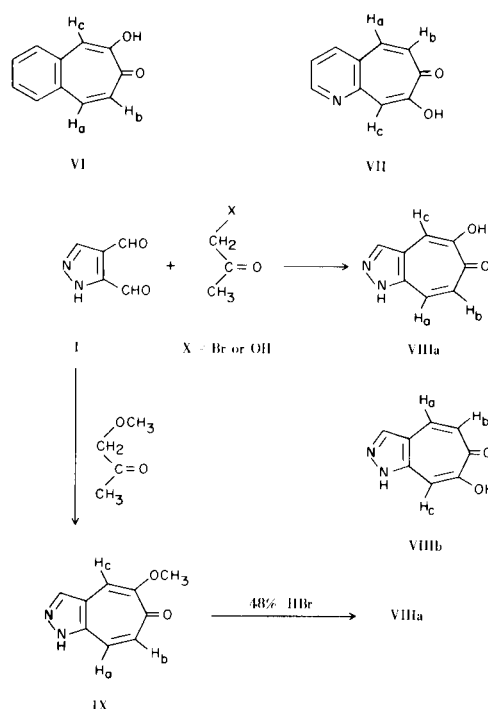
We reacted pyrazole-3,4-dicarboxaldehyde (I, Scheme I) (6) with dimethyl diglycolate in sodium methoxide which formed the new bicyclic structure, 1*H*-oxepino[4,5-*c*]pyrazole-5,7-dicarboxylic acid (II). Oxepinopyrazole II was very insoluble and recrystallized with difficulty from acetic acid or ethanol. It trapped a stoichiometric quantity of either solvent on crystallization and attempts to remove the solvent proved fruitless. For example, one mole of ethanol was irreversibly trapped per mole of oxepine II and the nuclear magnetic resonance spectrum clearly exhibited the ethanol spectrum (7) superimposed on the absorptions of II. The infrared spectrum showed the characteristic strong carbonyl group absorption at 1680 cm^{-1} as well as bands at 1660 (C=C stretching), 1260 and 1050 cm^{-1} (aromatic ether asymmetric stretching). These spectral findings compared favorably to those reported (8) for benzoxepins prepared by photochemical conversion of substituted 1,4-epoxy-1,4-dihydronaphthalene.

The only thiepinopyrazole reported (9) was 4,4,8,8-tetramethyl-4,5,7,8-tetrahydro-1*H*-thiepinopyrazole

REACTION SCHEME I



REACTION SCHEME II



zole. We attempted to prepare 1*H*-thiepinopyrazole-2,7-dicarboxylic acid by a sodium methoxide catalyzed condensation of the dialdehyde I with dimethyl thiepidiglycolate. The infrared spectrum of the product isolated (m.p. $205\text{--}206^\circ$) showed (cm^{-1}): 3150 (pyrazole NH), 1680 (carbonyl), 1650 (C=C), 1560 (C=N) and 650 (C-S single bond stretching). A comparison of these values with those of II indicated the thiepinopyrazole (III) probably formed but positive identification was impossible because it rapidly decomposed. This instability was analogous to that of 2,7-dicarboxy-4,5-benzothiepin which decomposed, almost immediately, into 2,3-naphthalenedicarboxylic acid (10,11). However, we were unable to isolate any 2-azaindole from the decomposition of III.

Some fully saturated representatives of azepinopyrazoles are known (12-15). Our attempts to condense dimethyl *N*-methyliminodiacetate with I, according to the procedure

used to prepare 1-methyl-2,7-dicarboxy-4,5-benzazepine (16), yielded only unreacted dialdehyde I.

Pyrazolo[3,4-*d*]pyridazine (V), previously described by Bastide and Lematre (17), was prepared by us from I with hydrazine hydrate in acidic media. The structure of V was supported by elemental and infrared spectral analysis.

Tarbell and his coworkers (18) obtained 4,5-benzotropolone (VI) by condensing phthalaldehyde with hydroxyacetone. Recently, this procedure applied to pyridine-2,3-dicarboxaldehyde afforded an 8-hydroxycyclohepta[*b*]pyridin-7-one (VII) (19). Our interest in heterocyclic analogs of non-benzenoid hydrocarbons (20) led us to condense the dialdehyde I with either hydroxyacetone or bromoacetone (Scheme II). This afforded the cyclohepta[*c*]pyrazole (VIII). Also, condensation of I with methoxyacetone (21) gave 5-methoxy-1*H*-cyclohepta[*c*]pyrazol-6-one (IX) which on hydrolysis yielded VIIIa. While the infrared and ultraviolet spectral data for VIII (see Experimental) was comparable to that reported for VI (18,22,23) and VII (24) the nmr spectra allowed us to distinguish isomer VIIIa from VIIIb. The nmr spectra of VI and VII were similar in that the absorption of the Hc proton singlet appeared farthest downfield. Thus, the chemical shift values for the tropolone rings, in VI: δ 7.18 (d, Hb), 7.48 (d, Ha) and 7.57 (s, Hc) and the cycloheptapyridine VII: δ 7.23 (d, Hb, $J = 12.5$ Hz), 7.76 (d, Ha) and 7.93 (s, Hc) compared with the values of the cycloheptapyrazolone (VIII): δ 6.68 (d, Hb, $J = 6$ Hz), 7.44 (s, Hc); 7.96 (d, Ha) showed that in the latter the Ha doublet was the one farthest downfield as a result of its proximity to the ring nitrogen. Therefore, the cycloheptapyrazolone was assigned structure VIIIa since isomer VIIIb would have shown the chemical shift for the Hc singlet farthest downfield, its nmr spectrum resembling that of VII.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Beckman IR-8 (potassium bromide pellets), ultraviolet spectra on a Bausch and Lomb Spectronic 505 in methanol and nuclear magnetic resonance spectra on a Varian A-60-A with TMS as internal standard, the chemical shifts reported in ppm (δ). Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Materials.

Pyrazole-3,4-dicarboxaldehyde was prepared as described in the literature (6). Diglycolic acid, thiadiglycolic acid, and imino-diacetic acid were purchased from K and K Laboratories, N. Y. and were used in the preparations of dimethyl diglycolate, b.p. 130-131°, 20 mm (lit. (25) b.p. 129-130°, 20 mm); dimethyl thiadiglycolate, b.p. 258-259° (lit. (26) b.p. 259-260°) and dimethyl *N*-methyliminodiacetate, b.p. 85-86°, 2 mm (lit. (27) b.p. 85-86°, 2 mm). Methoxyacetone was obtained by the method of

Mariella and Leech (21).

1*H*-Oxepino[4,5-*c*]pyrazole-5,7-dicarboxylic Acid (II).

A suspension of pyrazole-3,4-dicarboxaldehyde (I) (3.31 g., 0.027 mole) and dimethyl diglycolate (7.6 g., 0.045 mole) in 30 ml. of *t*-butyl alcohol was slowly added over a 1 hour period to a vigorously stirred solution of potassium (4 g., 0.10 g.-atom) dissolved in 110 ml. of *t*-butyl alcohol. After stirring 48 hours, the solution was evaporated under vacuum to a gummy solid. Solution of the solid in 40 ml. of distilled water and acidification of the clear orange solution to pH 1 with hydrochloric acid yielded a precipitate. It was filtered, washed with water, air dried and recrystallized from ethanol and the solid which precipitated vacuum dried (100°, 10 mm) for 24 hours to yield 1*H*-oxepino[4,5-*c*]pyrazole-5,7-dicarboxylic acid, which crystallized from ethanol as white crystals, m.p. 194-195° (2.1 g., 26%), nmr (deuteriopyridine-*d*₅) 11.30 (s, 2H, COOH); 7.40 (s, 1H, NH); 7.20 (s, 1H, pyrazole CH); 5.46 (d, 2H, oxepine ring); 4.20 (s, 1H, OH); 3.40 (q, 2H, CH₂); 1.20 (t, 3H, CH₃).

Anal. Calcd. for C₉H₆N₂O₅·CH₃CH₂OH: C, 49.25; H, 4.47; N, 10.44; O, 35.82; mol. wt. 268. Found: C, 48.94; H, 4.73; N, 10.44; O, 35.70; mol. wt. 272, 258.

Pyrazolo[3,4-*d*]pyridazine (V).

To a suspension of I (0.50 g., 0.004 mole) in 25 ml. of acidic (HCl, pH 2) 95% ethanol was added dropwise with stirring over 0.25 hour, hydrazine hydrate (0.16 g., 0.004 mole). The mixture was refluxed 1 hour on a steam bath, cooled and evaporated under vacuum to a gummy solid. Recrystallization from absolute ethanol gave V as yellow needles (0.25 g., 52%), m.p. 195-197°; ν (cm⁻¹) 3200 (NH), 1260, 1240, and 1180 (C=N).

Anal. Calcd. for C₅H₄N₄: C, 50.00; H, 3.33; N, 46.67. Found: C, 49.92; H, 3.30; N, 46.60.

1*H*,6*H*-5-Hydroxycyclohepta[*c*]pyrazol-6-one (VIIIa).

To a suspension of pyrazole-3,4-dicarboxaldehyde (I) (2.98 g., 0.024 mole) in 300 ml. of water was added in one portion, 12 ml. of 5*N* sodium hydroxide followed by dropwise addition with stirring of bromoacetone (or hydroxyacetone) (0.027 mole). The red solution was stirred 22 hours at room temperature, filtered, and the filtrate adjusted to pH 3-5 with 20% sulfuric acid. The precipitated solid was filtered, washed with water and dried 4 hours in a heated (100°) desiccator. Sublimation at 180° (0.25 mm) gave VIIIa in 21% yield (X = Br) and 26% yield (X = OH), m.p. 312-313°; ν max, cm⁻¹: 3175 (broad NH and OH), 1634 (-C=C-) tropolone, 1592 (-C=O); ν max, nm (log ϵ): 234 (4.24, pyrazole ring), 258 (4.47, tropolone ring), 283 (4.05), 346 (4.06), and 358 (4.08, conjugated ring carbonyl); nmr (dimethyl sulfoxide-*d*₆) δ (cf. structure VIIIa) 6.68 (d, Hb, $J = 6$ Hz), 7.44 (s, Hc), 7.96 (d, Ha, $J = 6$ Hz), 8.20 (s, 1H, pyrazole CH), 9.40 (broad band, 1H, OH), 13.72 (broad band, 1H, NH).

Anal. Calcd. for C₈H₆N₂O₂: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.21; H, 3.80; N, 17.28.

1*H*,6*H*-5-Methoxycyclohepta[*c*]pyrazol-6-one (IX).

A condensation of I (0.10 g., 0.008 mole) with methoxyacetone (0.8 g., 0.009 mole) in 70 ml. of water to which 8 ml. of 2*N* potassium hydroxide was added gave, after 18 hours stirring at room temperature, acidification to pH 4 with hydrochloric acid, filtration and sublimation at 190° (0.5 mm), 1*H*,6*H*-5-methoxycyclohepta[*c*]pyrazol-6-one (IX) in 53% yield, m.p. 288-289°; ν max, cm⁻¹: 3215 (NH), 1587 (C=O); ν max, nm (log ϵ): 232 (3.84), 258 (4.07), 280 (3.06), 342 (3.70); nmr (dimethyl

sulfoxide-d₆) δ 3.83 (s, 3H, OCH₃), 6.62 (d, 1 Hb, J = 10 Hz, tropone), 7.20 (s, 1 Hc, tropone), 7.68 (d, 1 Ha, J = 10 Hz, tropone), 8.12 (s, 1H, pyrazole CH).

Anal. Calcd. for C₉H₈N₂O₂: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.37; H, 4.60; N, 15.64.

Hydrolysis of IX in 60 ml. of refluxing 48% hydrobromic acid gave after neutralization with 5% potassium hydroxide and extraction with 3 x 25 ml. of ethyl acetate, drying (magnesium sulfate) and evaporation, a brown solid. Sublimation at 197° (0.75 mm) gave 18% of VIIIa, m.p. 311-312°. A mixture melting point with the cycloheptapyrazole isolated from the condensation with hydroxy- or bromoacetone showed no depression.

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