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Treatment of 5-amino-1-(2-aminophenyl)-1*H*-pyrazole-4-carbonitrile (**15**) with triethyl orthoformate produces 6*H*-pyrazolo[2,3-*a*][1,3,5]benzotriazepine-3-carbonitrile (**16**). Other members of this novel ring system result from treating **15** with triethyl orthoacetate and triethyl orthopropionate. These latter reactions, which yield homologs **17** and **19**, respectively, of **16**, also produce acyclic Schiff bases. These Schiff bases are useful in determining the position of the triazepine double bond in pyrazolobenzotriazepines **16**, **17** and **19**, using ¹³C nmr spectroscopy.

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In previous reports from this laboratory we have cited anomalies in syntheses expected to produce pyrazoles. When bromohydrazone **1** was treated with ethyl cyanoacetate and sodium ethoxide, the expected pyrazole **2** was not found. Instead, 5-bromo-2-phenylbenzoxazole (**3**) and 6-bromo-3-phenyl-1,2,4-benzotriazine (**4**) (1) were isolated. Pyrazole **2** was intended for use in the preparation of pyrazolobenzotriazepines.

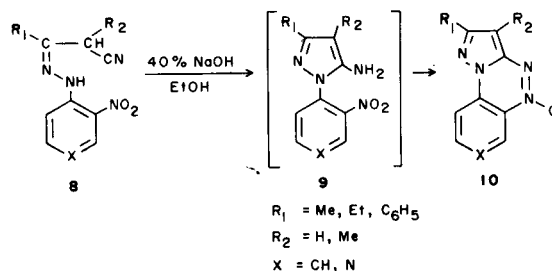
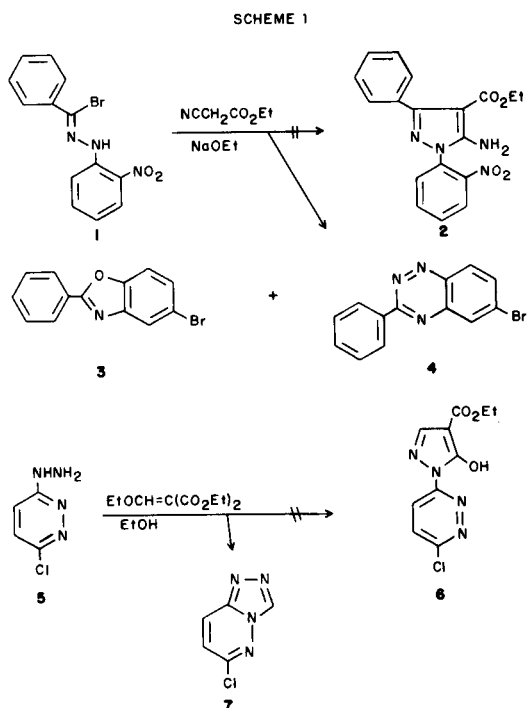
In another study, pyrazole formation was also thwarted when 3-chloro-6-hydrazinopyridazine (**5**) was treated with diethyl ethoxymethylenemalonate (2). Instead of the expected pyrazole **6**, 6-chlorotriazolo[4,3-*b*]pyridazine (**7**) was obtained in 75% yield.

Both of these above-mentioned anomalous reactions, which are shown in Scheme I, occur due to participation of a strategically placed functionality. In the former case,

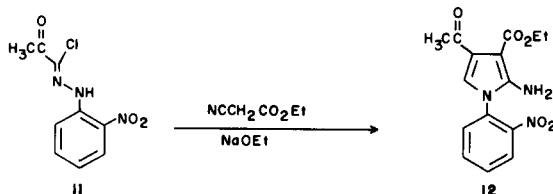
ortho nitro group participation is responsible (3), whereas in the latter case, participation of a pyridazine nitrogen leads to the anomalous product.

Another instance of nitro group involvement in the preparation of pyrazoles is reported by Hauptmann, Blattmann and Schindler (5) in their synthesis of pyrazolobenzotriazines and pyrazolopyridotriazines (general structure **10**). Treatment of hydrazononitriles **8** with 40% sodium hydroxide in ethanol led directly to **10** in good yield.

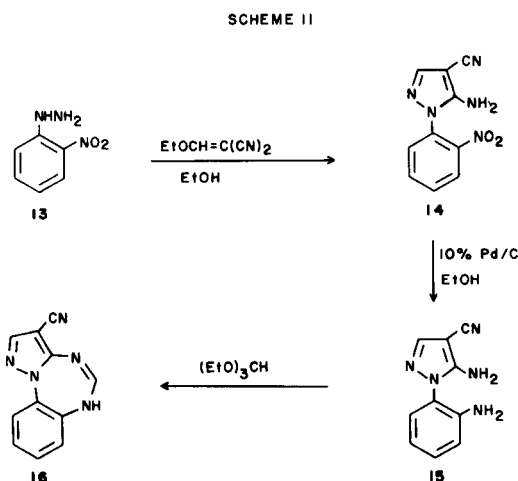
The nitro group participates in this instance by condensation with an amino functionality, whereas in Scheme I (top) we feel that nitro group involvement initiates with displacement of bromide ion by the nitro group (1). Nitro group participation in the preparation of other heterocyclic systems has also been documented (6).



However, nitro group involvement does not always occur, even when the potential exists. In response to our report of **3** and **4** being produced from **1**, Hassaneen, Abelhamid and Shawali (12) have investigated the reactions of a compound related to **1**, bearing the *N*-(2-nitrophenyl) moiety. These authors found that hydrazidoyl chloride **11** behaved quite normally (in that the nitro substituent remained inert) in the formation of pyrazole **12**, which was produced by treatment of **11** with ethyl cyanoacetate and sodium ethoxide. It is peculiar that we were unable to produce **2** from **1** in view of these results.



In addition, no involvement of the nitro group was observed when 2-nitrophenylhydrazine was treated with ethoxymethylenemalononitrile in ethanol. Thus, Hayashi, *et al.* (13) obtained 5-amino-1-(2-nitrophenyl)-1*H*-pyrazole-4-carbonitrile (**14**) in this fashion in good yield. We have repeated this reaction, and pyrazole **14** (Scheme II) has provided an entry into the novel 6*H*-pyrazolo[2,3-*a*][1,3,5]-benzotriazepine ring system (14). Catalytic hydrogenation of **14** produced diamino compound **15**, which was cleanly cyclized with triethyl orthoformate to yield pyrazolobenzotriazepine **16**.



Diamino compound **15** was also treated with triethyl orthoacetate and triethyl orthopropionate, as shown in Scheme III. The major products of these reactions were the respective pyrazolobenzotriazepines **17** and **19**. However, coproduced with **17** was the mono-Schiff base **18**, and with **19**, the bis-Schiff base **20**.

The ¹H nmr spectrum of compound **16** nicely demonstrated that the product was a pyrazolobenzotriazepine and not a pyrazolobenzotriazine (**22**, R = H), which was an alternate, potential product of cyclization. (Compound **22** could have arisen from **21**, a tautomer of **15**, by cyclization as shown in Scheme III.) In the ¹H nmr spectrum of **16**, coupling between the triazepine methine hydrogen and the adjacent hydrogen on nitrogen was observed. The methine doublet (*J* = 5 Hz) at δ 6.59 for **16** collapsed to a singlet when the hydrogen on nitrogen was exchanged with deuterium oxide.

A more difficult question to address was whether the

pyrazolobenzotriazepines were, in fact, the 4,5-double bond isomers as indicated for **16**, **17** and **19**, or the 5,6-double bond isomers indicated by general structure **23**. The ¹H nmr chemical shifts for the pyrazole hydrogens and the hydrogens *ortho* to the nitrogen substituents on the phenyl ring for the compounds prepared in this study are displayed in Table I. We initially felt that these data would be helpful in assigning the double bond position. However, chemical shift trends were not obvious, so ¹³C nmr analysis was utilized to answer this question. The structure of mono-Schiff base **18** was also unequivocally assigned using ¹³C nmr.

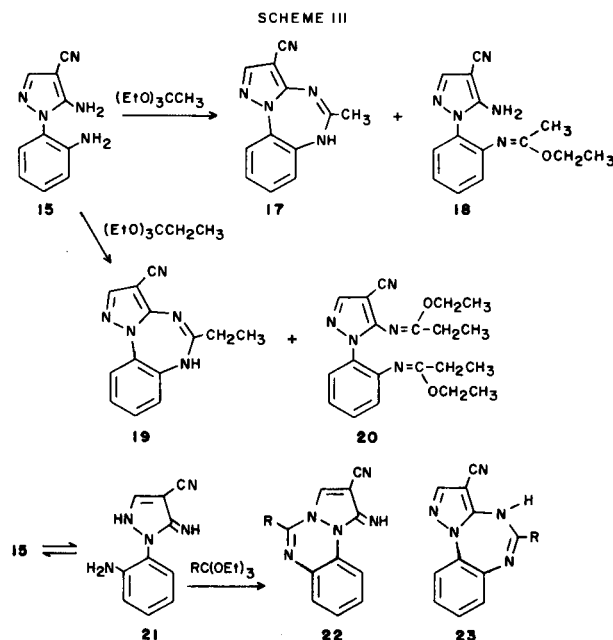


Table I

¹H NMR (Dimethylsulfoxide-*d*₆) Spectra of Pyrazoles

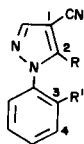
Compound	Pyrazole H (δ)	Phenyl H (δ) <i>ortho</i> to amino substituent
15	7.81	6.92
16	7.81	6.62
17	7.88	6.79
18	7.67	6.94
19	7.85	6.81
20	7.99	6.88

In Table II, the ¹³C chemical shifts for selected phenyl and pyrazole ring carbon atoms of compounds **15-20** (17) are listed. For bis-Schiff base **20**, whose structure was unambiguous from other spectral analysis, the C-1 signal appeared at 81.0 ppm and the C-4 signal at 122.3 ppm.

The C-4 signal for mono-Schiff base **18** was essentially unchanged (122.4 ppm) with respect to **20**, whereas the C-1 signal was substantially changed, appearing at 72.1 ppm, which was close to the position of 72.6 ppm of C-1 of diamino compound **15**. Thus, it was concluded that the mono-Schiff base was, indeed, structure **18**, and not the isomeric Schiff base which could have resulted from condensation of the pyrazole amino group with triethyl orthoacetate. Additional evidence for the presence of the amino group on the pyrazole ring of mono-Schiff base **18** came from the observation of long-range coupling between C-1 and the amino group protons in **18**, in that the C-1 signal was noticeably broadened (in a gated decoupling experiment). A similar coupling is observed in aniline, between C-2 and the amino group (21).

For all of the compounds of Table II, the C-2 signals appear at field positions which are relatively close, within a 1.7 ppm range. Of particular interest are the C-2 values for pyrazolobenzotriazepines **16**, **17** and **19**, which fall close to the C-2 value for bis-Schiff base **20**. This is in marked contrast to the large range span encompassed by the C-3 signals for the compounds of Table II. For pyrazolobenzotriazepines **16**, **17** and **19**, the C-3 signals appear at 12-14 ppm *upfield* with respect to Schiff bases **18** and **20** or diamino compound **15**. Thus, the triazepine double bond is *conjugated with the pyrazole*, as indicated in Schemes II and III for compound **16**, **17** and **19**, rather than with the phenyl ring, as indicated by general structure **23**.

Table II

¹³C NMR (Dimethylsulfoxide-*d*₆) Spectra of Pyrazoles

Compound	R	R'	C-1 (δ)	C-2 (δ)	C-3 (δ)	C-4 (δ)
15	NH ₂	NH ₂	72.6	151.8	144.5	116.6
16	N=CH-NH		90.5	153.4	131.7	120.0
17	N=C(Me)NH		89.4	152.4	132.4	120.2
18	NH ₂	N=C(Me)OEt	72.1	152.0	145.4	122.4
19	N=C(Et)NH		89.5	152.5	132.8	120.3
20	R=R'=N=C(Et)OEt		81.0	151.7	145.6	122.3

The iminoamino phenyl substituents of **16**, **17** and **19** have a *weaker deshielding* effect on C-3 than do the isoimino substituents of **18** and **20** or the amino substituent of **15**.

In summary, the synthesis of novel 6*H*-pyrazolo[2,3-*a*]-

[1,3,5]benzotriazepines has been described. The position of the triazepine double bond in our series of compounds was rigorously established using ¹³C nmr spectroscopy.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B or Beckman Model 4240 spectrophotometers, ¹H nmr spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, ¹³C nmr spectra with a Varian FT-80A spectrometer, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Dow Analytical Laboratories, Midland, MI.

5-Amino-1-(2-nitrophenyl)-1*H*-pyrazole-4 carbonitrile (**14**).

A solution of 30.0 g (0.195 mole) of 2-nitrophenylhydrazine (**13**) and 25.6 g (0.210 mole) of ethoxymethylenemalononitrile in 250 ml of ethanol was heated at reflux for 3 hours. The solution was concentrated and the resulting oil was triturated with ether to yield 37.0 g of solid. Recrystallization from toluene (2 liters) gave 32.7 g (73%) of **14**, mp 173.5-175° [lit (13) mp 174-175°]; ir (Nujol): 3340 and 3300 (NH), 2220 (C=N), 1650, and 1520, 1340 and 850 (NO₂) cm⁻¹; ¹H nmr (deuteriochloroform and dimethylsulfoxide-*d*₆): δ 8.30-7.43 (m, 5H, aromatic), 5.60 (broad s, 2H, NH₂, deuterium oxide-exchangeable); ms: (70 eV, chemical ionization, methane) 230 (M⁺ + 1), 258 (M⁺ + 29), 270 (M⁺ + 41).

Anal. Calcd. for C₁₀H₇N₃O₂: C, 52.40; H, 3.08; N, 30.56. Found: C, 52.63; H, 3.10; N, 30.23.

5-Amino-1-(2-aminophenyl)-1*H*-pyrazole-4-carbonitrile (**15**).

A solution of 8.50 g (37.1 mmoles) of **14** in 175 ml of ethanol was treated with 1 g of 10% Pd/C and hydrogenated at ca. 50 psi of hydrogen on a Parr apparatus until hydrogen uptake ceased (45 minutes). Two such batches were combined, the catalyst was removed by filtration, and the filtrate was concentrated to leave 16.0 g of solid. Recrystallization from ethanol afforded 10.1 g (68%) of **15**, mp 140-141°; ¹H nmr (dimethylsulfoxide-*d*₆): δ 7.81 (s, 1H, pyrazole), 7.37-6.60 (m, 4H, phenyl), 6.33 (s, 2H, NH₂), 5.00 (s, 2H, NH₂); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 151.8 (C-5), 144.5 (Ph C-2), 141.9 (C-3), 130.0 (Ph C-6), 127.6 (Ph C-4), 121.7 (Ph C-1), 116.6 (Ph C-3, C-5), 115.2 (CN), 72.6 (C-4); ms: (70 eV, electron impact) m/e 199 (molecular ion).

Anal. Calcd. for C₁₀H₇N₅: C, 60.29; H, 4.55; N, 35.16. Found: C, 60.60; H, 4.68; N, 35.16.

6(*H*)-Pyrazolo[2,3-*a*][1,3,5]benzotriazepine-3-carbonitrile (**16**).

A solution of 7.40 g (37.1 mmoles) of **15** in 70 ml of triethyl orthoformate was heated at reflux for 2 hours. The mixture (solid was present) was cooled and the yellow solid was collected and air-dried to yield 3.34 g (43%) of **16**, mp 240-241° (ethanol); ir (potassium bromide): 3300 (NH), 2230 (CN), 1630 cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 9.55 (d, J = 5 Hz, 1H, NH, collapses to a s with deuterium oxide), 7.81 (s, 1H, H at 2-position), 7.62-7.45 (m, 1H, H at 10 position), 7.15-6.73 (m, 2H, protons at 8- and 9-positions), 6.73-6.55 (m, 2H, protons at 5- and 7-positions, with d, J = 5 Hz, at 6.59 for H at 5-position which collapses to a singlet with deuterium oxide); ¹³C nmr (dimethylsulfoxide-*d*₆): δ 153.4 (C-3a), 150.0 (C-5), 143.3 (C-2), 131.7 (C-6a), 129.9 (C-10a), 128.6 (C-10), 124.6 (C-8), 121.5 (C-9), 120.0 (C-7), 113.2 (CN), 90.5 (C-3); ms: (70 eV, electron impact) m/e 209 (molecular ion).

Anal. Calcd. for C₁₁H₇N₅: C, 63.15; H, 3.37; N, 33.48. Found: C, 63.40; H, 3.40; N, 33.72.

Treatment of **15** with Triethyl Orthoacetate.

A mixture of 10.0 g (50.2 mmoles) of **15** and 80 ml of triethyl orthoacetate was heated at reflux. Solution resulted initially and a precipitate formed later. After 80 hours the mixture was concentrated to a smaller volume, cooled, and the solid was collected to give 6.40 g (57%) of 5-methyl-6*H*-pyrazolo[2,3-*a*][1,3,5]benzotriazepine-3-carbonitrile (**17**) as yellow needles, mp 248-249° (ethanol); ir (potassium bromide): 3315

(NH), 2225 (CN), 1650 cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 9.17 (s, 1H, NH), 7.88 (s, 1H, H at 2-position), 7.63-7.47 (m, 1H, H at 10-position), 7.20-6.73 (m, 3H, remaining aromatic), 1.99 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide- d_6): δ 161.1 (C-5), 152.4 (C-3a), 143.3 (C-2), 132.4 (C-6a), 129.7 (C-10a), 128.5 (C-10), 124.3 (C-8), 121.4 (C-9), 120.2 (C-7), 113.5 (CN), 89.4 (C-3), 24.6 (CH_3); ms: (70 eV, electron impact) m/e 223 (molecular ion).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3$: C, 64.56; H, 4.06; N, 31.38. Found: C, 64.50; H, 4.26; N, 31.33.

White crystals separated from the filtrate which were collected to yield 0.87 g (6%) of *N*-[2-(5-amino-4-cyano-1*H*-pyrazol-1-yl)phenyl]ethanimidic acid ethyl ester (**18**), mp 124° (benzene-hexane) (22); ir (potassium bromide): 3465, 3305 and 3180 (NH_2), 2215 (CN), 1660, 1625 cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 7.67 (s, 1H, pyrazole), 7.55-7.05 (m, 3H, protons at 4-, 5-, and 6-positions), 7.05-6.87 (m, 1H, H at 3-position), 4.04 (q, $J = 7$ Hz, 2H, CH_2), 1.73 (s, 3H, N = CCH_3), 1.13 (t, $J = 7$ Hz, 3H, CH_2CH_3); ^{13}C nmr (dimethylsulfoxide- d_6): δ 128.4 (Ph C-3), 161.8 (C-1), 152.0 (Pyr C-5), 145.4 (Ph C-1), 141.3 (Pyr C-3), 130.2 (Ph C-5), 128.8 (Ph C-2), 123.7 (Ph C-4), 122.4 (Ph C-6), 115.1 (CN), 72.1 (Pyr C-4), 61.3 (CH_2), 16.7 (C-2), 13.8 (CH_2CH_3); ms: (70 eV, electron impact) m/e 269 (molecular ion).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.17; H, 5.73; N, 26.12.

Treatment of **15** with Triethyl Orthopropionate.

A mixture of 10.0 g (50.2 mmoles) of **15** and 30 ml of triethyl orthopropionate was heated at reflux. Solution resulted quickly, but after 80 hours a precipitate was present. The mixture was cooled and the precipitate was collected and washed with ether to yield 5.40 g (45%) of 5-ethyl-6*H*-pyrazolo[2,3-*a*][1,3,5]benzotriazepine-3-carbonitrile (**19**), mp $222-223^\circ$ (ethanol); ir (potassium bromide): 3300 (NH), 2230 (CN), 1630 cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 9.04 (s, 1H, NH), 7.85 (s, 1H, H at 2-position), 7.65-7.45 (m, 1H, H at 10-position), 7.20-6.75 (m, 3H, remaining aromatic), 2.24 (q, $J = 7.5$ Hz, 2H, CH_2), 1.09 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide- d_6): δ 165.4 (C-5), 152.5 (C-3a), 143.3 (C-2), 132.8 (C-6a), 129.8 (C-10a), 124.3 (C-8), 121.4 (C-9), 120.3 (C-7), 113.4 (CN), 89.5 (C-3), 30.4 (CH_2), 11.0 (CH_3); ms: (70 eV, electron impact) m/e 237 (molecular ion).

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.60; H, 4.76; N, 29.80.

The filtrate, upon standing for two days, deposited white prisms which were collected and washed with ether to yield 1.95 g (11%) of *N*-[4-cyano-1-(2-(1-ethoxy-1-propylidene)amino)phenyl]-1*H*-pyrazol-5-yl]propanimidic acid ethyl ester (**20**), mp $86-87^\circ$; ir (potassium bromide): 2220 (CN), 1645 cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 7.99 (s, 1H, pyrazole), 7.52-7.00 (m, 3H, protons meta and para to pyrazole), 7.00-6.80 (m, 1H, H *ortho* to pyrazole), 4.25-3.82 (m, 4H, both OCH_2 groups), 2.45-1.97 (m, 4H, both N = CCH_2 groups), 1.22-0.88 (m, 12H, four CH_3 groups); ^{13}C nmr (dimethylsulfoxide- d_6): δ 170.2 (C-1), 164.6 (N = C at Ph C-2), 151.7 (Pyr C-5), 145.6 (Ph C-2), 141.2 (Pyr C-3), 130.4 (Ph C-4), 128.7 (Ph C-1), 128.0 (Ph C-6), 122.9 (Ph C-5), 122.3 (Ph C-3), 114.0 (CN), 81.0 (Pyr C-4), 63.0 (OCH_2), 61.0 (OCH_2), 24.4 (CCH_2CH_3), 23.6 (CCH_2CH_3), 13.8 (OCH_2CH_3), 13.4 (OCH_2CH_3), 10.3 (CCH_2CH_3), 9.9 (CCH_2CH_3); ms: (70 eV, electron impact) m/e 367 (molecular ion).

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.60; H, 6.97; N, 19.16.

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- (22) Schiff base **18** apparently cyclizes to pyrazolobenzotriazepine **17** upon heating. A sample of **18**, after melting at 124° in the melting point apparatus, was heated to 210° (bubbling was noticed). After cooling, the sample remelted at 248° .