# Reactions with 5-Aminopyrazoles. I. Synthesis of Halogen-Containing Fused Pyrazoles



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5-Amino-3-phenylpyrazole (I) and 5-amino-4-bromo-3-phenylpyrazole (II) reacted with ethyl acetoacetate and acetylacetone to give various pyrazolo[1,5-*a*]pyrimidines IV-VI and with benzoins to give different fused pyrazoles, namely, imidazo[1,2-*b*]pyrazoles IX, pyrrolo[2,3-*c*]pyrazoles X and pyrazolo[4,3-*b*][1,4]oxazines XII. Diazotized II was coupled with active methylene-containing nitriles to afford pyrazolo[5,1-*c*]-*as*-triazines XIV.

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In view of the considerable biological and medicinal activities of pyrazolopyrimidines [1,2], pyrazolotriazines [3] and of many fused pyrazoles it was thought of interest to synthesize some halogen-containing fused pyrazoles. For this purpose we started with 5-amino-4-bromo-3-phenylpyrazole (II) [4] prepared by the bromination of 5-amino-3-phenylpyrazole (I).

Products of condensation of aminopyrazoles with ethyl acetoacetate at the carbonyl or the carboxyl group have already been synthesized [5]. Condensation of II with ethyl acetoacetate in refluxing ethanol afforded the 5-acylamino derivative III whose structure was supported by: (a) it gave deep colour with ferric chloride, (b) its ir spectrum displayed a broad band at 3350-3000 $cm^{-1}$ (chelated NH and OH) and at 1640 (CO).

Cyclization of III by polyphosphoric acid gave the expected pyrazolo[1,5-*a*]pyrimidine IV which showed bands at 3420 $cm^{-1}$ (NH) and 1670 (CO) in its ir spectrum.

On the other hand and in accord with the findings of Dorn and Zubek [6,7], compound II condensed with ethyl acetoacetate in acetic acid at 100° to yield the isomeric pyrazolo[1,5-*a*]pyrimidine V which has a 4-pyridone structure.

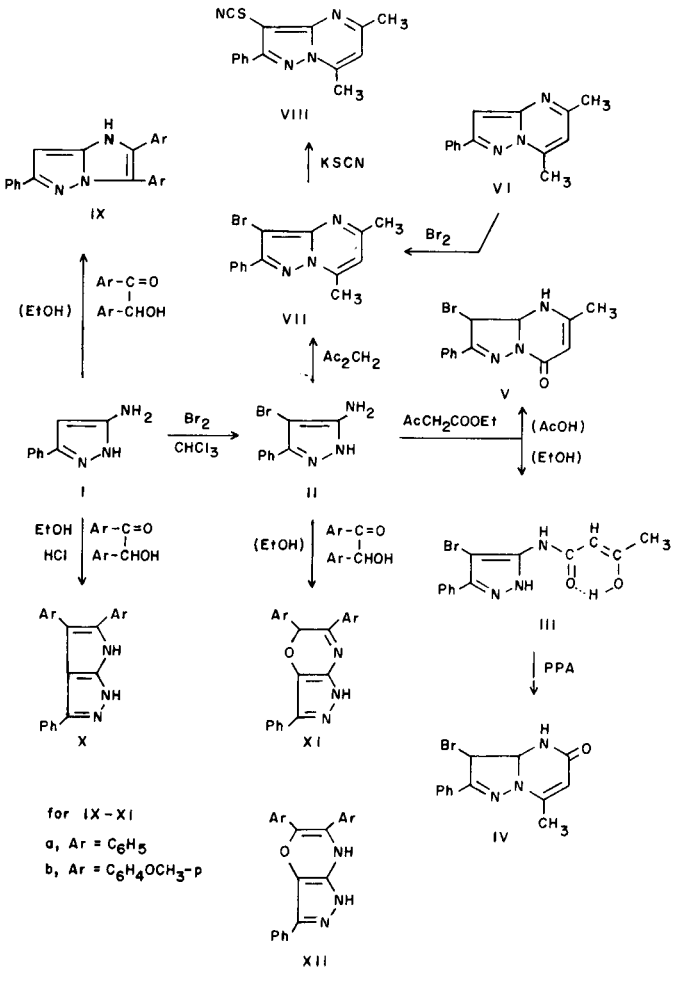
Compound II condensed also with acetylacetone to give the 3-bromopyrazolo[1,5-*a*]pyrimidine (VII). Formulation of VII was based on elemental analysis and pmr data. Furthermore, VII was obtained by the bromination of the pyrazolo[1,5-*a*]pyrimidine VI [8] with bromine in chloroform or with *N*-bromosuccinimide in carbon tetrachloride.

To explore the synthetic potentiality of VII for the synthesis of other 3-subsituted pyrazolo[1,5-*a*]pyrimidines, it was converted to the 3-thiocyanate derivative VIII by the reaction with potassium thiocyanate. The presence of the SCN group in VIII was indicated by the appearance of a peak at 2160 $cm^{-1}$ in its ir spectrum.

The reaction of I with benzoins in refluxing ethanol gave the imidazo[1,2-*b*]pyrazoles IXa,b. The ir spectrum of IXa exhibited bands at 3400 $cm^{-1}$ (NH), 1670, 1595 (C=C and C=N). Its pmr spectrum showed a signal for the pyrazole proton at $\delta$ 5.9 ppm.

On the other hand, I reacted wtih benzoins in ethanol-hydrochloric acid to afford the hydrochloride salts of pyrrolo[2,3-*c*]pyrazoles Xa,b. This structure was proved by the absence of a signal at $\delta$ 5-7.3 ppm characteristic of the pyrazole C-4 proton [9] in the pmr spectrum of Xa. The ir spectrum of Xa exhibited bands at 3400 $cm^{-1}$ (NH), 2300-2700 ($NH_2^+$), 1640, 1600 (C=C and C=N).

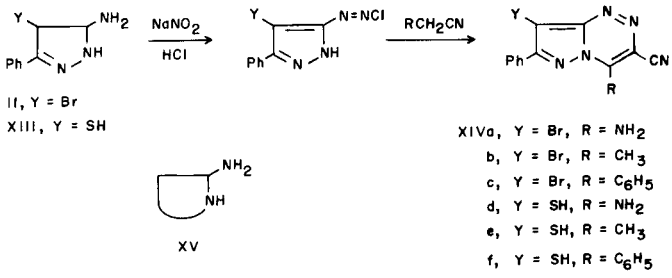
Chart 1



To synthesize the desired bromoimidazo[1,2-*b*]pyrazole the reaction of II with benzoins was undertaken. However, bromine-free products were obtained and these were formulated as the pyrazolo[4,3-*b*][1,4]oxazines XIIa,b, rather than XIa,b, due to the absence of the oxazine CH proton in the pmr spectra of these products which show no resonance in the high field region down to 7 ppm. The ir spectrum of XIIa exhibited absorption bands at 3330 $cm^{-1}$ (NH) and 1660, 1590 (C=C and C=N).

Synthesis of pyrazolo[5,1-*c*]-*as*-triazines was achieved by diazotization of II and of 5-amino-4-mercapto-3-phenylpyrazole (XIII), prepared by the action of sodium sulfide on II, and coupling of the diazotized compounds with active methylene-containing reagents (*cf.* Chart 2). Thus, diazotized II reacted with malononitrile, 3-iminobutyronitrile and benzoylacetonitrile to give the corresponding pyrazolo[5,1-*c*]-*as*-triazine derivatives XIVa-c, respectively.

Chart 2




Similarly, diazotized XIII reacted with the same nitriles to give XIVd-f. The ir spectra of compounds XIV clearly revealed the presence of the cyano group.

This method of synthesis was recently shown [10] to be of common use in the annellation of a triazine ring to heterocycles of the type XV. The synthesis of compounds of the type XIV by first converting diazotized 5-aminopyrazoles to the hydrazonyl chlorides and then reacting with the proper reagents is also noteworthy [11].

Compounds XIVd-f could be also prepared by the reaction of the corresponding 3-bromo derivatives XIVa-c with sodium sulfide in dimethylformamide.

## EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded (potassium bromide) with a Pye-Unicam SP 1000 spectrophotometer. The pmr spectra were taken in deuteriochloroform with a Varian 90 MHz EM 390 nmr spectrometer using TMS as internal standard.

5-Acetoacetamido-4-bromo-3-phenylpyrazole (III).

A solution of II [4] (0.01 mole) and ethyl acetoacetate (0.01 mole) in absolute ethanol (25 ml) was refluxed for 3 hours. The solid obtained after cooling was filtered off and crystallized from ethanol to give III, mp 135°, yield 72%; ir: 3000-3350 $cm^{-1}$ (chelated NH and OH), 1640 (CO), 1600 (C=N).

*Anal.* Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.5; H, 3.8; N, 13.0; Br, 24.8. Found: C, 48.3; H, 3.6; N, 12.9; Br, 24.7.

3-Bromo-7-methyl-2-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidin-5-one (IV).

A mixture of 1 g of III and 5 g of polyphosphoric acid was heated at 140-150° for 3 hours, cooled and poured on cold water. The resulting grey solid was filtered off, washed with water and crystallized from dimethylformamide to give IV, mp 269°, yield 68%; ir: 3420 $cm^{-1}$ (NH), 1670 (amide CO), 1630 and 1600 (C=C and C=N).

*Anal.* Calcd. for $C_{13}H_{10}BrN_3O$: C, 51.3; H, 3.3; N, 13.8; Br, 26.3. Found: C, 51.0; H, 3.4; N, 13.6; Br, 26.6.

3-Bromo-5-methyl-2-phenyl-4*H*,7*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (V).

A mixture of 1.2 g (5 mmoles) of II, 0.78 g (6 mmoles) of ethyl acetoacetate in 7 ml of glacial acetic acid was heated on the steam bath for 30 minutes. The white solid which separated hot was filtered off and recrystallized from acetic acid to give V, mp 286°, yield 75%; ir: 3430 $cm^{-1}$ (NH), 1665 (amide CO), 1620 and 1590 (C=C and C=N).

*Anal.* Calcd. for $C_{13}H_{10}BrN_3O$: C, 51.3; H, 3.3; N, 13.8; Br, 26.3. Found: C, 51.5; H, 3.4; N, 13.6; Br, 26.1.

3-Bromo-5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (VII).

Method A.

A solution of 3 mmoles of II and 3 mmoles of acetylacetone in 20 ml of absolute ethanol was refluxed for 3 hours and cooled. The solid that separated was collected and crystallized from ethanol to give VII, mp 180°, yield 78%; pmr: δ 2.6 ppm (s, $CH_3$, 3H), 2.8 (s, $CH_3$, 3H), 6.8 (s, H-6, 1H), 7.2-8.2 (m, aromatic, 5H).

*Anal.* Calcd. for $C_{14}H_{12}BrN_3$: C, 55.7; H, 4.0; N, 13.9; Br, 26.4. Found: C, 55.9; H, 4.1; N, 13.7; Br, 26.2.

Method B.

To a stirred suspension of 0.01 mole of VI [8] in 30 ml of chloroform was added dropwise 0.011 mole of bromine in 30 ml of chloroform. Stirring was continued for 15 minutes and the solid product was filtered off and identified as VII (mp and mixed mp), yield 87%.

Method C.

To a suspension of 0.01 mole of VI in 40 ml of carbon tetrachloride was added 0.011 mole of *N*-bromosuccinimide. The reaction mixture was heated to 50° and kept at this temperature for 15 minutes and was then filtered. To the filtrate was added petroleum ether (40-60°) and the solid product was filtered off and identified as VII.

5,7-Dimethyl-2-phenyl-3-thiocyanatopyrazolo[1,5-*a*]pyrimidine (VIII).

To a solution of 0.01 mole of VII in 50 ml of ethanol was added a solution of 0.01 mole of potassium thiocyanate in 5 ml of water. The reaction mixture was refluxed for 5 hours, concentrated and cooled. The solid obtained was filtered off and recrystallized from ethanol to give VIII, mp 160°, yield 82%; ir: 2160 $cm^{-1}$ (SCN), 1620 and 1590 (C=C and C=N).

*Anal.* Calcd. for $C_{15}H_{12}N_4S$: C, 64.3; H, 4.3; N, 20.0; S, 11.4. Found: C, 64.6; H, 4.1; N, 19.7; S, 11.4.

2,3-Diaryl-6-phenyl-1*H*-imidazo[1,2-*b*]pyrazoles (IXa,b).

A solution of 3 mmoles of I and 3 mmoles of benzoin or anisoin in 20 ml of absolute ethanol was refluxed for 5 hours, cooled and then poured on water. The solid obtained was filtered off and recrystallized from aqueous ethanol.

Compound IXa had mp 136°, yield 61%; ir: 3400 $cm^{-1}$ (NH), 1670, 1595 (C=C and C=N); pmr: δ 4.45 (broad s, NH, 1H), 5.9 (s, H-7, 1H), 7.25-7.9 (m, aromatic, 15H).

*Anal.* Calcd. for $C_{23}H_{17}N_3$: C, 82.4; H, 5.1; N, 12.5. Found: C, 82.7; H, 4.9; N, 12.4.

Compound IXb had mp 109°, yield 64%; ir: 3420 $cm^{-1}$ (NH), 1645, 1595 (C=C and C=N).

*Anal.* Calcd. for $C_{25}H_{21}N_3O_2$: C, 75.9; H, 5.4; N, 10.6. Found: C, 76.2; H, 5.2; N, 10.5.

4,5-Diaryl-3-phenyl-1*H*,6*H*-pyrrolo[2,3-*c*]pyrazoles (Xa,b).

A mixture of 5 mmoles of I, 5 mmoles of benzoin or anisoin, 20 ml of ethanol and 10 ml of concentrated hydrochloric acid was refluxed for 5 hours. The white solid that separated hot was filtered off and crystallized from ethanol to give the hydrochloride of Xa,b.

Compound Xa had mp 163°, yield 59%; ir: 3400 $cm^{-1}$ (NH), 1630, 1600 (C=C and C=N); pmr (DMSO-$d_6$): 6.4 ppm (broad s, NH, 1H), 7.3-8.0 (m, 16H, aromatic and NH).

*Anal.* Calcd. for $C_{23}H_{18}ClN_3$: C, 74.3; H, 4.9; N, 11.3. Found: C, 74.7; H, 5.0; N, 11.2.

Compound Xb had mp 159°, yield 60%; ir: 3380 $cm^{-1}$ (NH), 1610 and 1600 (C=C and C=N).

*Anal.* Calcd. for $C_{25}H_{22}ClN_3O_2$: C, 69.5; H, 5.1; N, 9.7. Found: C, 69.8; H, 5.3; N, 9.7.

5,6-Diaryl-3-phenyl-1*H*,7*H*-pyrazolo[4,3-*b*][1,4]oxazines (XIIa,b).

A solution of 3 mmoles of II and 3 mmoles of benzoin or anisoin in 20 ml of absolute ethanol was refluxed for 5 hours, cooled and then poured on water. The solid obtained was collected and recrystallized from aqueous ethanol.

Compound XIIa was obtained as beige crystals, mp 100°, yield 60%, ir: 3320 $cm^{-1}$ (NH), 1670, 1590 (C=C, C=N); pmr: $\delta$ 8.3 ppm (broad s, NH, 2H), 7.3-7.9 (m, aromatic, 15H).

*Anal.* Calcd. for $C_{23}H_{17}N_3O$: C, 78.6; H, 4.9; N, 12.0. Found: C, 78.9; H, 5.0; N, 11.8.

Compound XIIb was obtained as yellow needles, mp 128°, yield 62%; ir: 3380 $cm^{-1}$ (NH), 1645, 1590 (C=C and C=N).

*Anal.* Calcd. for $C_{25}H_{21}N_3O_3$: C, 73.0; H, 5.1; N, 10.2. Found: C, 72.7; H, 4.9; N, 10.1.

5-Amino-4-mercapto-3-phenylpyrazole (XIII).

Sodium sulfide (60 g, 0.25 mole) were dissolved in 200 ml of dimethylformamide by gentle warming and 23.8 g (0.1 mole) of II were added gradually while stirring. The reaction mixture was allowed to stand in a boiling water bath for 5 hours, then left overnight. After filtering the inorganic residue, solvent was removed under reduced pressure to give a semi solid product (12 g, 63%) which was used as such in diazotization without further purification.

Diazotization of the Aminopyrazoles II and XIII.

A suspension of II or XIII (0.1 mole) in ethanol (100 ml) was treated with concentrated hydrochloric acid (30 ml). The mixture was heated to get a clear solution and was then cooled to 0°. A solution of sodium nitrite (7 g, 0.1 mole) in 40 ml of water was added portionwise with stirring. The reaction mixture was allowed to stand in the ice bath for 10 minutes after which this diazonium salt solution was used for coupling with active methylene-containing reagents.

4-Substituted-8-bromo-3-cyano-7-phenylpyrazolo[5,1-*c*]-*as*-triazines (XIVa-c). General Procedure.

To a cooled solution of 0.1 mole of malononitrile, 3-iminobutyronitrile or benzoylacetonitrile in 100 ml of ethanol was added a solution of 7 g of sodium acetate in 20 ml of water followed by a solution of diazotized II (prepared from 0.1 mole of II as above). The resulting mixture was stirred at room temperature for 30 minutes. The solid obtained was filtered off, washed with water, dried and recrystallized to give XIVa-c, respectively.

Compound XIVa had mp 273° (dioxane), yield 85%; ir: 3445, 3350 $cm^{-1}$ ($NH_2$), 2240 (CN), 1660 ($\delta$ $NH_2$).

*Anal.* Calcd. for $C_{12}H_7BrN_6$: C, 45.7; H, 2.2; N, 26.7; Br, 25.3. Found: C, 45.5; H, 2.4; N, 26.4; Br, 25.1.

Compound XIVb had mp 182° (ethanol), yield 76%; ir: 2210 $cm^{-1}$ (CN).

*Anal.* Calcd. for $C_{13}H_8BrN_5$: C, 49.7; H, 2.6; N, 22.3; Br, 25.4. Found: C, 49.4; H, 2.8; N, 22.0; Br, 25.1.

Compound XIVc had mp 245° (ethanol), yield 80%; ir: 2250 $cm^{-1}$ (CN).

*Anal.* Calcd. for $C_{18}H_{10}BrN_5$: C, 57.5; H, 2.7; N, 18.6; Br, 21.2. Found: C, 57.2; H, 2.5; N, 18.9; Br, 21.1.

4-Substituted-3-cyano-8-mercapto-7-phenylpyrazolo[5,1-*c*]-*as*-triazines (XIVd-f).

Proceeding similarly as for XIVa-c, malononitrile, 3-iminobutyronitrile or benzoylacetonitrile were coupled with diazotized XIII to give XIVd-f, respectively.

Compound XIVd had mp 312° (ethanol), yield 68%; ir: 3450, 3350 $cm^{-1}$ ($NH_2$), 2240 (CN), 1650 ($\delta$ $NH_2$).

*Anal.* Calcd. for $C_{12}H_8N_6S$: C, 53.7; H, 3.0; N, 31.3; S, 12.0. Found: C, 53.5; H, 2.8; N, 31.1; S, 11.6.

Compound XIVe had mp 185° (methanol), yield 78%; ir: 2250 $cm^{-1}$ (CN).

*Anal.* Calcd. for $C_{13}H_9N_5S$: C, 58.4; H, 3.4; N, 26.2; S, 12.0. Found: C, 58.2; H, 3.5; N, 26.1; S, 11.7.

Compound XIVf had mp 233° (ethanol), yield 88%; ir: 2245 $cm^{-1}$ (CN).

*Anal.* Calcd. for $C_{18}H_{11}N_5S$: C, 65.6; H, 3.4; N, 21.3; S, 9.7. Found: C, 65.9; H, 3.2; N, 21.0; S, 9.5.

Formation of the pyrazolo[5,1-*c*]-*as*-triazines XIVd-f from XIVa-c and Sodium Sulfide.

Compounds XIVa-c (0.01 mole) were placed in 50 ml of dimethylformamide containing 6.5 g of sodium sulfide. The mixture was heated on a water bath for 5 hours and was then filtered from the solid inorganic material while hot. The solvent was removed from the filtrate under reduced pressure and the residue was crystallized to give products identified as XIVd-f (mp and mixed mp).

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