Reactions with Heterocyclic Amidines VIII. Synthesis of some New Imidazo[1,2-*b*]pyrazole Derivatives

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The reaction of benzoylacetonitrile (III), its phenylazo derivative (X), malononitrile and malononitrile derivatives with ethyl hydrazinoacetate was investigated. All the investigated compounds with the exception of phenylazobenzoylacetonitrile and phenylazomalononitrile afforded 1-ethoxycarbonylmethyl-3-aminopyrazole derivatives when treated with I. Compounds Xa and XVIII afforded imidazoypyrazole derivatives under the same experimental conditions.

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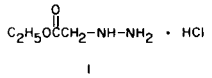
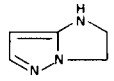
The interesting biological and medicinal activities of fused pyrazoles have initiated much recent research on the synthesis and chemistry of this class of compounds (1,4). In previous work from this laboratory we have described the scope and limitations of a new synthesis of pyrazolo[1,5-*a*]pyrimidines *via* the reaction of β-cyanoethylhydrazine with β-functional-nitriles (6-10). In conjunction with our work directed for the development of a new simple and efficient procedures for the synthesis of fused pyrazoles we have investigated possible utility of the reaction of ethyl hydrazinoacetate hydrochloride (I) with β-functional reagents for the synthesis of imidazo[1,2-*b*]-pyrazoles (II). To our knowledge the only reported synthesis of derivatives of this ring system has been described recently by Elguero, *et al* (11) *via* reaction of benzoylaceto-

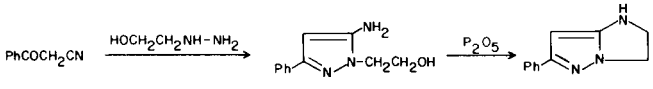


I



II

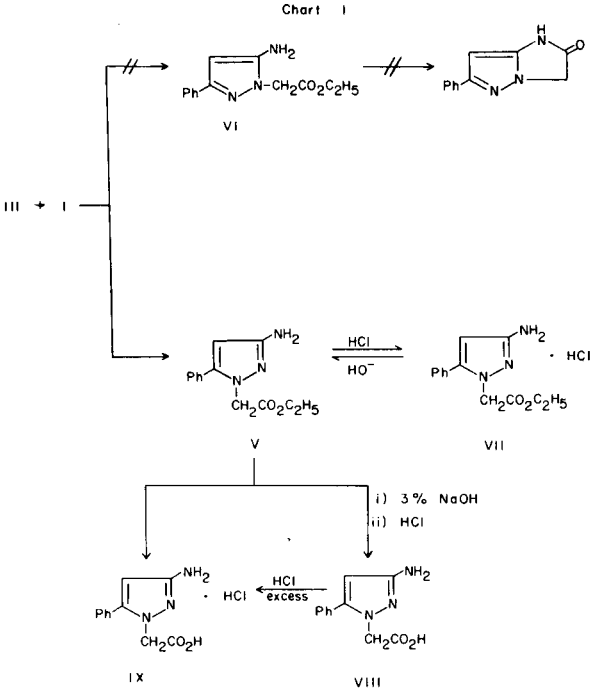
nitrile (III) with β-hydroxyethylhydrazine to yield 5-amino-1-β-hydroxyethyl-3-phenylpyrazole (IV) and subsequent cyclization of the latter (*cf.* Chart 1).



III IV

It has been found that III reacts with I in refluxing ethanol to yield a product for which structures V and isomeric VI seemed possible. Structure V was considered most likely for the reaction product based on its chemical bahaviour. Thus, whereas VI is expected to cyclize readily on reflux with acetic acid or heating above its melting point into the imidazo[1,2-*b*]pyrazole derivative (*cf.* Chart 1), the reaction product of I and III was recovered almost unaffected after treatment under both conditions.

Chart 1



Attempted cyclization by the action of concentrated hydrochloric acid afforded only the hydrochloride VII. Compound VII was reconverted into V on basefication. On the other hand, attempted cyclization of V by the action of 5% sodium hydroxide utilising our previously described procedure for the conversion of 5-amino-1-β-ethoxycarbonylethylpyrazoles into the corresponding pyrazolo-[1,5-*a*]pyrimidin-5-ones has resulted in the formation of the acid VIII (6). The acid VIII has afforded the hydrochloride IX on treatment with concentrated hydrochloric acid.

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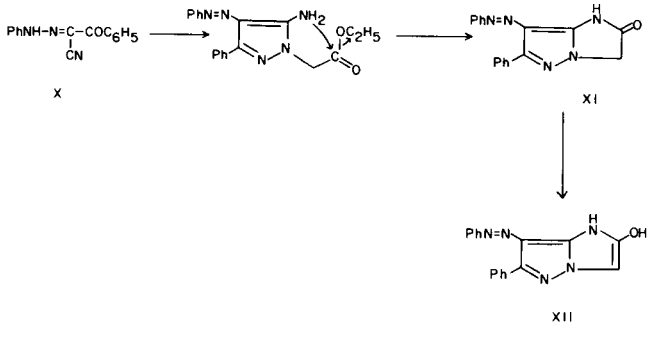
Attempts to synthesize either IV or V *via* the action of ethyl chloroacetone on 5-amino-3-phenylpyrazole were unsuccessful. Under a variety of alkylation conditions, 5-amino-3-phenylpyrazole was recovered almost unaffected.

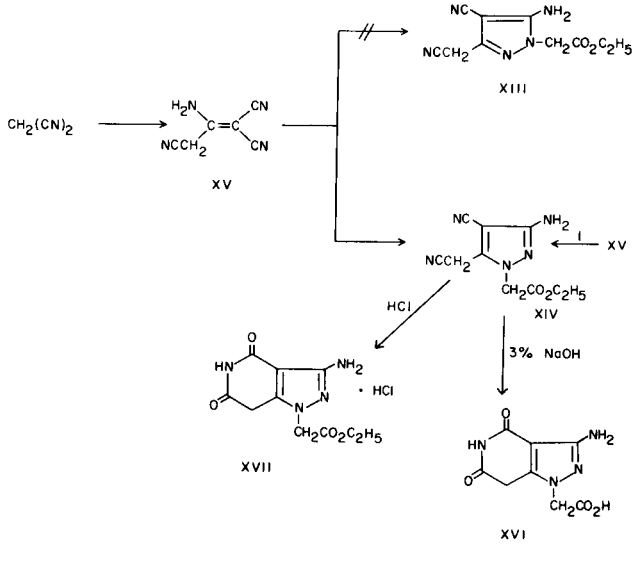
In contrast to the bahaviour of III, the arylhydrazono derivatives of 2,3-dioxo-3-phenylpyropionitrile (X) reacted with I to yield the imidazo[1,2-*b*]pyrazole derivatives which can be formulated as XI or XII. Structure XII was considered most likely for these products based on the ir spectral data for the reaction products which revealed the absence of CO stretching absorption for amide CO group and revealed a broad band extending from 2500 to 3300 cm^{-1} for OH dimer (12). The formation XI in this reaction may be assumed to proceed *via* the sequence demonstrated in Chart II. However, attempts to isolate intermediates for this reaction were unsuccessful.

In contrast to the behaviour of III and X, compound I reacted with malononitrile to afford a product for which structures XIII or XIV seemed possible based on

Chart II

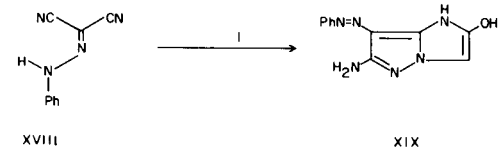


analytical and spectral data. Structure XIV was considered most likely for this product based on its chemical behaviour (see later). The formation of this product might be assumed to proceed *via* reaction with malononitrile dimer (XV) which exists in equilibrium with malononitrile. In support of this view we have found that XV reacts with I to yield XIV in excellent yield. Attempted cyclization of XIV by the action of 3% sodium hydroxide has afforded the carboxyl acid derivative XVI. On the other hand the hydrochloride XVII was obtained on attempted cyclization of XIV by the action of concentrated hydrochloric acid.



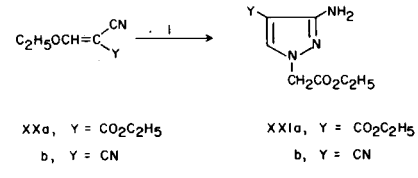
The formation of products resulting from reaction with malononitrile dimer is similar to the previously reported behaviour of malononitrile with hydrazines.

Similar to the behaviour of X, phenylhydrazono-



mesoxalonitrile (XVIII) reacted with I to yield the imidazo[1,2-*b*]pyrazole derivative XIX.

The behaviour of the ethoxymethylene derivatives of cyanoacylic acid (XXa,b) has also been investigated. It has been found that XXa,b reacts with I to yield the aminopyrazole derivatives XXIa,b.



It is well established that the keto function in III and in Xa-c is the most electrophilic center in these molecules. Also the vinyl ether moiety in IXa,b has been shown to be the most electrophilic reaction center. Since the substituted nitrogen atom in I might be considered a better nucleophilic in the reactions under consideration, the formation of V, XXa,b might be expected. However, these results are in contrast to previous findings that β-cyanoethylhydrazine reacts with the same reagents to yield products resulting from initial attack by the unsubstituted nitrogen atom (5-7). These results may indicate the existance of a delicate plance between steric considerations and the relative reactivity in the reaction between substituted hydrazines and β-functional reagents. In the reaction of ethyl hydrazinoacetate with β-functional reagents the reaction affords products resulting from electrophilic attack by the more basic nitrogen whereas in the reaction of β-cyanoethylhydrazine with the same reagents the reaction is totally dependent on steric considerations.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were obtained in potassium bromide on a Pye-Unicum SP 1000 spectrophotometer. ^{1}H Nmr spectra were obtained in DMSO-d_6 with a Varian A-60 spectrometer with TMS as the internal standard and chemical shifts are expressed as δ ppm. Analytical data were performed by the analytical data unit at Cairo University.

Ethyl Hydrazinoacetate (I).

This reagent was prepared after the procedure described by Carni, *et al.* (13). The reagent obtained by this method had m.p. 150-152° (Literature 150-152°). It also gave correct analytical and spectral data.

3-Amino-1-ethoxycarbonylmethyl-5-phenylpyrazole (V).

To a suspension of ethyl hydrazinoacetate hydrochloride (3 g., 0.02 mole) in ethanol (30 ml.), benzoylacetonitrile (2.9 g.) was added, then neutralized with sodium carbonate (1.06 g., 0.02 mole in 5 ml. of water). The reaction mixture was refluxed for 3 hours, then cooled and poured into ice cold water (50 ml.). The solid product, so obtained was collected by filtration and crystallised from an ethanol-water mixture.

Compound V formed colorless crystals m.p. 112°, yield 70%; ir: 3440, 3340, 3240, cm^{-1} (NH); 2910, 2960, 3000 cm^{-1} (CH_2 and CH_3); 1740 cm^{-1} (COOEt) 1640 cm^{-1}; (NH_2); ^{1}H nmr: δ 1.16 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 4.66 (s, 2H, CH_2-H), 5.16 (br, 2H, disappears after deuterium oxide exchange, NH_2), 5.60 (s, 1H, pyrazole C-4 proton); 7.16 ~ 7.60 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.7; H, 6.1; N, 17.1. Found: C, 64.0; H, 6.1; N, 17.3.

The hydrochloric of V (VII) was prepared by dissolving V (1.0 g.) in concentrates hydrochloric acid (5 ml., 35.5%). The mixture was boiled for ten minutes, then cooled. The solid product, so formed, was collected by filtration and crystallised from water. The hydrochloric VII formed colourless crystals, m.p. 224°, yield 90%; ir: 3430, 3320, 3230 cm^{-1}, (NH_2); 2500 ~ 3000 cm^{-1} (NH); 1745 cm^{-1} (ester CO) and 1650 (NH_2).

Anal. Calcd. for $C_{13}H_{16}ClO_2N_3$: C, 55.6; H, 5.7. Found: C, 55.3. H, 5.5.

3-Amino-1-carboxymethyl-5-phenylpyrazole (VIII).

A suspension of V (1.0 g.) in aqueous sodium hydroxide solution (5 ml., 5%) was refluxed for ten minutes. The reaction mixture was then cooled and neutralised by the addition of concentrated hydrochloric acid. The solid product, so formed was collected by filtration and crystallised from water.

Compound VIII formed colourless crystals, m.p. 187°; yield 80%; ir: 3420, 3320 and 3220 cm^{-1} (NH_2), 2400-3000 cm^{-1} (OH dimer) 1725 (carboxylic CO) and 1650 cm^{-1}; ^{1}H-nmr: δ 4.60 (s, 2H, CH_2-N), 5.16 (s, 1H, pyrazole C-5 proton); 6.66 (br, 3H, NH_2 and OH protons) and 7.16 ~ 7.60 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.8; H, 5.1. Found: C, 60.5; H, 5.5.

The hydrochloride (IX) was obtained on treatment of VIII with concentrated hydrochloric acid as has been described above for the preparation of VII. The resulting solid product was collected by filtration and crystallised from water. Compound IX formed colourless crystals, m.p. 142°, yield 70%, ir: broad band 3420-3340, 3200 (NH vibrations), 2400, 3000 cm^{-1} (OH dimer); 1725 (carboxyl CO) and 1650 cm^{-1} (NH_2).

Anal. Calcd. for $C_{11}H_{12}ClO_2N_3$: C, 52.2; H, 4.9. Found: C, 51.8; H, 4.7.

5-Hydroxy-2-phenyl-3-phenylazoimidazo[1,2-*b*]pyrazole (XI).

A suspension of I (3.0 g., 0.02 mole) in ethanol (50 ml.) was neutralised with sodium hydroxide (0.85 g. in 5 ml. water) and treated with X (3.0 g.). The reaction mixture was refluxed for two hours. The solid product, formed on cooling, was collected by filtration, washed several times with water and crystallised from ethanol. Compound XI formed yellow crystals, m.p. 187°, yield 50%; nmr: 3470-3400 (chelated NH); 2500, 2900 cm^{-1} (OH dimer) and 1630 cm^{-1} (N=N); ^{1}H-nmr: δ 3.36 (s, 1H, CH), 6.90-8.05 (br, 10H, $2C_6H_5$).

Anal. Calcd. for $C_{17}H_{13}ON_5$: C, 67.3; H, 4.3; N, 23.1. Found: C, 67.7; H, 4.7; N, 23.5.

3-Amino-4-cyano-5-cyanomethyl-1-ethoxycarbonylmethylpyrazole (XIV).

A suspension of I (3.0 g., 0.02 mole) in ethanol (30 ml.) was treated with malononitrile (2.4 g., 0.04 mole); then with 5 ml. of sodium carbonate solution (3.5 *N*). The reaction mixture was refluxed for three hours and evaporated *in vacuo*. The remaining product was triturated with water and collected by filtration and crystallised from water.

Compound XIV formed colourless crystals, m.p. 172°, yield 50%; ir: 3450, 3360, 3270, 3220 (NH); 3010, 2950, 2920, (CH_2 and CH_3); 2270 cm^{-1} (unconjugated CN) 2220 cm^{-1} (conjugated CN) 1745 ester CO and 1650 cm^{-1} (NH_2).

Anal. Calcd. for $C_{10}H_{11}O_2N_5$: C, 51.5; H, 4.7; N, 30.0. Found: C, 51.3; H, 4.8; N, 30.4.

Compound XIV was also obtained in 70%, yield by refluxing equimolecular amount of neutralised I and XV for one hour.

The hydrochloride XVII was obtained from XIV on treatment with concentrated hydrochloric acid.

Compound XVII formed brown crystals m.p. 285°; yield 60%; ir: 3490, 3360 cm^{-1} (NH), 2400-2800 cm^{-1} (OH dimer), broad band 1740, 1630 (CO and NH_2).

Anal. Calcd. for $C_{10}H_{13}ClN_4O_4$: C, 41.7; H, 4.5. Found: C, 42.0; H, 4.2.

3-Amino-1-carboxymethyl-4,5,6,7-tetrahydro-4,6-dioxopyrazolo[4,3-*c*]-pyridine (XVI).

Compound XVI was formed in 60% yield when XIV was treated with 5% sodium hydroxide solution utilising the experimental procedure described above for the conversion of V into VIII.

Compound XVI formed brown crystals, m.p. 280°; ir: 3490, 3385, 3270 and 3200 cm^{-1} (NH), 2980 cm^{-1} (CH_2), 2400-2750 (OH dimer), 1740, 1710, 1690 (CO groups) and 1635 (NH_2).

Anal. Calcd. for $C_8H_8O_4N_4$: C, 42.8; H, 3.6. Found: C, 42.5; H, 4.0.

2-Amino-5-hydroxy-3-phenylazoimidazo[1,2-*b*]pyrazole (XIX).

To a suspension of I (3.0 g., 0.02 mole) in ethanol (50 ml.) 0.02 mole of XVIII was added. The reaction mixture was then neutralised by addition of 1.06 g. of sodium carbonate dissolved in the least amount of water (~ 5 ml.). The mixture was refluxed for three hours and solid product formed during refluxing was collected by filtration and crystallised from ethanol.

Compound XIX formed red crystals, m.p. 285°, yield 50%; ir: 3500, 3100 cm^{-1} (NH and OH) and 1640, 1620 cm^{-1} NH_2 and N=N).

Anal. Calcd. for $C_{11}H_{10}ON_6$: C, 54.6; H, 4.2; N, 34.7. Found: C, 54.5; H, 4.0; N, 34.5.

3-Amino-1-ethoxycarbonylmethyl-4-substituted Pyrazoles (XXa,b).

A suspension of I (3.0 g., 0.02 mole) in ethanol (50 ml.) was treated with 0.02 mole of either of XXa,b then neutralised with 1.06 g. of sodium carbonate. The reaction mixture was refluxed for three hours then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid was collected by filtration and crystallised from water.

Compound XXIa formed orange crystals, 162°, yield 50%; ir: 3480, 3450, 3349, 3250 (NH), 3000, 2960, 2920 cm^{-1} (CH_2 and CH_3), 1750 cm^{-1} (ethoxycarbonylmethyl CO), 1710 (C-4 ester CO) and 1640 (NH_2); ^{1}H-nmr: δ 1.1 and 1.3 (2t, 6H, $2CH_3$); 4.16 (octet, 4H, $2CH_2$), 4.73 (s, 2H, CH_2-N), 6.30 (s, br, 2H, disappears after deuterium oxide exchange, NH_2) and 7.6 (s, 1H, C-4 proton).

Anal. Calcd. for $C_{10}H_{15}O_4N_3$: C, 49.8; H, 6.2; N, 17.4. Found: C, 49.5; H, 6.3; N, 17.8.

Compound XXIb formed colourless crystals, m.p. 101°, yield 50%; ir: 3500, 3380, 3100 cm^{-1} (NH) 2220 (conjugated CN), 1745 (ester CO), 1675 (NH_2); ^{1}H-nmr: δ 1.1 (t, 3H, CH_3), 4.16 (q, 2H, CH_2); 4.66 (s, 2H, CH_2-N), 6.66 (2H, disappears after deuterium oxide exchange, NH_2) and 7.50 (s, 1H, pyrazole C-5 proton).

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.5; H, 5.2. Found: C, 49.9; H, 5.5.

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