SYNTHESIS OF SOME NEW PYRAZOLO[1,5-*a*]PYRIMIDINE AND PYRAZOLO[1,5-*c*]-*as*-TRIAZINE DERIVATIVES*

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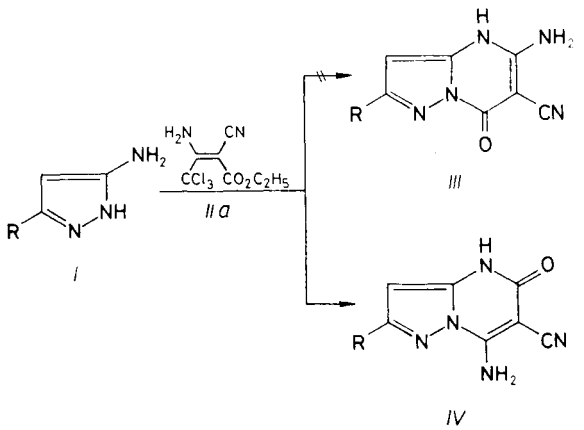
Several new pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*c*]-*as*-triazine derivatives were synthesized *via* the reaction of 3-antipyrinyl-5-aminopyrazole or its diazonium salt with enaminonitriles, enaminoesters and active methylene reagents. The action of hydrazine hydrate on the obtained polyfunctional products was also studied.

Although enaminonitriles and enaminoesters are versatile reagents for the synthesis of azole derivatives, very little attention was paid to the potential utility of *IIa, b* and *VIIIa, b* for the synthesis of fused azole derivatives. As a part of our program directed for synthesis of azole and fused azole derivatives of antipyrine[2,3], we report here the possible utility of *IIa, b*, *VIIIa, b* and other active methylene reagents for the synthesis of a variety of polyfunctionally substituted pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*c*]-*as*-triazine derivatives.

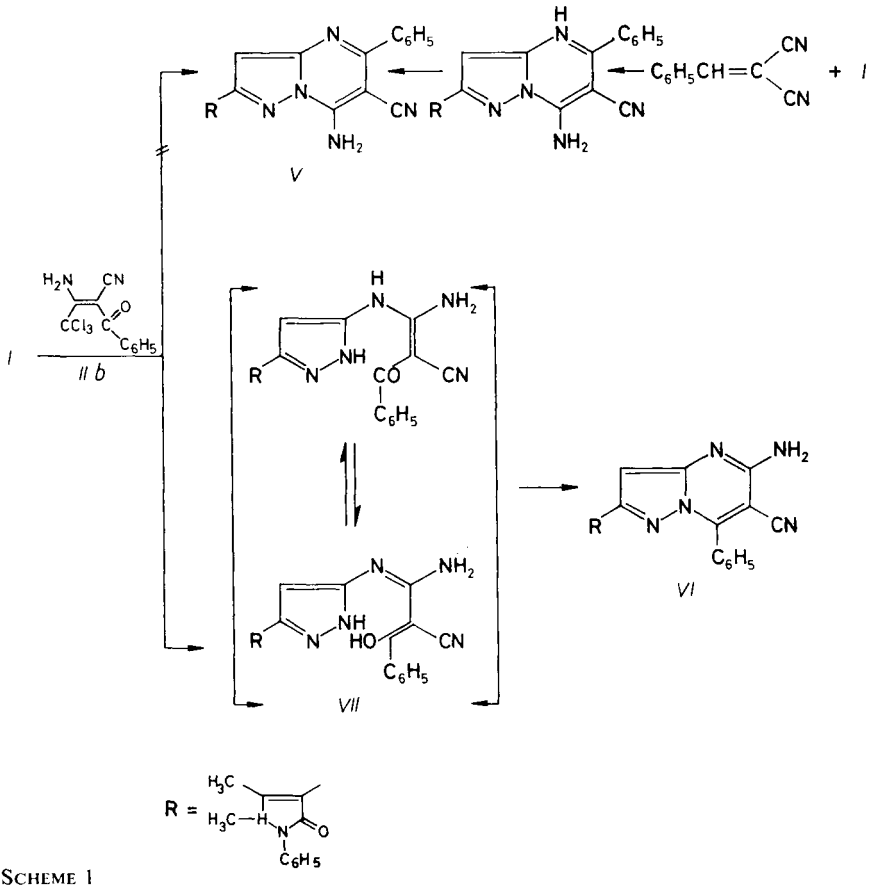
Now, 3-antipyrinyl-5-aminopyrazole[2] (*I*) reacted with ethyl β-trichloromethyl--β-aminomethylenecyanoacetate[4] (*IIa*) to yield a product resulting from elimination



* Part III in the series Reactions with Heterocyclic Amidines, Part II see ref.[1].

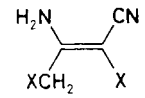
of ethanol and chloroform from the reactants. Although it seems quite difficult to exclude structure *III* completely for this product, structure *IV* seemed to be more likely on the basis of the IR spectrum which revealed a ring C=O group at 1 680 cm^{-1}, for structure *III* the ring carbonyl group should be obtained at higher frequency[5] (c. 1 700 cm^{-1}). Also, β-amino-β-trichloromethyl-α-benzoylacrylonitrile[6] (*IIb*) reacted with *I* to give a product of molecular formula $C_{24}H_{19}N_7O$. Two possible isomeric structures *V* and *VI* were considered. Structure *VI* was established based on the recently reported preparation[3] of *V* from the reaction of *I* with benzylidenemalononitrile in ethanol. The formation of *VI* in this reaction is assumed to proceed *via VII* followed by water elimination from the enolate form of *VII* (Scheme 1).

Recently, it has been reported by Elnagdi and coworkers[7-9], that coupling of *VIIIa* with aromatic or heterocyclic diazonium chlorides was resulted in the formation of the hydrazone *IX* which was cyclized to the pyridazin-6-ones *Xa* and *Xb* on treatment with ethanolic potassium hydroxide or acetic anhydride, respectively.

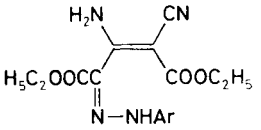


SCHEME 1

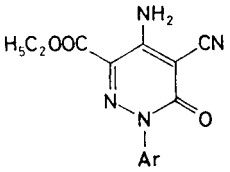
In the present work, compound *VIIIa* couples with diazotised aminopyrazole *XI* in aqueous ethanolic sodium acetate to yield a product of molecular formula $C_{22}H_{20}N_8O_4$. Two different structures *XIII* and *XIV* seemed possible. Structure *XIII* was established for the reaction product based on the ^{1}H NMR spectrum which revealed the absence of signal corresponding to the pyrazole NH. In contrast to the



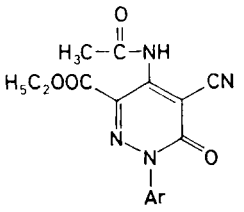
VIIIa, X = $COOC_2H_5$
VIIIb, X = CN



IX



Xa



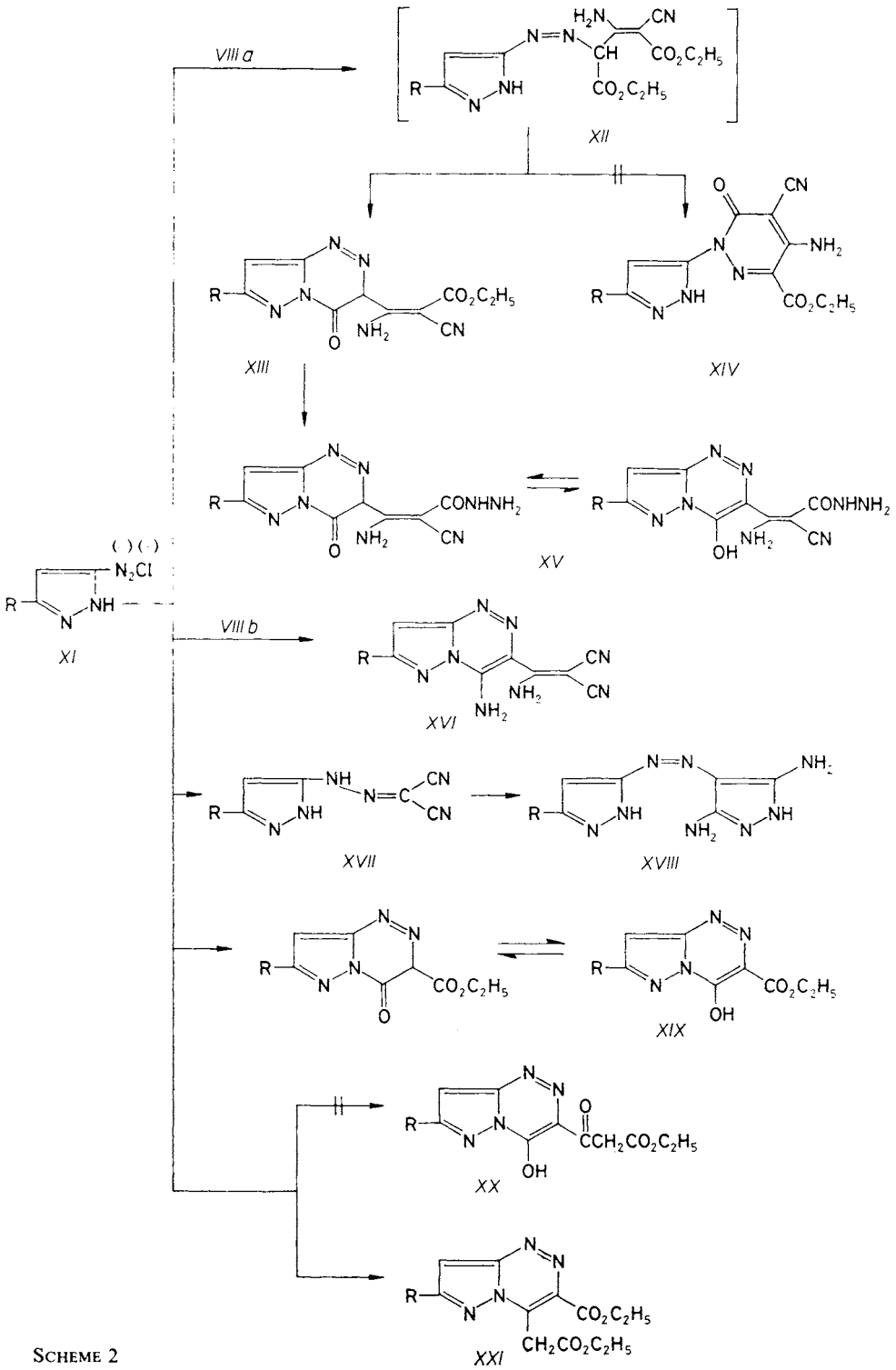
Xb

reported formation of *Xa* and *Xb* from the acyclic hydrazone *IX*, compound *XIII* formed directly without the isolation of *XII*. Compound *XIII* is assumed to be formed *via XII* which readily cyclized under the reaction conditions with the highly nucleophilic pyrazole NH *via* ethanol elimination.

Similarly, compound *XI* coupled with *VIIIb* to give *XVI* in good yield (Scheme 2).

In contrast to the reported behaviour of enaminonitriles and enaminoesters toward the action of hydrazines[10,11], compound *XIII* reacted with hydrazine hydrate to yield *XV* and not the expected cyclic parazole derivative. While *XVI* recovered unchanged on treatment with hydrazine hydrate, compound[12] *XVII* easily converted to the corresponding aminopyrazole *XVIII* under the action of the same reagent. The reactivity of the nitrile rather than the basicity of the amino function is the controlling factor in these reactions[13].

Compound *XI* was coupled also with diethyl malonate to yield the pyrazolo[1,5-*c*]--*as*-triazine *XIX*. Also, *XI* coupled with diethyl acetonedicarboxylate to afford a product for which structures *XX* or *XXI* were considered. Structure *XX* was ruled out based on elemental analysis and ^{1}H NMR spectrum of the reaction product which revealed the presence of two ester groups.



SCHEME 2

EXPERIMENTAL

All melting points are uncorrected. Recorded yields correspond to the pure products. IR spectra were recorded (KBr) on a Pye Unicam SP-1100 spectrophotometer. ^{1}H NMR were spectra measured on a Varian EM-360 spectrophotometer (60 MHz) using tetramethylsilane as internal standard and chemical shifts are expressed as δ values.

Microanalytical data were obtained from the microanalytical Data Unit at Cairo University.

Reaction of *I* with *IIa* and *IIb*

A suspension of 3-antipyrinyl-5-aminopyrazole (*I*) 2·7 g (0·01 mol) in dry pyridine (20 ml) was treated with (0·01 mol) of *IIa* or *IIb*. The mixture was refluxed for 3 h, then evaporatted *in vacuo*. The resulting solid product was collected by filtration and identificed as *IV* and *VI*, respectively.

7-*Amino*-2-*antipyrinyl*-6-*cyano*-4-5-*dihydropyrazolo*[1,5-*a*]-*pyrimidin*-5-*one* (IV) was obtained as yellow crystals from dimethylformamide with m.p. 281—283°C, yield 2·4 g (65%). For $C_{18}H_{15}N_7$ (361·4) calculated: 59·82% C, 4·18% H, 27·14% N; found 59·70% C, 4·45% H, 27·28% N. IR spectrum: 3 350, 3 270, 3 200 cm^{-1} (NH_2); 2 200 cm^{-1} (conjugated C≡N); 1 680 cm^{-1} (azolyl C=0); 1 610 cm^{-1} (antipyrinyl C=0); 1 600 cm^{-1} (δNH_2).

5-*Amino*-2-*antipyrinyl*-6-*cyano*-7-*phenylpyrazolo*[1,5-*a*]-*pyrimidine* (VI) was obtained as yellow crystals from dimethylformamide with m.p. > 300°C, yield 2·9 g (70%). For $C_{24}H_{19}N_7O$ (421·45) calculated: 68·39% C, 4·54% H, 23·27% N; found: 68·10% C, 4·81% H, 22·94% N. IR spectrum: 3 480, 3 400, 3 220 cm^{-1} (NH_2); 3 090, 2 970 cm^{-1} (two CH_3); 2 200 (conjugated C≡N); 1 660 cm^{-1} (antipyrinyl C=0); 1 600 cm^{-1} (δNH_2).

Preparation of *XIII*, *XVI*, *XIX*, and *XX*

A solution of activated methylene compound (0·01 mol) in ethanol (50 ml) was treated with a saturated sodium acetate solution (10 ml) and then with diazotized aminopyrazole *XI* (prepared from 2·7 g (0·01 mol) of the aminopyrazole hydrochloride and the equivalent quantity of $NaNO_2$ as has been previously described[12]). The mixture was left in the refrigerator for 24 h and the resulting solid was collected by filtration and crystallized.

(*E*)-2-*Amino*-1-*cyano*-1-*ethoxycarbonyl*-2-(2-*antipyrinyl*-7-*dihydropyrazolo*[1,5-*c*]-*as*-*triazin*-6-*yl*)-*ethene* (XIII) was obtained as yellow crystals from dimethylformamide with m.p. 278—280°C, yield 3·7 g (80%). For $C_{22}H_{20}N_8O_4$ (460·4) calculated: 57·38% C, 4·38% H, 24·34% N; found: 57·22% C, 4·18% H, 24·31% N. IR spectrum: 3 350, 3 320, 3 200 cm^{-1} (NH_2), 2 210 cm^{-1} (conjugated C≡N), 1 690, 1 670 cm^{-1} (ester and azolyl C=O), 1 640 cm^{-1} (antipyrinyl C=O). ^{1}H NMR spectrum: 1·3 ppm (t, 3 H, CH_3), 2·5 ppm (s, 3 H, CH_3), 3·3 ppm (s, 3 H, N—CH_3), 3·8 ppm (s, 1 H, triazine 6-H), 4·4 ppm (q, 2 H, CH_2), 6·6 ppm (s, 1 H, pyrazole H-4) and 7·3—7·7 ppm (m, 5 H, C_6H_5).

2-*Amino*-1,1-*dicyano*-2-(2-*antipyrinyl*-7-*aminopyrazolo*[1,5-*c*]-*as*-*triazin*-6-*yl*)*ethene* (*XVI*) was obtained as red crystals from acetic acid with m.p. >300°C, yield 3·5 g (85%). For $C_{20}H_{16}N_{10}O$ (412·4) calculated: 58·24% C, 3·91% H, 33·97% N; found: 58·32% C, 3·79% H, 34·08% N. IR spectrum: 3 400, 3 330, 3 200 cm^{-1} (NH_2), 2 210, 2 220 cm^{-1} (two conjugated C≡N), 1 640 cm^{-1} (antipyrinyl C=O), 1 610 cm^{-1} (NH_2).

2-*Antipyrinyl*-6-*ethoxycarbonyl*-7-*hydroxypyrazolo*[1,5-*c*]-*as*-triazine (*XIX*) was obtained as yellow crystals from dimethylformamide with m.p. 278—280°C, yield 2·9 g (75%). For $C_{19}H_{18}N_6O_4$ (394·4) calculated: 57·86% C, 4·60% H, 21·31% N; found: 57·82% C, 4·29% H, 21·45% N. IR spectrum: 3 300—2 400 cm^{-1} (OH), 1 750 cm^{-1} (C=O ester), 1 660 cm^{-1} (antipyrinyl C=O), 1 600 cm^{-1} (C=N and NH).

2-*Antipyrinyl*-6-*ethoxycarbonyl*-7-*ethoxycarbonylmethylpyrazolo*[1,5-*c*]-*as*-*triazine* (*XX*) was obtained as orange crystals from ethanol with m.p. 186–188°C, yield 3·2 g (70%). For $C_{23}H_{24}N_6O_5$ (464·5) calculated: 59·47% C, 5·21% H, 18·09% N; found: 59·38% C, 5·21% H, 18·26% N. IR spectrum: 3 090, 2 990, 2 930 cm^{-1} (CH_2 and CH_3), 1 780, 1 730 cm^{-1} (C=O esters), 1 680 cm^{-1} (antipyrinyl C=O), 1 610, 1 600 cm^{-1} (C=N and δ NH). ^1H NMR spectrum: 1·1–1·3 ppm (2 t, 6 H, 2 CH_3 esters), 2·6 ppm (s, 3 H, CH_3). 3·1 ppm (s, 3 H, N—CH_3), 4·1 ppm (s, 2 H, CH_2), 4·2–4·6 ppm (octet, 4 H, 2 CH_2 esters), 4·9 ppm (s, 1 H, pyrazole H-4), 7·3–7·5 ppm (m, 5 H, C_6H_5).

Reaction of *XII* and *XVII* with Hydrazine Hydrate

A solution of *XIII* or *XVII* (0·01 mol) in ethanol (20 ml) was treated with hydrazine hydrate (0·015 mol). The mixture was refluxed for 1 h and then left to cool. The solid was collected by filtration and crystallized from dimethylformamide.

3-*Amino*-2-*cyano*-2-(2-*antipyrinyl*-7-*hydroxypyrazolo*[1,5-*c*]-*as*-*triazin*-6-*yl*)*prop*-2-*enoic acid* (XV) was obtained as yellow crystals with m.p. >300°C, yield 2·4 g (55%). For $C_{20}H_{18}N_{10}O_3$ (446·4) calculated: 53·80% C, 4·06% H, 31·38% N; found: 53·72% C, 4·21% H, 31·56% N. IR spectrum: 3 600–2 600 cm^{-1} (OH and HN_2), 2 210 cm^{-1} (conjugated C=N), 1 680, 1 660 cm^{-1} (amide and antipyrinyl C=O), 1 600 cm^{-1} (δ NH_2).

3-*Antipyrinyl*-5-(3,5-*diaminopyrazol*-4-*yl*)*azopyrazole* (XVIII) was obtained as orange crystals with m.p. >300°C, yield 2·2 g (60%). For $C_{17}H_{18}N_{10}O$ (378·4) calculated: 53·96% C, 4·79% H, 37·02% N; found: 53·91% C, 4·79% H, 37·21% H. IR spectrum: 3 420, 3 360, 3 300 cm^{-1} (NH_2 and NH), 1 660 cm^{-1} (antipyrinyl C=O), 1 640 cm^{-1} (C=N), 1 600 cm^{-1} (δ NH_2).

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