New Heterocyclic Bridgehead Nitrogen Compounds Synthesis of 1-(*p*-Tosyl)pyrazolo[1,5-*a*]pyrimidines and Pyrazolo[5,1-*c*]-[1,2,4]-triazine Derivatives

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Interaction of 3-amino-1,5-dihydro-1-(*p*-tosyl)pyrazole with ethyl acetoacetate, acrylonitrile and acetyl acetone afforded the corresponding 1-(*p*-tosyl)pyrazolo[1,5-*a*]pyrimidine derivatives. Diazotization of the starting compound and subsequent coupling with bifunctionally active nitriles yielded the corresponding pyrazolo[5,1-*c*]-[1,2,4]-triazine derivatives. IR and ^{1}H NMR spectra for all of the hitherto prepared compounds are in good agreement with the proposed structures.

Schistosomiasis is considered to be one of the most difficult diseases to treat [1] and is a national problem in Egypt. Accordingly considerable attention has been directed toward the development of useful [2, 3] chemotherapeutic agents. Perusal of literature reveals the importance of pyrazolo[1,5-*a*]pyrimidine derivatives, especially those substituted with mercapto group [4, 5], as antischistosomal agents. Thus in continuation of our interest in synthesis of fused and/or isolated pyrimidine derivatives as potential chemotherapeutic agents [6—8], we report herein on the synthesis of new series of substituted pyrazolo-[1,5-*a*]pyrimidine derivatives and their aza analogues, namely, pyrazolo[5,1-*c*]-[1,2,4]-triazines that accomodate the pharmacologically active tosyl moiety aiming to synthesize novel products of extended and/or improved antischistosomiasis activity.

The synthesized compounds possess latent functional substituents and appear promising for utility in further chemical transformations and biological studies.

The general synthetic sequence followed for the preparation of these compounds is outlined in Scheme 1.

EXPERIMENTAL

Melting points are not corrected. The IR spectra (KBr) were measured on spectrophotometer SP 2000 (Pye—Unicam). The ^{1}H NMR spectra ($CDCl_3$) were recorded on spectrometer EM 360 (Varian; 60 MHz) with TMS as an internal standard.

7-Methyl-1,2,4,5-tetrahydro-1-(*p*-tosyl)pyrazolo-[1,5-*a*]pyrimidin-5-one (*II*)

A mixture of 3-amino-1,5-dihydro-1-(*p*-tosyl)-pyrazole (*I*) (0.01 mol) and ethyl acetoacetate (0.01 mol) was heated for 10 h at 160 °C. The reaction mixture was cooled, triturated with ethanol and the resulting solid product was crystallized from DMF—ethanol mixture to give *II* as yellow crystals in 63 % yield, m.p. = 210 °C. For $C_{14}H_{15}N_3O_3S$ w_i(calc.): 55.1 % C, 5.0 % H; w_i(found): 54.7 % C, 4.9 % H. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3300 ν(NH), 1680 ν(amidic CO), 1640 ν(C=C), 1350 $\nu_{as}(SO_2)$, 1150 $\nu_s(SO_2)$. ^{1}H NMR spectrum, δ: 1.9 and 2.3 (s, s, 6H, 2 × CH_3), 2.56 (d, 2H, CH_2), 5.40 (t, 1H, CH), 5.75 (s, 1H, C-6—H), 6.5—7.4 (m, 4H, H_{arom}), 9.1 (br s, 1H, NH).

1,2-Dihydro-5,7-dimethyl-1-(*p*-tosyl)pyrazolo-[1,5-*a*]pyrimidine (*IV*)

Compound *I* (0.01 mol) was condensed with acetylacetone (0.01 mol) utilizing the same experimental procedure as described above. The resulting reaction product was crystallized from dioxane as yellow crystals in 68 % yield, m.p. = 198 °C. For $C_{15}H_{17}N_3O_2S$ w_i(calc.): 59.4 % C, 5.7 % H; w_i(found): 58.9 % C, 5.6 % H. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1640 and 1620 ν(C=N and C=C), 1310 $\nu_{as}(SO_2)$, 1155 $\nu_s(SO_2)$. ^{1}H NMR spectrum, δ: 1.95 (s, 6H, 2 × CH_3 of pyrimidine moiety), 2.3 (s, 3H, tosyl—CH_3), 2.6 (d, 2H, CH_2), 5.45 (t, 1H, C-3—H), 5.8 (s, 1H, C-6—H), 6.4—7.4 (m, 4H, H_{arom}).

3-Bromo-1,2-dihydro-5,7-dimethyl-1-(*p*-tosyl)-pyrazolo[1,5-*a*]pyrimidine (*V*)

To a suspension of *IV* (0.01 mol) in carbon tetrachloride (50 cm^3) *N*-bromosuccinimide (0.013 mol) was added. The reaction mixture was heated at 60 °C and kept at this temperature for 15 min. Trituration with petroleum ether afforded the required

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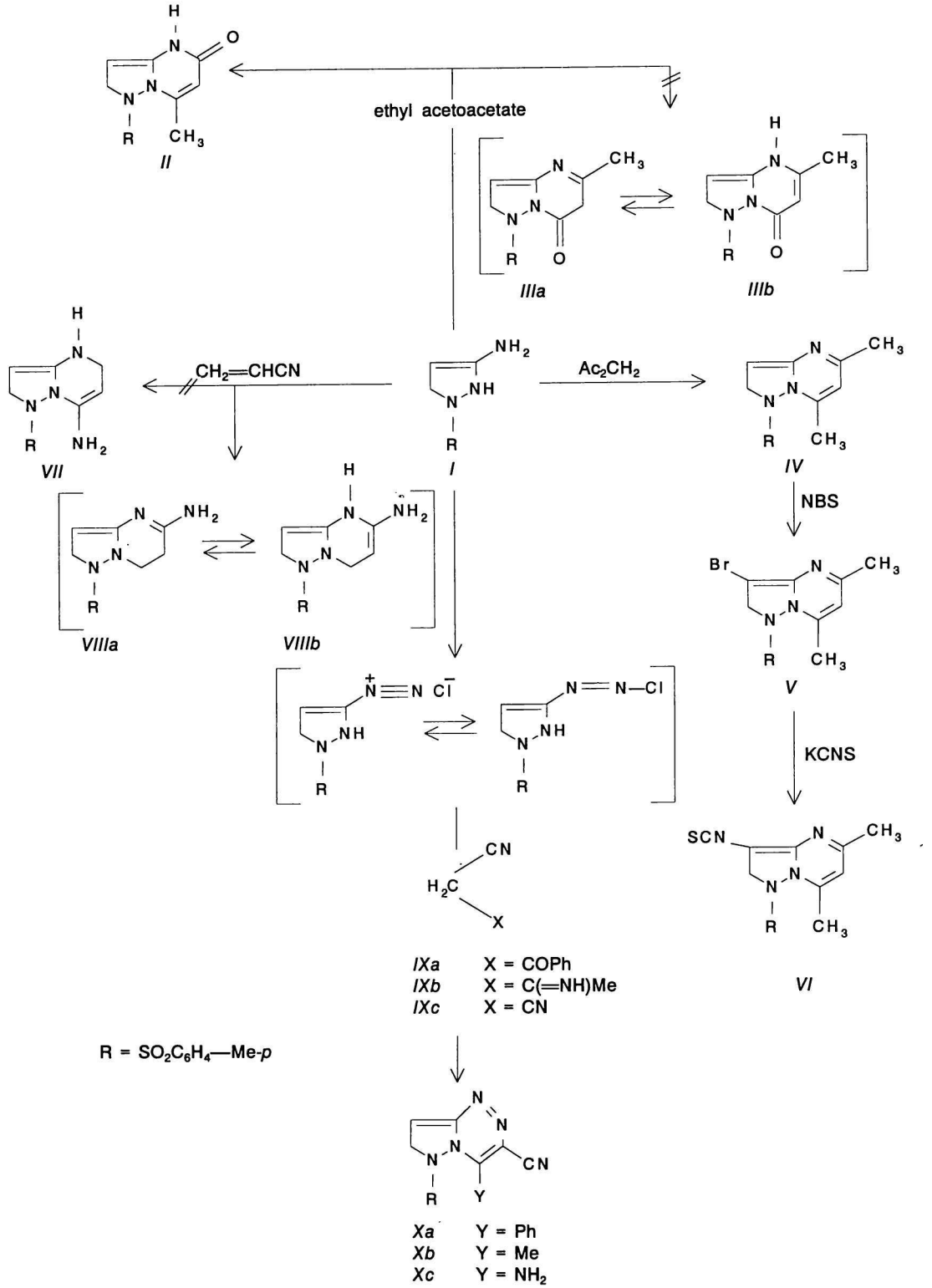

Scheme 1

product as yellow crystals in 77 % yield, m.p. = 178 °C. For $C_{15}H_{16}BrN_3O_2S$ w_i(calc.): 47.1 % C, 4.2 % H; w_i(found): 46.9 % C, 3.8 % H. ^{1}H NMR spectrum, δ: 1.95 (s, 6H, 2 × CH_3 of pyrimidine moiety), 2.3 (s, 3H, tosyl—CH_3), 2.65 (s, 2H, CH_2), 5.7 (s, 1H, C-6—H), 6.4—7.4 (m, 4H, H_{arom}).

1,2-Dihydro-5,7-dimethyl-3-isothiocyanato-1-(*p*-tosyl)pyrazolo[1,5-*a*]pyrimidine (*VI*)

A solution of *V* (0.01 mol) in ethanol (50 cm^3) was treated with potassium thiocyanate (0.01 mol) dissolved in water (5 cm^3). The reaction mixture was

refluxed for 5 h and the solvent was evaporated under reduced pressure. The resulting solid product was crystallized from ethanol as orange crystals in 73 % yield, m.p. = 203 °C. For $C_{16}H_{16}N_4O_2S_2$ w_i(calc.): 53.3 % C, 4.5 % H; w_i(found): 53.1 % C, 4.2 % H. IR spectrum, $\tilde{\nu}$/cm^{-1}: 2130 ν(N=C=S), 1640 and 1620 ν(C=N and C=C), 1310 $\nu_{as}(SO_2)$, 1155 $\nu_s(SO_2)$.

5-Amino-1,2,6,7-tetrahydro-1-(*p*-tosyl)pyrazolo-[1,5-*a*]pyrimidine (*VIII*)

To a solution of acrylonitrile (0.01 mol) in pyridine (15 cm^3), compound *I* (0.01 mol) was added and the reaction mixture was boiled under reflux for 6 h and concentrated under reduced pressure. Trituration with ethanol followed by allowing the mixture to stand at ambient temperature for 24 h afforded the product which was filtered and recrystallized from ethanol (yellow crystals) in 74 % yield, m.p. = 184 °C. For $C_{13}H_{16}N_4O_2S$ w_i(calc.): 53.4 % C, 5.5 % H; w_i(found): 53.4 % C, 5.3 % H. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3100—3500 ν(NH_2 and NH), 1310 $\nu_{as}(SO_2)$, 1160 $\nu_s(SO_2)$. ^{1}H NMR spectrum, δ: 2.3 (s, 3H, CH_3), 2.4 (s, 1H, NH), 2.65 (m, 4H, 2 × CH_2), 3.88 (t, 1H, C-6—H), 5.6 (t, 1H, C-3—H), 6.0 (br s, 2H, NH_2), 6.4—7.3 (m, 4H, H_{arom}).

7-Substituted 6-Cyano-1,2-dihydro-1-(*p*-tosyl)-pyrazolo[5,1-*c*]-[1,2,4]-triazines *Xa—Xc*

A cold diazonium salt solution, prepared from *I* (0.01 mol), was poured gradually with continuous stirring into a cold mixture of the appropriate active hydrogen reagent (0.01 mol) in ethanol (20 cm^3) in the presence of sodium acetate solution (1 g dissolved in 5 cm^3 of water). The reaction mixture was stirred at room temperature for 2 h and the solid product so formed was crystallized from ethanol as yellow to orange crystals in an average good yield (69—76 %).

Xa: M.p. = 230 °C. For $C_{19}H_{15}N_5O_2S$ w_i(calc.): 60.5 % C, 4.0 % H; w_i(found): 60.2 % C, 3.9 % H. IR spectrum, $\tilde{\nu}$/cm^{-1}: 2220 ν(CN), 1640 and 1633 ν(C=C and N=N), 1320 $\nu_{as}(SO_2)$, 1155 $\nu_s(SO_2)$.

Xb: M.p. = 195 °C. For $C_{14}H_{13}N_5O_2S$ w_i(calc.): 53.3 % C, 4.2 % H; w_i(found): 53.3 % C, 4.0 % H. ^{1}H NMR spectrum, δ: 1.9 (s, 3H, CH_3), 2.3 (s, 3H, tosyl—CH_3), 2.6 (d, 2H, CH_2), 5.6 (t, 1H, C-3—H), 6.4—7.4 (m, 4H, H_{arom}).

Xc: M.p. = 265 °C. For $C_{13}H_{12}N_6O_2S$ w_i(calc.): 49.4 % C, 3.8 % H; w_i(found): 49.6 % C, 3.65 % H. IR spectrum, $\tilde{\nu}$/ cm^{-1}: 3380—3450 ν(NH_2), 2225 ν(CN), 1640 ν(C=C), 1633 ν(N=N), 1320 $\nu_{as}(SO_2)$, 1155 $\nu_s(SO_2)$.

RESULTS AND DISCUSSION

Fusion of equimolar quantities of the *p*-tosyl aminopyrazole derivative (*I*) and ethyl acetoacetate at 160 °C yielded only one isolable product that was analyzed correctly for a molecular formula of $C_{14}H_{15}N_3O_3S$. The structure of this product may be formulated as *II* or its isomeric structure *III* (Scheme 1). Although structure *III* seemed convincing, depending on similarity to the well established behaviour of 5-aminopyrazoles towards β-keto esters [9], structure *II* was considered most likely based on spectral evidences, besides the characteristic absorption band at $\tilde{\nu}$ = 3300 cm^{-1} for NH group, IR spectrum for this product revealed another strong absorption at $\tilde{\nu}$ = 1680 cm^{-1} that might be ascribed to the ring carbonyl (amidic CO). For structure *III*, the band corresponding to the ring-carbonyl group should be obtained at higher wavenumber (*e.g.* 1700 cm^{-1}) [10].

Moreover, ^{1}H NMR spectrum of this pyrazolo-[1,5-*a*]pyrimidine derivative revealed two one-proton singlets at δ = 5.75 and 9.10 that might be attributed to pyrimidine ring CH and NH protons, respectively. For structure *III*, a group signal at about δ = 4.00 (two methylene group protons), similar to that previously reported, would have been expected [11, 12].

Chemical evidences that support structure *II* were drawn from the fact that the obtained product failed completely to undergo condensation reactions with aromatic aldehydes or to couple with benzene—diazonium salt solutions, reactions which proceed readily with activated methylene and methine functions, respectively, as in case of the pyrazolo-pyrimidine derivative *IIIa* and/or its tautomeric structure *IIIb* which accomodate the activating cyclic tertiary amidic linkage.

Similar to the well known behaviour of 3- or 5-aminopyrazoles, compound *I* condensed with acetylacetone to yield the corresponding pyrazolo-[1,5-*a*]pyrimidine derivatives *IV*. The structure of this product was inferred from analytical and spectral data (*cf.* Experimental).

Compound *IV* could be converted into *V* through treatment with *N*-bromosuccinimide (NBS). The latter derivative reacted readily with potassium thiocyanate to yield the corresponding isothiocyanate derivative *VI*. The presence of isothiocyanate function was inferred from IR spectral data which revealed the presence of an intense and broad absorption band at $\tilde{\nu}$ = 2130 cm^{-1} corresponding to stretching vibration of this moiety.

Compound *I* reacted also readily with acrylonitrile to yield a 1 : 1 adduct. However, in contrast to the expected cyanoethylation product, the IR spectrum of the obtained compound revealed the absence of absorption bands that might be ascribed to the cyano

group. Two isomeric structures seemed possible for the produced adduct (*cf.* structures *VII* and *VIII*). Although it is quite difficult to exclude structure *VII* completely for this product, structure *VIII* seemed to be more likely, not only on the basis of analogy to the reported behaviour of aminopyrazoles toward activated double bond systems [13—15] where cyanoethylation for such compounds involves the ring atom N-1 and not the amino group [9], but also according to ^{1}H NMR spectra which displayed a pattern (*cf.* Experimental) that could be intelligibly interpreted in terms of the proposed tautomeric structure *VIIIb*.

Diazotized compound *I* coupled with benzoylacetonitrile, 3-iminobutyronitrile or malononitrile to yield directly the corresponding pyrazolo[5,1-*c*]-[1,2,4]-triazine derivatives *Xa—Xc*. The formation of these fused-ring systems and not the acyclic hydrazones finds support from the previously reported work [5], where the reaction with these reagents was assumed to proceed, most likely, *via* a (4 + 2) dipolar cycloaddition sequence. The different possible mechanisms for the reaction of diazotized cyclic amidines with active hydrogen reagents have been critically discussed and reviewed [16].

The hitherto prepared products were characterized by elemental analysis and spectral measurements. The possibility of using these compounds as possible chemotherapeutic agents is for the time being under investigation. The results of this study together with toxicity of the prepared compounds will be published elsewhere.

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