Reactions of Heterocyclic β-Enamino Esters Synthesis of Pyranopyrimidine, Pyranopyridine, and *N*-(Pyran-2-yl)azetidinone Ring Systems

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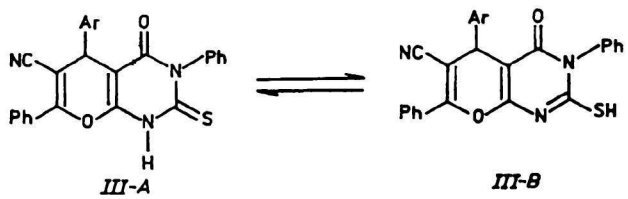
Reaction of 2-amino-5-cyano-3-ethoxycarbonyl-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran (β-enamino ester) with phenyl isothiocyanate, malononitrile, and amides afforded the corresponding pyranopyrimidine derivatives, respectively. Acetylation of β-enamino ester yielded the *N*-acetyl derivative which reacted with phenacyl bromide to give 2-[*N*-acetyl-*N*-(benzoylmethyl)-amino]-5-cyano-3-ethoxycarbonyl-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran. Treatment of this compound with sodium hydride in dry toluene gave 8-(benzoylmethyl)-3-cyano-5-hydroxy-4-(*p*-methoxyphenyl)-7-oxo-2-phenyl-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine. Cycloaddition reaction between Schiff bases of enamino ester and chloroacetyl chloride in the presence of triethylamine produced the substituted β-lactam ring structures, *e.g.* 4-aryl-3-chloro-*N*-[5-cyano-3-ethoxycarbonyl-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran-2-yl]-2-azetidinones. The structure of the hitherto prepared compounds was confirmed by spectral data and, whenever possible, by alternative synthetic routes.

It is well known that pyran moiety possesses pronounced biological properties [1]. On the other hand, substituted pyridines show acaricidal, insecticidal, and herbicidal activities [2]. Moreover, pyrimidines are important analgesic and anti-inflammatory [3, 4] agents. Thus compounds having a combination of such pyran, pyridine and/or pyrimidine moieties might afford less toxic and more potent drugs in the field of medicinal chemistry.

In continuation of our study on the chemistry of heterocyclic β-enamino esters and the synthesis of fused pyran ring systems [5—7] of pharmacological importance, we report herein on the use of 2-amino-5-cyano-3-ethoxycarbonyl-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran (*II*) as a key intermediate for the synthesis of new series of pyranopyrimidine, pyranopyridine, and *N*-(pyran-2-yl)azetidinone derivatives *III*—*XII*.

Reaction of *II* with phenyl isothiocyanate in dry acetone at room temperature afforded 6-cyano-3,7-diphenyl-5-(*p*-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydro-5*H*-pyrano[2,3-*d*]pyrimidine-2-thione (*III*) (Scheme 1). Besides absorption bands characteristic of ν(NH), ν(C≡N), ν(CO), ν(C=C), IR spectrum for this product revealed a strong absorption band at $\tilde{\nu}$ = 1200 cm^{-1} (ν(C=S)) and another weak absorption band at $\tilde{\nu}$ = 2425 cm^{-1} (ν(C—SH)). The presence of such absorption bands may be considered as an indication for the existence of structure *III*, predominantly, in the thione form (*A*) and in a tautomeric mixture [8] as well (*A* and *B*).

Fusion of compound *II* with malononitrile at 120 °C in the presence of catalytic amount of ammonium acetate yielded 6-cyano-2-cyanomethyl-5-(*p*-methoxyphenyl)-4-oxo-7-phenyl-3,4-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine (*IV*), the structure of which was confirmed from IR and ^{1}H NMR spectra. The absence of absorption due to amino and ester moieties and the appearance of new absorption



III-A *III-B*

bands at $\tilde{\nu}$ = 1650 cm^{-1} (ν(cyclic amide)) and 1620 cm^{-1} (ν(C=N)) in the IR spectrum of *IV* substantiate the assigned structure for this product. Further support was gathered from ^{1}H NMR spectrum which displayed a singlet at δ = 4.2 for $C\underline{H}_2$—CN.

Allowing the enamino ester *II* to react with formamide and/or benzamide gave the corresponding pyrano[2,3-*d*]pyrimidine derivatives *Va* and *Vb*, respectively. The infrared spectra of both derivatives displayed absorption bands around $\tilde{\nu}$ = 1620 and 1650 cm^{-1} assignable to stretching vibrations of the C=N and cyclic secondary amide moieties, respectively.

Compound *II* reacted (Scheme 2) with acetic anhydride to yield the corresponding acetyl derivative *VI*. IR spectrum of the product revealed

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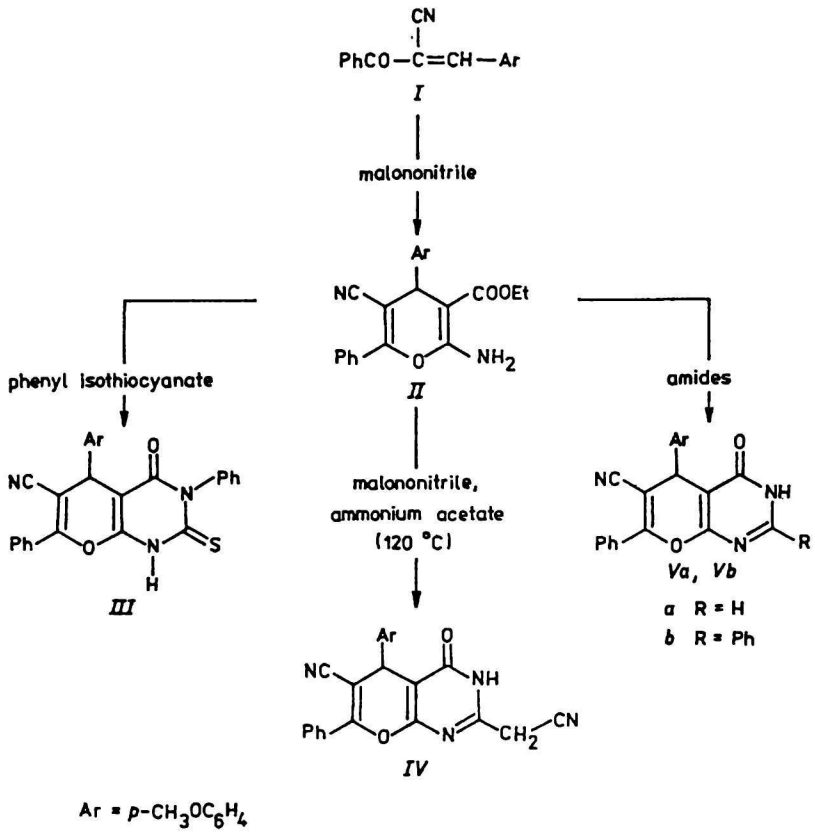


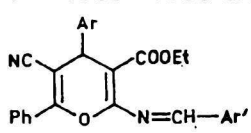
Scheme 1

new absorption band at $\tilde{\nu}$ = 1700 cm^{-1} that might be assigned to the acetylamino group in its structure. Reaction of the acetyl derivative *VI* with phenacyl bromide gave the corresponding *N*-alkylated derivative *VII*, its structure was based on elemental analyses and spectral data. Both IR and ^{1}H NMR spectra revealed the disappearance of NH proton of acetylamino group in the product. The latter product, when treated with sodium hydride in dry toluene afforded the *N*-benzoylmethylpyranopyridine derivative *VIII*. Besides correct elemental and spectral data, the structure *VIII* was confirmed through independent synthesis by fusion of compound *II* with diethyl malonate in an oil bath at 120 °C to give the ethoxycarbonylpyranopyridine derivative *IX*.

Hydrolysis of the latter product followed by decarboxylation yielded the pyranopyridine derivative *X* which in turn, when reacted with phenacyl bromide in ethanol, furnished the *N*-benzoylmethyl derivative *VIII*.

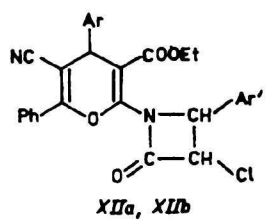
Condensation of β-enamino ester *II* with aromatic aldehydes gave the corresponding Schiff bases *XIa*—*XIc*. The structure of these products has been established from their analytical and spectral data. IR spectra for all these derivatives displayed a characteristic absorption band in the region of $\tilde{\nu}$ = 1625—1640 cm^{-1} that may be attributed to azomethine group in their structure.

β-Lactam ring structure is known [9] to be the most important part which is responsible for antibiotic activity of Penicillin and Cephalosporine C molecules. Cycloaddition of Schiff bases *XIa*, *XIb* with monochloro ketones (prepared *in situ* from chloroacetyl chloride and triethylamine) in dry benzene gave rise to *N*-(pyran-2-yl)-2-azetidinone derivatives *XIIa*, *XIIb*. IR spectra of these azetidinone derivatives displayed the stretching vibrational bands characteristic of amidic-carbonyl moiety of monocyclic β-lactam structure [10] at $\tilde{\nu}$ = 1700—1705 cm^{-1}.



XIa—*XIc*

a Ar' = p-NO_2—C_6H_4
b Ar' = p-$(CH_3)_2N$—C_6H_4
c Ar' = p-Cl—C_6H_4

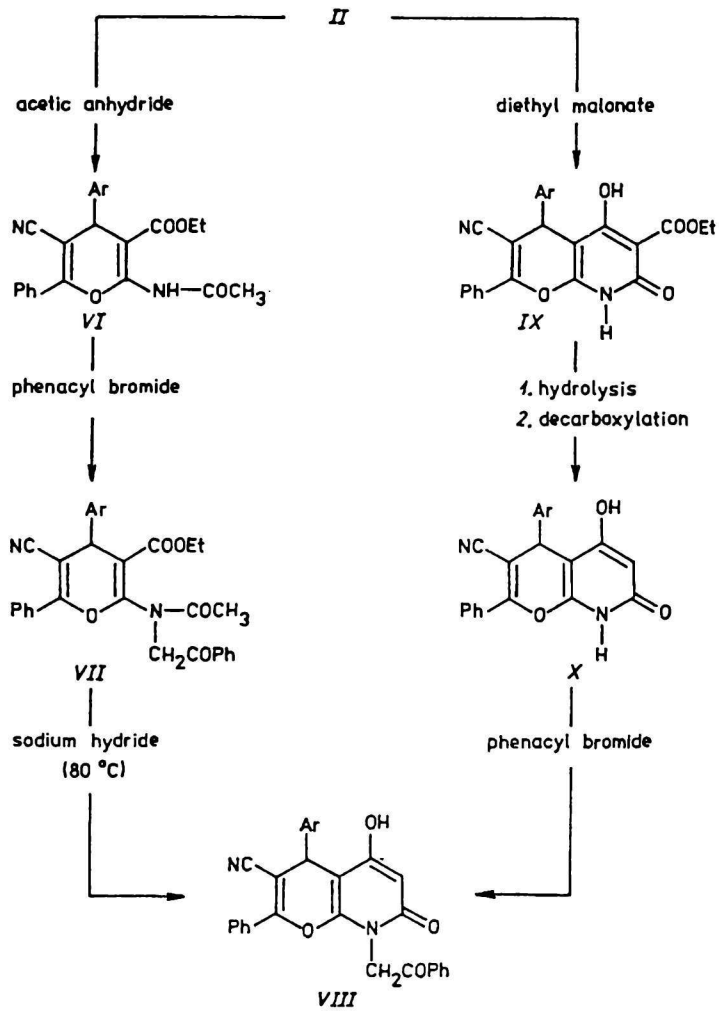


XIIa, *XIIb*

a Ar' = p-NO_2—C_6H_4
b Ar' = p-$(CH_3)_2N$—C_6H_4

EXPERIMENTAL

The starting compound *II* was obtained *via* α-cyanochalcone *I* as previously reported [11].



Scheme 2

All melting points of the twice recrystallized compounds are uncorrected. Infrared spectra were determined using KBr wafer technique on a Varian SP 2000 spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Varian model T-60 spectrometer using tetramethylsilane as internal standard. Physical data of the prepared compounds are listed in Table 1.

6-Cyano-3,7-diphenyl-5-(*p*-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydro-5*H*-pyrano[2,3-*d*]pyrimidine-2-thione (*III*)

Enamino ester *II* (1.9 g; 5 mmol) dissolved in acetone (30 cm^3) was mixed with phenyl isothiocyanate (5.2 mmol; 0.62 cm^3) and the whole mixture was stirred at room temperature for 1 h. The solid product that separated was collected by filtration, washed with acetone and water, dried and recrystallized from methanol to give the pure pyranopyrimidine derivative *III* as yellow crystals. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3100 ν(NH), 2425 ν(N=C—SH), 2220 ν(C≡N), 1685 ν(amidic CO), 1595 ν(C=C), 1200 ν(C=S), 1170 ν(C—O—C).

6-Cyano-2-cyanomethyl-5-(*p*-methoxyphenyl)-4-oxo-7-phenyl-3,4-dihydro-5*H*-pyrano-[2,3-*d*]pyrimidine (*IV*)

Ammonium acetate (0.2 g) was added to a mixture of malononitrile (2.2 mmol) and enamino ester *II* (0.75 g; 2 mmol). The whole mixture was fused in an oil bath at 120 °C for 2 h and cooled. The solid product so formed was boiled with water, cooled, filtered off, dried and recrystallized as yellow crystals from ethanol. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3120 ν(NH), 2220 ν(C≡N), 1650 ν(cyclic amide moiety), 1620 ν(C=N), 1560 ν(C=C), 1170 ν(C—O—C). ^{1}H NMR spectrum, δ: 3.8 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 5.0 (s, 1H, C-5—H), 6.8—8.3 (m, 10H, 9 H_{arom} + NH).

Table 1. Characterization Data of the Prepared Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	Yield/%	M.p./°C
III	$C_{27}H_{19}N_3O_3S$	69.66	4.11	55	187
	465.50	69.60	3.69		
IV	$C_{23}H_{16}N_4O_3$	69.69	4.07	70	115
	396.39	69.48	3.60		
Va	$C_{21}H_{15}N_3O_3$	70.58	4.23	57	260
	357.35	70.44	4.10		
Vb	$C_{27}H_{19}N_3O_3$	74.81	4.42	45	230
	433.44	74.53	4.31		
VI	$C_{24}H_{22}N_2O_5$	68.88	5.30	53	184
	418.44	68.50	5.12		
VII	$C_{32}H_{28}N_2O_6$	71.63	5.26	60	171
	536.56	71.30	5.20		
VIII	$C_{30}H_{22}N_2O_5$	73.46	4.52	69	201
	490.50	73.34	4.41		
IX	$C_{25}H_{20}N_2O_6$	67.56	4.54	71	189
	444.43	67.31	4.40		
X	$C_{22}H_{16}N_2O_4$	70.96	4.33	59	177
	372.37	71.10	4.23		
XIa	$C_{29}H_{23}N_3O_6$	68.36	4.55	72	180
	509.49	68.30	4.32		
XIb	$C_{31}H_{29}N_3O_4$	73.35	5.76	66	178
	507.56	73.01	5.51		
XIc	$C_{29}H_{23}N_2O_4Cl$	69.81	4.65	59	189
	498.94	69.52	4.40		
XIIa	$C_{31}H_{24}N_3O_7Cl$	63.54	4.13	46	255
	585.97	63.13	3.80		
XIIb	$C_{33}H_{30}N_3O_5Cl$	67.86	5.18	43	267
	584.04	67.50	4.83		

6-Cyano-5-(*p*-methoxyphenyl)-4-oxo-7-phenyl-3,4-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine Derivatives *Va*, *Vb*

These products were prepared by treatment of *II* with the corresponding carboxamides adopting the method of *Smith et al.* [12]. For *Va* IR spectrum, $\tilde{\nu}$/cm^{-1}: 3150, 2225, 1650, 1620, and 1170 assignable to stretching vibrations of NH, C≡N, cyclic amide, C=N, and C—O—C moieties, respectively. ^{1}H NMR spectrum, δ: 3.8 (s, 3H, OC<u>H</u>$_3$), 5.1 (s, 1H, C-5—H), 6.8—7.8 (m, 10H, H$_{arom}$), 8.5 (br, 1H, N<u>H</u>).

Both of the two products *Va*, *Vb* were obtained in yellow-coloured crystals by crystallization from ethanol.

2-Acetylamino-5-cyano-3-(ethoxycarbonyl)-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran (*VI*)

A solution of *II* (0.75 g; 2 mmol) in acetic anhydride (10 cm^3) was refluxed for 12 h and left to cool. The reaction mixture was then poured onto cold water (30 cm^3) and the solid product, formed on standing, was collected by filtration and recrystallized as colourless crystals from ethanol. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3120 ν(NH), 2220 ν(C≡N), 1725 ν(intramolecularly hydrogen-bonded ester group), 1700 ν(acetyl CO), 1595 ν(C=C), 1170 ν(C—O—C).

2-[*N*-Acetyl-*N*-(benzoylmethyl)amino]-5-cyano-3-(ethoxycarbonyl)-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran (*VII*)

To a solution of *VI* (2.1 g; 5 mmol) in ethanol (30 cm^3), phenacyl bromide (1 g; 5 mmol) was added and the mixture was refluxed for 2 h. Evaporation of solvent under reduced pressure followed by cooling gave white mass of *VII*. Recrystallization from ethanol afforded pure white crystals. IR spectrum, $\tilde{\nu}$/cm^{-1}: 2220 ν(C≡N), 1740 ν(ester CO), 1700 ν(acetyl CO), 1695 ν(ketonic CO), 1610 ν(C=C), 1170 ν(C—O—C). ^{1}H NMR spectrum, δ: 1.9 (t, 3H, CH$_2$C<u>H</u>$_3$), 3.1 (s, 3H, COC<u>H</u>$_3$), 3.8 (s, 3H, OC<u>H</u>$_3$), 4.0 (q, 2H, C<u>H</u>$_2$CH$_3$), 4.7 (s, 2H, COC<u>H</u>$_2$), 5.0 (s, 1H, C-4—H), 6.3—7.4 (m, 14H, H$_{arom}$).

8-(Benzoylmethyl)-3-cyano-5-hydroxy-4-(*p*-methoxyphenyl)-7-oxo-2-phenyl-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine (*VIII*)

A solution of *VII* (2.7 g; 5 mmol) in dry toluene (20 cm^3) was added dropwise during 1 h to a stirred solution of sodium hydride (5 mmol, 60 % oil dispersion) in dry toluene (10 cm^3) at 80 °C. The resulting reaction mixture was kept with stirring at this temperature for further 3 h and left to cool. Quenching with excess ethanol (20 cm^3) followed by pouring in cold water and acidification of the aqueous layer with hydrochloric acid afforded the required product *VIII* which was recrystallized as yellow crystals from ethanol. ^{1}H NMR spectrum, δ: 3.8 (s, 3H, OC<u>H</u>$_3$), 4.4 (s, 2H, N—C<u>H</u>$_2$), 4.66 (s, 1H, OH), 5.0 (s, 1H, C-4—H), 6.5—7.8 (m, 15H, H$_{arom}$).

3-Cyano-6-(ethoxycarbonyl)-5-hydroxy-4-(*p*-methoxyphenyl)-7-oxo-2-phenyl-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine (*IX*)

A mixture of *II* (1.5 g; 4 mmol) and diethyl malonate (0.64 cm^3; 4.2 mmol) were fused in an oil bath at 120 °C for 2 h and cooled. The obtained solid product was then recrystallized as yellowish white crystals from ethanol. IR spectrum, $\tilde{\nu}$/cm^{-1}:

3450 ν(enolic OH), 3150 ν(NH), 2225 ν(C≡N), 1720 ν(ester CO, hydrogen-bonded), 1665 ν(amidic CO), 1170 ν(C—O—C). ^{1}H NMR spectrum, δ: 2.1 (t, 3H, $CH_2C\underline{H}_3$), 3.8 (s, 3H, $OC\underline{H}_3$), 4.2 (q, 2H, $C\underline{H}_2CH_3$), 5.0 (s, 1H, C-4—H), 5.5 (s, 1H, OH), 6.8—8.0 (m, 10H, 9 H_{arom} + N$\underline{H}$).

3-Cyano-5-hydroxy-4-(*p*-methoxyphenyl)-7-oxo-2-phenyl-7,8-dihydro-4*H*-pyrano-[2,3-*b*]pyridine (*X*)

Sodium hydroxide solution (10 cm^3; 5 %) was added to a boiling solution of *IX* (2.2 g; 5 mmol) in ethanol (25 cm^3). The reaction mixture was refluxed for 2 h, cooled, acidified with dilute hydrochloric acid and boiled for further 2 h. The solid product, obtained on cooling, was filtered off, washed with water, dried and recrystallized from benzene to give *X* as white crystals.

Formation of Pyranopyridine Derivative *VIII* by the Reaction of *X* with Phenacyl Bromide

A mixture of *X* (0.8 g; 2 mmol), phenacyl bromide (0.4 g; 2 mmol) in ethanol (20 cm^3) was refluxed for 2 h. Evaporation of half quantity of the solvent under reduced pressure followed by cooling afforded a solid product which was filtered off, dried and recrystallized from ethanol to give yellow crystals of *VIII*. No depression in melting point was observed on admixing with authentic sample prepared from compound *VII*.

Formation of Schiff Bases *XIa—XIc* by the Reaction of *II* with Aromatic Aldehydes

These products were prepared as yellow-coloured crystals, adopting the general procedure used for preparation of Schiff bases.

4-Aryl-3-chloro-*N*-[5-cyano-3-ethoxycarbonyl-4-(*p*-methoxyphenyl)-6-phenyl-4*H*-pyran-2-yl]-2-azetidinone Derivatives *XIIa*, *XIIb*

To a mixture of Schiff bases *XIa*, *XIb* (5 mmol in each case) and triethylamine (1 mmol) in dry benzene (20 cm^3), monochloroacetyl chloride (1 mmol) was added dropwise while stirring and keeping the temperature below 25 °C. The mixture was stirred for 5 h and kept at room temperature for 5 d. The precipitated triethylammonium chloride was filtered and washed with dry benzene. The combined solvent and filtrate was washed with dilute hydrochloric acid and water, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave yellow solid which was recrystallized from ethanol to give the final product as yellow crystals.

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