SYNTHESIS OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING CHROMENE

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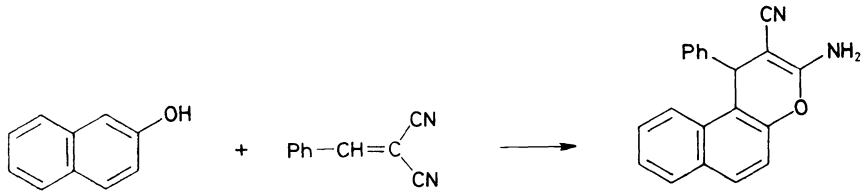
2-Amino-3-cyano-4*H*-phenyl-benzo[*f*]chromene (*I*) was reacted with formamide, acetic anhydride, and ethyl cyanoacetate to produce compounds (*II*—*IV*), respectively. Compound *IV* reacted with $HCONH_2$, $POCl_3$ and P_2S_5 to produce corresponding pyrimidobenzochromene (*V*), chloropyridobenzochromene (*VI*) and mercaptopyridobenzochromene (*VII*). Compound *VII* reacted with α-halocompounds to produce corresponding S-alkylated derivatives (*VIIIa* to *VIIIc*), and compound (*VI*) reacted with different amines to produce corresponding alkyl amino-, or aryl aminopyridobenzochromene (*IXa*—*IXc*) but in using hydrazine hydrate, pyrazolopyridobenzochromene (*X*) was obtained.

The synthesis[1-4] and biological[5-7] activity of chromenes have attracted significant attention in recent years, but chromenes fused with other heterocyclic ring have virtually been ignored. In this investigation 2-amino-4*H*-phenyl-benzo[*f*]chromene--3-carbonitrile (ref.[8]) was used as a starting material to prepare other heterocyclic rings fused with chromene.



I

2-Amino-4*H*-phenyl-benzo[*f*]chromene-3-carbonitrile (*I*) was obtained from the reaction of arylidinemalononitrile and β-naphthol in the presence of a catalytic amount of piperidine (Scheme 1). When refluxed with formamide, 1-amino-12*H*-phenyl--pyrimido[4,5-*b*]benzo[*f*]chromene (*II*) was produced. When compound *I* was refluxed with acetic anhydride, 1-diacetylamino-4*H*-phenyl-benzo[*f*]chromene-3-

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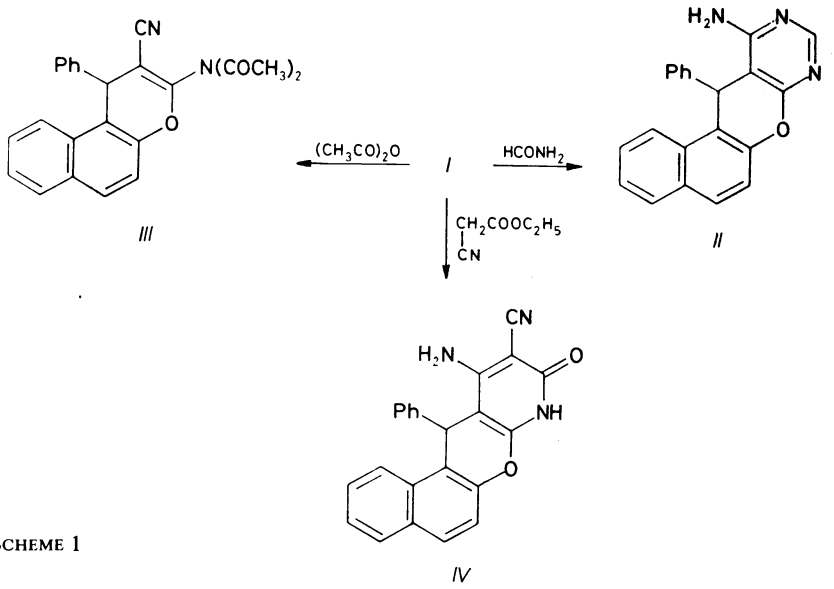
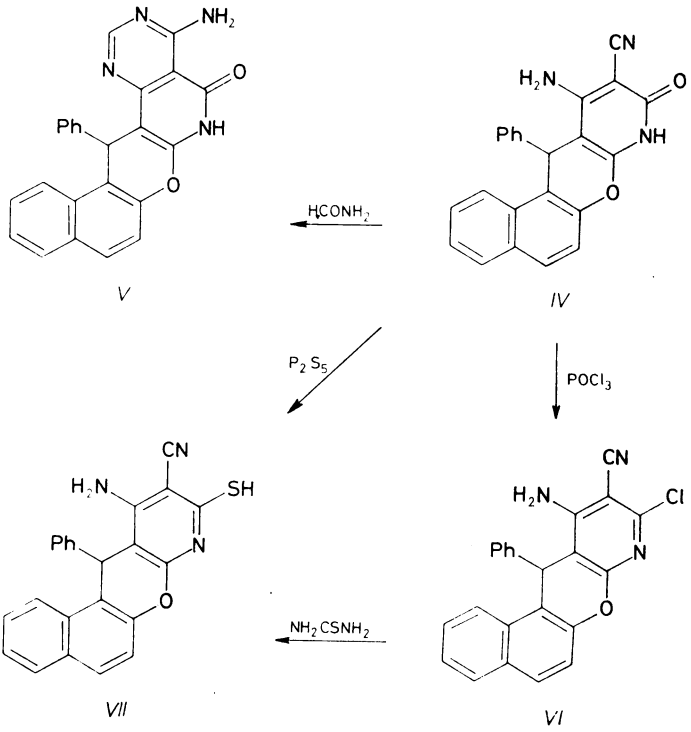


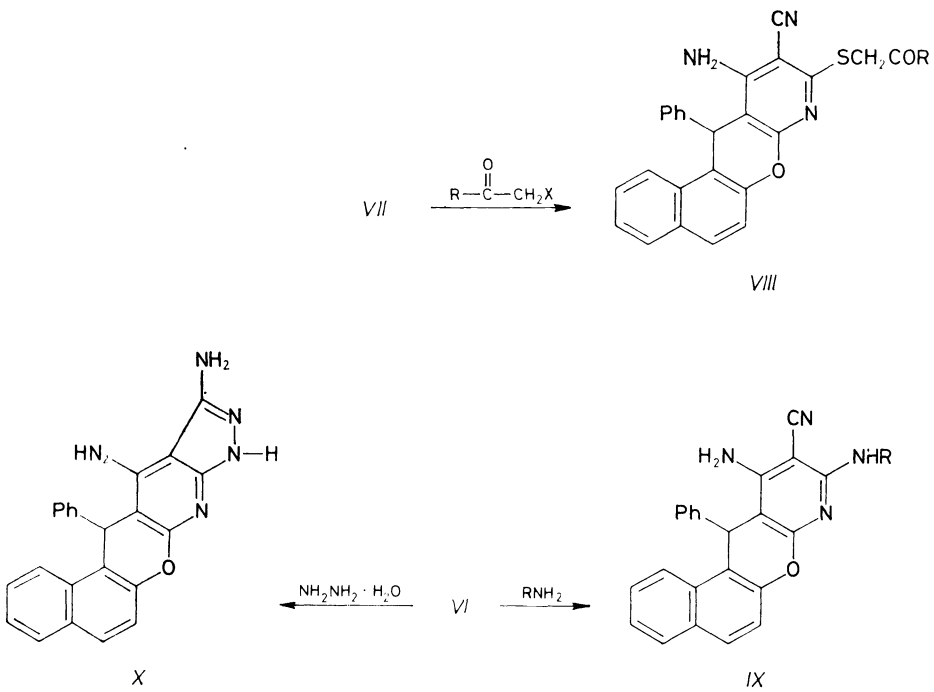
SCHEME 1



SCHEME 2

-carbonitrile (*III*) was obtained. By fusion with ethyl cyanoacetate compound *I* afforded 1-amino-3-hydroxy-12*H*-phenyl-pyrido[2,3-*b*]benzo[*f*]chromene-2-carbonitrile (*IV*).

4-Amino-14*H*-phenyl-pyrimido[5′,6′ : 3,4]pyrido[5,6-*b*]benzo[*f*]chromene (*V*) was obtained by refluxing compound (*IV*) with formamide. When compound *IV* was treated with phosphorus oxychloride, 1-amino-3-chloro-12*H*-phenyl-pyrido[2,3-*b*]-benzo[*f*]chromene-2-carbonitrile (*VI*) was produced, but when treated with phosphorus pentasulfide in refluxing pyridine, 1-amino-2-cyano-12*H*-phenyl-pyrido-[2,3-*b*]benzo[*f*]chromene-3-thiol (*VII*) was produced, which was identified by preparing it by the reaction of compound *V* with thiourea in refluxing ethanol followed by hydrolysis of thiouronium salt formed with sodium hydroxide and acidification with hydrochloric acid (Scheme 2).



SCHEME 3

When compound *VII* was allowed to react with halocompound, namely ethyl chloroacetate, phenacyl bromide and chloroacetanilide in refluxing ethanol in the presence of sodium acetate, the S-alkylation occurred, producing the corresponding S-alkylated derivatives *VIIIa* – *VIIIc* (Scheme 3). Compound *VI* reacted easily with

different amino compound. Reflux with aliphatic or aromatic amines produced the corresponding 1-amino-3-alkyl(aryl)amino-2-cyano-12*H*-phenyl-pyrido[2,3-*b*]benzo-[*f*]chromenes (*IX*). Use of the hydrazine instead of amines resulted the 1,13-diamino--12*H*-phenyl-pyrazolo[4',4' : 2,3]pyrido[5,6-*b*]benzo[*f*]chromene(*X*).

EXPERIMENTAL

Melting points reported are uncorrected and determined on Fisher–Johnes melting point apparatus. Elemental analysis were performed on Perkin–Elmer 240°C elemental analyser. IR spectra were recorded on a Perkin–Elmer spectrometer using KBr wafer technique. ^{1}H NMR spectra were recorded by 90 MHz Varian NMR spectrometer in $(CD_3)_2SO$ using tetramethylsilane as internal standard.

2-Amino-4*H*-phenyl-benzo[*f*]chromene-3-carbonitrile (*I*)

To a mixture of benzylidinemalononitrile (0·1 mol) and β-naphthol (0·1 mol) in ethanol (50 ml) few drops of piperidine were added. The mixture was refluxed for 1 h, the solid product was collected and recrystallized from acetic acid as white crystals, in 85% yield (25·3 g); m.p. 278°C (ref.[8] 278°C).

1-Amino-12*H*-phenyl-pyrimido[4,5-*b*]benzo[*f*]chromene (*II*)

Compound *I* (0·01 mol) in 10 ml formamide was refluxed for 4 h. The reaction mixture was allowed to cool, the product was filtered off, and recrystallized from ethanol as white crystals in 70% yield (2·3 g); m.p. 215°C. For $C_{21}H_{15}N_3O$ (325·4) calculated: 77·53% C, 4·65% H, 12·92% N; found: 77·88% C, 4·52% H, 13·15% N. IR ($\tilde{\nu}$, cm^{-1}): 3 400—3 300 (NH_2) and showed the disappearance of band characteristic of (C≡N); ^{1}H NMR (δ, $(CD_3)_2SO$): 7·0 to 8·2 m, 12 H (Ar–H); 6·1 s, 2 H (NH_2); 5·2 s, 1 H (CH pyran).

1-Diacetylamino-4*H*-phenyl-benzo[*f*]chromene-3-carbonitrile (*III*)

Compound *I* (0·01 mol) in 15 ml acetic anhydride was refluxed for 10 h and allowed to cool. The solid product was collected and recrystallized from acetic acid as white crystals. Yield 2·59 g (68%); m.p. 335°C. For $C_{24}H_{18}N_2O_3$ (382·4) calculated: 75·39% C, 4·71% H, 7·32% N; found: 75·58% C, 4·52% H, 7·62% N. IR ($\tilde{\nu}$, cm^{-1}): 2 220 (C≡N); 1 740, 1 780 (C=O); no band characteristic for NH_2 group.

1-Amino-3-hydroxy-12*H*-phenylpyrido[2,3-*b*]benzo[*f*]chromene (*IV*)

A mixture of compound *I* (0·01 mol) and ethyl cyanoacetate (0·01 mol) was fused at 180°C for 2 h. The reaction mixture was allowed to cool. The solid product was collected and recrystallized from acetic acid as pale brown crystals. Yield 2·37 g (65%); m.p. 275°C. For $C_{23}H_{15}N_3O_2$ (365·4) calculated: 75·61% C, 4·10% H, 11·50% N; found: 75·98% C, 3·84% H, 11·73% N. IR ($\tilde{\nu}$, cm^{-1}): 3 440, 3 340 and 3 190 (NH_2 and NH); 2 200 (C≡N) and 1 670 (C=O). ^{1}H NMR (δ, $CDCl_3$): 7·0—7·9 m, 11 H (Ar–H); 5·2 s, 1 H (pyran ring); 4·5 s, 2 H (NH_2).

4-Amino-14*H*-phenyl-pyrimido[5',6' : 3,4]pyrido[5,6-*b*]benzo[*f*]chromene (*V*)

Compound *IV* (0·01 mol) in 10 ml formamide was refiuxed for 5 h, then allowed to cool. The

solid product was collected and recrystallized from ethanol as brown crystals. Yield 2·2 g (60%); m.p. 220°C. For $C_{24}H_{16}N_4O_2$ (392·4) calculated: 73·46% C, 4·08% H, 14·28% N; found: 73·65% C, 3·85% H, 14·00% N. IR ($\tilde{\nu}$, cm^{-1}): 3 500—3 100 (NH_2 and OH); no band characteristic for C≡N group.

1-Amino-3-chloro-12*H*-phenyl-pyrido[2,3-*b*]benzo[*f*]chromene-2-carbonitrile (*VI*)

A mixture of compound *IV* (0·01 mol) and phosphorus oxychloride (10 ml) was refluxed for 5 h, then allowed to cool and poured onto ice. The solid product was collected and recrystallized from ethanol. Yield 2·56 g (66%) of yellowish white crystals; m.p. 190°C. For $C_{23}H_{14}ClN_3O$ (383·8) calculated: 71·96% C, 3·65% H, 9·25% Cl, 10·95% N; found: 72·18% C, 3·47% H, 9·52% Cl, 11·12% N. IR ($\tilde{\nu}$, cm^{-1}): 3 440, 3 340 (NH_2); 2 190 (C≡N); 1 640 (C=N).

1-Amino-2-cyano-12*H*-phenyl-pyrido[2,3-*b*]benzo[*f*]chromene-3-thiol (*VII*)

A) A mixture of compound *IV* (0·01 mol) and phosphorus pentasulfide (0·01 mol) in pyridine (30 ml) was refluxed for 5 h, allowed to cool, and poured into cold water. The solid product was collected and recrystallized from acetic acid as yellowish brown crystals. Yield 2·47 g (65%); m.p. 135—139°C.

B) A mixture of compound *VI* (0·01 mol) and thiourea (0·01 mol) in ethanol (30 ml) was refluxed for 5 h and allowed to cool. The solid product was collected, dissolved in NaOH solution (10% 100 ml) and then acidified with hydrochloric acid. The precipitated product was filtered off and recrystallized from acetic acid as yellowish brown crystals. Yield 2·66 g (70%); m.p. 138—139°C. For $C_{23}H_{15}N_3OS$ (381·5) calculated: 72·44% C, 3·93% H, 11·02% N, 8·39% S; found: 72·66% C, 4·18% H, 10·79% N, 8·39 S. IR ($\tilde{\nu}$, cm^{-1}): 3 440, 3 340 (NH_2); 2 190 (C≡N). ^1H NMR (δ, $CDCl_3$): 7·0—7·9 m, 11 H (Ar–H); 5·2 s, 1 H (pyran ring); 4·5 s, 1 H (SH); 4·9 s, 2 H (NH_2).

Reaction of Compound *VII* with α-Halocompounds

To a mixture of compound *VII* (0·01 mol) and α-halocompound (0·01 mol) in ethanol (30 ml), sodium acetate (2 g) was added, the mixture was refluxed for 3 h, then allowed to cool and poured into water. The solid product was collected and recrystallized from ethanol to give compounds *VIIIa*—*VIIIc*. The physical constants and spectral data of the products are presented in Table I.

Reaction of Compound *VI* with Aliphatic and Aromatic Amines

A mixture of compound *VI* (0·01 mol) and aliphatic or aromatic amine in ethanol (30 ml) was refluxed for 4 h, then allowed to cool. The solid product was collected and recrystallized from ethanol to give compounds *IXa*—*IXc*. Their physical constants and spectral data are represented in Table I.

1,13-Diamino-12*H*-phenyl-pyrazolo[4′,5′ : 2,3]pyrido[5,6-*b*]benzo[*f*]chromene (*X*)

A mixture of compound *VI* (0·01 mol) and hydrazine hydrate (0·01 mol) was refluxed in ethanol (30 ml) for 8 h, then allowed to cool. The solid product was filtered off and recrystallized from ethanol as yellowish brown crystals. Yield 2·46 g (65%); m.p. 260°C. For $C_{23}H_{17}N_5O$ (379·4) calculated: 72·82% C, 4·48% H, 18·46% N; found: 73·08% C, 4·71% H, 18·30% N. IR ($\tilde{\nu}$, cm^{-1}): 3 500—3 100 (2 NH_2, NH); no band characteristic of C≡N bond.

TABLE I

Physical and spectral data of compounds *VIIIa*—*IXc*

Compound R	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found % C	% H	% N	% S	Spectral data
VIIIa	259—261	$C_{27}H_{21}N_3O_3S$	69·37	4·49	8·99	6·85	IR: 1 740 (C=O), 2 220 (C≡N), 3 400—3 200 (NH_2);
OC_2H_5	78	(467·6)	69·00	4·67	9·15	6·67	^{1}H NMR: 1·5 s, 3 H (CH_3), 3·9 s, 2 H (CH_2 of ester group), 4·1 s, 2 H (SCH_2), 5·00 s, 1 H (CH of pyran ring), 6·7 s, 2 H (NH_2), 7·2—8·0 m, 11 H (Ar–H)
VIIIb	238—240	$C_{31}H_{21}N_3O_2S$	74·54	4·20	8·41	6·41	IR: 1 700 (C=O), 2 230 (C≡N), 3 400—3 200 (NH_2)
	84	(499·6)	74·80	4·00	8·30	6·67	
VIIIe	312	$C_{31}H_{22}N_4O_2S$	72·37	4·28	10·89	6·22	IR: 3 440—3 300 (NH_2 and NH), 2 190 (C≡N)
NHC_6H_5	68	(514·6)	72·09	4·52	11·12	5·98	
IXa	270	$C_{24}H_{18}N_4O$	76·19	4·76	14·81	—	IR: 3 450—3 300 (NH_2 and NH), 2 195 (C≡N)
CH_3	60	(378·4)	75·88	5·06	15·00	—	
IXb	265	$C_{29}H_{20}N_4O$	79·09	4·54	12·72	—	IR: 3 450—3 280 (NH_2 and NH), 2 190 (C=N);
C_6H_5	68	(440·5)	78·82	4·68	13·00	—	^{1}H NMR: 5·3 s, 1 H (CH of pyran ring), 6·8 s, 2 H (NH_2), 7·1—8·00 m, 16 H (Ar–H), 8·3 s, 1 H (NH)
IXc	210	$C_{31}H_{24}N_4O$	79·48	5·12	11·96	—	IR: 3 450—3 200 (NH_2 and NH), 2 180 (C≡N)
$CH_2CH_2C_6H_5$	70	(468·6)	79·67	4·88	12·18	—	

Antibacterial Activity Evaluation

Compounds *I*—*X* were screened for their antibacterial activity in vitro against a variety of Gram positive and Gram negative bacteria (*Staphylococcus aureus*, *Staphylococcus citreus*, *Pseudomonas pyocyanea*, *Klebsiella pneumoniae*, *Bacillus cereus*, *Proteus vulgaris*) by the agar diffusion technique[9]. Compound *VI* was found to be the most potent member of the series. It exhibits a significant activity against both *Bacillus cereus* and *Staphylococcus citreus*. All the remaining compounds were found to be devoid of any antibacterial activity.

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