Syntheses of Substituted Pyrazolo[3,4-*b*]quinolines, 3,4-Dihydro-4-oxopyrimido[4',5':4,5]theino[2,3-*b*]quinoline and Pyrido[1',2':1,2]pyrimido[4,5-*b*]quinoline [1]

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Syntheses of substituted pyrazolo[3,4-*b*]quinolines, 3,4-dihydro-4-oxopyrimido[4',5':4,5]theino[2,3-*b*]quinoline and 12-phenylpyrido[1',2':1,2[pyrimido[4,5-*b*]quinoline are described.

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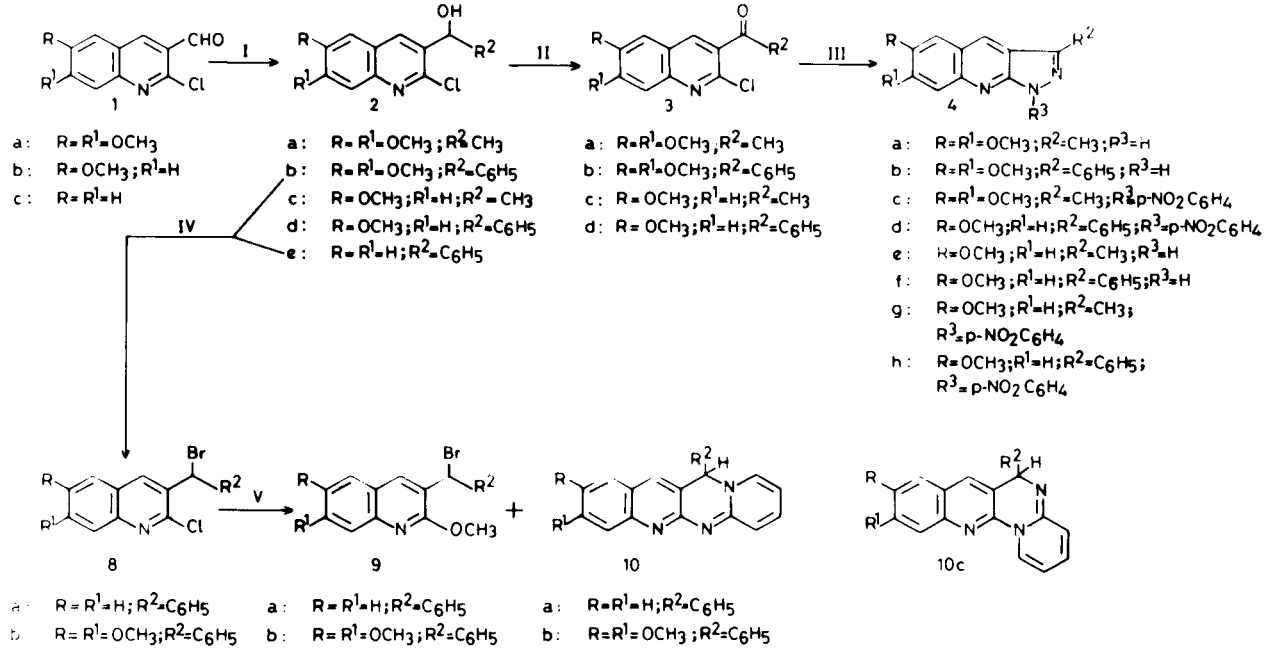
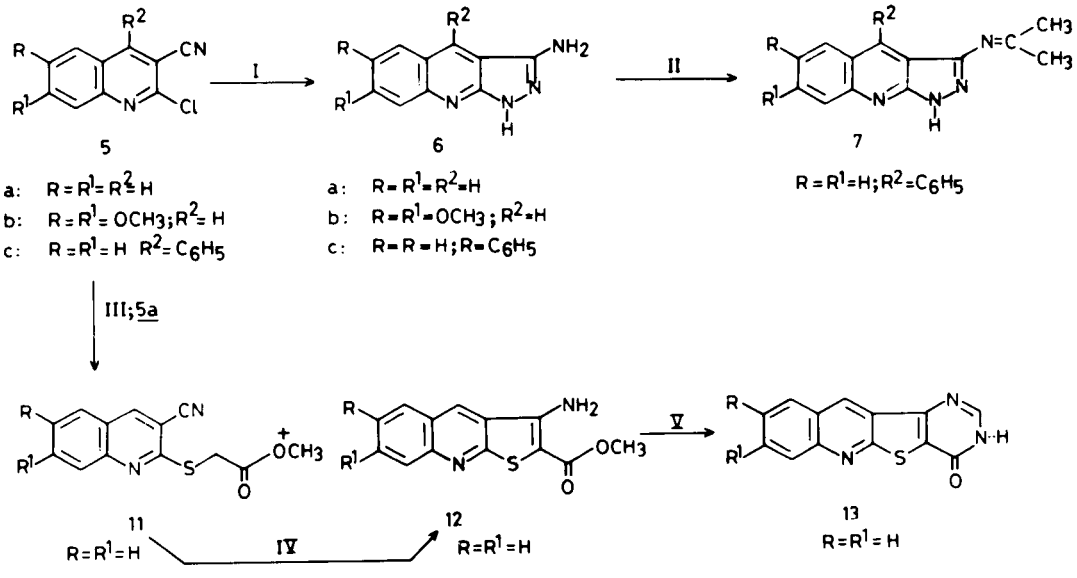
A number of reports concerning the synthetic utility of 2-chloro-3-formylquinolines (**1**) have appeared during the last few years [2-7]. Since this compound happens to be the starting material for the syntheses of various linear tri-and tetracyclic heterocycles of biological interest and in view of the present concern for evaluating the synthetic utility of **1**, the syntheses of the title compounds are presented here.

Ring closure of **1** with hydrazines or substituted hydrazines, an obvious route to tricyclic heterocycles, did not succeed [7] because the corresponding hydrazones had *E*-configuration. In principle, hydrazine or nitrogen-substituted hydrazine adduct of 3-acyl or aroyl quinolines, because of steric reasons, can be expected to facilitate a ring-closure. Indeed, a facile ring closure was observed in the reaction of 3-acyl or aroyl quinolines **3a-d** with hydrazine to yield pyrazolo[3,4-*b*]quinolines **4a-h** (Figure 1). However, ring closure of 2-chloro-3-cyanoquinoline **5a-c** with appropriate hydrazine proceeded smoothly to yield **6a-c** (Figure 2). The latter was found to exist predominently in the amino form as was evident from its derivatization to **7**. Another tricyclic heterocycle **12** (Figure 2) was conveniently prepared by reacting **5** with methyl thioglycolate and the intermediate compound **11** formed in the reaction, was also isolated. In presence of piperidine compound **11** in refluxing methanol, quantitatively cyclised to **12**.

Novel tetracyclic compounds **10a-b** (Figure 1) were synthesized from **2e** and **2b** which were obtained by the Grignard reaction [3] of **1c** and **1a**. Bromination of **2e** and **2b** with phosphorus tribromide furnished **8a-b**. Reaction of these halides with 2-aminopyridine yielded **10a-b** as major



I: Methyl or phenyl magnesium halide, ether:THF; II: Pyridinium Chlorochromate, CH_2Cl_2;
III: Hydrazine or p-nitrophenyl hydrazine, CH_3OH; IV: PBr_3, benzene; V: 2-Aminopyridine, CH_3OH, and $(C_2H_5)_3N$.



I: $NH_2NH_2.H_2O$, CH_3OH; II: Acetone; III: $SCH_2CO_2CH_3$, K_2CO_3, DMF; IV: Piperidine, CH_3OH;
V: Formamide.

Fig. 2

Table

Physical, Analytical and Spectral Data of Unknown Compounds

Compound	Mp °C	Yield %	Molecular formula	Analysis % Calcd./Found C	H	N	Spectral Data
4a [a]	220-222	40	$C_{13}H_{13}N_3O_2 \cdot \frac{1}{2} H_2O$	61.9 62.1	5.6 5.5	16.7 16.6	ir: 3350 (NH) and 1620 (−C=N) nmr (trifluoroacetic acid): δ2.5 (s, CH_3, 3H), 3.8 (s, OCH_3, 6H), 7.0-7.7 (m, C-8,5 and 4-H, 3H), 8.7 (broad, NH, 1H)
4b	225-226	50	$C_{18}H_{15}N_3O_2$	70.8 70.8	4.9 5.0	13.8 13.8	ir: 3400 (NH) and 1620 (−C=N) nmr (deuteriochloroform + deuteriodimethyl sulfoxide): δ 3.92 and 3.96 (2 singlets, OCH_3, 6H), 7.25 and 7.28 (2 singlets, C-5 and 8-H, 2H), 7.4 (d, aromatic, 3H), 7.9 (s, C-4H, 1H), 7.9-8.1 (m, aromatic, 2H), 8.8 (s, NH, 1H)
4c	216-218	40	$C_{19}H_{16}N_4O_4$	62.6 62.4	4.4 4.4	15.4 15.4	ir: 1610 (−C=N) nmr (trifluoroacetic acid): δ 2.1 (s, CH_3, 3H), 3.8 (s, OCH_3, 6H), 7.0-7.9 (m, C-8, 5,4-H and aromatic, 7H)
4d [b]	244-245 (dec)	40	$C_{24}H_{20}N_4O_5$	64.9 64.9	4.5 4.2	12.6 12.8	ir: 1600 (−C=N) nmr (deuteriochloroform): δ 3.9 and 4.0 (2 singlets, OCH_3, 6H), 6.8 (s, C-8H, 1H), 7.2 (s, C-5H, 1H), 7.3-8.3 (m, aromatic and C-4H, 10H)
4e [b]	230-231	40	$C_{12}H_{13}N_3O_2$	62.3 62.3	5.6 5.4	18.2 18.0	ir: 1620 (−C=N) nmr (deuteriochloroform + deuteriodimethyl sulfoxide): δ 1.9 (s, CH_3, 3H), 3.8 (s, OCH_3, 3H), 5.7 (s, NH, 1H), 7.0 (d, C-5H, 1H, J_m = 2.7 Hz), 7.2-7.4 (m, C-7 and 8-H, 2H), 8.0 (s, C-4H, 1H)
4f	234-235	50	$C_{17}H_{13}N_3O$	74.2 74.0	4.8 4.6	15.3 15.0	ir: 3100 (NH) and 1630 (−C=N) nmr (trifluoroacetic acid): δ 3.65 (s, OCH_3, 3H), 7.0-7.8 (m, C-7,8,5,4-H and aromatic, 9H), 9.2 (s, NH, 1H)
4g [c]	120 (dec)	35	$C_{18}H_{14}N_4O_3$	58.4 58.5	4.9 4.6	15.1 15.0	ir: 1600 (−C=N), 1500 (NO_2) nmr (deuteriochloroform + deuteriodimethyl sulfoxide): δ 2.4 (s, CH_3, 3H), 3.9 (s, OCH_3, 3H), 6.8-8.2 (m, C-4, 5,7,8-H and aromatic, 8H)
4h	220-222 (dec)	40	$C_{23}H_{16}N_4O_3$	69.7 69.5	4.0 4.0	14.1 14.0	ir: 1600 (−C=N) nmr (deuteriochloroform): δ 3.8 (s, OCH_3, 3H), 6.8 (d, C-5H, 1H, J_m = 1.8 Hz), 7.2-8.2 (m, aromatic and C-8,7 and 4-H, 12H)

Table (Continued)

Compound	Mp °C	Yield %	Molecular formula	Analysis % Calcd./Found C	H	N	Spectral Data
6a	178	70	$C_{16}H_8N_4$	65.2 65.0	4.4 4.2	30.4 30.4	ir: 3400 (NH_2) and 1640 (−C=N) nmr (deuteriodimethyl sulfoxide): δ 6.0 (broad, NH, 1H), 7.0-8.0 (m, aromatic, 4H), 8.3 (s, NH_2, 2H), 8.7 (s, C-4H, 1H)
6b	278	80	$C_{12}H_{12}N_4O_2$	59.0 59.0	5.0 5.0	22.9 22.7	ir: 3450 (NH_2), 3300 (NH) and 1640 (−C=N) nmr (deuteriodimethyl sulfoxide): δ 3.88 and 3.9 (2 singlets, OCH_3, 6H), 5.7 (broad, NH_2, 2H), 6.1 (broad, NH, 1H), 7.18 and 7.25 (2 singlets, C-8 and 5-H, 2H), 8.5 (s, C-4H, 1H)
6c	245	70	$C_{16}H_{12}N_4$	73.8 73.7	4.6 4.8	21.5 21.3	ir: 3450 (NH_2), 3300 (NH) and 1620 (−C=N) nmr (deuteriodimethyl sulfoxide): δ 4.5 (s, NH_2, 2H), 6.9 (broad, NH, 1H), 7.1-8.1 (m, aromatic, 9H)
7	150	90	$C_{19}H_{16}N_4$	76.0 76.3	5.3 5.5	18.7 18.9	ir: 3400 (NH) and 1620 (−C=N) nmr (deuteriochloroform): δ 2.0 (s, CH_3, 3H), 2.2 (s, CH_3, 3H), 3.8 (broad, NH, 1H), 6.9-8.0 (m, aromatic, 9H)
8a	oil	70	$C_{16}H_{11}Br$ ClN	57.7 57.9	3.3 3.6	4.2 4.0	ir: 1620 (−C=N) nmr (deuteriochloroform): δ 5.7 (s, CH, 1H), 7.1-8.2 (m, aromatic, 9H), 8.5 (s, C-4H, 1H)
8b	164-165	80	$C_{18}H_{15}Br$ $ClNO_2$	55.0 55.3	3.8 3.9	3.6 3.4	ir: 1630 (−C=N) nmr (deuteriochloroform): δ 3.80 and 3.82 (2 singlets OCH_3, 6H), 5.6 (s, CH, 1H), 7.0-8.1 (m, aromatic, 7H), 8.5 (s, C-4H, 1H)
9a	oil	15	$C_{17}H_{14}BrNO$	62.2 62.3	4.3 4.5	4.3 4.5	ir: 1610 (−C=N) nmr (deuteriochloroform): δ 3.8 and 3.82 (2 singlets, OCH_3, 6H), 5.6 (s, CH, 1H), 7.0-8.1 (m, aromatic, 7H), 8.5 (s, C-4H, 1H).
9b	105-106	10	$C_{19}H_{18}BrNO_3$	58.8 58.9	4.6 4.9	3.6 3.9	ir: 1620 (−C=N) nmr (deuteriochloroform): δ 4.0 (s, OCH_3, 9H), 5.2 (s, CH_3, 1H), 6.5-7.5 (m, aromatic, 7H), 8.1 (s, C-4H, 1H)
10a	oil	60	$C_{21}H_{15}N_3$	81.6 81.6	4.9 4.7	13.6 13.4	ir: 1640 and 1620 (−C=N) nmr (deuteriochloroform): δ 4.4 (s, CH, 1H), 6.4-6.6 (m, aromatic, 7H), 7.2-7.4 (m, aromatic, 3H), 7.9-8.1 (m, aromatic, 4H)
10b	42-44	65	$C_{23}H_{19}N_3O_2$	74.8 75.0	5.1 4.8	11.4 11.4	ir: 1640 and 1630 (−C=N) nmr (deuteriochloroform): δ 4.5 (broad, OCH_3 and CH, 7H), 6.3-6.7 (m, aromatic, 8H), 7.9-8.2 (m, aromatic, 4H)
11 [d]	136-137	15	—	—			—
12 [e]	262 dec	80	—	—			—
13 [f]	>300	80	$C_{13}H_7N_3SO$	61.7 61.5	2.8 3.0	16.6 16.4	ir: 3400 (NH) and 1660 (−C=O)

[a] Crystallized as hemihydrate. [b] Crystallized as hydrate. [c] Crystallized as dihydrate. [d] Mp 138-139 [11]. [e] Mp 263 [11]. [f] ^{1}H-NMR could not be recorded due to the poor solubility in common organic solvents.

products along with minor products **9a-b**. The other probable structure **10c** was ruled out on the basis of two observations made earlier. The first one relates to the exclusive formation of 1-alkyl-2-iminopyridine [8] in the reaction of 2-aminopyridine with alkyl halides. The second one is concerned with the displacement of only the bromine atom in the reaction of 3-bromomethyl-2-chloro quinolines with amines [9]. Yet another novel tetracyclic heterocycle **13** (Figure 2) was prepared by reacting **12** with formamide.

EXPERIMENTAL

Melting points were determined on an electrically heated block and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 157 grating instrument. The ^{1}H nmr spectra were recorded on a Perkin-Elmer R-32 spectrometer using tetramethylsilane as internal reference.

6-Alkoxy or 6,7-Dialkoxy-3-alkyl or aryl-(1*H*) or (1-substituted-phenyl)-pyrazolo[3,4-*b*]quinolines **4a-h**.

General Procedure.

A mixture of **3a-d** (0.01 mole), appropriately substituted hydrazines (0.015 mole) and methanol (40 ml) was refluxed under constant stirring for 2.5 hours. The solvent was removed *in vacuo*, the residue was diluted with water (20 ml) and the precipitated solid so obtained was purified by column chromatography over silica gel using chloroform-methanol mixture (9:1) as the eluant. Removal of the solvent gave compounds **4a-h** as pale yellow crystalline solids which were recrystallized from methanol.

3-Amino-1*H*-pyrazolo[3,4-*b*]quinoline (**6a**) and 3-Amino-6,7-dimethoxy-1*H*-pyrazolo[3,4-*b*]quinoline (**6b**).

General Procedure.

By following similar experimental procedure as described for the preparation of **4**, compounds **6a-b** were prepared from **5a-b**.

3-Amino-4-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**6c**).

It was prepared from **5c** by the same method as described for the preparation of **6a-b**. The starting material **5c**, in turn, was obtained by the Grignard reaction of **5a** with phenyl magnesium bromide [10].

3-(Isopropylidene)amino-4-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**7**).

A solution of **6c** (0.005 mole) in acetone (20 ml) was stirred at room temperature (30°) for 15 minutes. The separated solid was filtered and washed with water to yield **7** as a crystalline solid.

2-Chloro-3-[(α-phenyl)bromomethyl]quinoline (**8a**) and 2-chloro-6,7-dimethoxy-3[(α-phenyl)bromomethyl]quinoline (**8b**).

A mixture of **2e** or **2b** (0.01 mole), phosphorus tribromide (5 ml) and dry benzene (50 ml) was refluxed with stirring for 2.5 hours. Removal of the solvent followed by trituration of the residue with water furnished **8a** or **8b**, which were recrystallized from a mixture of chloroform-hexane.

2-Methoxy-3-[(α-phenyl)bromomethyl]quinoline (**9a**); 2,6,7-Trimethoxy-3-[(α-phenyl)bromomethyl]quinoline (**9b**) and 12-Phenylpyrido-[1′,2′:1,2]pyrimido[4,5-*b*]quinoline (**10a**); 8,9-Dimethoxy-12-phenylpyrido-[1′,2′:1,2]pyrimido[4,5-*b*]quinoline (**10b**).

To a well stirred solution of **8a** or **8b** (0.01 mole) in methanol (25 ml) were added triethylamine (0.2 ml) and 2-aminopyridine (0.015 mole). The reaction mixture was refluxed with stirring for 4 hours. The solvent was distilled off and the residue triturated with water (20 ml). The precipitated reaction product was purified by column chromatography over silica gel. Elution of the column with chloroform followed by a mixture of chloroform-ethyl acetate (8:2) yielded **9a-b** and **10a-b** respectively recrystallized from methanol.

3-Cyano-2-methoxycarbonylmethylthioquinoline (**11**) and Methyl 3-Aminotheino[2,3-*b*]quinoline-2-carboxylate (**12**).

A mixture of **5a** (0.001 mole), anhydrous potassium carbonate (0.0015 mole) and methyl mercaptoacetate (0.002 mole) in dry dimethylformamide (20 ml) was stirred at room temperature (30°) for 12 hours. Water (50 ml) was then added to the reaction mixture and the separated solid was filtered. It was purified by column chromatography over silica gel. Elution of the column with chloroform and with a mixture of chloroform-ethyl acetate (9:1) gave **11** and **12** respectively, recrystallized from methanol.

However, **11** could be quantitatively converted to **12** by refluxing a solution of **11** (0.001 mole) in methanol (25 ml) in presence of piperidine (0.1 ml).

3,4-Dihydro-4-oxopyrimido[4′,5′:4,5]theino[2,3-*b*]quinoline (**13**).

A mixture of **12** (0.0001 mole) and formamide (15 ml) was refluxed under stirring for 12 hours. The solution was cooled and poured onto crushed ice. The precipitated solid was recrystallized from methanol.

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