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Condensed heterotricycles: Synthesis of pyrazolo[3,4-*c*]quinoline derivatives†

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Pyrazol[3,4-*c*]quinoline **4a** is obtained from 4-(2-nitrophenyl)pyrazole-3-carboxylate (**3a**) by reduction followed by thermal cyclization. **4a** undergoes aminoalkylation uniquely at N(3) to form **4b-d**, as shown by ^{13}C NMR. Pyrazoles **3a** and **3c** are methylated at N(2) to **6a** and **6b** respectively which are reductively cyclized to pyrazoloquinolones **7a** and **7b**. The later are transformed into amino derivatives **8b-d** and **8g,h** via chloro compounds **8a** and **8f**. The amino alkoxypyrazoloquinoline (**8e**) is obtained from **8a** or the lactam **7a**. Cyclic hydroxamic acids **7c** and **7d** are prepared from the nitropyrazoles **6a** and **6b** by using $NaBH_4$ and Pd – C. A second synthesis of the pyrazolo[3,4-*c*]quinoline ring system consists of heating mercaptoacid (**8**) with methyl or phenyl hydrazine when **10a** or **10b** is obtained. Attempts to convert the pyrazole carboxylate **13a** into an isomeric pyrazoloisoquinoline system **12** via the isocyanate **13d** resulted only in the formation of bis-urea **14**.

As part of an ongoing programme of synthesis and biological evaluation of condensed heterotricycles[1], we took up a study of the pyrazolo (3,4-c) quinoline ring system. Syntheses reported in earlier literature[2] involving diazotisation of 3-aminolepidine offer access to the parent molecule, but with limited potentials for manipulation, whereas our new route reported herein leads to the pyrazolo-quinoline system with possibilities for derivatisation. Further our study highlights the use of ^{13}C NMR spectroscopy[3,4] for assignment of structures to products arising from substrates with multiple points of attack.

Addition of diazomethane to ethyl 2-nitro-(**1a**) and ethyl 2-nitro-4,5-dimethoxy (**1b**) cinnamate afforded the pyrazolines **2a** and **2b** which were oxidised by bromine to the pyrazoles **3a** and **3c** respectively[5]. Catalytic reduction of **3a** gave the amine **3b** which was cyclized thermally to pyrazoloquinoline **4a**. Attempts to convert the lactam to the iminochloride for further derivatisation failed. However, it could be converted to aminoalkyl derivatives **4b-d** by reaction with one molar equivalent of the respective chloride. Although there are potentially four sites of alkylation, *viz.* 2-5, the products formed under the reaction conditions were uniquely the 3-aminoalkyl derivatives. Crucial diagnostic data were the presence of a C = O band in the IR spectrum and signals in the ^{13}C NMR spectra for C-4 around δ 155 ppm as a singlet and for C-1 around 130 ppm as a large doublet ($^1J_{CH}$ 190 Hz) with no further fine structure. 4-Alkyl derivatives would lack a C = O group; 5-alkyl derivatives would exhibit $^3J_{CH}$ coupling for the C = O carbon signal in the ^{13}C NMR spectrum, while 2-alkyl derivatives would be characterized by the presence in the ^{13}C NMR spectrum of a large doublet for C-1, with further fine structure due to the three bond coupling with the protons on the substituent at N-2[3,4]. Treatment of the sodium salt of **4a** with excess methyliodide gave a product which was probably a mixture of **5** as the HI salt ($C_{12}H_{11}N_3O \cdot HI$; M^+ at m/z 213) and a small percentage of **4e** ($C_{11}H_9N_3O$; M^+ at m/z 199; IR: 1670 cm^{-1} (C = O), the formation of **5** from **4e** being based on analogy with the behaviour of **7a** (see below).

Methylation of pyrazoles **3a** and **3c** afforded 1-methyl-4-aryl pyrazole-3-carboxylates **6a** and **6b**. The structures are deduced from the fact that in their ^{13}C NMR spectra, the signals due to C-5 around δ 131 ppm were seen as a large doublet ($^1J_{CH}$ 186 Hz), exhibiting further quartet structure ($^3J_{CH}$ (CH_3) 3 Hz). **6a** and **6b** were transformed readily into **7a** and **7b** respectively by catalytic hydrogenation in ethanol solution and evaporation. As expected, in the ^{13}C NMR spectrum of **7a**, the signal of C-1 was a doublet ($^1J_{CH}$ 190 Hz) with further quartet structure ($^3J_{CH}$ 3 Hz). **7a** and **7b** were converted readily into the chloro derivatives **8a** and **8f** which were further

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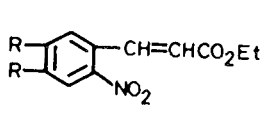
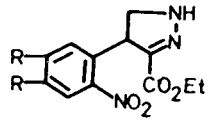


1a : R = H
1b : R = OMe



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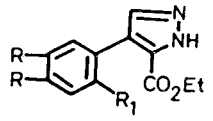
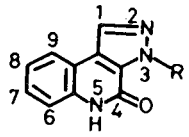
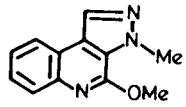
2b : R = OMe



3a : R = H ; R_1 = NO_2
3b : R = H ; R_1 = NH_2
3c : R = OMe ; R_1 = NO_2



4a : R = H
4b : R = CH_2CH_2N O
4c : R = $CH_2CH_2NEt_2$
4d : R = $(CH_2)_3NMe_2$
4e : R = Me



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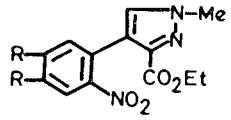
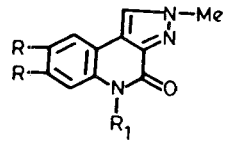
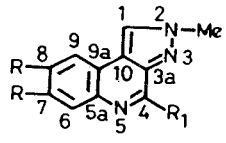


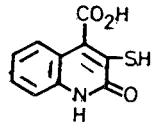
6a : R = H
6b : R = OMe



7a : R = R_1 = H
7b : R = OMe ; R_1 = H
7c : R = H ; R_1 = OH
7d : R = OMe ; R_1 = OH



8a : R = H ; R_1 = Cl
8b : R = H ; R_1 = 4-methyl-1-piperazinyl
8c : R = H ; R_1 = 4-morpholinyl
8d : R = H ; R_1 = NEt_2
8e : R = H ; R_1 = $O(CH_2)_3NMe_2$
8f : R = OMe ; R_1 = Cl
8g : R = OMe ; R_1 = 1-pyrrolidinyl
8h : R = OMe ; R_1 = $NHNH_2$



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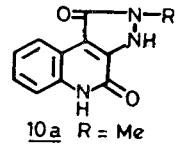
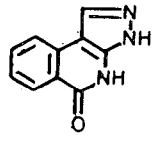


10a R = Me
10b R = Ph



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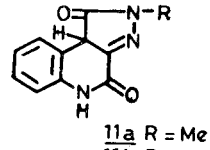
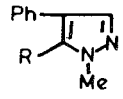
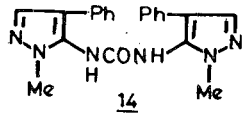


11a R = Me
11b R = Ph



13a : R = CO_2Et
13b : R = CO_2H
13c : R = CONHOH
13d : R = NCO
13e : R = NH_2
13f : R = CON_3



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transformed to various derivatives **8b-d**, **8g** and **8h**. A complete analysis of the ^{13}C NMR spectrum of **8g** is given in the experimental section. In the ^1H NMR spectra of **8b-d** and **8g**, belonging to the 2-methyl series, the signal due to H(1) suffered a larger downfield shift ($\Delta\delta$ 0.5 ppm), compared to that in **4c,d** of the 3-alkyl series ($\Delta\delta$ 0.3 ppm) in changing over from $CDCl_3$ to DMSO-d_6 as the solvent. This is in keeping with observations on isomeric alkyl nitromidazoles[4] and pyrazoles[6]. Treatment of the sodium salt of **7a** with 3-dimethylaminopropyl chloride led to the O-alkylated product **8e** (no C=O band in IR) which was also obtained from **8a** with the sodium salt of 3-dimethylaminopropanol. Reduction of the nitro esters **6a** and **6b** with sodium borohydride in the presence of palladised charcoal led to the formation of the cyclic hydroxamic acids **7c** and **7d** respectively.

The pyrazolo[3,4-*c*]quinoline ring system has been constructed by heating 3-mercapto-carbostyryl-4-carboxylic acid **9** with phenyl hydrazine[7]. In addition to repeating this, we have also used methyl hydrazine. The product from the former reaction has been formulated as **11b**[7]. We prefer structures **10a** and **10b** to **11a** and **11b** for the products because in their ^1H NMR spectra in DMSO-d_6 and in the ^{13}C NMR spectrum of the methyl hydrazine product, signals due to *CH*(CO) were not seen. On the other hand, both showed signals for *two* exchangeable hydrogens, one around 11 ppm due to H(5)

Table 1—Physical data of compounds **4-10**

Compd	Mol. formula	Mol. wt.	IR (Nujol) cm^{-1}	^1H NMR data	Selected ^{13}C NMR data
4a	$C_{10}H_7N_3$	185.20	1690 (CO)	[a]11.58 (s, N-5H); 8.52 (s, C-1H); 8.00 (m, C-9H), 6.98-7.53 (m, 4H, C-6 to C-8H + N-3H)	[a]155.0 (s, C-4), 130.8 (d × d; C-1. $^1J_{CH}$ 192; $^2J_{CH}$ 6 Hz).
4b	$C_{16}H_{18}N_4O_2$	298.34	1660 (CO)	[a]11.66 (s, N-5H); 8.42 (s, C-1H); 8.01 (m, C-9H); 7.13-7.53 (m, 3H, C-6 to C-8H); 4.84 (t, N-3 CH_2); 3.49 (m, CH_2OCH_2); 2.81 (t, $CH_2-N<$); 2.46 (m, $-N<^{CH_2}_{CH_2}$)	[a]154.6 (s, C-4); 131.1 (d, C-1; $^1J_{CH}$ 191 Hz)
4c	$C_{16}H_{20}N_4O$	284.36	1660 (CO)	[b]12.34 (s, N-5H); 7.11-7.51 (s, C-1H); 7.77 (m; C-9H); 7.11-7.51 (m, 3H, C-6 to C-8H); 4.86 (t, N-3 CH_2); 3.00 (t, CH_2NEt_2); 2.72 (q, 4H, $2CH_2CH_3$); 1.04 (t, $2CH_3$); 8.33 (C-1H).	
4d	$C_{15}H_{18}N_4O$	270.33	1650 (CO)	[b]11.0 (s, N-5H); 8.15 (s, C-1H); 7.87 (m, C-9H); 7.00-7.47 (m, 3H, C-6 to C-8H); 4.90 (t, N-3 CH_2); 1.80-2.60 (m, 4H, $CH_2CH_2NMe_2$); 2.5 2.25 (s, 6H, $2NCH_3$); 8.30 (C-1H).	[a+b]155.2 (s, C-4); 131.7 (d, C-1; $^1J_{CH}$ 186 Hz).
7a	$C_{11}H_9N_3O$	199.21	1680 (CO)	[a+b]11.33 (s, N-5H); 8.55 (s, C-1H); 7.80 (m, C-9H); 6.90-7.60 (m, 3H, C-6 to C-8H); 4.20 (s, N-2 CH_3)	[a]157.0 (s, C-4); 126.05 (dxq; C-1; $^1J_{CH}$ 192; $^3J_{CH}$ 3 Hz).
7b	$C_{13}H_{13}N_3O_3$	259.26	1660 (CO)		
7c	$C_{11}H_9N_3O_2$	215.21	1630 (CO)	[a]11.09 (s, N − OH); 8.69 (s, C-1H); 7.94 (m, C-9H); 7.69 (m, C-6H); 7.56 (m, C-7H); 7.24 (m, C-8H); 4.15 (s, N − CH_3).	[a]153.0 (s, C-5); 126.05 (dxq; C-1; $^1J_{CH}$ 190 $^3J_{CH}$ 3 Hz).
7d	$C_{13}H_{13}N_3O_4$	275.22	1610 (CO)	[a]11.06 (broad s, N − OH); 8.59 (s, C-1H); 7.53 (s, C-9H); 7.22 (s, C-6H); 4.13 (s, N − CH_3); 3.85 (s, 6H, 2OMe).	
8b	$C_{16}H_{19}N_5$	281.38		[b]8.05 (s, C-1H); 7.06-7.81 (m, 4H, C-6 to C-9H); 4.31 (t, 4H, $=C-N<^{CH_2}_{CH_2}$); 4.17 (s, N-2 CH_3); 2.60 (t, 4H, CH_2N-CH_2); 2.36 (s, $<^{CH_2}_{CH_2}>N$ Me) CH_3); 8.60 (C-1H)	
8c	$C_{15}H_{16}N_4O$	268.32		[b]8.03 (s, C-1H); 7.12-7.81 (m, 4H, C-6 to C-9 H); 4.27 (t, 4H, CH_2OCH_2); 4.14 (s, N − CH_3); 3.89 (t, 4H, CH_2NCH_2); 8.60 (C-1H)	[b]123.0 (d × q; $^1J_{CH}$ 186; $^3J_{CH}$ 3Hz
8d	$C_{15}H_{18}N_4$	254.33		[b]7.32-8.01 (m, 4H, C-6 to C-9H); 7.89 (s, C-1H); 4.33 (q, 4H, NCH_2); 4.13 (s, NCH_3); 1.56 (t, CH_2 CH_2CH_3; 8.60 (C-1H)	
8g	$C_{17}H_{20}N_4O_2$	312.37		[b]7.91 (s, C-1H); 7.19, 7.11 (2s, C-6H, C-9H); 4.12 (s, N-$2CH_3$); 4.04 (m, CH_2NCH_2); 3.97, 3.93 (2s, 2 OCH_3); 1.97 (m, 4H, $-N-CH_2CH_2CH_2$); 8.48 (C-1H).	[b]121.7 (dxq; C-1; $^1J_{CH}$ 185; $^3J_{CH}$ 3Hz
8e	$C_{16}H_{20}N_4O$	284.36		[b]8.02 (s, C-1H); 7.83 (m, C-9H); 7.10-7.83 (m, 3H, C-6 to C-8H); 4.72 (t, OCH_2); 4.15 (s, N-3CH); 1.8-2.70 (m, $CH_2CH_2NMe_2$); 2.30 (s, 6H, 2N − CH_3).	
10a	$C_{11}H_9N_3O_2$ (M^+ 215)	215.11	1680, 1610	[a]11.47 (s, N-5H); 8.10 (m, C-9H); 7.03-7.40 (m, 3H; C-6 to C-8H).	
10b	$C_{16}H_{11}N_3O_2$ (M^+ 277)	277.28	1670, 1620	[a]11.84 (s, N-5H); 8.27 (m, C-9H); 7.0-8.0 (m, 8H, C-6 to C-8H + C_6H_5).	

Satisfactory C,H,N analyses were obtained for all the compounds

[a]in DMSO-d_6; [b]in $CDCl_3$

and the other as a broad one due to NH below 6 ppm due to exchange with moisture in the solvent. Further the ^{13}C NMR spectrum of **10a**, showed two C = O carbon signals, one as a singlet at 158.2 (C-4) and the other as a finely split multiple at 156.4 ppm (C-1).

We made one futile attempt to use the ester **13a** for the synthesis of the isomeric pyrazoloisoquinoline system **12**, though the acid **13b**, acid chloride, hydroxamic acid **13c** and isocyanate **13d**. Treatment of the acid chloride with hydroxylamine in aqueous alkaline medium gave amine **13e** directly. Pyrolysis of the azide **13f** afforded the symmetrical urea **14** instead of the isocyanate **13d**.

Experimental Procedure

Ethyl 4-(2-*nitrophenyl*)-4,5-*dihydropyrazole*-3-*carboxylate* (**2a**) *and its* 3,4-*dimethoxy derivative* (**2b**)

To a solution of ethyl 2-nitrocinnamate (12.8 g, 60 mmole) in ether (50 ml) was added ethereal diazomethane (from 20 g nitrosomethyl urea, 60 ml 50% aq. KOH and 200 ml ether) and the mixture left overnight. On removal of ether, a residue was obtained which was crystallized from ether-hexane. Recrystallisation from the same mixture afforded **2a** (7.9 g; 50%) m.p. 94-96°. **2b** similarly prepared was a gum and used as such for the next experiment.

Ethyl 4-(2-*nitrophenyl*)*pyrazole*-3-*carboxylate* (**3a**) *and its* 3,4-*dimethoxy derivative* **3c**

Ester **2a** (2.1 g, 8 mmole) in ether (120 ml) was treated with bromine (1.4 g, 9 mmole) in the same solvent (20 ml). The solution was set aside at room temperature for 4 hr and evaporated. The residue was washed with water and crystallised from ethanol to give **3a** (1.5 g; 58%), m.p. 182-84°.

The free acid was obtained from the ester by hydrolysis with aqueous alcoholic alkali; m.p. 227-9° (from aq. ethanol) (Found: C, 51.75; H, 3.35; N, 18.1. $C_{10}H_7N_3O_4$ requires C, 51.5; H, 3.05; N, 18.0%).

Similarly was prepared **3c** in an overall yield of 60% and crystallised from methanol-acetone; m.p. 235-6°. This was also obtained by nitration of ethyl 4-(3,4-dimethoxyphenyl)pyrazole-3-carboxylate, m.p. 160-2° (Found: C, 61.1; H, 6.2; N, 10.3. $C_{14}H_{16}N_2O_4$ requires C, 60.85; H, 5.85; N, 10.15%) prepared by addition of diazomethane to ethyl 3,4-dimethoxy cinnamate followed by oxidation with bromine.

Ethyl 4-(2-*aminophenyl*)*pyrazole*-3-*carboxylate* (**3b**)

Ester **3a** (1g) was dissolved in ethanol (50 ml) and shaken with hydrogen at 1 atmospheric pressure in the presence of platinum catalyst (from 0.1 g PtO_2). The catalyst was filtered off and the filtrate evaporated. The residue was crystallised from ether to give **3b** (0.9 g), m.p. > 300°.

Pyrazoloquinolone (**4a**)

The above ester (6 g) was heated to its melting point. The initial melt solidified and was ground with ethanol and filtered to yield **4a** (4.5 g, 94%), m.p. > 300°.

Aminoalkyl pyrazoloquinolones (**4b-d**)

Pyrazoloquinolone **4a** (3.7 g, 20 mmole) in hot DMF (50 ml) was stirred with sodium hydride (50% suspension in mineral oil, 1 g) at 50° for 1 hr and then treated with N-(2-chloroethyl)morpholine (3 g, 20 mmole). The mixture was stirred at 60° overnight and filtered. The filtrate was evaporated and the residue treated with water and filtered. The precipitate was crystallised from chloroform-ethanol to give **4b** (3.5 g, 59%), m.p. 270-1°.

Similarly was prepared the diethylaminoethyl derivative **4c** in 32% yield; m.p. 173-75° (from ether) forming a tosylate ($C_{23}H_{28}N_4O_4S$) m.p. 194-96°C (from ethanol) and dimethylaminopropyl derivative **4d** (50%), m.p. 168-70° (from ether-hexane).

Dimethylpyrazoloquinoline (**5**)

To the sodium salt of **4a** [prepared from **4a** (1.1 g, 6 mmole) and 50% sodium hydride (300 mg)] in DMF (20 ml), methyl iodide (5 ml) was added and the mixture stirred at 50° for 16 hr. It was then filtered and the solvent removed from the filtrate. The residue obtained was treated with water again and filtered. The filtrate was made acidic when the HI salt of **5** was precipitated along with some **4e**. This was filtered off and crystallised from MeOH; yield 0.2 g, m.p. 222° (d) (Found: C, 42.6; H, 3.75; N, 12.55. $C_{12}H_{12}IN_3O$ requires C, 42.25; H, 3.5; N, 12.3%).

Methyl pyrazoloquinolone **7a** *and its dimethoxy derivative* **7b**

Ester **3a** (2.1 g, 8 mmole) in dioxane (25 ml) at 50° was treated with sodium hydride (50% suspension in mineral oil; 0.4 g, 8.3 mmole) and the resultant sodium salt stirred with methyl iodide (2 ml) at 50° overnight. The mixture was filtered and the filtrate evaporated to dryness. The residue was crystallized from hexane and it was recrystallised from ethanol to give **6a** (2g, 91%), m.p. 129-131°. Similarly was prepared the dimethoxy derivative **6b** in 66% yield; m.p. 153-5° (from ethanol).

Reduction of ester **6a** (11 g, 40 mmole) in ethanol

(250 ml) with hydrogen at atmospheric pressure and room temperature using platinum catalyst (from 0.5 g PtO_2), filtration, evaporation of the filtrate and heating of the residue at 100° for 3 hr yielded pyrazoloquinolone **7a** (5.9 g, 74%), m.p. 285-57° (from methanol). Likewise ester **6b** was reduced in methanol solution and cyclised to **7b** in 85% yield; m.p. > 300° (from DMF-ethanol).

4-Chloro-2-methylpyrazoloquinolone (**8a**) *and its dimethoxy derivative* (**8f**)

Quinolone **7a** (5 g, 25 mmol) and phosphorous oxychloride (30 ml) were heated together under reflux for 3 hr. Excess reagent was removed *in vacuo* and the residue treated with ammonia. Extraction with chloroform and evaporation of the extract afforded **8a** (5.1 g, 94%), m.p. 148-49° (from $CHCl_3$ – hexane).

The dimethoxy derivative **8f** was similarly prepared from **7b** in 90% yield m.p. 255-56° (from chloroform).

4-Amino-2-methyl pyrazoloquinolones (**8b-d**), **8g** and **8h**)

Chloro derivative **8a** (3.3 g, 15 mmol) and N-methyl piperazine (3.0 g, 30 mmole) were heated together at 100° for 4 hr. The solution was diluted with water and filtered to give piperazinopyrazoloquinoline **8b** (4.0 g, 95%), m.p. 85-89°, yielding a ditosylate, ($C_{30}H_{35}N_5O_6S_2 \cdot H_2O$), m.p. 176° (from ethanol).

8c was similarly prepared in 92% yield; m.p. 129-131° (from methanol); tosylate ($C_{22}H_{24}N_4O_4S$), m.p. 273-75° (from methanol).

8d was obtained in 60% yield from **8a** using excess diethyl amine at 100° in an autoclave for 16 hr and characterized as the tosylate ($C_{22}H_{26}N_4O_3S \cdot H_2O$) m.p. 182-84° (from ethanol-ether).

The displacement reaction of chloride in **8f** was conducted in chloroform-ethanol mixture to give pyrrolidino derivative **8g** as tosylate ($C_{24}H_{28}N_4O_5S \cdot H_2O$) in 75% yield; m.p. 278-79° (from ethanol); ^{13}C of base in $CDCl_3$: δ 149.4 (C-8, qui, J 3.7 Hz), 148.5 (C-4, s), 145.3 (C-7; qui, J 3.7 Hz), 139.5 (C-5a; d × d; J 3.2, 7.9 Hz), 138.2 (C-3a; d; J 7.4 Hz), 123.2 (C-9a; d × d; J 5.2, 8.9 Hz), 121.7 (C-1; d × q; J 188, 2.8 Hz), 110.7 (C-10; d; J 5.6 Hz), 109.3 (C-6; d; J 158 Hz), 104.7 (C-9; d; J 155 Hz), 56.3 (O – CH_3; q; J 144 Hz), 55.9 (O – CH_3, q; J, 144 Hz), 48.5 (N – CH_2; t; J 143 Hz), 40.0 (N – CH_3; q; J 140 Hz), 25.4 ppm (N CH_2CH_2; t; J 132 Hz), and the hydrazino derivative **8h** (85%), m.p. 216-8° (from methanol).

Dimethylaminopropyloxypyrazoloquinoline (**8e**)

To a stirred solution of 3-dimethylaminopropanol (0.8 g, 8 mmole) in dioxane (10 ml) was added with stirring, sodium hydride (50% suspension in mineral oil, 0.4 g, 8 mmole). After 30 min, a solution of chloro compound **8a** (1.3 g, 6 mmole) in dioxane (25 ml) was added. The mixture was stirred at 60° overnight and filtered. The filtrate was evaporated to dryness and the residual oil separated into neutral (0.15 g) and basic (0.7 g) parts. The latter gave the dipicrate of **8e** ($C_{28}H_{26}N_{10}O_{15}$), m.p. 178-80° (from acetone-methanol).

This was also obtained in 32% yield by treating pyrazoloquinolone **7a** with sodium hydride in DMF followed by 3-dimethylaminopropyl chloride.

5-Hydroxy-2-methyl pyrazoloquinolones (**7c**) *and* (**7d**)

Nitroester **6a** (2.75 g, 10 mmole) in methanol (25 ml) was added to a stirred suspension of 10% Pd – C (50 mg) in water (25 ml) containing sodium borohydride (0.8 g) in an atmosphere of nitrogen. After 15 min, the mixture was filtered and the filtrate made acidic. The precipitate was filtered off and crystallised from chloroform-methanol to give **7c** (1.1 g, 51%), m.p. 284-46°, giving a deep red ferric reaction; M^+ 215.

Similarly nitroester **6b** afforded **7d** in 65% yield; m.p. 282-3°; M^+ 275.

Pyrazoloquinolinediones (**10a**) *and* (**10b**)

Mercaptoquinoline carboxylic acid **9** (3.3 g, 15 mmole) and methyl hydrazine (2.3 g, 50 mmole) were heated together in ethanol (50ml) under reflux for 1 hr. After removal of solvent, the residue was acidified with 2*N* HCl. The precipitate was filtered off and recrystallised from DMF-ether to afford **10a** (1.5 g, 70%), m.p. > 300°.

Likewise **9** (1.1 g, 5 mmole) and phenylhydrazine (1.1 g, 10 mmole) gave **10b** in 60% yield, m.p. > 300° (from acetone-ethanol).

1-Methyl-4-phenylpyrazole-3-carboxylic acid (**13b**)

Ethyl 4-phenylpyrazole-3-carboxylate was methylated using the conditions employed for **6a** in 92% yield to give **13a**, m.p. 89-91° (from ethanol).

Hydrolysis using aq. alcoholic sodium hydroxide gave the free acid **13b**, m.p. 127-29° (from chloroform-hexane).

Action of hydroxylamine on acid chloride of (**13b**)

The above acid (2.0 g, 10 mmole) was refluxed with thionyl chloride (20 ml) and benzene (20 ml) for 2 hr. After evaporation, the acid chloride was dissolved in dry ether (20ml) and the solution added to an ice-cold solutionof hydroxyl amine hydrochloride (0.8 g) and sodium hydroxide (0.9 g) in water

(20 ml) with stirring. After 3 hr the crystalline precipitate was filtered off and recrystallised from ether to give **13e** (0.5 g, 30%), m.p. 116-19°; NMR($CDCl_3$) 7.30-7.60 (m, 5 aromatic H), 7.25 (s, pyrazole H), 3.72 (NCH_3), 3.63 (s, 2H, disappears with D_2O); M^+ 173.

Curtius degradation of acid (**13b**)

Acid chloride from the acid **13b** (2.5 g) was dissolved in acetone (20 ml) and the solution cooled to − 5°. Sodium azide (1.0 g) in water (5 ml) was added with stirring. After 30 min, water (500 ml) was poured in and the oily azide **13f** extracted into benzene (100 ml). The dried benzene extract was heated gently under reflux until nitrogen evolution ceased. After a further 2 hr reflux, the solvent was evaporated off and the residue extracted with hexane. The insoluble part was crystallised from chloroform-hexane to give the bis-urea **14** (1.2 g, 55%), m.p. 205-7°.

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