Synthesis, Molecular, and Crystal Structure of a New, Unexpected Polycyclic System: 5,12:10,12-Dimethano-12*H*-pyrazolo[3,4-*b*]pyrazolo[4',3':6,7]-azepino[2,3-*f*]azocine†

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By reacting 1-phenyl-3-R-5-methylaminopyrazoles (**1a**, **b**) and hexane-2,5-dione (**2**) in acetic acid compounds (**4a**, **b**), containing the title system, were obtained. They were characterized by elemental analysis, n.m.r. spectroscopy and, for (**4a**), *X*-ray crystallography of a single crystal. The structure is characterized by a fused hexacyclic system which includes two *N*-phenyl-substituted pyrazole rings adjacent to two azepine ones in the half-chair conformation and, finally, two five-membered fused rings.

Benzazepine derivatives show a wide range of pharmacological properties such as fungicidal,[1] analgesic,[2] antihypertensive,[3] renal vasodilator,[4] antidepressant,[5] and other central nervous system activity.[6] Moreover, some pyrazolo[3,4-*b*]azepin-7-ones exhibit significant anti-inflammatory and analgesic effects in mice.[7]

As a part of our programme devoted to obtaining compounds with analgesic and/or anti-inflammatory activity, and with low side effects,[8,9] we sought to synthesize novel pyrazolo[3,4-*b*]azepine derivatives (**3**) and screen these for their pharmacological properties.

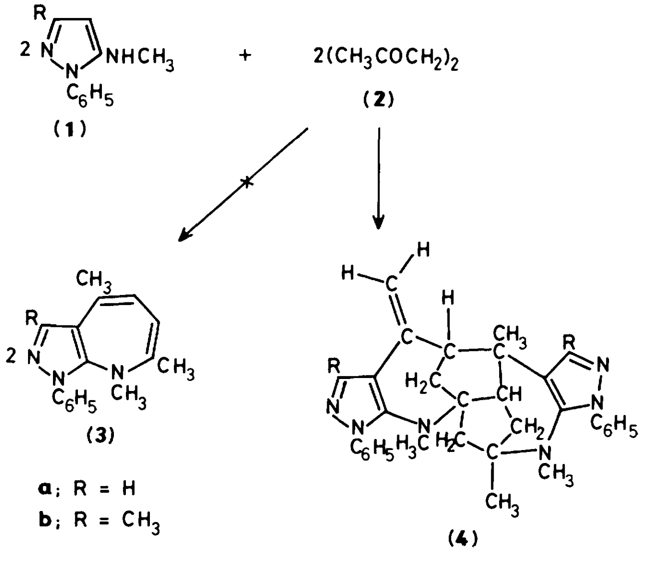
In order to achieve this goal we reacted 1-phenyl-3-R-5-methylaminopyrazoles (**1a**, **b**) and hexane-2,5-dione (**2**) in acetic acid under reflux (see Scheme 1). The 5-amino group of the pyrazole nucleus must be alkylated to avoid the formation of 1-(pyrazol-5-yl)pyrrole derivatives as reported for the analogous 1-methyl-3-R-5-aminopyrazoles.[10] However, we obtained unexpected products rather than the pyrazoloazepines (**3a**, **b**). To these we assigned structures (**4a**, **b**) on the basis of analytical and spectroscopic data and [for compound (**4a**)] *X*-ray analysis.

The molecular formulae of (**4a**, **b**) suggest that two hexane-2,5-dione molecules and two methylaminopyrazoles condensed to give compound (**4**) with the elimination of four molecules of water.

The i.r. spectra for (**4a**, **b**) do not show absorption for the methylamino group and the u.v. spectra above 200 nm, practically identical, are not informative.

The 300 MHz ^1H n.m.r. spectrum (Table 1) of compound (**4a**) showed, in addition to other signals, distinct resonances for two tertiary methyls, two *N*-methyl groups, one exocyclic methylene, two protons in the 3-position of the pyrazole nucleus (δ 7.40 and 7.71), and finally ten aromatic protons. The spectrum was analysed with the first-order approximation and the proton assignments (Table 1) are based on coupling constant sequences evaluated with the relationships between the coupling constants and dihedral angles (Dreiding molecular models).

9-H showed coupling only with 21a-H (J 9.2 Hz) (see Figure 1 and Scheme 1) and 19-H coupled only with 20a-H (J 6.4 Hz). Moreover the 20b-H signals were doublets with a geminal coupling constant of 13.8 Hz and a long-range coupling of 2.8 Hz with 18b-H. This long-range coupling is a result of the reciprocal positions of 18b- and 20b-H in the W-shaped sequence[11] for $H_bC(18)C(17)C(20)H_b$.



Scheme 1.

The ^1H n.m.r. spectrum of compound (**4b**) (Table 1) was similar to that of (**4a**) with the addition of signals for two methyl groups and the absence of the singlets at δ 7.40 and 7.71. However, the spectrum showed the exocyclic methylene proton signals as a poorly separated double doublet with $\Delta\delta$ 0.03 whereas for compound (**4a**) the spectrum produced two distinct doublets (δ_H 4.77 and 5.17; J 1.8 Hz) with $\Delta\delta$ 0.40 p.p.m.

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† The numbering of this system is according to IUPAC recommendations and is different from that used in the crystallographic numbering scheme.

Table 1. ^1H N.m.r. chemical shifts and multiplicities of compounds (**4a** and **b**). Designations for hydrogen atoms refer to the crystallographic numbering shown in Figure 1

	(**4a**)	(**4b**)
Me(36)	1.24 (s)	1.31 (s)
Me(22)	1.44 (s)	1.42 (s)
NMe(37)	2.39 (s)	2.41 (s)
NMe(38)	2.37 (s)	2.35 (s)
2Me(39, 40)		2.36 (s)
H(18a)	1.52 (d) (*J* 12.8 Hz)	1.49 (d) (*J* 12.8 Hz)
H(20a)	1.87 (dd) (*J* 13.8, 6.4 Hz)	1.90 (dd) (*J* 13.8, 6.4 Hz)
H(21a)	1.95 (dd) (*J* 13.6, 9.2 Hz)	1.94 (dd) (*J* 13.6, 9.2 Hz)
H(21b)	2.12 (d) (*J* 13.6 Hz)	2.21 (d) (*J* 13.6 Hz)
H(20b)	2.22 (dd) (*J* 13.8, 2.8 Hz)	2.30 (dd) (*J* 13.8, 2.6 Hz)
H(18b)	2.46 (dd) (*J* 12.8, 2.8 Hz)	2.43 (dd) (*J* 12.8, 2.6 Hz)
H(9)	2.57 (d) (*J* 9.2 Hz)	2.54 (d) (*J* 9.2 Hz)
H(19)	2.77 (d) (*J* 6.4 Hz)	2.85 (d) (*J* 6.4 Hz)
H(23a)*	4.77 (d) (*J* 1.8 Hz)	5.0 (d) (*J* 1.8 Hz)
H(23b)*	5.17 (d) (*J* 1.8 Hz)	5.03 (d) (*J* 1.8 Hz)
H(6)	7.71 (s)	
H(12)	7.40 (s)	
10H-2Ar	7.20—7.72 (m)	6.85—7.40 (m)

* Assignment may be reversed.

Table 2. ^{13}C N.m.r. chemical shifts (p.p.m.) and multiplicities of compounds (**4a** and **b**). Designations for carbon atoms refer to the crystallographic numbering scheme shown in Figure 1

	(**4a**)	(**4b**)
C(1)	79.05 (s)	78.12 (s)
C(3)	147.21 (s)	147.33 (s)
C(6)	139.21 (d)	147.88 (s)
C(7)	116.23 (s)	112.98 (s)
C(8)	140.53 (s)	140.36 (s)
C(9)	59.72 (d)	62.33 (d)
C(10)	46.70 (s)	47.37 (s)
C(11)	113.11 (s)	111.29 (s)
C(12)	138.88 (d)	147.33 (s)
C(15)	144.66 (s)	145.64 (s)
C(17)	67.47 (s)	67.14 (s)
C(18)	39.85 (t)	39.49 (t)
C(19)	62.46 (d)	62.33 (d)
C(20)	45.98 (t)	45.77 (t)
C(21)	35.84 (t)	37.00 (t)
C(22)	24.66 (q)	24.17 (q)
C(23)	109.59 (t)	112.31 (t)
2C(24, 28)	123.22 (d)	123.58 (d)
2C(25, 27)	129.01 (d)	128.96 (d)
C(26)	126.62 (d)	126.27 (d)
C(29)	141.45 (s)	142.51 (s)
2C(30, 34)	123.99 (d)	123.84 (d)
2C(31, 33)	129.01 (d)	129.07 (d)
C(32)	126.62 (d)	126.44 (d)
C(35)	141.45 (s)	141.39 (s)
C(36)	26.15 (q)	25.93 (q)
C(37)	34.82 (q)	35.22 (q)
C(38)	37.20 (q)	36.74 (q)
C(39)		17.15 (q)
C(40)		15.71 (q)

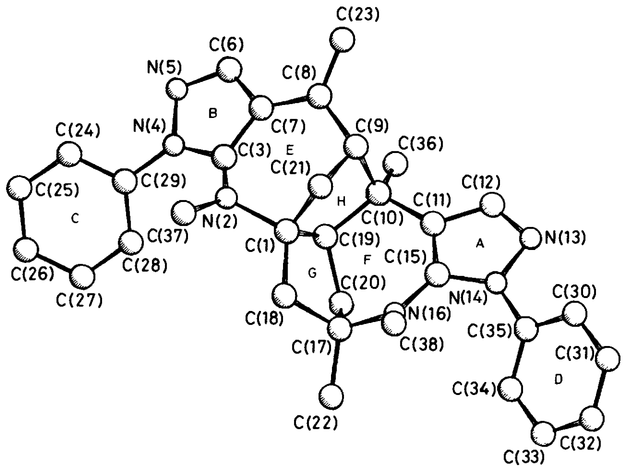


Figure 1. Perspective of the molecule (hydrogen omitted for sake of clarity) with atom and ring numbering scheme

The ^{13}C n.m.r. spectra (Table 2) indicated some differences for the exocyclic methylene carbon atom. In fact, C(23) of compound (**4b**) showed a downfield shift of 2.72 p.p.m. compared with that for (**4a**). This discrepancy may be explained by a different conformation in ring E for the two compounds (see Figure 1). In fact, C(9), C(21), and C(1) in ring E in compound (**4b**) compared with (**4a**) show $\Delta\delta$ values of 2.61, 1.16 (downfield), and 0.93 (upfield) p.p.m. respectively, while no significant variations can be observed for the remaining carbon atoms.

An *X*-ray crystallographic analysis was carried out to establish the structure of compound (**4a**). This was not possible for (**4b**) because no good single crystal was obtained. Figure 1 shows a perspective view of one molecule of (**4a**) with the atom numbering scheme (hydrogen atoms are omitted for clarity). Selected interatomic distances and angles are reported in Table 3.

The molecular structure is characterized by the presence of two penta-atomic *N*-phenyl-substituted planar systems (A and B in Figure 1) which stabilize the conformations (see below) of the adjacent seven-membered rings E and F. These have between them the two fused five-membered rings G and H.

There is a wide range of N–C bond distances: N(2)–C(1) 1.480(7) and N(16)–C(17) 1.478(7) Å correspond to the standard N(sp^3)–C(sp^3) distance and N(2)–C(37) 1.466(7) and N(16)–C(38) 1.465(7) Å are not far from it, especially as the angles around N(16) are closer to planarity than pyramidality (see Table 3). N(5)–C(6) 1.300(9) and N(13)–C(12) 1.318(10) Å are very close to the double-bond value of 1.27 Å (ref. 12), while N(4)–C(3) 1.376(8), N(4)–C(29) 1.395(6), N(2)–C(3) 1.398(7), N(14)–C(35) 1.401(6), N(14)–C(15) 1.379(7), and N(16)–C(15) 1.382(7) Å are intermediate between single- and double-bond lengths.

Examination of the bond lengths involving each of two heterocyclic penta-atomic rings (A and B) indicates conjugated systems. For ring B this extends from C(23) and ends on one side at N(2) and on the other side at C(29). In fact C(8)–C(23) 1.352(6) Å is longer than a pure C=C bond and C(7)–C(8) 1.457(6), C(3)–C(7) 1.376(7), and C(6)–C(7) 1.409(9) Å, with C(3)–N(4) and N(4)–C(29) quoted above, are indicative of a mesomeric effect in this system. The N(4)–N(5) [1.379(7) Å] and N(13)–N(14) [1.367(7) Å] bond lengths are close to single bond values.

The conformation of the adjacent seven-membered ring E (see Figure 1) can be described as half-chair. [The torsion angles C(3)–N(2)–C(1)–C(21) and C(7)–C(8)–C(9)–C(21) are

Table 3. Bond distances (Å) and angles (°) with e.s.d.s in parentheses

N(4)–N(5)	1.379(7)	C(8)–C(23)	1.352(6)
N(4)–C(3)	1.376(8)	C(8)–C(9)	1.517(7)
N(4)–C(29)	1.395(6)	C(9)–C(21)	1.523(7)
N(5)–C(6)	1.301(9)	C(9)–C(10)	1.562(6)
N(2)–C(3)	1.398(7)	C(21)–C(1)	1.541(7)
N(2)–C(1)	1.480(7)	C(1)–C(19)	1.537(7)
N(2)–C(37)	1.466(7)	C(1)–C(18)	1.544(7)
N(16)–C(17)	1.478(7)	C(19)–C(20)	1.538(6)
N(16)–C(38)	1.465(7)	C(19)–C(10)	1.548(6)
N(16)–C(15)	1.382(7)	C(36)–C(10)	1.527(8)
N(13)–N(14)	1.367(7)	C(20)–C(17)	1.521(7)
N(13)–C(12)	1.318(10)	C(18)–C(17)	1.536(7)
N(14)–C(15)	1.379(7)	C(17)–C(22)	1.531(6)
N(14)–C(35)	1.401(6)	C(10)–C(11)	1.501(7)
C(6)–C(7)	1.409(9)	C(15)–C(11)	1.389(8)
C(7)–C(8)	1.457(6)	C(11)–C(12)	1.403(9)
C(7)–C(3)	1.376(7)		

C(3)–N(4)–C(29)	131.1(4)	N(2)–C(1)–C(19)	110.3(4)
N(5)–N(4)–C(29)	117.3(4)	C(19)–C(1)–C(18)	104.5(4)
N(5)–N(4)–C(3)	111.4(4)	C(1)–C(19)–C(10)	108.0(4)
N(4)–N(5)–C(6)	103.3(5)	C(1)–C(19)–C(20)	106.1(4)
C(1)–N(2)–C(37)	114.0(4)	C(20)–C(19)–C(10)	115.8(4)
C(3)–N(2)–C(37)	113.5(4)	C(19)–C(20)–C(17)	105.2(4)
C(3)–N(2)–C(1)	115.2(4)	C(1)–C(18)–C(17)	106.1(4)
C(38)–N(16)–C(15)	117.4(4)	C(20)–C(17)–C(18)	100.5(4)
C(17)–N(16)–C(15)	122.3(4)	N(16)–C(17)–C(18)	113.1(4)
C(17)–N(16)–C(38)	116.8(4)	N(16)–C(17)–C(20)	111.3(4)
N(14)–N(13)–C(12)	103.7(5)	C(18)–C(17)–C(22)	111.6(4)
N(13)–N(14)–C(35)	116.6(4)	C(20)–C(17)–C(22)	112.1(4)
N(13)–N(14)–C(15)	111.6(5)	N(16)–C(17)–C(22)	108.1(4)
C(15)–N(14)–C(35)	131.6(5)	C(19)–C(10)–C(36)	111.5(4)
N(5)–C(6)–C(7)	115.0(6)	C(9)–C(10)–C(36)	113.0(4)
C(6)–C(7)–C(3)	103.1(5)	C(9)–C(10)–C(19)	102.4(4)
C(6)–C(7)–C(8)	126.1(5)	C(36)–C(10)–C(11)	109.6(4)
C(8)–C(7)–C(3)	130.8(4)	C(19)–C(10)–C(11)	112.3(3)
C(7)–C(8)–C(9)	120.2(4)	C(9)–C(10)–C(11)	107.9(4)
C(7)–C(8)–C(23)	120.5(4)	N(16)–C(15)–N(14)	120.6(5)
C(23)–C(8)–C(9)	119.3(4)	N(14)–C(15)–C(11)	107.0(4)
C(8)–C(9)–C(10)	114.2(4)	N(16)–C(15)–C(11)	132.5(5)
C(8)–C(9)–C(21)	112.9(4)	C(10)–C(11)–C(15)	129.8(4)
C(21)–C(9)–C(10)	103.1(4)	C(15)–C(11)–C(12)	103.2(5)
N(2)–C(3)–C(7)	134.1(5)	C(10)–C(11)–C(12)	126.9(5)
N(4)–C(3)–C(7)	107.1(4)	N(13)–C(12)–C(11)	114.5(6)
N(4)–C(3)–N(2)	118.7(5)	N(4)–C(29)–C(28)	121.1(4)
C(9)–C(21)–C(1)	104.6(4)	N(4)–C(29)–C(24)	119.2(3)
N(2)–C(1)–C(21)	113.1(4)	N(14)–C(35)–C(34)	121.4(4)
C(21)–C(1)–C(18)	113.6(4)	N(14)–C(35)–C(30)	118.5(3)
C(21)–C(1)–C(19)	105.0(4)		
N(2)–C(1)–C(18)	109.9(4)		

respectively 62.1(6) and −49.4(6)°; C(8)–C(7)–C(3)–N(2) is 2(1)°.]

The other heterocyclic penta-atomic ring A has bond lengths comparable with ring B but the adjacent system is slightly different having C(10)–C(36) 1.527(8) and C(10)–C(11) 1.501(7) Å for single bonds. The other corresponding C–C and N–C bond lengths are similar.

In consequence the conformation of the seven-membered ring F is slightly different from the E with the two torsion angles [C(15)–N(16)–C(17)–C(20)] −9.18(7) and [C(20)–C(19)–C(10)–C(11)] −24.8(6)°. Least-squares planes through the two rings are more indicative of a half-chair conformation for ring E and chair conformation for ring F (ref. 13).

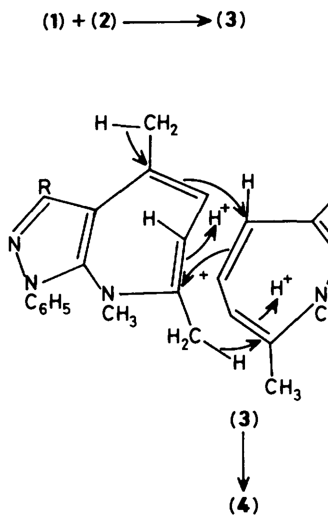
In fact N(2), C(3), C(7), and C(8) (ring E) are coplanar and the remaining members of the ring have the following deviations: C(1) 0.526(3), C(9) 0.418(3), and C(21) −0.290(3) Å. In ring F the planar part is related to C(10), C(11), C(15), N(16) and from this plane the deviations of the other atoms are C(17) 0.700(3), C(19), 0.575(3), and C(20) −1.556(3) Å.

The four planar systems (rings A—D) are characterized by the dihedral angles $\widehat{\text{AB}}$ 19.6(2), $\widehat{\text{AD}}$ 41.1(2), $\widehat{\text{CB}}$ 140.5(2), and $\widehat{\text{CD}}$ 150.7(1)°.

The two fused penta-atomic rings G and H formed by C(sp^3) hybridized atoms have the expected C–C single bond distances and as a consequence they are not planar. The conformation of the G ring is characterized by the Q and Φ puckering parameters 0.409(5) Å and −105.2(7)° and that of H ring by Q 0.405(5) Å and Φ −112.0(7)°. Then we assign a half-chair conformation to them.

The crystal packing (see Figure 2) is determined by van der Waals forces and all intermolecular contracts agree with those predicted from radii sum rules.

The production of compounds (**4a**, **b**) can be rationalized through the formation of the intermediates (**3a**, **b**) followed by a bimolecular addition reaction (see Scheme 2). Monitoring by t.l.c. of the reaction mixture for (**1a**) and (**2**) after 15 h showed distinct spots for compound (**4a**) and the starting methylaminopyrazole (**1a**) but not for the possible intermediate (**3a**). This suggests a two-stage reaction, slow formation of the intermediate (**3**) followed by very fast proton-catalysed bimolecular addition.



Scheme 2.

In order to demonstrate this reaction mechanism we tried to synthesize the intermediate (**3**), to use it as a starting product for the addition reaction in acetic acid. We reacted 5-methylaminopyrazole (**1a**) and hexane-2,5-dione for 45 h in toluene under reflux, with a small amount of toluene-*p*-sulphonic acid, using a Dean–Stark trap as water separator, but only the starting aminopyrazole was isolated.

At this point an indirect approach was made to test the proposed mechanism. Because the postulated bimolecular addition reaction is catalysed by two protons supplied by acetic acid (see Scheme 2), two deuterium atoms should be introduced into compound (**4**) by CH_3COOD.

The amine (**1a**) and hexane-2,5-dione were reacted in CH_3COOD and a deuteriated product was isolated. The ^1H n.m.r. spectrum did not show the two methyls at δ *ca.* 1.4 and other protons were missing compared with the spectrum of the undeuteriated compound. Moreover, the mass spectrum produced a set of peaks indicating that the product is a mixture of deuteriated compounds with deuterium incorporation ranging from 7 to 12 atoms. Furthermore, a solution of

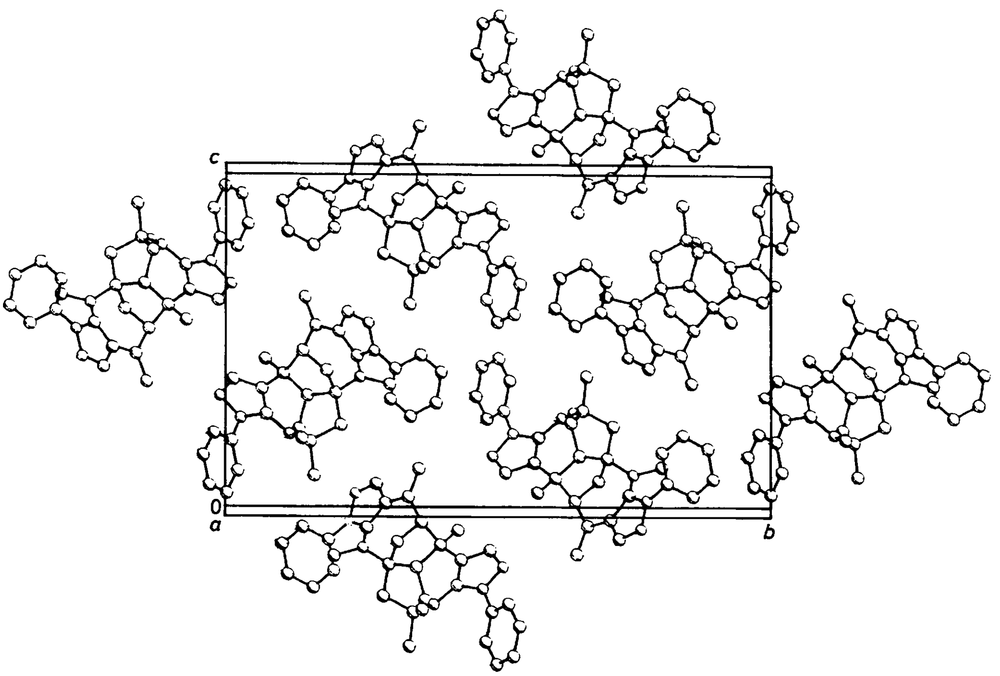


Figure 2. Packing diagram viewed down the *a* axis

hexane-2,5-dione in CD_3COOD was refluxed for 40 h and the ^1H n.m.r. spectrum showed an intense signal at δ 11.45 for CD_3COOH, indicating a large amount of deuterium exchange. Because the deuterium incorporation in compound (**4a**) is attributable mainly to the exchanged hexane-2,5-dione, it is not, unfortunately, possible to establish the exact role of the acidic medium.

Finally, because derivative (**4a**) contains two pyrazoloazepine systems, which are reported to have analgesic and anti-inflammatory activities,[7] this compound was tested for these pharmacological properties. At the dose levels of 50 and 100 mg kg^{-1} in rats no activity was noted.[14]

Experimental

M.p.s were determined on a Büchi–Tottoli apparatus and are uncorrected. I.r. spectra were recorded on a JASCO spectrophotometer for hexachlorobutadiene solutions. ^1H and ^{13}C n.m.r. spectra of (**4a, b**) were obtained for $CDCl_3$ solutions (tetramethylsilane as internal standard) on Varian CXP300 (300 MHz) and Varian FT 80A (20 MHz) spectrometers, respectively. ^{13}C N.m.r. assignments were made on the basis of substitution character and off-resonance decoupling experiments. Mass measurements at low resolution were obtained on a JEOL JMS-01-SG-2 mass spectrometer operating at 75 eV.

Reaction of 1-*Phenyl*-3-R-5-*methylaminopyrazoles* (**1a, b**) *with Hexane*-2,5-*dione* (**2**): *General Procedure.*—A solution of the amine (**1a**)[15] or (**1b**)[16] (10 mmol) and hexane-2,5-dione (**2**) (10 mmol) in acetic acid (25 ml) was heated under reflux [45 h for (**1a**), 30 h for (**1b**)]. The solution was concentrated under reduced pressure to small volume, cold water (100 ml) was added, and the pH adjusted to 8 with aqueous sodium hydroxide. The mixture was extracted with chloroform (2 × 100 ml), and the combined extracts dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue was chromatographed following the flash chromatography procedure:[17] diameter of the column 5 cm, silica gel (32—63 μm) (200 g), eluant ethyl acetate–light petroleum (b.p. 40—70 °C) 2:3, fractions each 50 ml.

The first 12 fractions were rejected and the combined fractions 13—19 were evaporated under reduced pressure. The residue was recrystallized from ethanol (95% v/v) to give (**4a, b**) as crystals.

1,4,5,5a,6,7,10,11,11a,13-*Decahydro*-5a,6,10,13-*tetramethyl*-4-*methylene*-1,9-*diphenyl*-5,12:10,12-*dimethano*-12H-*pyrazolo*[3,4-b]*pyrazolo*[4′,3′:6,7]*azepino*[2,3-f]*azocine* (**4a**). This had a yield of 13.5%, m.p. 280—282 °C (Found: C, 76.55; H, 6.9; N, 16.6. $C_{32}H_{34}N_6$ requires C, 76.5; H, 6.8; N, 16.7%); *m/z* 502(19%) (M^+), 252(100), and 237(10.8). ^1H and ^{13}C n.m.r. data (Tables 1 and 2).

1,4,5,5a,6,7,10,11,11a,13-*Decahydro*-3,5a,6,9,10,13-*hexamethyl*-4-*methylene*-1,9-*diphenyl*-5,12:10,12-*dimethano*-12H-*pyrazolo*[3,4-b]*pyrazolo*[4′,3′:6,7]*azepino*[2,3-*f*]*azocine* (**4b**). This had a yield of 27%, m.p. 263—265 °C (Found: C, 76.9; H, 7.4; N, 15.8. $C_{34}H_{38}N_6$ requires C, 76.9; H, 7.2; N, 15.8%); *m/z* 530(20%) (M^+), 266(100), and 251(5). ^1H and ^{13}C n.m.r. data (Tables 1 and 2).

Reaction of 1-*Phenyl*-5-*methylaminopyrazole* **1a**) *with Hexane*-2,5-*dione in* CH_3COOD.—The amine (**1a**) and the hexane-2,5-dione (**2**) were reacted in CH_3COOD, by the above procedure, to give variable deuteriated derivatives of compound (**4a**), *m/z* 509(5.1%), 510 (10.6), 511 (16.6), 512(20.2), 513(19.1), and 514(13.6).

Crystal Structure Analysis.—*Crystal data.* $C_{32}H_{34}N_6$, m = 502.7, monoclinic, a = 7.256(2), b = 24.506(3), c = 15.253(3) Å, β = 93.61(2)°, U = 2 706.8(5) Å^3, Z = 4, D = 1.23 g cm^{-3}, F(000) = 1 072, space group $P2_1/c$, μ = 0.70 cm^{-1} for Mo-K_α radiation, λ = 0.710 69 Å.

Crystals of compound (**4a**), suitable for *X*-ray analysis, were obtained by the liquid diffusion method using as solvent–precipitant pairs chloroform and light petroleum (b.p. 40—70 °C). A crystal of dimensions 0.2 × 0.3 × 0.25 mm was used for the measurement at room temperature (23 °C) on a Siemens–Stoe four-circle diffractometer. Accurate unit-cell dimensions and crystal orientation matrices were obtained from least-squares refinement of 2θ, ω, χ, and φ values of 22 reflections in the range 10° < 2θ < 20°. Crystal and electronic stability was confirmed by the constancy of three reference reflections (2, −7, 4; −2, 7, −4; −4, −2, −2) whose intensities were monitored every 120 min taken from 4 207 reflections, measured with the ω–2θ scan technique in the range $3° \leqq 2\theta \leqq 48°$. 2 016 Having a net intensity $I \geqq 3\sigma(I)$ were used in the structure refinement. Lorentz and polarization corrections, but not absorption corrections, were made.

Structure determination. The structure was solved by direct methods with the MULTAN 80 system[18] and subsequent calculations were carried out by the SHELX-76 (ref. 19) and PARST[20] systems of programs. All the hydrogen atoms were introduced at idealized positions (C–H 0.98 Å) with a common thermal factor $U = 0.06$ Å^2. The structure was refined by the full-matrix least-squares method; anisotropic temperature factors were introduced for all non-hydrogen atoms except those belonging to the aromatic rings. These were refined as rigid groups and restricted to their normal geometry (D_6 symmetry, C–C 1.395 Å) by using the group refinement procedure. Each ring was assigned six variable positional parameters, and each ring carbon atom was assigned an individual isotropic thermal parameter. Final $R = [\Sigma|F_0| - |F_c|]/\Sigma|F_0| = 0.068$ and $R_w = [\Sigma(|F_0| - |F_c|)^2/\Sigma_w|F_0|^2]^{\frac{1}{2}} = 0.074$. The weighting scheme used in the last refinement cycles was $w = 2.489/[\sigma^2(F_0) + 0.001\ 367(F_0)^2]$, and the parameters varied were 256.

In the final difference the largest peak was 0.38 e Å^{-3}. Scattering factors were taken from ref. 21.

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References

1 B. R. Vogt (Squib, E. R. and Sons, Inc.), U.S.P. 3 985 731/1976, Appl. 484 908/1974 (*Chem. Abstr.*, 1977, **86**, P55304h).
2 Sanwa Kagaku Kenkyusho Co., Ltd., Jap. P. 59 13 761-[8413,761]/1984, Appl. 82/122 232/1982 (*Chem. Abstr.*, 1984, **101**, P7057m).
3 R. M. Demarinis, J. P. Hieble, and W. D. Matthews (Smithkline Beckman Corp.), Eur. Pat. Appl. EP 108 170/1984, Appl. 82/305 361/1982 (*Chem. Abstr.*, 1984, **101**, P72633k).
4 M. L. Brenner (Smithkline Corp.), Eur. Pat. Appl. EP 44 709/1982, U.S. Appl. 169 696/1980 (*Chem. Abstr.*, 1982, **97**, P6180h).
5 R. I. Fryer, E. J. Trybulski, and A. Walser (Hoffmann-La Roche), Eur. Pat. App. EP 41 627/1981, U.S. Appl. 150 508/1980 (*Chem. Abstr.*, 1982, **96**, P122656w).
6 P. E. Reyel and J. L. A. Rollet (Alphachemie), Fr. 1 472 930/1967 (*Chem. Abstr.*, 1968, **68**, P59453g).
7 S. C. Sharma and B. M. Lynch, *Can. J. Chem.*, 1979, **57**, 3034.
8 G. Daidone, S. Plescia, B. Maggio, M. Matera, and E. Bousquet, *Farmaco Ed. Sci.*, 1985, **40**, 178.
9 S. Plescia, M. L. Bajardi, D. Raffa, G. Daidone, M. Matera, A. Caruso, and M. Amico-Roxas, *Eur. J. Med. Chem.-Chem. Ther.*, 1986, **21**, 291.
10 I. Hori and M. Igarashi, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2856.
11 D. W. Mathieson, 'Nuclear Magnetic Resonance for Organic Chemists,' Academic Press, London–New York, 1967, p. 146.
12 Y. D. Dunitz, '*X*-Ray Analysis and the Structure of Organic Molecules,' Cornell Univ. Press, Ithaca, 1979.
13 E. Toromanoff, *Tetrahedron*, 1980, **36**, 2809.
14 L. Puglisi, unpublished results.
15 K. Eichenberger, R. F. Zurcher, A. Rossi, M. Wilhelm, and P. Schmidt, *Helv. Chim. Acta*, 1965, **48**, 524.
16 S. Plescia, G. Daidone, V. Sprio, E. Aiello, G. Dattolo, and G. Cirrincione, *J. Heterocycl. Chem.*, 1978, **15**, 1287.
17 W. C. Still, M. Khan, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
18 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data, 1980, University of York and Louvain.
19 G. M. Sheldrick, SHELX 76, Program for Crystal Structure Determinations, University of Cambridge.
20 M. Nardelli, *Comput. Chem.*, 1983, **7**, 95.
21 'International Tables of *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. IV, pp. 102—104.

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