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REACTION OF D-GALACTOSE PHENYLHYDRAZONE WITH NITROALKENES: SYNTHESIS OF PENTAHYDROXYPENTYLPYRAZOLES*

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ABSTRACT

D-Galactose phenylhydrazone reacts with 1- and 2-substituted and 1,2-disubstituted nitroalkenes, with loss of the nitro group, to give moderate yields of 3-(D-*galacto*-pentitol-1-yl)-1-phenylpyrazoles variously substituted at positions 4, 5, and 4,5, and a mechanism is proposed. Acetylation of these products affords pentaacetates and periodate oxidation gave the corresponding 1-phenylpyrazole-3-carbaldehyde derivatives, some of which were oxidised to the carboxylic acids. U.v., i.r., and n.m.r. data confirm the proposed structures.

INTRODUCTION

C-Nucleosides and their analogoues are of interest because of their biological properties[1–3]. *C*-Pentahydroxypentylpyrazoles can be transformed into *C*-nucleosides[4], although not as easily as other *C*-polyhydroxyalkylheterocycles[5]. Such pyrazole *C*-nucleoside precursors have been synthesised from acetylenic sugars and hydrazine[4] or from aldohexose arylhydrazones and acetylenic esters[6]. We now report the synthesis of 3-(pentahydroxypentyl)pyrazoles from D-galactose phenylhydrazone and nitroalkenes.

On the basis of the results[7] of the reactions of aldehyde phenylhydrazones with β-nitrostyrene, it was anticipated that sugar arylhydrazones and nitroalkenes would react to give 4-nitropyrazoles. However, a preliminary study[8] of the reaction of D-galactose phenyl(or *p*-tolyl)hydrazone with two 1-phenyl-2-nitroalkenes indicated that the products did not contain a nitro group and that the regioselectivity varied. These results prompted a wider study of the reaction.

RESULTS AND DISCUSSION

D-Galactose phenylhydrazone (**1**) reacted with a variety of nitroalkenes (**2a–k**) in *N*,*N*-dimethylformamide at room temperature, to give, after several days,

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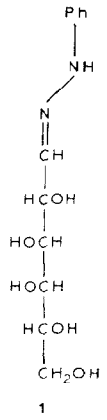

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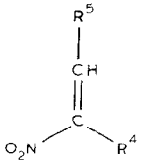
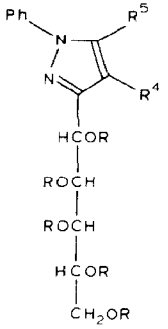
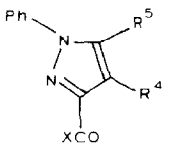


2a–k



3a–j,l,m R = H
4a–j,l,m R = Ac



5a–h,j,m X = H
6a–d,f–h,l,m X = OH

Symbol	R^4	R^5
a	H	Me
b	Me	Me
c	H	^{i}Pr
d	$-(CH_2)_4-$	
e	Ph	Ph
f	H	p-Me$-C_6H_4-$
g	Me	p-Me$-C_6H_4-$
h	Me	p-MeO$-C_6H_4-$
i	H	p-$O_2N-C_6H_4-$
j	COOMe	Ph
k	Br	Ph
l	COOH	Ph
m	NO_2	Ph

3-(D-*galacto*-pentitol-1-yl)pyrazoles (**3a–j,m**) in moderate yields. As in the preliminary studies, the products did not contain a nitro group, except that from the reaction of **1** with β-bromo-β-nitrostyrene (**2k**), which led to **3m**. The 4-carboxypyrazole **3l** was easily obtained by saponification of **3j**. Each of the compounds **3a–j,l,m** gave a penta-acetate (**4a–j,l,m**) and the consumption of periodate confirmed the presence of the pentitol side-chain. The D-*galacto* configuration was assigned on the basis of that of **1**. Periodate oxidation of the (pentitol-1-yl)pyrazoles **3a–h,j,m** gave the corresponding pyrazole-3-carbaldehydes (**5a–h,j,m**) in high yields, the last one as an aldehyde hydrate. Several of these aldehydes (**5a–d,f–h,j,m**) were oxidised with moist silver oxide to yield the pyrazole-3-carboxylic acids **6a–d,f–h,l,m**; in the case of **5j**, simultaneous saponification led to **6l**.

Each of the products **3**, except **3e**, was dextrorotatory. The u.v. absorptions for the series **3, 5,** and **6** are summarised in Table **1**. The 1,5-diarylpyrazoles **3e–h,j,l** had λ_{max} in the range 250–258 nm, as do other 1,5-diarylpyrazoles[9,10], but the nitro

TABLE I

U.V. ABSORPTION BANDS[a] FOR COMPOUNDS **3, 5,** AND **6**

Compound	λ_{max} *(nm)*	ε *(L.mol^{-1})*	*Compound*	λ_{max} *(nm)*	ε *(L.mol^{-1})*
3a	243	6,400	**5e**	233sh	23,000
3b	249	8,200	**5f**	247	16,800
3c	244, 267sh[b]	9,600, 7,900	**5g**	245	25,600
3d	254	7,200	**5h**	249	25,800
3e	230sh, 256, 335	20,000, 16,100, 2,500	**5j**	245	13,000
3f	254	12,400	**5m**	217sh, 275	14,700, 6,700
3g	255	17,800	**6a**	227	11,500
3h	256	23,700	**6b**	221, 252	8,000, 11,000
3i	222, 295	26,600, 17,400	**6c**	239	10,800
3j	253	20,400	**6d**	220sh, 257	11,400, 8,500
3l	253	14,800	**6f**	233	17,000
3m	218, 278	22,000, 8,400	**6g**	259	21,000
5a	244	5,600	**6h**	234, 260sh	22,300, 16,800
5b	223, 247	13,500, 14,400	**6l**	229sh, 257	18,300, 8,500
5c	243	15,200	**6m**	222sh, 272sh	20,600, 6,800
5d	223, 254	12,000, 11,400			

[a]In MeOH. [b]sh, shoulder.

group in **3i** and **3m** caused a bathochromic shift of 20–40 nm. The triphenyl derivative **3e** had an additional absorption at longer wavelength, and the monophenyl derivatives had λ_{max} in the range 243–254 nm as observed[11,12] for related compounds.

The conjugated nitro group in the aldehyde **5m** caused a bathochromic shift of λ_{max} in comparison with the other pyrazole-3-carbaldehydes (see Table I), which had λ_{max} in the range 233–254 nm, showing a small hypsochromic shift with regard to the respective 3-(pentitol-1-yl)pyrazoles (**3**).

The 1,5-diarylpyrazole-3-carboxylic acids **6f–h,l** had λ_{max} in the range 233–260 nm, but the 4-nitropyrazole **6m** absorbed at higher wavelength (see above) and the monophenyl derivatives absorbed mainly in the range 227–257 nm.

The members of the series **3–6** had i.r. bands typical of the pyrazole ring and the appropriate functional groups (Table II). The pyrazole C=N stretching gives rise to a band[4] at 1570–1530 cm^{-1}. One or two bands at 945–905 cm^{-1} are assigned to pyrazole ring bending[13].

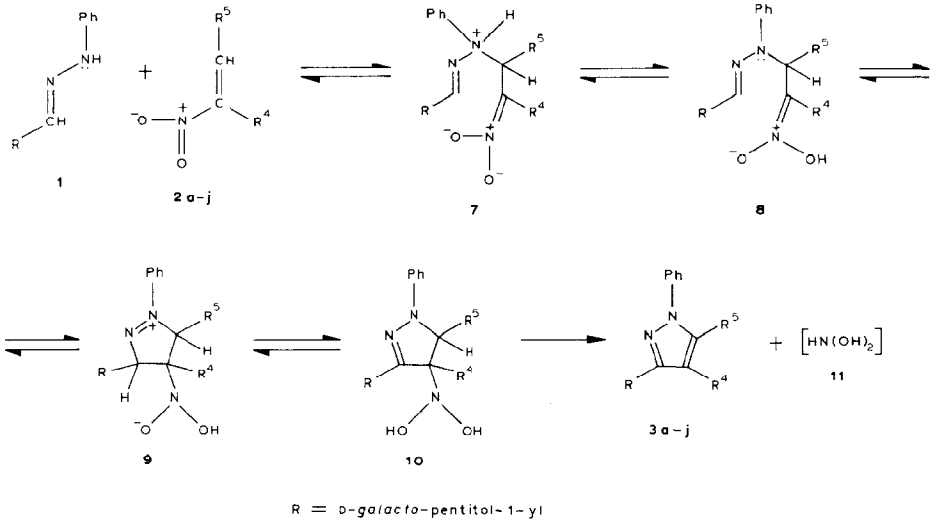
The ^{1}H-n.m.r. data are recorded in Table III. Assignments are based on literature data for related compounds and on double-resonance and/or deuteration experiments. The unique pyrazole proton in **3a,c,f,i,** the penta-acetates **4a,c,f,i,** the aldehydes **5a,c,f,** and the carboxylic acids **6a,c,f** resonated in the range δ 6.32–7.37 in agreement with the data reported for H-4 in other 1-phenylpyrazoles[9,10,14–17] (*cf.* δ 7.85–8.78 for H-5 in such systems[14–19]), thus emphasising the high regioselectivity of the reactions giving the compounds **3**. Comparison of observed J values with those calculated from modifications[20–23] of the Karplus equation indicates that the C-1,2,3,4 portion of the penta-acetoxypentyl chain of compounds **4** adopts

TABLE II

TYPICAL I.R. ABSORPTION BANDS FOR COMPOUNDS **3**, **4**, **5**, AND **6**[a]

Compound	*νO–H*	*Ester νC=O*	*Aldehyde νC=O*	*Carboxylic acid νC=O*	*Pyrazole νC=N*	*Pyrazole ring bending*
3a	3280br, s[b]				1545m	915m
3b	3300br, s				1570m	940w, 915m
3c	3380br, s				1545m	905w
3d	3300br, s				1570w	910w
3e	3350br, s				1550w	918m
3f	3450br, s				1555w	913m
3g	3420br, s				1545w	932w, 918m
3h	3590d 3440br, s				1554sh	920sh
3i[c]	3480br, s				1537w	920w
3j	3390br, s	1720s			1547s	938w
3l	3400br, s			1680s 1676s	1546m	925w, 915w
3m[d]	3360br, s				1553sh	915w
4a		1740br, s			1545m	912m
4b		1750br, s 1720m			1560m	930w, 916m
4c		1760sh 1740br, s			1540m	944w, 910m
4d		1760s 1753s 1740s			1576w	920w
4e		1745s			1550w	915w
4f		1750s			n.o.	928w
4g		1745s			n.o.	938w, 920w
4h		1740br, s			1565w	940w, 920w
4i[e]		1740s			1535sh	907w
4j		1750s 1705s			1545br, m	930w
4l	3300–2400w	1745br, s		1696sh	1540w	925w, 915w
4m[f]		1745br, s			1558m	920w
5a			1695s		1545m	915m
5b			1687s		1565m	910m
5c			1700s		1535w	920m
5d			1690s 1670sh		1570m	930m
5e			1700s 1690s		1540w	918w
5f			1695s		1545w	912w
5g			1690s		n.o.	912w
5h			1742sh 1738s		1555w	910w
5j		1710s	1690s		1542sh	920w
5m[g]	3410br, m				1550s	914w
6a	3200–2200m			1675br, s	1540m	920m
6b	3280–2300m			1684br, s 1650sh	1560w	910m
6c	3600–2300s			1695br, s	1535w	920w, 908m
6d	3600–2300m			1670s	1555w	910w
6f	3600–2300m			1700sh 1685s	1550w	910w
6g	3600–2300m			1680br, s	n.o.	930w, 915w
6h	3600–2300m			1685s	1546w	938w, 910w
6l	3600–2300m			1720br, m 1620br, s	1530sh	922sh
6m[h]	3300–2300m			1700s	1550sh	913w

[a]Recorded for KBr discs. [b]br, broad; s, strong; m, medium; w, weak; sh, shoulder; n.o., not observed. [c]The nitro group gives rise to strong bands at 1518 and 1342 cm^{-1} (asym. and sym. stretching). [d]As in *c*, at 1548 and 1347 cm^{-1}. [e]As in *c*, at 1510 and 1364 cm^{-1}. [f]As in *c*, at 1558 and 1367 cm^{-1}. [g]Aldehyde hydrate; the nitro group gives rise to strong absorptions at 1550 and 1352 cm^{-1}. [h]As in *c*, at 1515 and 1365 cm^{-1}.



R = D-*galacto*-pentitol-1-yl

preferentially a planar zigzag conformation in solution, but no preferential conformation around the C-4–C-5 bond in solution could be assigned.

The ^{13}C-n.m.r. data for **3b** are summarised in Table IV. Assignments are based on multiplicities and literature data[8,24,25] for related compounds. The δ value (124.0) observed for the phenyl *ortho*-carbon nuclei indicates[26] that Me-5 reduces the conjugation between the rings by steric hindrance to coplanarity.

The loss of the nitro group during the formation of **3a–j** is similar to that observed in the formation of other heterocyclic systems from nitroalkenes[27,28], and can be rationalised as indicated in the annexed scheme (**7**→**10**). The aminic nitrogen of **1** acts as a nucleophile in attacking the β carbon atom of **2a–j** to give the adduct **7**, which tautomerises to give **8**. Cyclisation of **8** by attack of the π electrons of the hydrazone moiety, to give the nitronic acid **9**, and subsequent proton migration leads to the pyrazoline derivative **10**, aromatisation of which by loss of dihydroxylamine (**11**) yields **3a–j**. The alternative mechanism, involving nucleophilic attack of the azomethine carbon of **1** on the nitroalkene, would yield the isomer of **3** with R^4 and R^5 interchanged. Moreover, Le Fevre and Hamelin[29] have established that *C*-alkyl hydrazones (or the isomeric azo compounds), formed first in the reaction of simple phenylhydrazones with electron-deficient olefins under neutral conditions, do not cyclise. It is considered[29] more probable that 1,3-dipolar addition of the isomeric ylids, in equilibrium with the hydrazones, to the olefins occurs. This mechanism would explain the formation of two products with both types of orientation. This last mechanism seems to be of little importance in our work, since the Griess–Ilosvay assay[30] for nitrite ion was negative and 1,3-dipolar addition would require the elimination of nitrous acid. The exception was **2k**, which lost bromide ion instead of the nitro group, and can be explained in the annexed scheme (**12**→**14**). The intermediate adduct **7k**, after tautomerisation to

TABLE III

^{1}H-N.M.R. CHEMICAL SHIFTS (δ, P.P.M.)[a] AND COUPLING CONSTANTS (J, Hz) FOR COMPOUNDS **3**[b], **4**[c], **5**[c], AND **6**[c]

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	*OH*	*OAc*	*N-Ph*	R^4	R^5
3a[d]	← 3.30–5.05m (11 H) →								7.53s	6.35s	2.33s
3b[e]	4.94d $J_{1,2}$ 2.0	3.76dd $J_{2,3}$ 8.8	3.59dd $J_{3,4}$ 1.5	3.78ddd $J_{4,5}$ 6.1 $J_{4,5'}$ 6.7	3.45dd $J_{5,5'}$ 10.8	3.42dd	4.10–4.55bs (5 H)		7.48s	2.05s	2.22s
3c[e]	6.13d $J_{1,2}$ 4.4	← 3.44–4.92m (10 H) →							7.40–7.56m	6.32s	3.02h 1.11d 1.10d *J* 6.8
3d[e]	4.95dd $J_{1,2}$ 2.0	3.75ddd $J_{2,3}$ 8.7	3.59ddd $J_{3,4}$ 1.5	3.81dddd $J_{4,5}$ 6.2 $J_{4,5'}$ 7.3	3.48ddd $J_{5,5'}$ 10.8	3.41ddd	4.71d 1[f] 4.36d 2 4.24d 3		7.31–7.55m	← 1.70bs (4 H) →	
	$J_{1,OH}$ 6.8	$J_{2,OH}$ 6.6	$J_{3,OH}$ 7.4	$J_{4,OH}$ 6.1	$J_{5,OH}$ =	$J_{5',OH}$ = 5.6	4.22d 4 4.47t 5			← 2.50–2.71m (4 H) →	
3e[e]	4.95s	← 2.78–4.57m (10 H) →							← 7.06–7.54m (7.27bs) (15 H) →		
3f[e]	6.20bs	← 3.30–3.86m, 4.10–4.84m, 4.90–5.20m (10 H) →							7.22–7.40m	6.62s	7.10d 7.16d *J* 8.2 2.33s
3g[e]	5.05d *J* 7.0	← 3.42–3.48m, 3.64m, 3.79–3.85m (5 H) →					4.25d *J* 5.8 4.28d *J* 7.5 4.43d *J* 6.4 4.46t *J* 5.6 4.84d *J* 7.0		7.03–7.35m[g]	2.07s	7.03–7.35m[g]

3h[e]	5.05s ←			3.48–3.84m (5 H)		→ 4.12–4.96bs (5 H)			7.15–7.33m	2.07s	6.96d 7.10d *J* 8.8 3.76s
3i[e]	5.04s[h] ←			3.43–4.50m, 5.04s[h] ←(9 H)→			→		7.24–7.43m	6.85s	7.47d 8.23d *J* 8.8
3j[d]	5.38d *J* 10 ←			3.05–4.75m (10 H)			→		7.18s[g]	3.48s	7.18s[g]
3l[e]	5.36d *J* 1.7 ←			3.17–3.82m[i]		4.09–4.16m (2 H) 3.17–3.82m[i]	→		7.16–7.37m[g]	4.50bs	7.16–7.37m[g]
3m[d]	5.52d *J* 8.8 ←			3.30–5.00m (3.48s) (10 H)			→		7.20–7.62m[g]		7.20–7.62m[g]
4a[e]	6.09d $J_{1,2}$ 2.6	5.62dd $J_{2,3}$ 9.6	5.51dd $J_{3,4}$ 2.0	5.33ddd $J_{4,5}$ 4.9 $J_{4,5'}$ 7.4	4.31dd $J_{5,5'}$ 11.6	3.90dd		2.05s 2.08s 2.11s 2.18s 2.20s	7.39–7.52m	7.37s	2.32s
4b[e]	6.11d $J_{1,2}$ 3.3	5.59dd $J_{2,3}$ 8.8	5.52dd $J_{3,4}$ 2.3	5.27ddd $J_{4,5}$ 4.8 $J_{4,5'}$ 7.3	4.28dd $J_{5,5'}$ 11.6	3.93dd		2.00s 2.02s 2.05s 2.10s 2.11s	7.32–7.47m	2.12s	2.16s
4c[e]	6.12d $J_{1,2}$ 2.1	5.58dd $J_{2,3}$ 9.5	5.49dd $J_{3,4}$ 1.8	5.32ddd $J_{4,5}$ 4.8 $J_{4,5'}$ 7.6	4.32dd $J_{5,5'}$ 11.7	3.86dd		1.97s 2.02s 2.05s 2.12s	7.34–7.46m	7.28s	2.97h 1.12d 1.15d *J* 7.0
4d[e]	6.12d $J_{1,2}$ 3.4	5.64dd $J_{2,3}$ 9.0	5.52dd $J_{3,4}$ 2.4	5.29ddd $J_{4,5}$ 4.8 $J_{4,5'}$ 7.3	4.28dd $J_{5,5'}$ 11.6	3.93dd		2.00s 2.01s 2.05s 2.10s 2.12s	7.41s 7.43s	←1.68–1.88m (4 H)→ ←2.26–2.76m (4 H)→	
4e[e]	6.11d $J_{1,2}$ 2.7	5.48dd $J_{2,3}$ 8.8	5.41dd $J_{3,4}$ 2.9	5.23ddd $J_{4,5}$ 4.6 $J_{4,5'}$ 7.1	4.26dd $J_{5,5'}$ 11.7	3.92dd		1.91s 2.01s 2.02s (6 H) 2.07s	← 6.99–7.35m (15 H) →		

Table III (continued)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	*OH*	*OAc*	*N-Ph*	R^4	R^5
4f[e]	6.17d $J_{1,2}$ 2.7	5.66dd $J_{2,3}$ 9.6	5.54dd $J_{3,4}$ 2.0	5.34ddd $J_{4,5}$ 5.0 $J_{4,5'}$ 7.5	4.31dd $J_{5,5'}$ 11.6	3.90dd		2.01s 2.03s 2.07s 2.13s 2.16s	7.27s	6.38s	7.05d 7.29d *J* 2.9 2.33s
4g[e]	6.21d $J_{1,2}$ 3.6	5.67dd $J_{2,3}$ 8.9	5.56dd $J_{3,4}$ 2.5	5.29ddd $J_{4,5}$ 4.8 $J_{4,5'}$ 7.2	4.30dd $J_{5,5'}$ 11.7	3.94dd		2.00s 2.03s 2.12s 2.13s 2.15s	7.10–7.28m[g]	2.07s[f]	6.99d 7.27d[g] *J* 8.0 2.34s
4h[e]	6.21d $J_{1,2}$ 3.7	5.67dd $J_{2,3}$ 8.9	5.56dd $J_{3,4}$ 2.6	5.28ddd $J_{4,5}$ 4.7 $J_{4,5'}$ 7.2	4.30dd $J_{5,5'}$ 11.7	3.94dd		2.00s 2.03s 2.11s 2.13s 2.15s	7.06–7.27m	2.06s[f]	6.84d 7.03d *J* 8.7 3.80s
4i[e]	6.16d $J_{1,2}$ 2.5	5.65dd $J_{2,3}$ 9.6	5.55dd $J_{3,4}$ 2.1	5.35ddd $J_{4,5}$ 4.9 $J_{4,5'}$ 7.3	4.32dd $J_{5,5'}$ 11.6	3.91dd		2.00s 2.03s 2.07s 2.13s 2.16s	7.24–7.43m	6.56s	7.32d 8.13d *J* 8.8
4j[e]	6.64d $J_{1,2}$ 2.0	5.76dd $J_{2,3}$ 9.8	5.64dd $J_{3,4}$ 2.1	5.43ddd $J_{4,5}$ 4.9 $J_{4,5'}$ 7.5	4.34dd $J_{5,5'}$ 11.5	3.96dd		1.95s 2.03s 2.06s 2.22s 2.30s	7.10–7.50m[g]	3.74s	7.10–7.50m[g]
4l[e]	6.60d $J_{1,2}$ 1.8	5.61dd $J_{2,3}$ 9.8	5.54dd[g] $J_{3,4}$ 1.5	5.44ddd[g] $J_{4,5}$ 4.9 $J_{4,5'}$ 7.5	4.30dd $J_{5,5'}$ 11.6	3.93dd		1.92s 1.94s 2.04s (6 H) 2.20s	7.12–7.42m[g]	n.r.[k]	7.12–7.42m[g]
4m[e]	6.56bs $J_{1,2}$ <1	5.70d[f] $J_{2,3}$ 10.0	5.65d[f] $J_{3,4}$ <1	5.47ddd[m] $J_{4,5}$ 4.9 $J_{4,5'}$ 7.8	4.36dd $J_{5,5'}$ 11.7	3.96dd		1.92s 2.00s 2.02s 2.20s (6 H)	6.95–7.50m[g]		6.95–7.50m[g]

Compound	*3-CHO*	*N-Ph*	*R*[4]	*R*[5]	*Compound*	*3-COOH*	*N-Ph*	*R*[4]	*R*[5]
5a[d]	10.12s	7.45s	6.72s (1 H)	2.32s (3 H)	**6a**[e]	6.40–6.80bs	7.48s	6.80s (1 H)	2.36s (3 H)
5b[d]	10.16s	7.33s	2.15s (3 H)	2.21s (3 H)	**6b**[e]	8.46bs	7.46s	2.25s (3 H)	2.31s (3 H)
5c[e]	10.01s	7.42–7.55m	6.77s (1 H)	3.04h[n] 1.19d *J* 6.8	**6c**[e]	4.20–6.30bs	7.40–7.54m	6.34s (1 H)	3.00h[n] 1.18d *J* 6.7
5d[d]	10.07s	7.60s	← 1.70–2.15m (4 H) 2.65–3.15m (4 H) →		**6d**[e]	8.86bs	7.32–7.52m	← 1.81bs (4 H) 2.71bs, 2.85bs →	
5e[e]	10.16s	←	7.01–7.39m (15 H) →		**6f**[e]	7.55bs	7.35s	7.06s (1 H)	7.10s (4 H) 2.34s (3 H)
5f[e]	10.08s	7.12s	7.00s (1 H)	7.35–7.40m 2.35s (3 H)	**6g**[e]	4.20–5.24bs	7.29s	2.34s (3 H)	7.04d 7.17d *J* 8.2
5g[e]	10.17s	7.27–7.33m	2.34s (3 H)	7.05d 7.18d *J* 8.2 2.37s	**6h**[e]	n.r.[k]	7.29s	2.33s (3 H)	2.37s (3 H) 6.88d 7.08d
5h[e]	10.17s	7.27–7.34m	2.34s (3 H)	6.90d 7.09d *J* 8.7 3.83s	**6i**[e]	5.09bs[h]	7.26m[g]	5.09bs[h]	*J* 8.7 3.82s (3 H) 7.26m[g]
5j[d]	10.40s	7.20bs[g]	3.86s (3 H)	7.20bs[g]	**6m**[e]	4.95bs	7.26–7.46m[g]		7.26–7.46m[g]
5m[d]	10.50s	7.30–7.70m[g]		7.30–7.70m[g]					

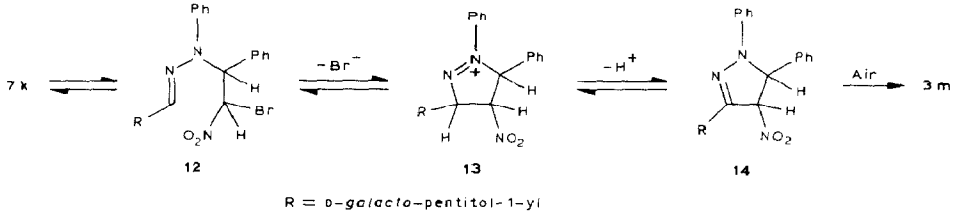
[a]Me_4Si as internal reference. [b]In $(CD_3)_2SO$. [c]In $CDCl_3$. [d]At 60 MHz. [e]At 200 MHz. [f]Locant at the side chain. [g]Overlapped signals. [h]As in *g*, total intensity, 2 H. [i]As in *g*, total intensity, 8 H. [j]This assignment may be interchanged with one of the AcO signals. [k]Not recorded. [l]The internal peaks overlap. [m]Poor resolved peaks. [n]Pseudoquintet.

TABLE IV

^{13}C-N.M.R. CHEMICAL SHIFTS (δ, P.P.M.)[a], MULTIPLICITIES, AND ASSIGNMENTS FOR **3b**

Chemical shift and multiplicity	*Assignment*
8.4q	pyrazole 4-CH_3
10.4q	pyrazole 5-CH_3
63.0t	C-5 of the alditol chain
66.4d	C-1
68.9d	C-4
70.0d	C-3
73.0d	C-2
113.0s	pyrazole C-4
124.0d	phenyl *ortho*-C
126.8d	phenyl *para*-C
129.0d	phenyl *meta*-C
135.9s	pyrazole C-5
139.7s	phenyl *ipso*-C
152.8s	pyrazole C-3

[a]Internal Me_4Si.



R = D-*galacto*-pentitol-1-yl

12, cyclises to give **13**, which is deprotonated to give the pyrazoline **14**. In this case, air oxidation must be accepted.

EXPERIMENTAL

General methods. — Solvents were evaporated *in vacuo* at <45°. Melting points were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. T.l.c. was performed on Silica Gel HF_{254} (Merck) with 10:1 dichloromethane–methanol and detection with u.v. light. Column chromatography was conducted on Silica Gel 60 (Merck, 63–200 μm) with the eluant stated and the flash technique[31]. I.r. spectra were recorded with Perkin–Elmer 299 or 1310 spectrophotometers, using KBr discs for solids and films for liquids. U.v. spectra were recorded with a Perkin–Elmer 545 spectrophotometer. ^{1}H-N.m.r. spectra (60 and 200 MHz, internal Me_4Si) were recorded with a Perkin–Elmer R-12B and a Varian XL-200 spectrometer, respectively. Coupling constants were measured directly from the spectra and assignments were confirmed by deuteration and/or double-resonance experiments. ^{13}C-N.m.r.

spectra (50.3 MHz) were recorded with a Varian XL-200 spectrometer; chemical shifts were assigned from APT[32] spectra and are relative to that of internal Me_4Si. Consumption of periodate was determined by a method based on the Fleury and Lange[33] procedure.

*Preparation of 3-(*D-galacto-*pentitol-1-yl)-1-phenylpyrazoles* (**3**). — Nitroalkene (**2a–k**) was added to a solution of an equimolecular amount of D-galactose phenylhydrazone[34] (**1**) in *N,N*-dimethylformamide. The mixture was kept for several days at room temperature and monitored by t.l.c. The solvent was then evaporated *in vacuo* (<1 Torr), the residue was treated with ethyl acetate, and the product was recrystallised from methanol.

The following amounts and conditions were used.

Starting nitroalkene (g, mmol)	*$HCONMe_2$ (mL)*	*Time (days)*	*Product*	*Yield of pure product (g, %)*
2a[35] (2.61, 30)	10	5	**3a**	3.46, 37[a]
2b[36] (3.03, 30)	12	7[b]	**3b**	5.72, 59
2c[c] (3.45, 30)	15	13	**3c**	3.58, 35
2d[37] (3.81, 30)	12	15	**3d**	4.63, 44
2e[38] (5.63, 25)	12	15	**3e**	2.59, 23[d]
2f[e] (4.69, 30)	15	20	**3f**	4.03, 35[f]
2g[40] (5.90, 33)	13	18	**3g**	5.41, 41
2h[41] (5.79, 30)	12	20	**3h**	6.81, 55
2i[g] (4.27, 22)	20	18	**3i**	0.83, 8.7
2j[42] (4.14, 20)	12	7	**3j**	3.64, 42
2k[43] (4.56, 20)	10	12	**3m**	1.10, 13[a]

[a]From water. [b]At 30°. [c]Prepared from nitromethane and isobutyraldehyde by a procedure similar to that described[36] for other nitroalkenes. 3-Methyl-1-nitrobutanol (b.p. 104–109°/50 Torr) was dehydrated with phthalic anhydride to give 41% (overall yield) of 3-methyl-1-nitro-1-butene, b.p. 71–73°/20 Torr. [d]Yield of crude product, 5.14 g (46%); m.p. 114–119°. [e]Prepared from *p*-tolualdehyde and nitromethane, as described for β-nitrostyrene[39], **2f** had m.p. 102° (from ethanol). [f]From ethyl acetate. [g]Prepared from *p*-nitrobenzaldehyde and nitromethane, as described for β-nitrostyrene[39], **2i** had m.p. 200–201° (from acetone).

The following compounds were prepared, for which the spectral data are given in Tables I–IV.

5-Methyl-3-(D-*galacto*-pentitol-1-yl)-1-phenylpyrazole (**3a**), m.p. 154–155° (from water), $[\alpha]_D^{20}$ +30° (*c* 1.2, pyridine); periodate consumption, 4.01 mol (Found: C, 57.59; H, 6.70; N, 8.97. $C_{15}H_{20}N_2O_5 \cdot 0.25\ H_2O$ calc.: C, 57.59; H, 6.61; N, 8.96%).

4,5-Dimethyl-3-(D-*galacto*-pentitol-1-yl)-1-phenylpyrazole (**3b**), m.p. 180–181°, $[\alpha]_D^{25}$ +16° (*c* 1.1, pyridine); periodate consumption, 3.84 mol (Found: C, 59.81; H, 7.14; N, 8.72. $C_{16}H_{22}N_2O_5$ calc.: C, 59.61; H, 6.88; N, 8.69%).

5-Isopropyl-3-(D-*galacto*-pentitol-1-yl)-1-phenylpyrazole (**3c**), m.p. 156–157°, $[\alpha]_D^{25}$ +24° (*c* 1.3, pyridine); periodate consumption, 3.97 mol (Found: C, 60.41; H, 7.27; N, 8.48. $C_{17}H_{24}N_2O_5$ calc.: C, 60.70; H, 7.19; N, 8.33%).

4,5,6,7-Tetrahydro-3-(D-*galacto*-pentitol-1-yl)-1-phenyl-1*H*-indazole (**3d**), m.p. 187–188°, $[\alpha]_D^{25}$ +25° (*c* 1, pyridine); periodate consumption, 3.98 mol (Found: C, 62.05; H, 7.09; N, 8.21. $C_{18}H_{24}N_2O_5$ calc.: C, 62.05; H, 6.94; N, 8.04%).

3-(D-*galacto*-Pentitol-1-yl)-1,4,5-triphenylpyrazole (**3e**), m.p. 157–158°, $[\alpha]_D^{22}$ −23° (*c* 1.2, pyridine); periodate consumption, 3.87 mol. The elemental analysis gave no satisfactory results.

3-(D-*galacto*-Pentitol-1-yl)-1-phenyl-5-(*p*-tolyl)pyrazole (**3f**), m.p. 147–148° (from ethyl acetate), $[\alpha]_D^{25}$ +33° (*c* 1.1, pyridine); periodate consumption, 3.86 mol. The elemental analysis gave no satisfactory results.

4-Methyl-3-(D-*galacto*-pentitol-1-yl)-1-phenyl-5-(*p*-tolyl)pyrazole (**3g**), m.p. 168–169°, $[\alpha]_D^{22}$ +25° (*c* 1.2, pyridine); periodate consumption, 3.91 mol (Found: C, 66.45; H, 6.59; N, 7.11. $C_{22}H_{26}N_2O_5$ calc.: C, 66.31; H, 6.58; N, 7.03%).

5-(*p*-Methoxyphenyl)-4-methyl-3-(D-*galacto*-pentitol-1-yl)-1-phenylpyrazole (**3h**), m.p. 172–173°, $[\alpha]_D^{22}$ +16° (*c* 1, pyridine); periodate consumption, 4.02 mol (Found: C, 64.00; H, 6.39; N, 6.56. $C_{22}H_{26}N_2O_6$ calc.: C, 63.75; H, 6.32; N, 6.76%).

5-(*p*-Nitrophenyl)-3-(D-*galacto*-pentitol-1-yl)-1-phenylpyrazole (**3i**), m.p. 198–200°, $[\alpha]_D^{22}$ +48° (*c* 0.8, pyridine); periodate consumption, 2.92 mol (Found: C, 55.26; H, 5.36; N, 9.39. $C_{20}H_{21}N_3O_7 \cdot H_2O$ calc.: C, 55.42; H, 5.35; N, 9.70%).

4-Methoxycarbonyl-3-(D-*galacto*-pentitol-1-yl)-1,5-diphenylpyrazole (**3j**), m.p. 170–171°, $[\alpha]_D^{24}$ +9° (*c* 1.2, pyridine); periodate consumption, 3.98 mol (Found: C, 59.98; H, 5.54; N, 6.21. $C_{22}H_{24}N_2O_7 \cdot 0.5\ H_2O$ calc.: C, 60.40; H, 5.76; N, 6.40%).

4-Nitro-3-(D-*galacto*-pentitol-1-yl)-1,5-diphenylpyrazole (**3m**), m.p. 184–185° (from water), $[\alpha]_D^{20}$ +3° (*c* 0.3, pyridine); periodate consumption, 4.0 mol (Found: C, 57.44; H, 5.17; N, 10.20. $C_{20}H_{21}N_3O_7$ calc.: C, 57.83; H, 5.10; N, 10.12%).

*3-(*D-galacto-*Pentitol-1-yl)-1,5-diphenylpyrazole-4-carboxylic acid* (**3l**). — M NaOH (1 mL) was added to a boiling solution of **3j** (340 mg, 0.78 mmol) in water (20 mL), and the mixture was heated for 6 h under reflux and then acidified to pH 3–4 with hydrochloric acid. The precipitate (318 mg, 98%) was recrystallised from methanol to afford **3l** (298 mg, 92%), m.p. 238–239°, $[\alpha]_D^{22}$ +5° (*c* 0.9, pyridine); periodate consumption, 3.95 mol (Found: C, 60.71; H, 5.64; N, 6.32. $C_{21}H_{22}N_2O_7$ calc.: C, 60.86; H, 5.35; N, 6.76%). For the spectral data, see Tables I–III.

Acetylation of compounds **3**. — Compounds **3(a–j,l,m)** were conventionally treated in pyridine with acetic anhydride for 48 h at 0°. After precipitation in ice–water, crude products were recrystallised from ethanol–water.

The amounts used and the yields of pure products were as follows.

Starting compound (g, mmol)		*Ac_2O (mL)*	*Pyridine (mL)*	*Product*	*Yield (g, %)*
3a	(0.24, 0.77)	2.4	2.4	**4a**	0.33, 83
3b	(0.31, 0.96)	3.1	3.1	**4b**	0.50, 97
3c	(0.25, 0.74)	2.5	2.5	**4c**	0.31, 76
3d	(0.26, 0.75)	2.6	2.6	**4d**	0.40, 96
3e	(0.21, 0.46)	2.1	2.1	**4e**	0.16, 52
3f	(0.30, 0.78)	3.0	3.0	**4f**	0.34, 73
3g	(0.22, 0.55)	2.2	2.2	**4g**	0.32, 96
3h	(0.28, 0.66)	2.8	2.8	**4h**	0.38, 92
3i	(0.15, 0.34)	1.5	1.5	**4i**	0.19, 89
3j	(0.25, 0.57)	2.5	2.5	**4j**	0.30, 83
3l	(0.05, 0.12)	0.7	0.7	**4l**	0.06, 85
3m	(0.25, 0.60)	2.5	2.5	**4m**	0.22, 58

The following compounds were prepared, for which the spectral data are given in Tables II and III.

5-Methyl-3-(D-*galacto*-penta-acetoxypentyl)-1-phenylpyrazole (**4a**), m.p. 133–134°, $[\alpha]_D^{20}$ +51° (*c* 0.9, chloroform) (Found: C, 57.68; H, 5.76; N, 5.20. $C_{25}H_{30}N_2O_{10}$ calc.: C, 57.91; H, 5.83; N, 5.40%).

4,5-Dimethyl-3-(D-*galacto*-penta-acetoxypentyl)-1-phenylpyrazole (**4b**), m.p. 110–111°, $[\alpha]_D^{20}$ +42° (*c* 1.2, chloroform) (Found: C, 58.60; H, 6.16; N, 4.86. $C_{26}H_{32}N_2O_{10}$ calc.: C, 58.64; H, 6.06; N, 5.26%).

5-Isopropyl-3-(D-*galacto*-penta-acetoxypentyl)-1-phenylpyrazole (**4c**), m.p. 104–105°, $[\alpha]_D^{22}$ +49° (*c* 1.2, chloroform) (Found: C, 59.08; H, 6.18; N, 5.02. $C_{27}H_{34}N_2O_{10}$ calc.: C, 59.33; H, 6.27; N, 5.13%).

4,5,6,7-Tetrahydro-3-(D-*galacto*-penta-acetoxypentyl)-1-phenyl-1*H*-indazole (**4d**), m.p. 155–156°, $[\alpha]_D^{25}$ +57° (*c* 1.1, chloroform) (Found: C, 60.08; H, 6.38; N, 5.14. $C_{28}H_{34}N_2O_{10}$ calc.: C, 60.21; H, 6.14; N, 5.02%).

3-(D-*galacto*-Penta-acetoxypentyl)-1,4,5-triphenylpyrazole (**4e**), m.p. 98–99°, $[\alpha]_D^{22}$ −4° (*c* 1, chloroform) (Found: C, 65.83; H, 5.59; N, 4.60. $C_{36}H_{36}N_2O_{10}$ calc.: C, 65.84; H, 5.53; N, 4.27%).

3-(D-*galacto*-Penta-acetoxypentyl)-1-phenyl-5-(*p*-tolyl)pyrazole (**4f**), m.p. 140–141°, $[\alpha]_D^{22}$ +54° (*c* 0.8, chloroform) (Found: C, 62.35; H, 5.62; N, 4.72. $C_{31}H_{34}N_2O_{10}$ calc.: C, 62.60; H, 5.76; N, 4.71%).

4-Methyl-3-(D-*galacto*-penta-acetoxypentyl)-1-phenyl-5-(*p*-tolyl)pyrazole (**4g**), m.p. 123–124°, $[\alpha]_D^{22}$ +55° (*c* 0.8, chloroform) (Found: C, 62.84; H, 6.06; N, 4.64. $C_{32}H_{36}N_2O_{10}$ calc.: C, 63.15; H, 5.96; N, 4.60%).

5-(*p*-Methoxyphenyl)-4-methyl-3-(D-*galacto*-penta-acetoxypentyl)-1-phenylpyrazole (**4h**), m.p. 107–108°, $[\alpha]_D^{22}$ +57.5° (*c* 1.1, chloroform) (Found: C, 61.88; H, 6.13; N, 4.58. $C_{32}H_{36}N_2O_{11}$ calc.: C, 61.53; H, 5.81; N, 4.48%).

5-(*p*-Nitrophenyl)-3-(D-*galacto*-penta-acetoxypentyl)-1-phenylpyrazole (**4i**), m.p. 84–85°, $[\alpha]_D^{22}$ +56° (*c* 1, chloroform) (Found: C, 57.26; H, 4.86; N, 6.50. $C_{30}H_{31}N_3O_{12}$ calc.: C, 57.60; H, 4.99; N, 6.72%).

4-Methoxycarbonyl-3-(D-*galacto*-penta-acetoxypentyl)-1,5-diphenylpyrazole (**4j**), m.p. 115–116°, $[\alpha]_D^{24}$ +24° (*c* 0.9, chloroform) (Found: C, 59.97; H, 5.25; N, 4.14. $C_{32}H_{34}N_2O_{12}$ calc.: C, 60.18; H, 5.37; N, 4.39%).

3-(D-*galacto*-Penta-acetoxypentyl)-1,5-diphenylpyrazole-4-carboxylic acid (**4l**), m.p. 151–152°, $[\alpha]_D^{22}$ +19° (*c* 0.9, chloroform) (Found: C, 59.85; H, 5.46; N, 4.23. $C_{31}H_{32}N_2O_{12}$ calc.: C, 59.61; H, 5.16; N, 4.49%).

4-Nitro-3-(D-*galacto*-penta-acetoxypentyl)-1,5-diphenylpyrazole (**4m**), m.p. 135–136°, $[\alpha]_D^{20}$ −7° (*c* 0.9, chloroform) (Found: C, 57.74; H, 5.08; N, 6.97. $C_{30}H_{31}N_3O_{12}$ calc.: C, 57.60; H, 4.99; N, 6.72%).

Preparation of 1-phenylpyrazole-3-carbaldehydes (**5a–h,j,m**). — A solution of sodium metaperiodate in water (50 mL) was added to a suspension of the substrate (**3a–h,j,m**) in water (50 mL), and the mixture was covered with ether (50 mL) and stirred at room temperature. The aqueous layer was removed and extracted with several portions of ether. The combined and dried (Na_2SO_4) ethereal layers were concentrated, and the residue was purified to give the aldehyde.

The following amounts and conditions were used.

Starting compound (g, mmol)		*$NaIO_4$ (g, mmol)*	*Stirring time (h)*	*Ether (mL)*	*Product*	*Yield (g, %)*
3a	(0.90, 2.88)	2.57, 12.0	1	4 × 30	**5a**	0.47, 88[a]
3b	(1.00, 3.10)	2.74, 12.8	3	3 × 25	**5b**	0.55, 89[b]
3c	(1.02, 3.03)	2.67, 12.5	1	3 × 40	**5c**	0.64, 98[c]
3d	(1.05, 3.0)	2.66, 12.4	1	3 × 25	**5d**	0.55, 80[c]
3e	(0.60, 1.34)	1.19, 5.54	3	2 × 50	**5e**	0.39, 89[c]
3f	(1.00, 2.60)	2.30, 10.8	4	3 × 50	**5f**	0.65, 95[d]
3g	(1.00, 2.51)	2.21, 10.35	3	3 × 40	**5g**	0.64, 92[c]
3h	(1.00, 2.40)	2.13, 9.95	3	2 × 50	**5h**	0.54, 76[e]
3j	(0.78, 1.78)	1.57, 7.34	2	3 × 30	**5j**	0.50, 91[b]
3m	(0.36, 0.86)	0.70, 3.30	3	3 × 25	**5m**[f]	0.195, 73[b]

[a]After flash chromatography[31] (ether–hexane, 1:3). [b]From ether–hexane. [c]After column chromatography (ether–hexane, 1:1). [d]After column chromatography (ether–hexane, 2:1). [e]After column chromatography (ether–hexane, 3:2). [f]As a *gem*-diol.

The following compounds were prepared, for which the spectral data are given in Tables I–III.

5-Methyl-1-phenylpyrazole-3-carbaldehyde (**5a**) was isolated as a yellow oil.

4,5-Dimethyl-1-phenylpyrazole-3-carbaldehyde (**5b**), m.p. 87–88° (Found: C, 71.80; H, 6.18; N, 13.80. $C_{12}H_{12}N_2O$ calc.: C, 71.98; H, 6.04; N, 13.99%).

5-Isopropyl-1-phenylpyrazole-3-carbaldehyde (**5c**) was isolated as a nearly colourless oil.

4,5,6,7-Tetrahydro-1-phenyl-1*H*-indazole-3-carbaldehyde (**5d**), m.p. 55–56° (Found: C, 74.61; H, 6.43; N, 12.32. $C_{14}H_{14}N_2O$ calc.: C, 74.31; H, 6.24; N, 12.38%).

1,4,5-Triphenylpyrazole-3-carbaldehyde (**5e**), m.p. 176–177° (Found: C, 81.15; H, 5.13; N, 8.46. $C_{22}H_{16}N_2O$ calc.: C, 81.46; H, 4.97; N, 8.64%).

1-Phenyl-5-(*p*-tolyl)pyrazole-3-carbaldehyde (**5f**) was isolated as a yellow oil.

4-Methyl-1-phenyl-5-(*p*-tolyl)pyrazole-3-carbaldehyde (**5g**), m.p. 111–112° (Found: C, 77.92; H, 5.96; N, 9.85. $C_{18}H_{16}N_2O$ calc.: C, 78.24; H, 5.84; N, 10.14%).

5-(*p*-Methoxyphenyl)-4-methyl-1-phenylpyrazole-3-carbaldehyde (**5h**) was isolated as an oil.

4-Methoxycarbonyl-1,5-diphenylpyrazole-3-carbaldehyde (**5j**), m.p. 120–121° (Found: C, 70.28; H, 4.82; N, 9.27. $C_{18}H_{14}N_2O_3$ calc.: C, 70.58; H, 4.61; N, 9.15%).

4-Nitro-1,5-diphenylpyrazole-3-carbaldehyde (**5m**) hydrate, m.p. 84–85° (Found: C, 61.35; H, 4.43; N, 13.17. $C_{16}H_{13}N_3O_4$ calc.: C, 61.73; H, 4.21; N, 13.50%).

Preparation of 1-phenylpyrazole-3-carboxylic acids (**6a–d,f–h,l,m**). — A mixture of the aldehyde (**5a–d,f–h,l,m**), aqueous silver nitrate, and M NaOH was boiled under reflux for several hours and filtered whilst hot, and the solid residue was washed with a few mL of hot water. The filtrate was then acidified to pH 3–4 with nitric acid, to precipitate crude product that was recrystallised from ethanol–water.

The following amounts and conditions were used.

Starting compound (g, mmol)		*$AgNO_3$[a] (g, mmol)*	*M NaOH (mL)*	*Reflux time (h)*	*Product*	*Yield (g, %)*
5a	(0.20, 1.07)	0.40, 2.35	4.0	15	**6a**[b]	0.14, 60
5b	(0.20, 1.0)	0.37, 2.2	3.5	6	**6b**	0.15, 71
5c	(0.14, 0.65)	0.24, 1.44	2.5	15	**6c**	0.073, 48
5d	(0.23, 1.0)	0.37, 2.2	3.5	15	**6d**	0.16, 65
5f	(0.26, 1.0)	0.37, 2.2	4.0	9	**6f**	0.22, 80
5g	(0.27, 0.98)	0.37, 2.2	4.0	8	**6g**	0.12, 40
5h	(0.26, 0.87)	0.33, 1.93	3.5	14	**6h**	0.19, 70
5j	(0.26, 0.85)	0.32, 1.88	3.0	6	**6l**[b]	0.23, 82
5m	(0.27, 0.86)	0.34, 2.0	3.5	13	**6m**	0.16, 57

[a]Dissolved in water (0.5–1.0 mL). [b]As a monohydrate.

The following compounds were prepared, for which the u.v., i.r., and n.m.r. data are given in Tables I–III.

5-Methyl-1-phenylpyrazole-3-carboxylic acid (**6a**), as a monohydrate, m.p. 132–133°; lit.[44] m.p. 134–136° (Found: C, 60.31; H, 5.28; N, 12.64. $C_{11}H_{10}N_2O_2 \cdot H_2O$ calc.: C, 59.99; H, 5.49; N, 12.72%).

4,5-Dimethyl-1-phenylpyrazole-3-carboxylic acid (**6b**), m.p. 162–163° (Found: C, 66.63; H, 5.72; N, 12.73. $C_{12}H_{12}N_2O_2$ calc.: C, 66.65; H, 5.59; N, 12.96%).

5-Isopropyl-1-phenylpyrazole-3-carboxylic acid (**6c**), m.p. 142–143° (Found: C, 67.62; H, 5.97; N, 12.40. $C_{13}H_{14}N_2O_2$ calc.: C, 67.81; H, 6.13; N, 12.17%).

4,5,6,7-Tetrahydro-1-phenyl-1*H*-indazole-3-carboxylic acid (**6d**), m.p. 153–154° (Found: C, 69.70; H, 5.84; N, 11.41. $C_{14}H_{14}N_2O_2$ calc.: C, 69.40; H, 5.82; N, 11.56%).

1-Phenyl-5-(*p*-tolyl)pyrazole-3-carboxylic acid (**6f**), m.p. 174–175° (Found: C, 71.71; H, 4.85; N, 10.41. $C_{17}H_{14}N_2O_2 \cdot 0.5\ H_2O$ calc.: C, 71.06; H, 5.26; N, 9.75%).

4-Methyl-1-phenyl-5-(*p*-tolyl)pyrazole-3-carboxylic acid (**6g**), m.p. 194–195° (Found: C, 67.63; H, 5.20; N, 9.17. $C_{18}H_{16}N_2O_2 \cdot 1.5\ H_2O$ calc.: C, 67.69; H, 5.99; N, 8.77%).

5-(*p*-Methoxyphenyl)-4-methyl-1-phenylpyrazole-3-carboxylic acid (**6h**), m.p. 164–165° (Found: C, 70.16; H, 5.37; N, 9.21. $C_{18}H_{16}N_2O_3$ calc.: C, 70.12; H, 5.23; N, 9.09%).

1,5-Diphenylpyrazole-3,4-dicarboxylic acid (**6l**) monohydrate had m.p. 222–223°; lit.[45] m.p. 217–218° (Found: C, 62.32; H, 4.28; N, 8.12. $C_{17}H_{12}N_2O_4 \cdot H_2O$ calc.: C, 62.57; H, 4.32; N, 8.59%).

4-Nitro-1,5-diphenylpyrazole-3-carboxylic acid (**6m**), m.p. 197–198° (Found: C, 62.26; H, 3.80; N, 13.63. $C_{16}H_{11}N_3O_4$ calc.: C, 62.13; H, 3.58; N, 13.59%).

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