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REACTION OF D-MANNOSE ARYLHYDRAZONES WITH DIMETHYL ACETYLENEDICARBOXYLATE: SYNTHESIS OF PENTAHYDROXYPENTYLPYRAZOLES

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ABSTRACT

The reactions of D-mannose arylhydrazones with dimethyl acetylenedicarboxylate under acidic conditions afforded the respective pentahydroxypentylpyrazoles. With the phenyl- and *p*-tolyl-hydrazones, the respective enehydrazones were also obtained. The new pyrazole derivatives gave penta-acetates and oxidation with sodium periodate gave pyrazole-3-carbaldehydes. The ^{1}H-n.m.r. coupling constants of the penta-acetates indicated that each polyol side-chain adopted a planar zigzag conformation.

INTRODUCTION

Aldohexose aryl- or alkyl-hydrazones react with dimethyl acetylenedicarboxylate (DMADC) in neutral medium, to afford[1,2] the respective enehydrazones, as unique products, in moderate yields. Each product contains a pentahydroxypentyl side-chain, and the configurations around both the C=C and C=N bonds were proved to be *E*. The reaction is complex and there is some controversy[3–5] about its mechanism. With simple aldehyde hydrazones, a pyrazole derivative is one of the products[3–5], the formation of which requires an addition reaction followed by dehydrogenation.

Few pentahydroxypentylpyrazoles have been described[6]. Tronchet *et al.*[7] synthesised *C*-glycosylpyrazoles from active acetylenic compounds and *O*-protected 2,5-anhydropentose arylhydrazones having one bromine substituent on C-1 as the leaving group. We now report the synthesis of pentahydroxypentylpyrazoles by the acid-catalysed reaction of D-mannose arylhydrazones and DMADC.

RESULTS AND DISCUSSION

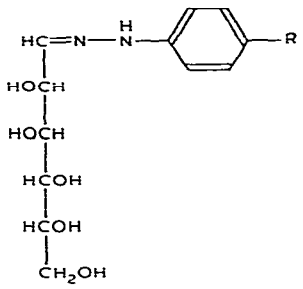
The phenylhydrazone (**1a**), *p*-tolylhydrazone (**1b**), and *p*-bromophenylhydrazone

TABLE I

CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J, Hz) FOR COMPOUNDS **4a**, **4b**, **4c**, **5a**, **5b**, AND **5c** AT 90 MHz[a,b]

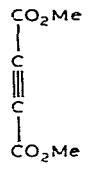
Compound	*AcO*	*MeO_2C-4*	*MeO_2C-5*	*H-1'*	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-5''*	*OH*	*Phenyl*	*p-Subst.*
4a[c]	—	3.82s	3.86s	5.12d[e] $J_{1',2'} \sim 9.0$			← 4.3–3.4m →			5.3–4.9d 4.5–3.2m	7.55s (5 H)	—
4b[c]	—	3.82s	3.86s	5.12d[e] $J_{1',2'} \sim 9.0$			← 4.5–3.3m →			5.3–4.9d 4.5–3.3m	7.40s (4 H)	2.41s (3 H)
4c[c]	—	3.82s	3.87s	5.12d[e] $J_{1',2'} \sim 9.0$			← 4.5–3.3m →			5.3–4.9d 4.5–3.2m	7.9–7.4m (4 H)	—
5a[d]	2.18s (3 H) 2.10s (3 H) 2.06s (6 H) 1.89s (3 H)	3.82s	3.91s	6.37d $J_{1',2'} \sim 9.1$	5.89dd $J_{2',3'} \sim 2.0$	5.67dd $J_{3',4'} \sim 9.0$	5.15m $J_{4',5'} \sim 3.0$ $J_{4',5''}$ 5.5	4.30dd $J_{5',5''} \sim 12.3$	4.10dd	—	7.46s (5 H)	—
5b[d]	2.18s (3 H) 2.11s (3 H) 2.07s (6 H) 1.90 (3 H)	3.83s	3.91s	6.35d $J_{1',2'} \sim 9.0$	5.87dd $J_{2',3'} \sim 2.5$	5.67dd $J_{3',4'} \sim 9.0$	5.16m $J_{4',5'} \sim 3.0$ $J_{4',5''} \sim 5.3$	4.29dd $J_{5',5''} \sim 12.3$	4.09dd	—	7.5–7.2m (4 H)	2.42s (3 H)
5c[d]	2.15s (3 H) 2.07s (3 H) 2.02s (6 H) 1.86s (3 H)	3.82s	3.88s	6.32d $J_{1',2'} \sim 9.0$	5.83dd $J_{2',3'} \sim 2.0$	5.67dd $J_{3',4'} \sim 9.0$	5.15m $J_{4',5'} \sim 3.0$ $J_{4',5''} \sim 5.5$	4.28dd $J_{5',5''} \sim 12.2$	4.08dd	—	7.6–7.2m (4 H)	—

[a]The spectrometer was locked on the signal of internal Me_4Si. [b]The spectra were recorded at 35.5°. Signal multiplicities: s, singlet; d, doublet; m, multiplet. [c]In $(CD_3)_2SO$. [d]In $CDCl_3$. [e]After shaking with D_2O.



1

a R = H
b R = Me
c R = Br



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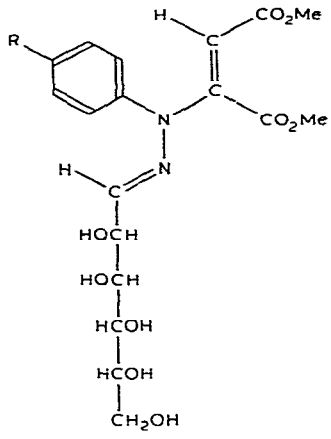
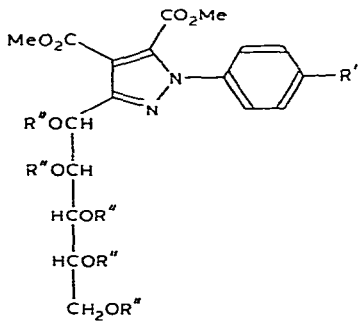


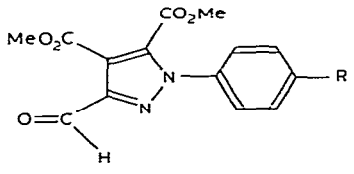
3

a R = H
b R = Me



4 R'' = H
5 R'' = Ac

a R' = H
b R' = Me
c R' = Br



6

a R = H
b R = Me
c R = Br

(**1c**) derivatives of D-mannose were used, and the reactions with DMADC (**2**) were performed at room temperature in *N*,*N*-dimethylformamide containing acetic acid, to give 14–23% of the corresponding pentahydroxypentylpyrazoles (**4a–c**). The formation of these products involved an oxidation stage and, although air was bubbled through each reaction mixture, substantially the same results were obtained without an air-stream. The reactions were monitored by t.l.c. The enehydrazones **3a** and **3b** were also isolated from **1a** or **1b**, respectively, but they are best prepared in the absence of acetic acid[1]. Compounds **3a** and **3b** did not cyclise under the conditions used for the preparation of the pyrazoles and hence they are not intermediates in the formation of the latter products.

Each pentahydroxypentylpyrazole (**4**) gave a penta-acetate (**5**), and oxidation with sodium metaperiodate afforded a 3-formylpyrazole (**6**) in high yield. Since it is

difficult to introduce a formyl group at C-3 of the pyrazole ring[8], the latter reaction may be useful in synthesis.

The analytical and spectroscopic data were consistent with the proposed structures **4**. Periodate oxidation indicated the presence of five contiguous hydroxyl-groups; the $[\alpha]_D$ values were low, reflecting the acyclic polyol side-chains, and their signs accorded with the Richtmyer–Hudson rules[9]. In the ^{1}H-n.m.r. spectra (Table I), the methoxycarbonyl groups gave rise to two singlets with $\Delta\delta$ values of 0.03–0.04 p.p.m., as observed[3,4] for dimethyl pyrazole-4,5-dicarboxylates lacking the polyol side-chain. For the enehydrazones **3**, this shift was ten times[1,2,10] as large (Table II). The aromatic protons of **4a** and **4b** gave a sharp singlet, as is usual in 5-substituted 1-arylpyrazoles[11], but, for **4c**, a multiplet typical of a *p*-disubstituted benzene was observed. The lack of signals corresponding to H-4 and H-5 of the heterocycle rules out a pyrazoline structure.

TABLE II

COMPARATIVE SPECTRAL DATA[a] FOR ENEHYDRAZONES (3a,3b) AND PYRAZOLE DERIVATIVES (4a,4b)

Compound	*^{1}H-N.m.r. (δ, p.p.m.; J in Hz)*			*I.r. (ν, cm^{-1})*		*U.v. (λ, nm)*
	CO_2Me	*HC=N*	*HC=C*	*C=O (ester)*	*C=N*	
3a	3.51s	6.54d	4.45s	1715	1635	303
	3.79s	$J \sim 6.4$		1700		(ε 31,000)
3b	3.51s	6.54d	4.45s	1715	1630	303
	3.79s	$J \sim 6.5$		1700		(ε 31,000)
4a	3.82s	—	—	1715	1530	254
	3.86s					(ε 7,600)
4b	3.82s	—	—	1720	1530	261
	3.86s					(ε 11,500)

[a]Recorded under similar conditions.

Pyrazoles (**4**) and the corresponding enehydrazones (**3**) can be distinguished by their ν(C=N) values (Table II). Table II also shows a great difference between their u.v. spectra, as expected.

The ^{1}H-n.m.r. data for the penta-acetates (**5**) indicated the conformation of the polyol side-chain. The observed coupling constants were consistent with anti-periplanar conformations for H-1′,2′ and H-3′,4′, and the synclinal conformation for H-2′,3′. Consequently, these compounds tend to adopt a planar zigzag conformation in solution, as do other D-*manno*-pentitol-1-yl heterocycles[12].

EXPERIMENTAL

General methods. — Solutions were concentrated *in vacuo* at <40°. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical

rotations were measured with a Perkin–Elmer 141 polarimeter (10-cm cell). I.r. spectra were recorded, for KBr discs, with a Perkin–Elmer 399 grating spectrophotometer. U.v. spectra were recorded with a Spektralphotometer DMR 11 Zeiss instrument. ^{1}H-N.m.r. spectra (90 MHz) were recorded at 35.5° with a Perkin–Elmer R-32 spectrometer (locked on the signal of internal Me_4Si), and coupling constants were measured directly from spectra recorded at 300-Hz sweep-width. T.l.c. was performed on silica gel GF_{254} (Merck) with benzene–ethanol (3:1), and detection with u.v. light and iodine vapour. Consumption of periodate was determined by a method based on the Fleury and Lange[13] procedure.

Dimethyl 3-(D-manno-*pentitol-1-yl*)*-1-phenylpyrazole-4,5-dicarboxylate* (**4a**). — Acetic acid (0.16 mL) and DMADC (**2**; 0.5 mL, 4 mmol) were added to a stirred suspension of D-mannose phenylhydrazone[14] (**1a**; 0.73 g, 2.7 mmol) in *N,N*-dimethylformamide (20 mL). The mixture was stirred at room temperature until the solid had dissolved (3 days), and then stored for 1 month. The solvent was removed *in vacuo*, and the residue was extracted with ether (5 × 10 mL). The resulting syrup was treated with ethyl acetate (25 mL), and the solid residue (**4a**, 117 mg) was collected and washed with cold ethyl acetate. The combined filtrate and washings were concentrated and, after storage for 3–5 days in a refrigerator, more (130 mg) **4a** was obtained (total yield, 23%), m.p. 172–173° (from ethanol); $[\alpha]_D^{18}$ −19°, $[\alpha]_{578}^{18}$ −20°, $[\alpha]_{546}^{18}$ −25°, $[\alpha]_{436}^{18}$ −40°, $[\alpha]_{365}^{18}$ −143° (*c* 0.5, pyridine); λ_{max}^{MeOH} 254 nm (ε 7,600); ν_{max} 1715 (ester C=O) and 1530 cm^{-1} (C=N). See Table I for p.m.r. data.

Anal. Calc. for $C_{18}H_{22}N_2O_9$: C, 52.68; H, 5.40; N, 6.82; reduction equiv., 51.30. Found: C, 52.83; H, 5.47; N, 6.45; reduction equiv., 50.00.

The enehydrazone **3a** (334 mg, 30%) crystallised from the mother liquors.

Dimethyl 3-(*penta*-O-*acetyl*-D-manno-*pentitol-1-yl*)*-1-phenylpyrazole-4,5-dicarboxylate* (**5a**). — A solution of **4a** (0.10 g, 0.24 mmol) in pyridine (1 mL) was treated with acetic anhydride (0.7 mL) overnight at ~0° and then poured into ice–water (20 mL), to yield **5a** (0.11 g, 73%), m.p. 96–97° (from ethanol–water, 3:1); $[\alpha]_D^{25}$ +27°, $[\alpha]_{578}^{25}$ +29°, $[\alpha]_{546}^{25}$ +34°, $[\alpha]_{436}^{25}$ +63°, $[\alpha]_{365}^{25}$ +112° (*c* 0.375, chloroform); ν_{max} 1740 (ester C=O plus acetate) and 1530 cm^{-1} (C=N). See Table I for p.m.r. data.

Anal. Calc. for $C_{28}H_{32}N_2O_{14}$: C, 54.19; H, 5.20; N, 4.51. Found: C, 54.31; H, 5.32; N, 4.48.

Dimethyl 3-formyl-1-phenylpyrazole-4,5-dicarboxylate (**6a**). — A solution of sodium metaperiodate (0.5 g) in water (15 mL) was added to a stirred suspension of **4a** (0.20 g, 0.49 mmol) in ether (15 mL), and the mixture was stirred for 1 h. The organic phase was separated and the aqueous phase was extracted with ether (2 × 15 mL). The combined and dried (Na_2SO_4) extracts were concentrated, to yield **6a** (115 mg, 82%), m.p. 105–106° (from ether–light petroleum, 1:1); λ_{max}^{MeOH} 246 nm (ε 11,400); ν_{max} 1740 and 1725 (ester C=O), 1690 (aldehyde C=O), and 1530 cm^{-1} (C=N). P.m.r. data ($CDCl_3$): δ 3.86, 3.98 (2 s, 6 H, 2 CO_2Me), 7.52 (s, 5 H, Ph), and 10.30 (s, 1 H, CHO).

Anal. Calc. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.48; H, 4.25; N, 9.68.

Dimethyl 3-(D-manno-*pentitol-1-yl*)*-1-*(p-*tolyl*)pyrazole-4,5-dicarboxylate* (**4b**). — Acetic acid (4 mL) and DMADC (**2**; 8.5 mL, 66.5 mmol) were added to a suspension of D-mannose *p*-tolylhydrazone[15] (**1b**: 8.0 g. 28.2 mmol) in *N,N*-dimethylformamide (180 mL). The mixture was stirred until the solid had dissolved (3–4 days), and then kept at room temperature for 12–15 days. The solvent was then removed under diminished pressure, the resulting syrup was triturated with ether (4 × 100 mL), and a solution in ethyl acetate (125 mL) was kept at room temperature for 24 h, to yield a mixture (3.3 g) of **4b** and **3b**, which was recrystallised from ethanol (25 mL), to give **4b** (0.9 g). m.p. 176–177° (softening at 159–160°) (from ethanol). The mother liquor was concentrated to half volume, yielding, after several days, more of the mixture (1.5 g), which was treated as described above, to afford **4b** (0.7 g; total yield, 14%); $[\alpha]_D^{32}$ −18°, $[\alpha]_{578}^{32}$ −19°, $[\alpha]_{546}^{32}$ −22°, $[\alpha]_{436}^{32}$ −39°, $[\alpha]_{365}^{32}$ −87° (*c* 0.5, pyridine); λ_{max}^{MeOH} 261 nm (ε 11,500); ν_{max} 1720 (ester C=O) and 1530 cm^{-1} (C=N). See Table I for p.m.r. data.

Anal. Calc. for $C_{19}H_{24}N_2O_9$: C, 53.77; H, 5.70; N, 6.60; reduction equiv., 53.05. Found: C, 53.80; H, 5.65; N, 6.51; reduction equiv., 53.33.

The acyclic product **3b** (3.8 g, 32%) crystallised later from the ethanolic solution.

Dimethyl 3-(*penta-*O*-acetyl-*D-manno-*pentitol-1-yl*)*-1-*(p-*tolyl*)pyrazole-4,5-dicarboxylate* (**5b**). — Conventional treatment of **4b** (0.10 g, ~0.24 mmol) with pyridine (1 mL) and acetic anhydride (0.7 mL) yielded **5b** (115 mg, 77%), m.p. 123–124°: $[\alpha]_D^{32}$ +21°, $[\alpha]_{578}^{32}$ +23°, $[\alpha]_{546}^{32}$ +24°, $[\alpha]_{436}^{32}$ +55.5°, $[\alpha]_{365}^{32}$ +107° (*c* 0.5, chloroform); ν_{max} 1740 (ester C=O plus acetate) and 1530 cm^{-1} (C=N). See Table I for p.m.r. data.

Anal. Calc. for $C_{29}H_{34}N_2O_{14}\cdot H_2O$: C, 53.37; H, 5.56; N, 4.29. Found: C, 53.62; H, 5.27; N, 4.24.

Dimethyl 3-formyl-1-(p-*tolyl*)*pyrazole-4,5-dicarboxylate* (**6b**). — A solution of sodium metaperiodate (0.5 g) in water (15 mL) was stirred with a suspension of **4b** (0.20 g, 0.47 mmol) in ether (15 mL) at room temperature for 1 h. The aqueous phase was extracted with ether (2 × 15 mL). The combined and dried (Na_2SO_4) extracts were concentrated to a syrup, which was crystallised from ether–light petroleum, to yield **6b** (95 mg, 67%), m.p. 81–82°; λ_{max}^{MeOH} 253 nm (ε 11,600); ν_{max} 1740–1700 (ester C=O plus aldehyde) and 1530 cm^{-1} (C=N). P.m.r. data ($CDCl_3$): δ 2.42 (s, 3 H, Me), 3.85, 3.97 (2 s, 6 H, 2 CO_2Me), 7.10–7.45 (m, 4 H, aromatic protons), and 10.20 (s, 1 H, CHO).

Anal. Calc. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.62; H, 4.78; N, 9.41.

Dimethyl 1-(p-*bromophenyl*)*-3-*(D-manno-*pentitol-1-yl*)*pyrazole-4,5-dicarboxylate* (**4c**). — DMADC (**2**; 7 mL, 54 mmol) was added with continuous stirring to a suspension of the arylhydrazone[16] **1c** (8.0 g, 23 mmol) in *N,N*-dimethylformamide (180 mL) containing acetic acid (3.3 mL). After the solid had dissolved (5 days), the solution was kept at room temperature for 1 month and then concentrated *in vacuo*.

The resulting, brown syrup was extracted with ether (4 × 100 mL), and then a solution in ethyl acetate (150 mL) was kept at room temperature overnight. The solid was collected, and washed with cold ethyl acetate, to give **4c** (0.9 g). Storage of the mother liquors gave more **4c** (1.0 g; total yield, 17%), m.p. 193–194° (softening at 151–152°) (from methanol); $[\alpha]_D^{32}$ −15°, $[\alpha]_{578}^{32}$ −16°, $[\alpha]_{546}^{32}$ −17.5°, $[\alpha]_{436}^{32}$ −32°, $[\alpha]_{365}^{32}$ −63° (*c* 0.5, pyridine); λ_{max}^{MeOH} 262 nm (ε 14,800); ν_{max} 1730, 1715 (ester C=O), and 1530 cm^{-1} (C=N). See Table I for p.m.r. data.

Anal. Calc. for $C_{18}H_{21}BrN_2O_9$: C, 44.19; H, 4.33; Br, 16.33; N, 5.72; reduction equiv., 61.16. Found: C, 44.14; H, 4.36; Br, 15.32; N, 5.65; reduction equiv., 62.00.

Dimethyl 1-(p-*bromophenyl*)*-3-*(*penta*-O-*acetyl*-D-manno-*pentitol-1-yl*)*pyrazole-4,5-dicarboxylate* (**5c**). — Conventional treatment of **4c** (0.10 g, 0.20 mmol) with pyridine (1 mL) and acetic anhydride (0.7 mL) yielded **5c** (0.13 g, 88%), m.p. 107–108° (from ethanol–water); $[\alpha]_D^{27}$ +27.5°, $[\alpha]_{578}^{27}$ +29°, $[\alpha]_{546}^{27}$ +33°, $[\alpha]_{436}^{27}$ +65°, $[\alpha]_{365}^{27}$ +121° (*c* 0.46, chloroform); ν_{max} 1740–1715 (ester C=O plus acetate) and 1530 cm^{-1} (C=N). See Table I for p.m.r. data.

Anal. Calc. for $C_{28}H_{31}BrN_2O_{14}$: C, 48.08; H, 4.47; Br, 11.42; N, 4.00. Found: C, 48.04; H, 4.46; Br, 11.23; N, 4.00.

Dimethyl 1-(p-*bromophenyl*)*-3-formylpyrazole-4,5-dicarboxylate* (**6c**). — By the procedure described for the oxidation of **4b**, **4c** (0.20 g, 0.40 mmol) was converted into **6c** (0.12 g, 77%), m.p. 101–102° (from ether–light petroleum 1:2); λ_{max}^{MeOH} 257 nm (ε 13,700); ν_{max} 1715 (ester C=O), 1690 (C=O aldehyde), and 1530 cm^{-1} (C=N). P.m.r. data ($CDCl_3$): δ 3.85, 3.95 (2 s, 6 H, 2 CO_2Me), 7.19–7.70 (m, 4 H, aromatic protons), and 10.20 (s, 1 H, CHO).

Anal. Calc. for $C_{14}H_{11}BrN_2O_5$: C, 45.80; H, 3.02; Br, 21.76; N, 7.63. Found: C, 45.72; H, 3.10; Br, 21.38; N, 7.69.

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REFERENCES

1 M. Gómez Guillén, L. M. Vázquez de Miguel, and J. C. Palacios Albarrán, *An. Quim.*, *76C (1980)* 34–40.
2 M. Gómez Guillén, L. M. Vázquez de Miguel, and J. Velázquez Jiménez, *An. Quim.*, 78C (1982) 89–92.
3 M. K. Saxena, M. N. Gudi, and M. V. George, *Tetrahedron*, 29 (1973) 101–105.
4 H. Ogura, K. Kubo, Y. Watanabe, and I. Itoh, *Chem. Pharm. Bull.*, 21 (1973) 2026–2030.
5 R. Baumes, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. Fr.*, (1974) 2547–2555; (1976) 260–264.
6 J. G. Buchanan, M. E. Chacón-Fuertes, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, (1979) 244–248; J. G. Buchanan, M. E. Chacón-Fuertes, A. Stobie, and R. H. Wightman, *ibid.*, (1980) 2561–2566: J. G. Buchanan, S. J. Moorhouse, and R. H. Wightman, *ibid.*, (1981) 2258–2266.

7 J. M. J. TRONCHET, F. PERRET, F. BARBALAT-REY, AND T. NGUYEN-XUAN, *Carbohydr. Res.*, 46 (1976) 19–31; J. M. J. TRONCHET AND F. PERRET, *Helv. Chim. Acta*, 55 (1972) 2121–2133.
8 K. SCHOFIELD, M. R. GRIMMETT, AND B. R. T. KEENE, *The Azoles*, Cambridge University Press, 1976, p. 31.
9 N. K. RICHTMYER AND C. S. HUDSON, *J. Am. Chem. Soc.*, 64 (1942) 1612–1613.
10 W. SUCROW, C. MENTZEL, AND M. SLOPIANKA, *Chem. Ber.*, 107 (1974) 1318–1328.
11 Ref. 8, p. 22.
12 A. M. SELDES, E. G. GROS, I. M. E.THIEL, AND J. O. DEFERRARI, *Carbohydr. Res.*, 39 (1975) 11–18.
13 P. F. FLEURY AND J. LANGE, *J. Pharm. Chim.*, 17 (1933) 107–113, 196–208.
14 C. L. BUTLER AND L. H. CRETCHER, *J. Am. Chem. Soc.*, 51 (1929) 3161–3165.
15 *Beilstein's Handbuch der Organischen Chemie*, XV (EI), 156.
16 K. BJAMER, S. DAHN, S. FURBERG, AND C. S. PETERSEN, *Acta Chem. Scand.*, 17 (1963) 559–561.