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PUMMERER REARRANGEMENT OF THIOANHYDRO-HEXITOL SULFOXIDES

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Abstract—Pummerer rearrangement of the 2.5-di-O-acetyl-1.4:3.6-bis(thioanhydro)-D-iditol-disulfoxide (**1**) isomers gave besides 2-acetyl-thieno-[3.2-b]thiophene (**9**). 2-acetyl-5-acetoxy-thieno[3.2-b]thiophene (**3**) as main product. These compounds can be formed only by addition of acetic anhydride to an ylide inter-intermediate, a fact which enables a more detailed description of the reaction mechanism. Sodium periodate and iodate display a catalytic effect on the rearrangement, yielding a mixture of 2-acetoxy- (**6**) and 3-acetoxy-thieno[3.2-b]thiophene (**7**), which are the expected decomposition products of the normal Pummerer reaction. Ferric chloride seems to catalyse an oxido-reduction process, leading mainly to 2-acetyl-thieno-[3.2-b]thiophene.

INTRODUCTION

THE REARRANGEMENT of sulfoxides to α-acyloxy-sulfides on treatment with anhydrides of carboxylic acids (Pummerer reaction[1]) was first applied to carbohydrate sulfoxides by Lindberg and Lundström[2] in 1968. As their experiments were on methylglycosides carrying a methylsulfinyl group at C-6, O-acylated monothioacetals were obtained. McCormick and McElhinney[3] extended the same reaction to thioanhydro-tetritol sulfoxides of tetrahydrothiophene structure, converting them into acylated thiofuranoses. The Pummerer reaction of the isomeric 1.4:3.6-bis[thioanhydro]hexitol disulfoxides[4] (**1**) which should lead to the proper bicyclic hemithioacetales **2** is investigated here.

RESULTS

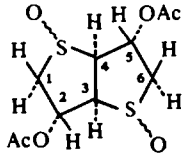
The reaction of the 2.5-di-O-acetyl-1.4:3.6-bis[thioanhydro]-D-iditol (R, R)- or -(R, S)-disulfoxide[4] (**1**) in Ac_2O at 110° was monitored by TLC. After consumption of starting material 2-acetyl-5-acetoxy-thieno[3.2-b]thiophene (**3**) was separated from the dark blue mixture with traces of the corresponding 2-acetyl derivative **9**. The structure of compound **3** was proved by spectroscopic methods, comparing the obtained data with those of the 2-acetyl derivative **9**, the structure of which was established unambigously by Challenger *et al.*[5,6] According to analytical and MS data compound **3** contained one Ac and one AcO group, this was supported by the appearance of two different carbonyl absorptions in the IR and by two different δ CH_3 values in the NMR spectrum (Table 1). Location of the two substituents on the thienothiophene skeleton in position 2 (Ac) and 5 (AcO) was made by NMR and MS interpretation. The two aromatic protons gave separate singlets, excluding a vicinal position as in compound **5** which would show an AB type spectrum. That means, that the Ac and AcO groups must be located on different rings. As the chemical shift of the proton adjacent to the Ac group was the same as in the corresponding 2-acetyl derivative **9** (δ 7·80 and δ 7·79 ppm resp.) the Ac group in **3** should occupy the same position. Location of the AcO group was made possible by comparing the chemical

shift of the adjacent proton with that of the 2- and 3-acetoxy isomers **6** and **7**, described below. If this proton is vicinal to the sulphur atom, its signal is paramagnetically shifted compared to the one in β-position (δ 7·34 and δ 6·95 ppm, Table 1). As the signal of the corresponding proton of compound **3** appears at 6·99 ppm, the AcO group must

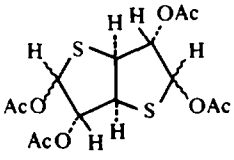
TABLE 1. NMR and IR DATA OF THIENO[3.2-b]THIOPHENE DERIVATIVES

Comp.	NMR data (CCl_4)							IR data
	δH_2	δH_3	νH_5	δH_6	δAc	δAcO	$J_{5,6}$	$\nu C=O$
3	—	7·80	—	6·99	2·58	2·36	—	1760; 1645
6	—	6·95	7·24	7·14	—	2·28	5·0	1755
7	7·34	—	7·35	7·20	—	2·30	5·0	1770
8	3·87	—	7·18	7·00	—	—	5·0	1700
9	—	7·79	7·53	7·24	2·50	—	5·5	1650

be located in the α-position (C-5). The mass spectrum of **3** shows an intensive peak (44%) at *m/e* 240 due to the molecular ion. The base peak (*m/e* 198) arises by elimination of ketene from the enol acetate part of the molecule, a process described to yield an enol.[14] This enol formed could generate a radical at position 2 by π-electron rearrangement in the case of a 5-acetoxy group only, this is assumed to be the driving force of the consecutive loss of the Me radical from the 2-acetyl-group, leading to the abundant ion (55%) at *m/e* 183.



1



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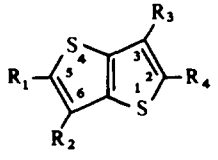
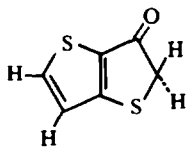




8

3 $R_2 = R_3 = H$; $R_1 = AcO$; $R_4 = Ac$
4 $R_1 = R_3 = H$; $R_2 = AcO$; $R_4 = Ac$
5 $R_1 = R_2 = H$; $R_3 = AcO$; $R_4 = Ac$
6 $R_1 = R_2 = R_3 = H$; $R_4 = AcO$
7 $R_1 = R_2 = R_4 = H$; $R_3 = AcO$
9 $R_1 = R_2 = R_3 = H$; $R_4 = Ac$
10 $R_1 = R_2 = R_3 = R_4 = H$

When the Pummerer reaction was carried out in the presence of 2% of $NaIO_4$ or $NaIO_3$, neither of the acetyl derivatives **3** and **9** could be detected by TLC, GLC analysis of the mixture revealed two components of similar volatility (ratio 3:7). The major component was obtained as crystals and proved to be 2-acetoxy-thieno-[3.2-b]thiophene (**6**). The other component, obtained as liquid by GLC, turned out to be the corresponding 3-acetoxy isomer **7**. Its structure could be proved chemically, as it was quite unstable and decomposed slowly in solution to the known[6] 3-oxo-compound **8**.

Carrying out the Pummerer reaction in the presence of $FeCl_3$ (known to accelerate remarkably both, the rate of racemisation of sulfoxides[7] and that of the Pummerer reaction[8]) the 2-acetyl derivative **9** was obtained as the main component along with a small amount of the acetoxy isomers **6** and **7**.

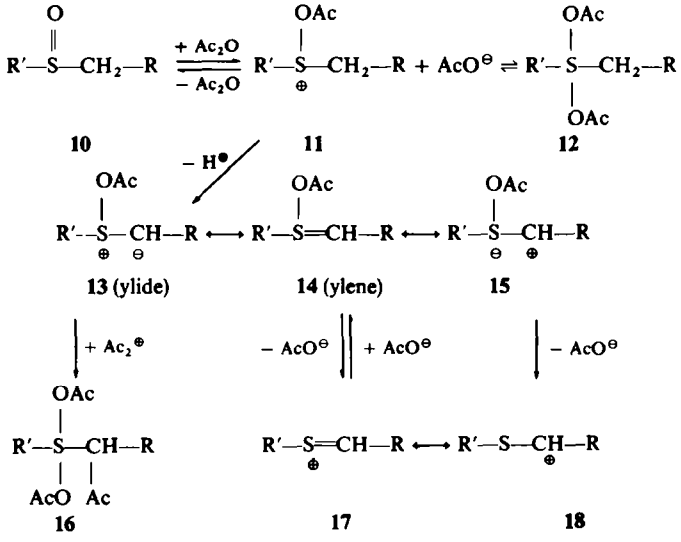
DISCUSSION

Among the thieno-thiophene derivatives **3**, **6**, **7** and **9** only the AcO isomers **6** and **7** can be formed *via* the hypothetical Pummerer rearrangement product **2** which may be unstable under the reaction conditions employed.[9, 10]

The Ac derivative **3** could be formed from compound **6** in a subsequent substitution reaction, as thieno[3·2-b]thiophenes are known to undergo similar reactions.[5] This supposition had to be ruled out, as the pure AcO derivatives **6** and **7** remained unchanged under the reaction conditions of the Pummerer rearrangement.

Formation of compounds **3** and **9** as well as the different course of the reaction in the presence of $NaIO_4$ or $NaIO_3$ can be explained, however, by taking into consideration a reaction mechanism slightly different from that, suggested by Kise and Oae (Scheme 1).[11]

Scheme 1. Suggested reaction mechanism for the Pummerer rearrangement



10 **11** **12**

13 (ylide) **14** (ylene) **15**

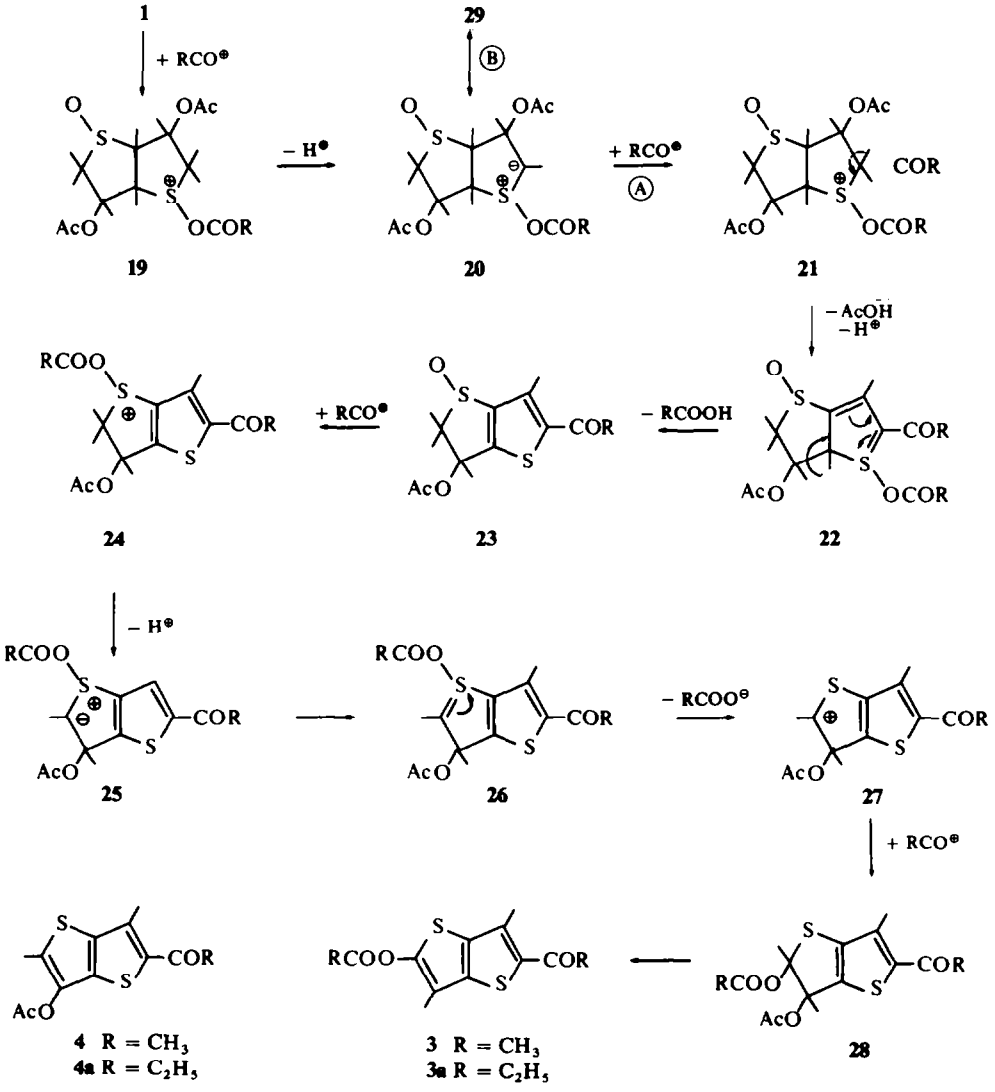
16 **17** **18**

Proton removal from the intermediate **11**, which is the rate determining step of the Pummerer reaction[11, 12] should lead first to the ylide[11–13] **13**, representing an extreme electron distribution of a mesomeric system, including the charge free ylene **14** and the

ionic counterpart **15**. The course of the Pummerer reaction is, however, an immediate collapse of the generated ylide **13** to the ylene **14**, from which the key ion **18** can be formed *via* intermediate **17** and **15** respectively. If the ylide **13** is relatively stable—as presumed in the case of halosulphonium salts[12]—it can be attacked by one mole of Ac_2O, resulting in an α-acetyl-derivative (**16**). Neither the compounds nor their decomposition products have been detected in Pummerer type reactions thus far, proving the high instability of the ylide intermediate (**13**).

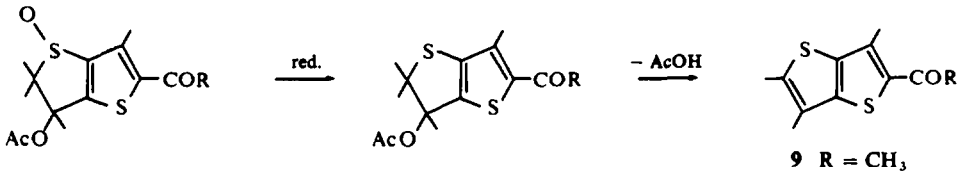
Applying the mechanism depicted in Scheme 1, to the Pummerer reaction of the disulfoxides (**1**) it can be supposed, that first one molecule-half will react to give the ylide **20** which—depending on the conditions employed—can be transformed *via* pathway A (Scheme 2) by attack of an acyl cation to the intermediate **21** or it can enter

SCHEME 2



pathway B (Scheme 4), collapsing to the ylene (**29**). By pathway A the addition product **21** can yield the monosulfoxide **23** by losing a proton and AcOH. The intact sulfoxide ring of this intermediate can undergo a "normal" Pummerer rearrangement, affording the diaciloxy derivative (**28**) from which both acetyl-acetoxy isomers **3**

SCHEME 3

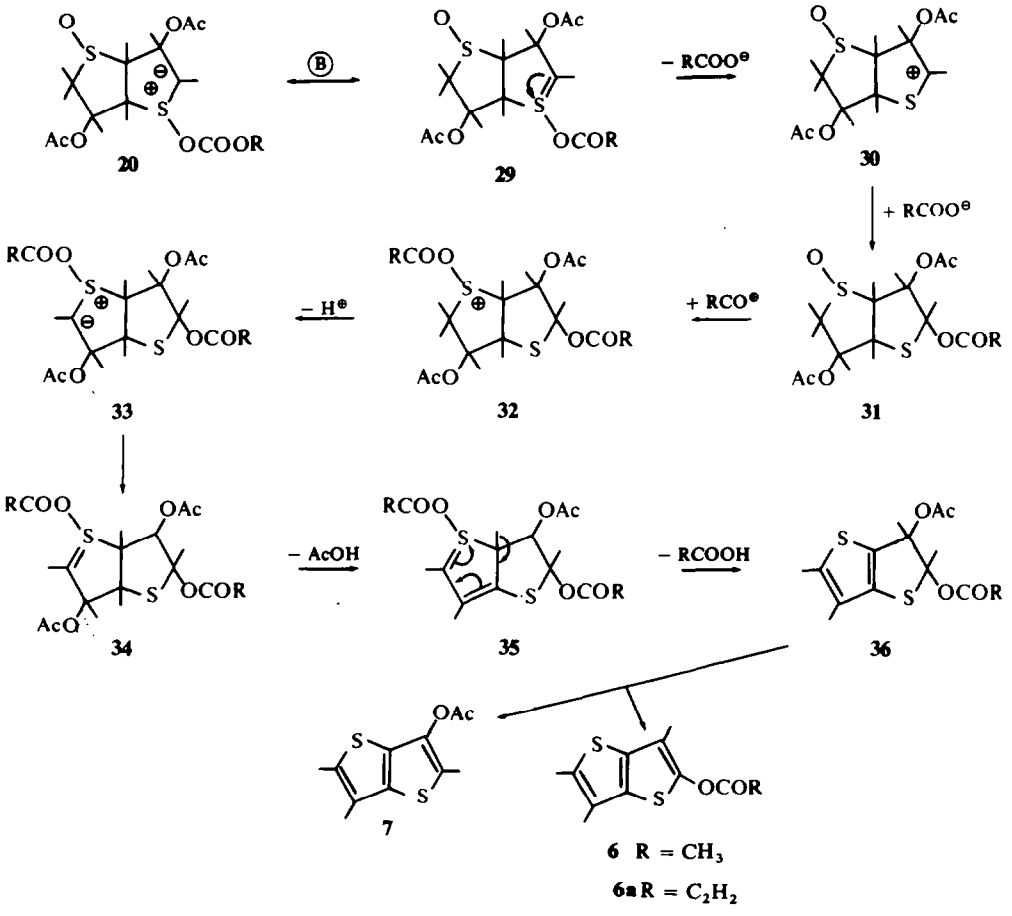


23

9 R = CH_3
9a R = C_2H_5

and **4** can be formed, differing only in the position of the AcO groups. If the reaction was carried out with Ac_2O only the 5-acetoxy-isomer **3** was isolated, but NMR investigation of the mother liquor revealed the presence of a small amount of compound **4**, which, could not be separated. As none of the AcO isomers (**6**, **7**) could be detected,

SCHEME 4



20 **29** **30** **33** **32** **31** **34** **35** **36**

7

6 R = CH_3
6a R = C_2H_2

the ylide intermediate **20** must be stable enough to enter into the addition reaction according to pathway A.

If the sulfoxide group of the intermediate **23** is reduced during the reaction, subsequent removal of AcOH should lead to compound **9** (Scheme 3), which was obtained as a byproduct. The dark blue colour of the reaction mixture and the formed amorphous black material may be due to such an oxidation process.

Pathway B (Scheme 4) represents the expected course of the Pummerer reaction, as both rings undergo a normal rearrangement and the loss of AcOH will result in the 2- and 3-acetoxy derivatives (**6** and **7**). As these compounds are formed only in the presence of $NaIO_4$ or $NaIO_3$, these salts must have a catalytic effect on the reactions, employed in pathway B. The catalytic role of these salts may be due to their ability to form complexes with anions, speeding up the decomposition of the ylene **29** to the cation **30**, by binding the acetate ion.

The catalytic role of $FeCl_3$ must be different, as the intermediate **20** undergoes a further rearrangement mainly *via* pathway A (Scheme 2)—as without catalyst—but the hypothetical sulfoxide **23** is completely reduced to give after loss of AcOH (Scheme 3) the 2-acetyl derivative **9**. The ferric salts may catalise the oxido-reduction process involved in this reaction.

In further experiments propionic acid anhydride was used instead of Ac_2O in the Pummerer reaction. MS investigation of the crude reaction product revealed the presence of the following compounds, due to peaks corresponding to their molecular ions: **3a**, **4a**, **6a**, **7**, **8**, **9a**, and **10**. This allows the conclusion to be drawn, that in propionic anhydride the Pummerer rearrangement proceeds simultaneously *via* route A (Scheme 2) and B (Scheme 4), affording the predicted derivatives **3a**, **4a**, **6a** and **7**, respectively. Compound **9a** is formed in the reductive side reaction (Scheme 3). Similar reduction of intermediate **31** will lead to a triester, from which thieno[3·2-b]thiophene (**10**) is formed by loss of three moles of carbonic acid.

EXPERIMENTAL

M.ps are uncorrected. TLC was carried out on Kieselgel G coated microscope slides using CCl_4/EtOAc 5:1 (A) as solvent. Detection was by 0·1 M $KMnO_4$ in 2 N H_2SO_4 (1:1). NMR spectra were recorded at 60 MHz with a Varian A-60D spectrometer, using TMS as internal standard. Mass spectra were recorded on a Varian MAT SM-1 instrument. Preparative GLC was carried out on a F-21 Perkin Elmer gaschromatograph, using a 3·5 mm × 2 m U shaped glass column, packed with 0·77 w/w % OV-1 on 100–120 mesh AW-DMCS. Temperatures: inlet 250°, column 140°; Carrier: nitrogen, 45 ml/min.

All evaporations were carried out in a rotary evaporator under diminished pressure, after drying the organic solutions over sodium sulphate.

Pummerer reaction without catalyst. The (R, R)- (m.p. 238–240°) or (R, S)- (m.p. 171–172°) disulfoxide[4] **1** (1·5 g) was dissolved by heating to 110° in Ac_2O anhydride (15 ml) and kept at this temperature for 20 h. The blue-black mixture—giving on TLC (solvent A) beside a faint spot of R_f 0·60 a green-blue spot of R_f 0·05 only—was evaporated. The residue was treated with $CHCl_3$, the insoluble black material filtered (0·35 g), the filtrate washed with 5% $NaHCO_3$ aq and water and was evaporated after being dried and treated with charcoal. The semisolid residue gave after treating with ether 0·5 g (42·4%) crude ester (m.p. 155–160) which on recrystallisation from EtOH (15 ml) afforded compound **3** as pale yellow needles (0·32 g, 27·1%), m.p. 164–165°. R_f 0·50 (green-blue spot, solvent A). *m/e* 240 (M); 198 (M-CH_2CO, 100%); 183 (M-CH_2CO—Me). (Found: C, 49·72; H, 3·60; S, 26·50. $C_{10}H_8O_3S_2$ requires: C, 49·98; H, 3·36; S, 26·69%).

The etheral filtrate gave on evaporation a brown syrup (0·75 g), chromatographed on silica (CCl_4) using solvent A. The fractions giving on TLC the spot of R_f 0·60 were combined and afforded on evaporation and subsequent recrystallisation from EtOH (2 ml) compound **9** (0·05 g, 5·6), m.p. 124–126°. (lit[5] m.p.

124·5–125°). *m/e* 182 (M); 167 (M-Me. 100%); 139 (M-CH_3CO). On treatment with phenylhydrazine (0·1 ml) in 50% AcOH (5 ml) on the steam bath for 1 h the phenylhydrazone (0·05 g) separated, which after recrystallisation from EtOH had m.p. 164–165°. (lit[5] m.p. 165·5–166°).

Pummerer reaction in the presence of sodium periodate or iodate. The mixture described above was kept in the presence of $NaIO_4$ or $NaIO_3$ (30 mg) at 110° for 12 h. TLC investigation revealed only one blue spot (R_f 0·90; solvent A), but GLC showed the presence of two compounds (ratio 3:7) with retention times of 3 and 4 min. The residue, gained after evaporation of the blue-black solution was treated with water-$CHCl_3$. The organic solution was washed with $NaHCO_3$ and water, dried and evaporated. The black residue was dissolved in $CHCl_3$ and "filtered" through silica (100 g) ($CHCl_3$) by washing with $CHCl_3$. Evaporation of the first 100 ml of the eluent yielded a mixture of the acetoxy isomers **6** and **7** as semisolid material (0·5 g, 51·5%). The pure 2-acetoxy derivative **6** was obtained (0·22 g, 22·4%) by treating this mixture with light petroleum, m.p. 66–68°. R_f 0·90 (Blue spot, solvent A). GLC retention time 4 min.

Pure 3-acetoxy isomer **7** was obtained by prep. GLC of the mother liquor as a colorless liquid. R_f 0·90 (Blue spot, solvent A). GLC retention time 3 min. Both isomers gave qualitatively identical mass spectra, differing in the relative intensities of some peaks only: *m/e* 198 (M); 156 (M-CH_2CO, 100%); 43 (CH_3CO). (Found for **6**: C, 48·81; H, 3·00; S, 32·24. For **7**: C, 48·62; H, 2·97; S, 32·15. $C_8H_6O_2S_2$ requires: C, 48·46; H, 3·05; S, 32·35%).

When the crude evaporated mixture was purified by normal column chromatography, the deacetylated derivative **8** was obtained, due to decomposition of the 3-acetoxy isomer **7** during this process. The composition of the fractions was determined by NMR spectroscopy (Table I) and those, containing mainly the ketone **8** were combined and evaporated. The residue was treated with light petroleum to give pure compound **8**, m.p. 95–96°. (lit.[6] m.p. 98–98·5°). R_f 0·90 (brown spot, solvent A). GLC retention time 0·6 min.

Pummerer reaction in the presence of $FeCl_3$ as catalyst. The mixture described above for the normal Pummerer reaction was heated for 12 h at 110° in the presence of $FeCl_3$ (0·05 g). The residue, obtained after evaporation was treated with $CHCl_3$ and filtered with charcoal. The filtrate was washed with $NaHCO_3$ and water, dried and evaporated. The semisolid residue (0·8 g) was chromatographed on a silica column (CCl_4) using solvent A for elution. The fractions, containing the component of R_f 0·90 gave on evaporation a mixture of the acetoxy isomers **6** and **7** (0·09 g, 9·3%), and those, containing the main component of R_f 0·60 gave on evaporation the 2-acetyl-derivative **9** (0·25 g, 28%), which after recrystallisation from EtOH had m.p. 124–126 and gave no depression with compound **9** described above.

Pummerer reaction in propionic acid anhydride. This reaction was carried out as described above for the normal Pummerer reaction, using propionic acid anhydride instead of Ac_2O. The semisolid residue, which remained after evaporation of $CHCl_3$ solution was investigated by mass spectrometry without further purification.

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REFERENCES

[1] J. A. Smythe. *J. Chem. Soc.* 349 (1909); R. Pummerer. *Der. Dtsch. Chem. Ges.* **43** 1401 (1910)
[2] B. Lindberg and H. Lundström. *Acta Chem. Scand.* **22** 1861 (1968)
[3] J. E. McCormick and R. S. McElhinney. *Chem. Comm.* 171 (1969)
[4] J. Kuszmann and P. Sohár. *Carbohyd. Res.* (in press)
[5] F. Challenger and G. M. Gibson. *J. Chem. Soc.* 305 (1940)
[6] F. Challenger and J. L. Holmes. *Ibid.* 1837 (1953)
[6] F. Challenger and J. L. Holmes. *Ibid.* 1837 (1953); S. Gronowitz and P. Moses. *Acta Chem. Scand.* **16** 155 (1962)
[7] E. Johnson. *Tetrahedron Letters* 3655 (1967)
[8] S. Oae and M. Kise; *Bull. Chem. Soc. Jap.* **43** 1416 (1970)
[9] L. Horner and P. Kaiser. *Ann.* **626** 19 (1959)
[10] R. L. Whistler and D. J. Hoffman. *Carbohyd. Res.* **11** 137 (1969)
[11] M. Kise and S. Oae. *Bull. Chem. Soc. Jap.* **43** 1426 (1970)
[12] C. R. Johnson and W. G. Phillips. *J. Amer. Chem. Soc.* **91** 682 (1969)
[13] G. A. Russel and E. T. Sabourin. *J. Org. Chem.* **34** 2336 (1969)
[14] H. Nakata and A. Tatematsu: *Org. Mass Spectrometry* **4**. 211 (1970)