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γ-LACTONES AND γ-THIOLACTONES—I

A NOVEL ROUTE TO 6-OXABICYCLO[3.2.1]OCTAN-7-ONE AND 6-THIABICYCLO[3.2.1]OCTAN-7-ONE DERIVATIVES

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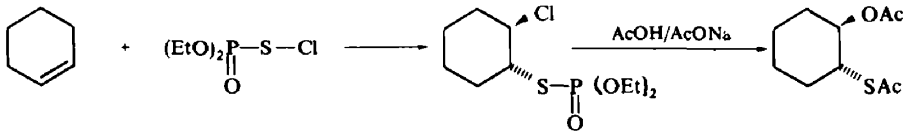
Abstract—Acetolysis of the adduct of diethoxyoxophosphoranesulphenyl chloride (I) and cyclohexene-4-carboxylic acid chloride (IV), yields, via an intramolecular reaction, nearly equal amounts of 4-acetylthio-6-oxabicyclo[3.2.1]octan-7-one (XIV) and 4-acetoxy-6-thiabicyclo[3.2.1]octan-7-one (XVIII) and accounts for about 90% of the products. The 4-acetylthio group in XIV and the 4-acetoxy group in XVIII occupy axial positions. The results testify to the high stereoselectivity of the acetolysis. A mechanism for the reactions involved has been proposed.

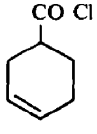
INTRODUCTION

A NEW method for the preparation of monothioglycol-1,2 acetates from olefins[1] involved the addition of diethoxyoxophosphoranesulphenyl chloride[2] (I) to cyclohexene, yielding O,O-diethyl-S-(*trans*-2-chlorocyclohexyl)phosphorothioate[3] (II). On acetolysis, this adduct afforded *trans*-2-hydroxycyclohexanethiol diacetate[1] (III).



I II III

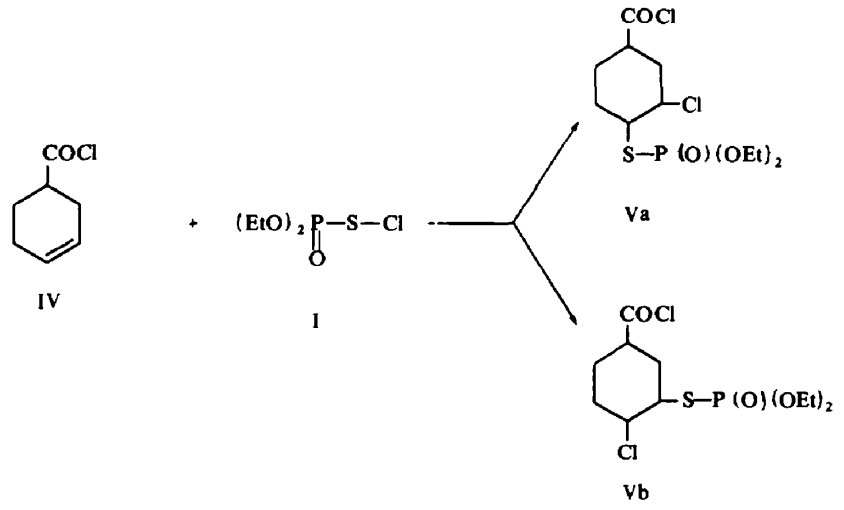
In the present paper, the acetolysis of the adduct of the chloride I and cyclohexene-4-carboxylic acid chloride (IV) is described.



IV

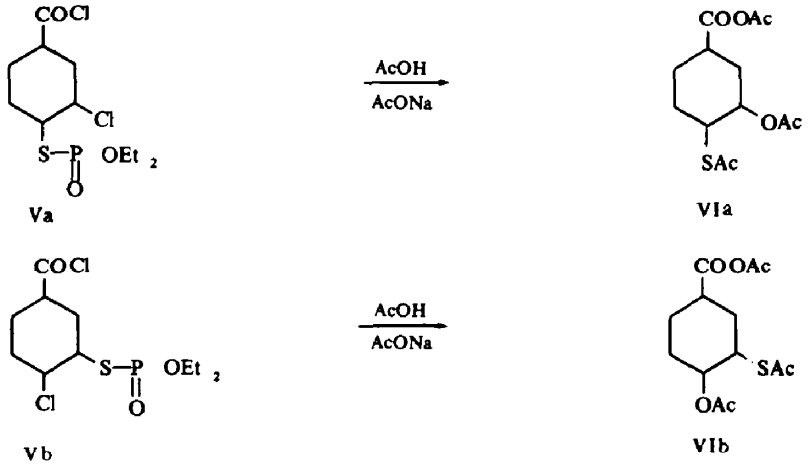
RESULTS AND DISCUSSION

The addition of sulphenyl chloride I to the double bond of chloroanhydride IV results in a mixture of isomers with the possible structures Va and Vb (for clarity, the stereoisomerism due to existence of three asymmetric centers was neglected).



During the acetolysis of the mixture of Va and Vb precipitation of sodium chloride was observed at room temperature, immediately after addition of acetic acid and sodium acetate. As the sodium chloride results from the displacement of the Cl atom at the carbonyl group by an acetoxy group, acetolysis of the adducts Va and Vb should yield the mixed anhydrides VIa and VIb.

The products of acetolysis were isolated by vacuum distillation. By means of TLC,



the distillate was shown to contain three products which were separated by means of column chromatography, yielding a crystalline compound A (ca. 50%), a liquid B (ca. 40%) and a liquid C (ca. 10%). The structures of compounds A and B have been determined. Elucidation of the structure of compound C will be the subject of a separate publication.

Compounds A and B are isomers with the molecular formula $C_9H_{12}O_3S$ which when compared with the anticipated product of acetolysis, $C_{13}H_{18}O_6S$ has lost

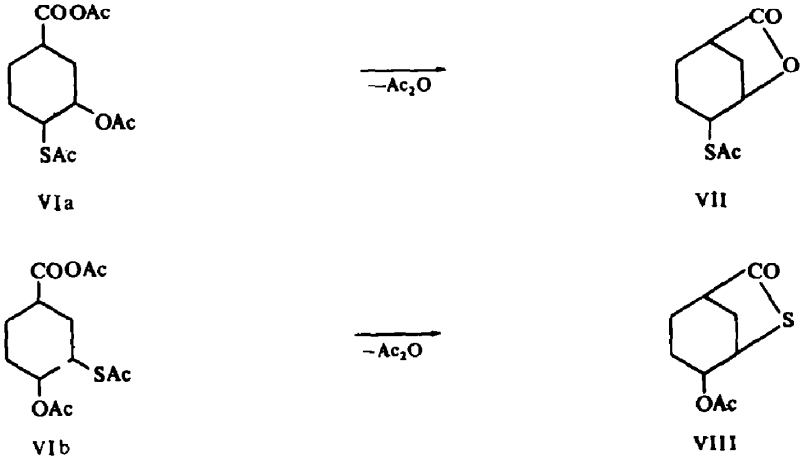
$C_4H_6O_3$ ((probably one molecule of acetic anhydride). It is noteworthy that neither decomposition nor evolution of volatile substances had been observed during distillation.

Determination of the structure and configuration of isomers A and B

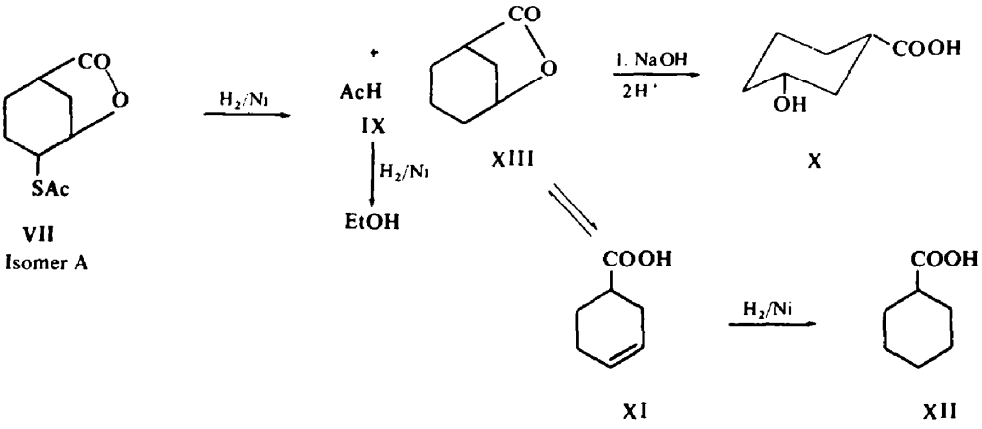
Isomer A. The crystalline product of acetolysis, m.p. 75–76°, b.p. 90–92° at 0·01 mm Hg, exhibits in the IR spectrum absorption bands at 1781 cm^{-1} (due to the CO group of a γ-lactone) and at 1687 cm^{-1} (due to the CO group of the thiolester); the absence of a band within 1220–1250 cm^{-1} indicates that no acetate group is present.

Isomer B. The main liquid product of acetolysis was a colourless oil, b.p. 74–76° at 0·005 mm Hg, m.p. ca. 20°. The IR spectrum exhibits characteristic absorption bands at 1733 cm^{-1} (due to the CO group of the ester), 1705 cm^{-1} (due to the CO group of the γ-thiolactone[4]), 1220 cm^{-1} (due to the O—C bond of the acetyl residue).

On the basis of the IR spectral data, we assigned the γ-lactone structure VII to isomer A and the γ-thiolactone structure VIII to isomer B.

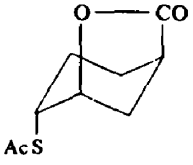


In accordance with the *trans*-addition of chloride I to cyclohexene,[3] and the retention of the configuration during acetolysis of adduct II,[1] the O and S atoms in the cyclohexane ring should be in *trans*-configuration. This was confirmed in isomer A by hydrolysis which yielded a glassy polymer.[5] *cis*-1,2-O,S-Diesters afford *cis*-1,2-monothioglycols which fail to undergo polymerization,[6] under the conditions of hydrolysis. Similarly, mild alkaline hydrolysis of isomer B yielded a polymer which again confirmed the *trans*-configuration of the O and S atoms in the cyclohexane ring.[5,6] Further evidence of this configuration was obtained by mild hydrolysis of the desulphuration products. The isomer A yielded acetaldehyde (IX), *cis*-3-hydroxy-cyclohexane carboxylic acid (X), cyclohexene-4-carboxylic acid (XI) and cyclohexane carboxylic acid (XII). These compounds were recognized by comparison with authentic samples prepared by independent syntheses. The formation of these products is illustrated by the following scheme:



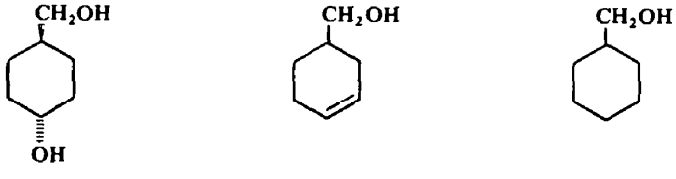
The formation of acetaldehyde in desulphuration of the isomer A indicates the presence of an acetothioxy group, whereas *cis*-3-hydroxycyclohexane carboxylic acid (X) is evidence of a γ-lactone grouping. Cyclohexene-4-carboxylic acid (XI) is an isomer of γ-lactone XIII[7] and is in equilibrium with the latter (lactoenoic tautomerism). Hydrogenation of the acid XI, under the conditions of desulphuration, to cyclohexane carboxylic acid (XII) shifts the tautomeric equilibrium towards the acid XI.

In accordance with this data isomer A has the configuration XIV:

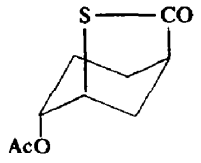


Isomer A: XIV

Desulphuration of isomer B followed by alkaline hydrolysis of the products yielded the following alcohols—*trans*-4-hydroxymethylcyclohexanol (XV), cyclohex-3-enylcarbinol (XVI) and cyclohexylcarbinol (XVII)—identical with authentic compounds obtained by independent syntheses.



The presence of *trans*-4-hydroxymethylcyclohexanol (XV) supports the structure XVIII assigned to isomer B (*trans*-configuration of the substituents 1,4 and *cis*-position of the substituents 1,3):



Isomer B: XVIII

The NMR spectra of the isomers A and B confirm the assigned structures XIV and XVIII.

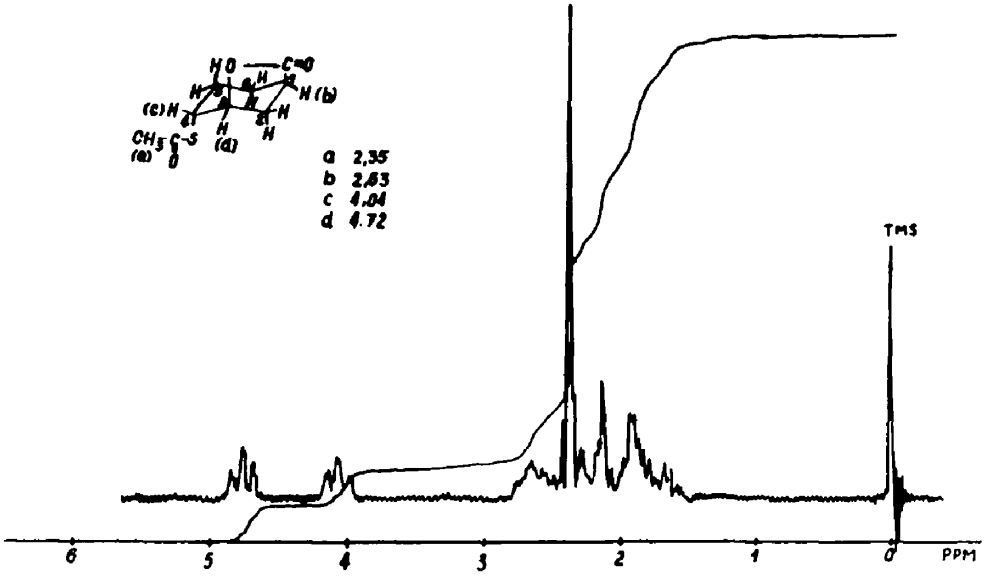


FIG. 1 The NMR spectrum of isomer A.

The NMR spectrum of the isomer A exhibits characteristic signals—three protons of the acetylthio group (singlet 2·35 δ), the proton in position α to the carbonyl group of γ-lactone (multiplet 2·63 δ), the proton in position α to the acetylthio group (triplet 4·04 δ), the proton in position α to the oxygen atom in the lactone ring (triplet 4·72 δ) and six protons of the methylene groups (absorption within the range 1·48–2·45 δ).

The equatorial position of the H atom on the C_3 carbon atom follows from its spin–spin splitting. Dihedral angles between the planes formed by the H—C_3—C_4 and C_3—C_4—H bonds, as well as by the H—C_3—C_2 and C_3—C_2—H (equatorial) bonds, measured on Dreiding models, are about 30° and 40°, respectively. This results in two approximately equal coupling constants and in splitting of the signal of proton on the C_3 carbon atom into a triplet ($J \cong 4{\cdot}5$ c/s). Since the dihedral angle

between the planes formed by the H—C_3—C_2 and C_3—C_2—H (axial) bonds approaches 90°, the coupling between these protons is less than 1 c/s, and it is reflected by broadening of the individual lines of the triplet.

By virtue of analogous reasoning, an equatorial position is assigned to the H atom on the C_4 carbon atom, since its signal also occurs as a triplet ($J \cong 4{\cdot}5$ c/s) with broadened lines.

Similar relationships concerning spin–spin splittings are recorded in the literature[8] for an analogous γ-lactone system.

The NMR spectrum of the isomer B is also consistent with the assigned structure XVIII.

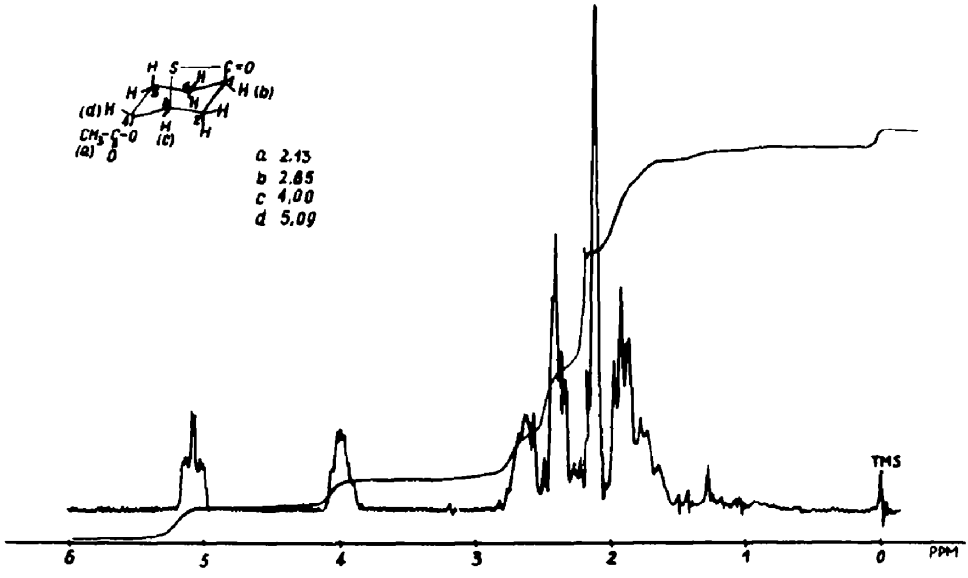


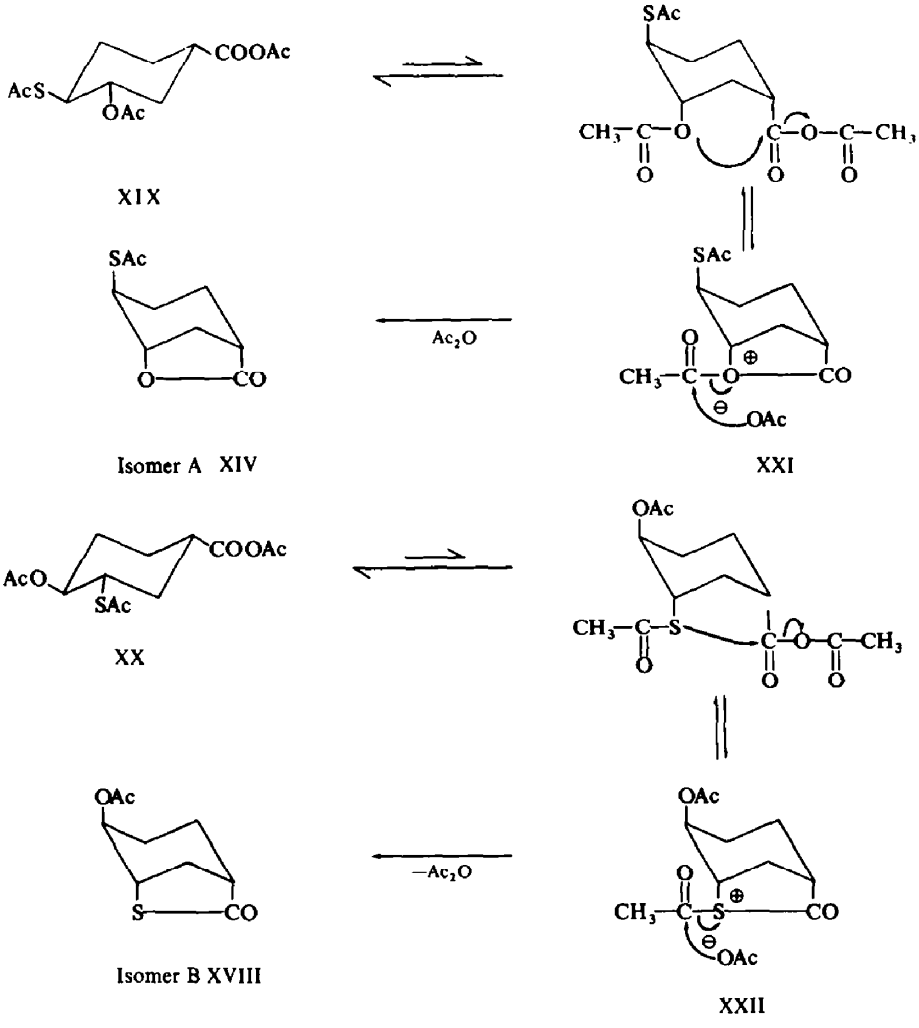
FIG. 2 The NMR spectrum of the isomer B.

The NMR spectrum exhibits characteristic signals—three protons of the acetoxy group (singlet 2·13 δ), protons in position α to the carbonyl group of γ-thiolactone (multiplet 2·65 δ), the proton in position α to the S atom in the thiolactone ring (multiplet 4·00 δ), the proton in position α to the acetoxy group (poorly resolved triplet 5·09 δ), six protons of the methylene groups (absorption within the range 1·18–2·53 δ).

The signal of proton on the C_4 carbon atom is a triplet ($J \cong 4{\cdot}2$ c/s) with broadened lines (about 1 c/s). Taking into account coupling constant values, an equatorial position is assigned to the foregoing proton at the C_4 carbon atom.

The signal of the proton on the C_3 carbon atom occurs as a unresolved multiplet; however the halfheight width of the signal (ca. 8·4 c/s) indicates the occurrence of coupling constants approximating those of the proton on the C_4 carbon atom and, consequently, it suggests an equatorial position of this H atom.

The following mechanism of γ-lactone XIV or γ-thiolactone XVIII formation from mixed anhydrides XIX and XX is proposed:



Formation of isomers A and B can be explained only on assumption of triequatorial conformation of the mixed anhydrides XIX and XX. Formation of a γ-lactone and a γ-thiolactone involves the attack of the nucleophilic O or S atom of the axial acetoxy or acetylthio group on the C atom of the axial carbonyl group in position 3. In the subsequent stage, the acetate ion attacks the carbonyl carbon atom of the acetyl residue in the oxonium cation (XXI) or sulphonium cation (XXII), with simultaneous splitting off of a γ-lactone or γ-thiolactone molecule.

It is noteworthy that about 90% of the products of acetolysis (isomers A and B) originate from triequatorial mixed anhydrides (XIX and XX); this fact emphasizes the marked stereoselectivity of the acetolysis.

EXPERIMENTAL

M.ps and b.ps were uncorrected. IR spectra were recorded on a Hilger H-800 or Perkin–Elmer 137 spectrophotometer. NMR spectra were taken on a Varian V-4300 unit, at 60 MHz, in $CDCl_3$ soln, with TMS used as internal standard. Chemical shifts were denoted in the scale (ppm), i.e. δ for TMS = 0, and the coupling constants were given in c/s.

Gas chromatography was performed on a Griffine George VPC Mark II B unit (column: glycol polyadipate on celite, temp. 148°, flow rate: 1·5 l N_2/hr, detector: catharometer).

TLC was carried out on silica gel G according to Stahl (Merck). Thickness of the layer 0·5 mm. The plates were dried at 120° for 30 min.

Starting materials. Compound IV b.p. 77·5° at 20 mm Hg; n_D^{20} 1·4884 was obtained from cyclohexene-4-carboxylic acid.[9] Compound I, b.p. 70–73° at 1·5 mm Hg; n_D^{20} 6·4684 was prepared by action of sulphuryl chloride on triethyl thiophosphate.[2] Anhyd AcOH was obtained according to Winstein.[10] Raney-nickel W-2 used for desulphuration was prepared according to Mozingo.[11]

1. *Addition of chloride* I *to acid chloride* IV

A soln of I (24·5 g, 0·12 mol) in anhyd benzene (30 ml) was added dropwise to a soln of IV (17·35 g, 0·12 mol) in anhyd benzene (30 ml) at 0–5°. After decolourization of the soln, the solvent was removed by distillation, whereupon the product was distilled (31·7 g; 75·8%; b.p. 126–129° at 0·02 mm Hg; n_D^{20} 1·5115); IR: $\nu_{max}^{(film)}$ 2941, 1780, 1718, 1470, 1433, 1380, 1337, 1250, 1156, 1013, 970, 950, 909, 893, 869, 855, 806, 704, 685 cm^{-1} (Perkin–Elmer). (Found: C, 37·97; H, 5·66; P, 9·11. Calc. for $C_{11}H_{19}O_4PSCl_2$: C, 37·83; H, 5·49; P, 8·87%).

2. *Acetylosis of adduct* V

The adduct V (52·4 g, 0·15 mol) was added to a soln of anhyd AcONa (100 g) in anhyd AcOH (300 ml). NaCl was immediately precipitated. The mixture was refluxed about 60 hr. AcOH was distilled off under reduced press. After addition of water (1500 ml), the residue was extracted with benzene. The solvent was distilled off, and the reaction products were separated by distillation yielding: a liquid fraction (18 g; b.p. 75–77° at 0·01 mm Hg; n_D^{20} 1·5256) and a crystalline fraction (6·5 g; b.p. 90–92° at 0·01 mm Hg). During distillation, neither decomposition nor evolution of gaseous products were observed, no Ac_2O or AcOH were found in the dry ice trap.

Redistillation of the liquid fraction (18 g) afforded: a liquid fraction (11·9 g; b.p. 85° at 0·005 mm Hg; n_D^{20} 1·5252 and a crystalline fraction (4·2 g; b.p. 90° at 0·005 mm Hg). Crystalline fractions resulting from both distillations (10·6 g) were recrystallized from a mixture of ether and pet. ether (50–60°) (m.p. 75–76°).

In the liquid fraction (n_D^{20} 1·5252), the presence of three constituents was disclosed by TLC (a mixture of isooctane and isopropyl ether 1:1 was used as the developing system. The chromatograms were developed 3 times. The spots were detected by spraying with a methanolic soln of hydroxylamine, followed by spraying with 1% aq soln of $FeCl_3$: constituent 1 (isomer A—identical with the crystalline product of acetolysis (m.p. 75–76°) R_f 0·43; constituent 2 (Isomer B)—the main product of the investigated liquid fraction R_f 0·58; constituent 3 (compound C) R_f 0·51.

The liquid fraction (n_D^{20} 1·5252) was separated by chromatography (column length 50 cm, diam 30 mm, filled with silica gel 100–200 μ activated at 140° during 3 hr. A mixture of isooctane and isopropyl ether (2:1) was used as eluent. After careful removal of the solvent, the liquid fraction (1·05 g) yielded: isomer B (0·75 g), compound C (0·14 g) and isomer A (0·08 g) which indicated the approximate composition of the liquid fraction: isomer B (73%), compound C (18%) and isomer A (9%). The liquid fraction represented about 55% of the products resulting from acetolysis, whereas the remaining 45% were accounted for by the crystalline fraction (isomer A); consequently, the total products of acetolysis ca. 40% of isomer B, ca. 10% of compound C and ca. 50% of isomer A.

Isomer A: m.p. 75–76°; b.p. 90–92° at 0·01 mm Hg; R_f 0·43 (isopropyl ether–isooctane 1:1); IR ν_{max} 2961, 2877, 1781, 1687, 1440, 1344, 1316, 1260, 1157, 1119, 1095, 1067, 1035, 990, 955, 934, 908 cm^{-1} (5% solution in CCl_4), Hilger H-800. The NMR spectrum and its interpretation are given above. Found: C, 54·10; H, 6·00; S, 15·76. Calc. for $C_9H_{12}O_3S$: C, 54·00; H, 6·04; S, 16·01%).

Isomer B: m.p. ca. 20°; b.p. 74–76° at 0·05 mm Hg; n_D^{20} 1·4982; R_f 0·58 (isopropyl ether–isooctane 1:1) IR: ν_{max} 2955, 2874, 1733, 1705, 1432, 1355, 1256, 1220, 1186, 1170, 1104, 1059, 1013, 1000, 974, 936 cm^{-1} (5% solution in CCl_4), Hilger H-800. The NMR spectrum and its interpretation are given above. (Found: C, 54·24; H, 6·02; S, 15·85. Calc. for $C_9H_{12}O_3S$; 54·00; H, 6·04; S, 16·01%).

3. *Desulphuration of isomer* A

(i) A mixture of isomer A (3·2 g), Raney-Ni (30 g) and EtOH (150 ml) was refluxed during 6 hr. After the Ni had been filtered off, EtOH was removed by distillation. After addition of 2,4-DNP to the distillate, a ppt identified as 2,4-dinitrophenylhydrazone of acetaldehyde was obtained (m.p. 166–167° from H_2O and EtOH) (Found: N, 24·46 Calc. for $C_8H_8N_2O_4$: N, 24·99%).

A sample of the residual oil obtained after removal of EtOH failed to react with 2,4-DNP. 20% KOH aq (30 ml) was added to the residual oil (2 g), and the mixture was allowed to stand for 12 hr at room temp, whereupon the oil dissolved. The soln was acidified and extracted with benzene. The substance obtained from the extract (1·2 g; b.p. 117–119° at 13 mm Hg; m.p. ca. 30°) was identified as XII (lit.:[12] m.p. 29–30°), by comparison with the authentic sample obtained by independent synthesis. (Found C, 66·42; H, 9·74. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·44%). The amide of XII (m.p. 186°, lit.:[12] 185–186°) was crystallized from H_2O. (Found: C, 65·82; H, 10·66; N, 11·30. Calc. for $C_7H_{13}ON$: C, 66·10; H, 10·30; N, 11·01%). After removing XII, the acidified aqueous layer was saturated with $(NH_4)_2SO_4$ and continuously extracted with ether during 24 hr. The substance obtained from the ether extract (0·5 g; m.p. 131–132°, from EtOAc) was identified as X (lit.:[13] 130–131°) by comparison with X obtained by an independent pathway.[17,13] (Found: C, 58·33; H, 8·52. Calc. for $C_7H_{12}O_3$: C, 58·31; H, 8·39%). The *p*-bromophenacyl ester of X had m.p. 136–137° from a mixture of EtOH and H_2O; (lit.:[14] m.p. 136–136·5°) undepressed on admixture with the sample obtained independently. (Found: C, 52·48; H, 4·55, Calc. for $C_{15}H_{17}O_4Br$: C, 52·80; H, 5·02%).

(ii) A mixture of isomer A (1·8 g), Raney-Ni (7 g) and EtOH (100 ml) was refluxed for 4 hr. After removal of Ni by filtration, EtOH was distilled off. The residual oil (0·8 g) was treated with 20% KOH aq (20 ml) at room temp during 12 hr.

The alkaline soln was acidified and extracted with benzene. The oily substance (0·55 g; n_D^{20} 1·4774) obtained from the benzene extract was proved by TLC to be identical with XI synthesized by an independent method.[9] The adduct of Br_2 to XI, m.p. 83–84° was crystallized from formic acid; lit.:[15] m.p. 84–86°. (Found: C, 29·08; H, 3·37. Calc. for $C_7H_{10}O_2Br_2$: C, 29·40; H, 3·53%). After separation of the extract of XI, X was isolated from the acidified aqueous soln as in experiment 3(i).

4. *Desulphuration of isomer* B

A mixture of isomer B (2·5 g), Raney-Ni (25 g) and EtOH (100 ml) was refluxed for 5 hr. Ni was removed by filtration and EtOH by distillation. In the distillate, no acetaldehyde (IX) was detected with 2,4-DNP. The residual oil (1·5 g) containing no aldehydes (test with 2,4-DNP), was hydrolyzed with 20% KOH aq (20 ml) at room temp during 12 hr. The soln was neutralized with conc HCl, and the undissolved oil was extracted with benzene. A liquid obtained from the extract (0·5 g; b.p. 78–80° at 16 mm Hg) consisted of XVII (70%) and XVI (30%), as determined by gas-chromatographic comparison with authentic compounds. The residual aqueous soln was saturated with $(NH_4)_2SO_4$ and continuously extracted with ether for 24 hr. The resulting crystalline substance (0·7 g) m.p. 103° from EtOAc, was identified as XV (lit.:[16] m.p. 103°), by comparison with independently synthesized XV.[16] (Found: C, 64·71; H, 10·77. Calc. for $C_7H_{14}O_2$: C, 64·58; H, 10·84%).

5. *Alkaline hydrolysis of isomer* A

A mixture of isomer A (2 g), MeOH (6 ml) and 2N NaOH (20 ml) was heated under reflux for 2 hr,[6] whereupon MeOH was removed by distillation. After acidification, an ether-insoluble glassy polymer was obtained.

6. *Alkaline hydrolysis of isomer* B

Hydrolysis of isomer B similarly performed also yielded an ether-insoluble polymer.

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REFERENCES

[1] B. Bochwic, A Frankowski and A. Kuś, *Bull. Acad. polon. Sci., Sér. Sci. Chim.* in press.
[2] J. Michalski and A. Skowrońska, *Chem. & Ind.*, 1199 (1958).
[3] B. Bochwic and A. Kuś, *Bull. Acad. polon. Sci., Sér. Sci. Chim.* in press.
[4] F. Korte and H. Christoph, *Chem. Ber.* **94**, 1966 (1961).

[5] C. C. J. Culvenor, W. Davies and N. S. Heath, *J. Chem. Soc.* 282 (1949).
[6] H. Behringer and W. Kley. *Liebigs Ann.* **595**, 160 (1955).
[7] R. P. Linstead and H. N. Rydon, *J. Chem. Soc.* 580 (1933).
[8] H. Bhacca, M. E. Wolff and R. Kwok, *J. Am. Chem. Soc.* **84**, 4976 (1962).
[9] A. A. Petrov, N. P. Sopov, *Zh. Obshchei Khim.* **17**, 2228 (1947).
[10] A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.* **78**, 2770 (1956).
[11] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *Ibid.* **65**, 1013 (1943).
[12] J. S. Lumsden, *J. Chem. Soc.* 90 (1905).
[13] M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.* **75**, 1846 (1953).
[14] R. Lukeš, J. Trojánek and K. Bláha, *Chem. listy*, **49**, 717 (1955).
[15] R. Grewe, A. Heinke and C. Sommer, *Chem. Ber.* **89**, 1978 (1956).
[16] L. N. Owen and P. A. Robins, *J. Chem. Soc.* 326 (1949).
[17] W. F. Clarke and L. N. Owen, *Ibid.*, 2108 (1950).