STEREOCHEMISTRY OF DIDIOXOLANYL SYSTEMS

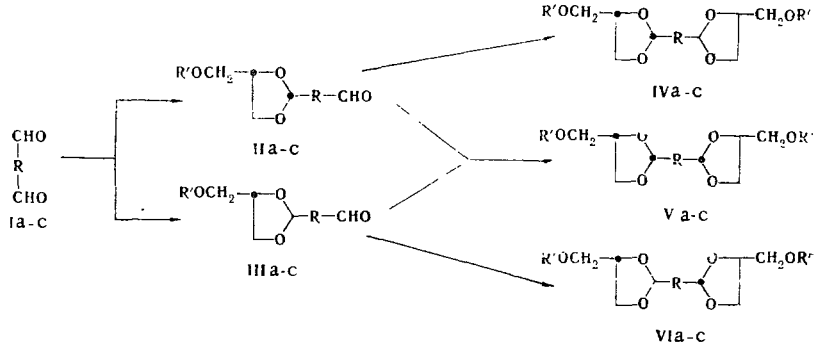
II.* ISOMERS OF CYCLIC ACETALS OF p-PHTHALALDEHYDE, 2,5-DIFORMYLFURAN, AND 2,5-DIFORMYLTHIOPHENE

G. P. Sokolov and S. A. Giller†

UDC 547.729.07:541.634:543.422.25

Diastereomeric cyclic mono- and diacetals of p-phthalaldehyde, 2,5-diformylfuran, and 2,5-diformylthiophene were synthesized under conditions of thermodynamic and kinetic control. The ratios of the diastereomers and their configurations were determined by PMR spectroscopy.

In commencing our study of the isomerism of substituted cyclic diacetals of dialdehydes of the aromatic and heterocyclic series we were guided by a previously proposed scheme [1], which specified the use of the enantiomers of O-p-tosyl-sn-glycerol in the acetalization of aldehydes; this makes possible to limit the number of resulting diastereomers to three:



I–VI a R = p-phenylene; b R = 2,5-furandiyl; c R = 2,5-thiophenediyl; R' = p-tosyl

Acetalization does not go to completion in the preparation of the diacetal of p-phthalaldehyde (Ia) and 3-O-p-tosyl-sn-glycerol in the presence of an acid catalyst at the boiling point of toluene under conditions of thermodynamic control [2]. A mixture of the diastereomers of 1,4-bis(4-O-p-tosyloxymethyl-1,3-dioxolan-2-yl)benzene (IVa, Va, and VIa) in 68% yield, monoacetals IIa and IIIa, and starting dialdehyde Ia is formed. The mixture of diacetals IVa, Va, and VIa contains dioxolane rings with cis and trans configurations in a ratio of 55 : 45 (the assignment of the isomers to the cis or trans configuration and their quantitative ratios are given on the basis of the difference in the chemical shifts and integral curves of the acetal protons in the PMR spectrum). The same ratio of the configurations is also retained in the formation of isomers IIa and IIIa, the method for the preparation of which is based on the use of a fivefold excess of the dialdehyde. The following ratio of compounds with cis-anti-cis (IVa), cis-syn-trans (Va) and trans-anti-trans (VIa) fused rings can be assumed in the mixture on the basis of this: 30 : 50 : 20. The diastereomers obtained give a common spot on the thin-layer chromatogram. The most soluble isomer (VIa) can be isolated only by repeated recrystallization. In contrast to them, the isomers of monoacetal IIa and IIIa are separated by means of column chromatography.

A mixture of diacetals in 56% yield, similar with respect to the cis-trans configurations to the mixture of diacetals formed under the conditions of thermodynamic control, was formed under conditions of kinetic control

* See [1] for communication I.

† Deceased.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1330-1333, October, 1976. Original article submitted November 17, 1975; revision submitted February 16, 1965.

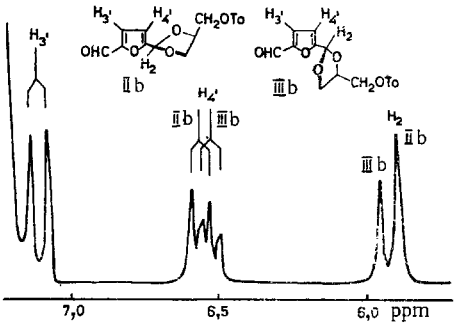


Fig. 1. Spectrum of a mixture of 5-(4-O-p-tosyloxymethyl-1,3-dioxolan-2-yl)furfural isomers (IIb, IIIb).

in the presence of anhydrous copper sulfate [2] after shaking the starting materials for 70 h. However, during monitoring of the acetalization by means of thin-layer chromatography (TLC) it was noted that the rate of formation of cis isomer IIa in the initial step is higher than the rate of formation of trans isomer IIIa. By using excess dialdehyde and interrupting the reaction when the ratio of IIa to IIIa is 95 : 5 one can obtain pure acetal IIa by ordinary recrystallization.

2,5-Diformylfuran (Ib) on acetalization under conditions of thermodynamic control gives a mixture of uncrystallizable diacetal diastereomers IVb, Vb, and VIb (70% yield) and monoacetal diastereomers IIb and IIIb. The ratio of the cis-trans configurations of the dioxolane rings in the mixture of diacetals is 1 : 1. However, when the monoacetals are prepared with excess starting aldehyde, the percentage of the cis isomer exceeds that of the trans isomer by a factor of 1.5. Evidence for the presence of two isomers is provided not only by two signals of acetal protons but also by protons of signals of protons of the furan ring (see Fig. 1). Thus the 3'-H protons give a doublet with $J = 3.3$ Hz (δ 7.09 ppm) and the 4'-H protons give two doublets with $J = 3.3$ Hz (δ 6.55 ppm for the cis isomer and 6.52 ppm for the trans isomer). The signal of the 4'-H proton of the trans isomers is broadened due to coupling with the acetal 2-H proton. The same protons of the furan ring in the mixture of diastereomers of the diacetal give a common signal at 6.36 ppm. Aldehyde Ib is acetalized exceptionally slowly under conditions of kinetic control.

2,5-Diformylthiophene (Ic) under conditions of thermodynamic control forms a mixture of diacetal diastereomers IVc, Vc, and VIc (65% yield) and monoacetal diastereomers IIc and IIIc. In contrast to derivatives Ia and Ib, the ratio of the cis-trans configurations of the dioxolane rings in the latter case is 45 : 55. Pure trans-anti-trans isomer VIc can be isolated from the mixture of diacetals by crystallization. Monoacetal diastereomers IIc and IIIc, although they do give two spots on the thin-layer chromatogram, are not separated with a column becuase of their close R_f values. Only pure trans isomer IIIc can be isolated by recrystallization of the mixture. The trans configuration predominates in the mixture of monoacetal isomers (54 : 46). The 3'-H and 4'-H protons of the thiophene ring give one signal at 6.98 ppm in the PMR spectrum of the mixture of diacetals, but the signals of the same protons in the mixture of monoacetals are overlapped by the signals of the phenyl rings.

Under conditions of kinetic control in the acetalization of aldehyde Ic the formation of cis isomer IIc, as in the case of Ia, proceeds more rapidly than the formation of the trans isomer, i.e., the cis configuration is kinetically preferable but not to such an extent as to obtain the pure cis isomer. The mixture of isomers isolated after 6 h contains 76% of the cis and 25% of the trans isomers of the monoacetal.

Thus the usual kinetic preferableness of the cis configurations of the 1,3-dioxolane ring is observed in the investigated series of compounds, but, in contrast to the cyclic acetals of aliphatic aldehydes [3], the thermodynamic stability of the trans configuration increases in the series of aromatic and heterocyclic dialdehydes.

We thank Yu. Yu. Popelis for recording the PMR spectra.

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried on Silufol UV-254 plates [hexane–ethyl acetate (2 : 1) for p-phthalaldehyde, and hexane–acetone (2 : 1) for the remaining dialdehydes]. The chromatograms were developed in UV light or with a 2% solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid. The melting points were determined with the microheating stage of a Boëtius system. The optical rotations were determined with

a Perkin–Elmer 141 polarimeter. The PMR spectra of 10% solutions of the compounds in $CDCl_3$ were recorded with a Perkin–Elmer R-12A spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

3-O-p-Tosyl-sn-glycerol was obtained by the method in [4] and had mp 58-59° and $[\alpha]_D^{20} = -13.9 \pm 0.3°$ [c 5, dimethylformamide (DMF)].

General Method for the Preparation of the Diacetals. Thermodynamic Control. A 0.005-mole sample of the dialdehyde, 2.5 g (0.01 mole) of 3-O-p-tosyl-sn-glycerol, and 0.1 g of p-toluenesulfonic acid in 150 ml of toluene was refluxed in a flask equipped with a Dean–Stark trap for 30 min after which it was cooled rapidly and shaken with an aqueous solution of hydroxylamine and sodium hydroxide until the unchanged dialdehyde and monoacetals vanished. The organic layer was separated, washed with water, and dried with sodium sulfate, and the toluene was removed by distillation.

Mixture of 1,4-Bis-(4-O-p-tosyloxymethyl-1,3-dioxolan-2-yl)benzene Isomers (IVa, Va, and VIa). The mixture was recrystallized from 100 ml of alcohol to give 2.0 g (68%) of a product with mp 100-115°, R_f 0.11, and $[\alpha]_D^{20} - 2.6 \pm 0.3$ (c 5, DMF). PMR spectrum: δ 5.77 (2-H, cis) and 5.86 ppm (2-H, trans).

Repeated recrystallization from alcohol gave pure 1,4-bis(4R-O-p-tosyloxymethyl-1,3-dioxolan-2S-yl)-benzene (VIa) with mp 148-148.5°, R_f 0.11, and $[\alpha]_D^{20} + 19.1 \pm 0.3°$ (c 5, DMF). PMR spectrum: δ 5.86 ppm (2-H). Found: C 57.0; H 5.0%. $C_{28}H_{30}O_{10}S_2$. Calculated: C 56.9; H 5.1%.

Mixture of 2,5-Bis(4-O-p-tosyloxymethyl-1,3-dioxolan-2-yl)furan Isomers (IVb, Vb, and VIb). The mixture was worked up to give 2.0 g (70%) of a viscous uncrystallizable oil with R_f 0.21 and $[\alpha]_D^{20} - 4.5 \pm 0.3°$ (c 5, DMF). PMR spectrum: δ 5.83 (2-H, cis) and 5.91 ppm (2-H, trans). Found: C 53.5; H 4.9%. $C_{26}H_{28}O_{11}S_2$. Calculated: C 53.7; H 4.9%.

Mixture of 2,5-Bis(4-O-p-tosyloxymethyl-1,3-dioxolan-2-yl)thiophene Isomers (IVc, Vc, and VIc). This mixture was worked up to give 1.9 g (63%) of a partially crystallizable substance with R_f 0.22 and $[\alpha]_D^{20} + 0.2 \pm 0.3°$ (c 5, DMF). PMR spectrum: δ 5.97 (2-H, cis) and 6.05 ppm (2-H, trans).

Recrystallization from alcohol gave pure 2,5-bis(4R-O-p-tosyloxymethyl-1,3-dioxolan-2S-yl)thiophene (VIc) [0.35 g (12%)] with mp 126-127°, R_f 0.22, and $[\alpha]_D^{20} + 31.4 \pm 0.3$ (c 5, DMF). PMR spectrum: δ 6.05 ppm (2-H). Found: C 52.2; H 4.7%. $C_{26}H_{28}O_{10}S_3$. Calculated: C 52.4; H 4.7%.

General Method for the Preparation of the Monoacetals. Thermodynamic Control. A solution of 0.25 mole of the dialdehyde, 1.23 g (0.005 mole) of 3-O-p-tosyl-sn-glycerol and 0.1 g of p-toluenesulfonic acid in 100 ml of toluene was refluxed in a flask equipped with a Dean–Stark trap for 15 min, after which it was cooled and treated with 150-200 ml of petroleum ether. The mixture was allowed to stand at 0° overnight, and the precipitated dialdehyde was removed by filtration. The residual solution was washed by shaking with a solution of 1.5-2.0 g of sodium pyrosulfite in 20 ml of water (the purification was monitored by TLC). The aqueous layer was separated, and the organic layer was dried with sodium sulfate and decolorized with charcoal, after which the solvent was removed by distillation.

Mixture of 4-(4-O-p-Tosyloxymethyl-1,3-dioxolan-2-yl)benzaldehyde Isomers (IIa, IIIa). The crude mixture was triturated with petroleum ether and filtered to give 0.9 g of a product with mp 65-75° and $[\alpha]_D^{20} - 2.5 \pm 0.3°$ (c 5, DMF). PMR spectrum: δ 5.81 (2-H, cis) and 5.88 ppm (2-H, trans). Isomers IIa and IIIa were separated with a chromatographic column filled with silica gel (0.2-mm particles) with elution by hexane–ethyl acetate (2 : 1). 4-(4R-O-p-Tosyloxymethyl-1,3-dioxolan-2S-yl)benzaldehyde (IIIa) had mp 84-85° (from 75% ethanol), R_f 0.32, and $[\alpha]_D^{20} + 19.4 \pm 0.3°$ (c 5, DMF). Found: C 59.6; H 5.1%. $C_{18}H_{18}O_6S$. Calculated: C 59.6; H 5.0%. 4-(4R-O-p-Tosyloxymethyl-1,3-dioxolan-2R-yl)benzaldehyde (IIa) had mp 95-98° (from 75% ethanol), R_f 0.25, and $[\alpha]_D^{20} - 19.4 \pm 0.3°$ (c 5, DMF). Found: C 59.5; H 5.1%. $C_{18}H_{18}O_6S$. Calculated: C 59.6; H 5.0%.

Mixture of 5-(4-O-p-Tosyloxymethyl-1,3-dioxolan-2-yl)furfural Isomers (IIb, IIIb). Workup of the reaction mixture gave 0.2 g of an uncrystallizable oil. The product was purified with a column filled with silica gel with elution by hexane–acetone (2 : 1). The purified acetal was crystallized to give a product with mp 57-62°, R_f 0.29, and $[\alpha]_D^{20} - 12.0 \pm 0.3°$ (c 5, DMF). PMR spectrum: δ 5.89 (2-H, cis) and 5.94 ppm (2-H, trans). Found: C 54.2; H 4.7%. $C_{16}H_{16}O_7S$. Calculated: C 54.3; H 4.6%.

Mixture of 2-(4-O-p-Tosyloxymethyl-1,3-dioxolan-2-yl)-5-formylthiophene Isomers (IIc, IIIc). The reaction mixture was worked up to give 0.8 g of an uncrystallizable oil, which was purified by chromatography as in the preceding experiment. The purified acetal was crystallized to give a product with mp 75-85°, R_f 0.29 and 0.32, and $[\alpha]_D^{20} - 5.7 \pm 0.3°$ (c 5.29, DMF). PMR spectrum: δ 6.05 (2-H, cis) and 6.15 ppm (2-H, trans). Recrystallization from 65% ethanol gave pure 2-(4R-O-p-tosyloxymethyl-1,3-dioxolan-2S-yl)-5-formylthiophene (IIIc)

with mp 96-97°, R_f 0.32, and $[\alpha]_D^{20}+33.4\pm0.3°$ (c 5, DMF). Found: 51.7; H 4.5%. $C_{16}H_{16}O_6S_2$. Calculated: C 51.8; H 4.4%.

Kinetic Control. A mixture of 0.025 mole of the dialdehyde, 1.23 g (0.005 mole) of 3-O-p-tosyl-sn-glycerol, 5 g of anhydrous copper sulfate, and 100 ml of toluene was shaken for 6 h (the formation of the isomers was monitored by TLC), after which it was filtered, and the solution was worked up as in the method involving thermodynamic control.

Aldehyde Ia yielded 0.45 g of a mixture consisting of 95% cis isomer IIa and 5% trans isomer IIIa with mp 88-95° and $[\alpha]_D^{20}-17.6°$ (c 5, DMF). Recrystallization from 75% ethanol gave pure IIa.

Aldehyde Ic yielded 0.5 g of a mixture consisting of 75% cis isomer IIc and 25% trans isomer IIIc as an uncrystallizable oil with $[\alpha]_D^{20}-18.6°$ (c 4.1, DMF).

LITERATURE CITED

1. G. P. Sokolov and S. A. Giller, Khim. Geterotsikl. Soedin., No. 12, 1608 (1973).
2. N. K. Kochetkov, A. F. Bochkova, B. A. Dmitriev, A. I. Usov, O. S. Chizhov, and V. N. Shibaev, Chemistry of Carbohydrates [in Russian], Khimiya, Moscow (1967), p. 170.
3. W. E. Willy, G. Binsch, and E. Y. Eliel, J. Am. Chem. Soc., 92, 5394 (1970).
4. D. J. Triggle and B. Bellen, Can. J. Chem., 40, 1201 (1962).

BEHAVIOR OF 2-NITROSO-4-NITROPROPIOPHENONE UNDER CONDITIONS OF CYCLIZATION TO HALOANTHRANILS

S. S. Mochalov, T. P. Surikova, and Yu. S. Shabarov

UDC 547.786.3.07

The cyclization of 2-nitroso-4-nitropropiophenone under the influence of hydrogen chloride proceeds in a more complex manner than in the cases previously described for other 4-substituted-2-nitrosopropiophenones: three, rather than two, haloanthranils are formed, and their formation is accompanied simultaneously by a number of redox transformations. This fact is explained by a decrease in the ability of the carbonyl group in the investigated ketone to undergo protonation.

It has been shown [1] that the formation of anthranils is practically the only pathway in the reaction of triphenylphosphine with 4-substituted o-nitrosoacylbenzenes. A side product – 2-amino-4-nitropropiophenone (III) – is formed in appreciable quantities (~17%) along with 6-nitro-3-ethylanthranil (II) only in the case of 2-nitroso-4-nitropropiophenone (I). This result provided evidence that the presence of a nitro group in the benzene ring of the starting nitroso ketone can have a substantial effect on the direction of the reaction.

In the present research we have studied the behavior of nitroso ketone I when it is treated with hydrogen chloride in benzene under conditions for which the previously investigated o-nitrosoacylbenzenes were readily converted to the correspondong 5- and 7-haloanthranils [2]. It was found that in this case also the conversion of I proceeds in a more complex manner. First, three haloanthranils, rather than two as previously shown for other o-nitro ketones [2], are formed; second, one observed simultaneous intermolecular redox transformations*

*Similar reactions are also observed during the cyclization of some nitroso ketones under the influence of hydrogen bromide in benzene and hydrogen chloride in methanol [3].

M. V. Lomonosov Moscow State University. N. I. Pirogov Second Moscow State Medical Institute.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1334-1337, October, 1976. Original article submitted September 30, 1975.