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STEREOISOMERS OF CYCLOPENTANO-TETRAHYDROPYRAN

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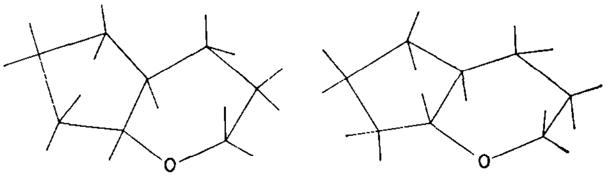
Abstract—*Cis*- and *trans*-cyclopentano(b)tetrahydropyrans were prepared and the validity of Auwers-Skita's rule confirmed. The relatively low differences of the constants of the substances prepared were explained, with regard to the analogous hydrindans, by a more planar arrangement of the rings. During the cyclization reaction, which was carried out by means of chromatography on aluminium oxide, a significant sterically conducting influence of the absorbens was noted.

THE *cis*- and *trans*-hydrindans I and II (C—C length 1·54 Å, bond angle 109°) can be compared with models on similar systems, containing a heteroatom, e.g. oxygen (C—O length 1·42 Å, C—O—C bond angle 111°) instead of a carbon atom, and we find on cyclopentano(b)tetrahydropyrans or 1-oxabicyclo(0,3,4) nonanes that the heterocyclic ring will have a somewhat more planar arrangement than the corresponding hydrocarbons. Assuming that the differences in the structures of the isomers are proportional to those in the physical constants, we may well expect smaller differences between isomers with a heteroatom than between the analogous structures containing carbon atoms only.



III IV

cyclopentano(b)tetrahydropyran
cis-(III) *trans*-(IV)*
FIG. 1.

In order to ascertain the influence of the heteroatom on the physical properties of these compounds, an attempt was made to prepare both isomers of oxabicyclononane (III and IV) by sterically defined reactions. 2-Carbethoxycyclopentanone (V), used as the starting material for the synthesis, was converted to 2-carbethoxy-2-(3′-bromopropyl)-cyclopentanone (VI) according to Mayer[1]; the compound obtained was hydrolysed to 2-(3′-bromopropyl)-cyclopentanone (VIII). As VII may undergo cyclization to spiro-3,4-octane-4-one[1] by action of strong bases, 2-(3′-acetoxypropyl)-

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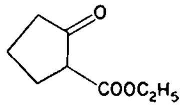
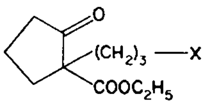
* Both isomers are supposed to be in conformation with the heterocyclic ring in the chair (Z) form.

[1] R. Mayer, G. Wenschuh, W. Töpelmann, *Chem. Ber.* **91**, 1616 (1958).

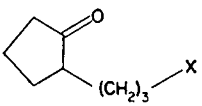
cyclopentanone (VIII) was first prepared. This compound was converted by means of an alkaline alcoholysis to the 2-(3′-hydroxypropyl)-cyclopentanone (IX). From the reaction mixture, chiefly when a great excess of the base was used, a hydrocarbon $C_{16}H_{20}$ was isolated as a secondary product, the nature of which will be a subject of further studies.



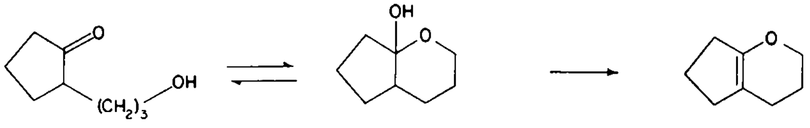
V



X=-Br(VI)
-OCOCH3(XI)



X=-Br(VII)
-OCOCH3(VIII)



IX IXa X

According to the I.R.-spectra (presence of a tertiary hydroxylic group), IX is probably in equilibrium with the cyclic structure IX a; the equilibrium being shifted towards IX. By the dehydrating action of acids, 1-oxa(0,3,4)bicyclononane-8-ene and 2-allylcyclopentanone are formed.

Zelinskij and Elagina[2] consider X to be a component of the reaction mixture, when compound VI is hydrolysed with diluted hydrochloric acid; but in a later communication Mayer[1] could not confirm this.

Vinyl ether X is, with regard to its planar structure, suitable for the preparation of the *cis*-isomer of 1-oxa(0,3,4)bicyclononane (III); the catalytic hydrogenation using 5 per cent palladium on barium sulphate, carried out under atmospheric pressure, yielded the *cis*-isomer, without trace of the *trans*-isomer (according to the I.R.-spectra).

As the yields were not satisfactory, a direct hydrolysis of 2-(3′-acetoxypropyl)-carbethoxycyclopentanone (XI) was tried. During the hydrolysis, the acetate VIII is first formed, being then hydrolysed to the alcohol IX. No cyclization to the spirolacton system occurs, and the decarboxylation proves to be rapid. Owing to the difficulties in the preparation of acetoxybromopropane, this method was abandoned. Unsatisfactory results were also obtained with the reaction of carbethoxycyclopentanone with 3-bromopropanol. A re-esterification of the carbethoxy-group on the one hand and some alcoholytic cleavage of the cycle on the other hand were observed.

As starting material for the synthesis of the *trans*-isomer IV, the bromocyclopentanone VII was used. During the reaction with a threefold excess of lithium aluminium hydride (LAH) in tetrahydrofuran, VII was converted in high yield into the *trans*-2-propylcyclopentanol, especially when suspended LAH was used. 2-(3′-Bromopropyl)cyclopentanol (XII) was prepared in satisfactory yield by reduction of

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[2] N. D. Zelinskij, N. V. Elagina, *Dokl. Akad. Nauk SSSR* **86**, 1117 (1952).

VII with a small excess of LAH in ethyl ether. On the basis of a *trans*-structure for 2-propylcyclopentanol,[3,4] a *trans*-structure has also been attributed to XII.

By the action of a water or methanolic potassium hydroxide on the bromohydrin XII, either 2-allylcyclopentanol or the desired *trans*-isomer IV, contaminated by the *cis*-isomer (5–10 per cent) results. This is in accordance with the steric purity of the bromohydrin XII. During the chromatography on aluminium oxide (activity 1·5), the freshly distilled bromohydrin XII undergoes cyclization to cyclopentano(b)-tetrahydropyran, which, after distillation, contains 35 ± 10 per cent of the *cis*-isomer according to the I.R.-spectra, the main product being the *trans*-isomer. Here, an interesting steric influence was observed during the reaction on the column of the aluminium oxide. The isomers obtained are stable by themselves during chromatography. A certain analogy may be found for instance in the catalytic hydrogenation.

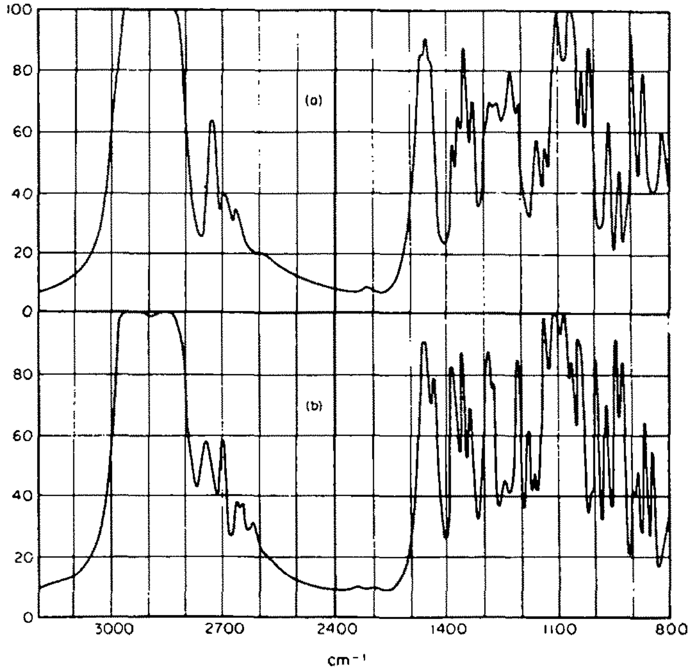

FIG. 2. Infra-red spectra of (a) *cis*-oxa (0,3,4) bicyclononane (III) and (b) *trans*-oxa (0,3,4) bicyclononane (IV) (90 ± 5% sterical purity).

The steric purity of the *trans*-isomer is sufficient for the determination that the boiling points of the two isomers differ by ±1° only, further, that the *cis*-isomer has, being thermodynamically less stable, a higher refraction index, which is in agreement with Auwers–Skita's rule.[5,6] A relatively small difference in the physical constants of the two isomers corresponds to the theoretic assumption of a higher degree of planarity, when compared with the analogous hydrindans.[7,8]

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[3] J. Colonge and A. Orsac, *Bull. Soc. Chim. Fr.* 1074 (1953).

[4] J. Blanchard and M. J. Jefraim, *J. Amer. Chem. Soc.* **78**, 2783 (1956).

[5] K. V. Auwers, *Liebigs Ann.* **420**, 91 (1920).

[6] A. Skita, *Ber. Dtsch. Chem. ges.* **53**, 1792 (1920).

[7] W. Hückel, *Liebigs Ann.* **518**, 166 (1935).

[8] W. Hückel and M. Sachs, *Liebigs Ann.* **420**, 21 (1920).

EXPERIMENTAL

2-*Carbethoxycyclopentanone* (V) was prepared in 68% yield by the condensation of the ethyl ester of the adipic acid using powdered sodium according to the literature.[9]

	b.p.	n_D^{20}	b.p.	n_D^{20}
cis-1-Oxa (0,3,4) bicyclononane	53°/15	1,4672	±1°	0,0028
trans (5–10% *cis*-isomer)	52°/14	1,4646		
with extrap. ad 0%		1,4644		
cis-Bicyclo (0,3,4) nonane	167°	1,4713	8°	0,0075
trans	159°	1,4638		

2-*Carbethoxy*-2-(3′-*bromopropyl*)*cyclopentanone* (VI) was prepared in a 34% yield; b.p.$_2$ 140–144° but according to the literature[1] a yield of 50%, b.p.$_{1-2}$ 135–138° was reported.

2-(3′-*Bromopropyl*)-*cyclopentanone* (VII), was prepared[1] in a 66% yield, b.p.$_{3\cdot5}$ 107° but the literature gives[1] 80%, b.p.$_{1-2}$ 98–105° and another ref.[2]: b.p.$_2$ 100°.

2-(3′-*Acetoxypropyl*)*cyclopentanone* (VIII)

A solution of the bromoderivative VII (37 g, 0·18 mole) in 96% ethanol (100 ml) was mixed with acetic acid (1 ml) and powdered anhydrous potassium acetate (21·2 g, 0·216 mole) and the reaction mixture heated on a boiling water bath for 5 hr. The potassium bromide formed during the reaction was filtered off, the organic solvents were removed by distillation under reduced press, the inorganic salts precipitated by ethyl ether and finally the organic layer fractionally distilled. The product (b.p.$_3$ 106–108°, n_D^{20} 1,4802) was obtained in a yield of 27 g (81%, calculated on the acetoxy derivative VIII). (Found: C, 65·0; H, 8·7 $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·8%).

2-(3′-*Hydroxypropyl*)*cyclopentanone* (IX)

A solution of the acetate VIII (34 g, 0·185 mole) in 150 ml 7% ethanolic potassium hydroxide was kept at room temp. for 24 hr, the ethanol removed under reduced press, the residue diluted with ether; and after filtration the solvent evaporated. The residual liquid (30 g), was chromatographed on a column of 300 g neutral aluminium oxide (activity 1·5) and 0·5 g of a liquid b.p.$_{18}$ 52–53° was eluated with pet ether, and according to chromatography on a thin layer of aluminium oxide, was the impure vinylether (X). Elution with benzene gave 5 g of hydrocarbon b.p.$_{0\cdot6-0\cdot7}$ 77–78°. (Found: C, 90·2; H, 9·5. $C_{16}H_{20}$ requires: C, 90·5; H, 9·5%). By elution with ether a mixture was obtained, which could not be separated by repeated chromatography or distillation. Finally, elution with methanol 20 g of the desired alcohol (IX) were obtained in a yield of 17 g after distillation, b.p.$_{0\cdot5-0\cdot6}$ 87–89°, n_D^{20} 1,4750. (Found: C, 67·7%; H, 9·8. $C_8H_{14}O_2$ requires: C, 67·6; H, 9·9%).

1-*Oxa-bicyclo*(0,3,4)*nonane* 8 (X)

A solution of hydroxypropylcyclopentanone (IX) in benzene (100 ml) was heated with *p*-toluensulfonic acid (0·1 g) to boiling point and water azeotropically distilled off. The expected amount of water was obtained in 45 min. After cooling, the dark solution was shaken with a saturated solution of sodium bicarbonate, the water layer extracted with ether and the ethereal extract mixed with a benzene layer. After drying with anhydrous magnesium sulphate, the solvents were distilled off over a 15 cm microcolumn and the residue chromatographed on neutral aluminium oxide (activity 1·5). Using pet ether, 5 g of a substance were obtained, yielding 1·7 g after redistillation (yield 10·5%). The substance is considerably volatile with all organic solvents and has a camphor-like odour. B.p.$_{14}$ 54–55°, n_D^{20} 1·4715. (Found: C, 77·2; H, 9·9. $C_{18}H_{12}O$ requires: C,77·4; H, 9·7%).

cis-1-*Oxa-bicyclo*(0,3,4)*nonane* (III)

Substance X (1·5 g) was hydrogenated in methanol (5 ml) under atm press was with 2 g of 5% Pd on $BaSO_4$. The theoretical consumption of hydrogen was obtained after 6 hr. After filtration the solvent was removed and the residue chromatographed on aluminium oxide (activity 1·5). By elution

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[9] *Organic Syntheses* Col. Vol. II. p. 116.

with pet ether, 1 g was obtained and after distillation, 0·6 g (III), b.p.$_{15}$ 53°. n_D^{20} 1,4672. (Found: C, 76·2; H, 11·5; $C_8H_{14}O$ requires: C, 76·1; H, 11·2%).

2-(3'*Acetoxypropyl*)2-*carbethoxycyclopentanone* (XI)

A·mixture of K-salt carbethoxycyclopentanone (19 g) and 1-acetoxy-3-brompropane[10] (18 g) in anhydrous benzene (25 g) was stirred during boiling for 8 hr. After cooling, the potassium bromide was filtered off and the solution fractionally distilled. (Found: C, 60·8; H, 7·7. $C_{13}H_{20}O_5$ requires: C, 60·9; H, 7·9%). B.p.$_3$ 157–158°, yield 12 g (46%).

Hydrolysis of XI. Compound XI (7·36 g; 25·6 mole) were mixed with 10 ml of 18% HO (50 mmoles) and heated to boiling for 20 min. After cooling, the solution was neutralized with a sodium carbonate solution to pH 7 and four times extracted with 10 ml of ether; the ethereal extract after removal of the solvent gave a residue (3·6 g), which was chromatographed on 60 g Al_2O_3 (activity 1·5 g). By elution with hexane, 0·1 g of a liquid was obtained, which was identified as impure vinyl ether X; 1·2 g of a substance were eluted with benzene b.p.$_{0·2}$ 76–78°, which is, according to the analyses and I.R.-spectra, identical with the acetate VIII; and 0·55 g of a mixture of acetate VIII and alcohol IX were eluted with ether and resulted from splitting on the column. Using methanol, 0·6 g of alcohol IX were obtained.

2-(3'-*Brompropyl*)*cyclopentanol*(XII)

To the bromoketone VII (9·52 g), 35 ml of a 2% solution of lithium aluminidum hydride in ethyl ether was added dropwise. After standing for 2 hr, the reaction mixture was decomposed with ice and hydrochloric acid and extracted with ether, and finally the ethereal extract was shaken with bicarbonate solution and fractionally distilled. The yield was 6·6 g (69%) of XII, b.p.$_{0·5}$ 83–84°, n_D^{19} 1,5062, the oily liquid decomposing on standing. (Found: C, 46·6; H, 7·1. $C_8H_{15}O$ Br requires: C, 46·4; H, 7·3%).

trans-1-*Oxa-bicyclo*(0,3,4)*nonane* (IV)

(A) The bromohydrin XII (8 g 39 mmoles) was shaken in a vibration apparatus with 20% KOH (30 ml) for 5 hr, the mixture then extracted with ether and the extract, after removing the solvents, was distilled on a 10 cm column. The yield was 0·5 g of the substance, b.p.$_{14}$ 52°, n_D^{20} 1,4646, containing according to the I.R.-spectra 5–10% of the *cis*-isomer. Calculation was carried out on the basis of absorption at 900 and 1016 cm^{-1}. (Found: C, 76·1; H, 11·2. $C_8H_{12}O$ requires: C, 76·1; H, 11·2).

(B) On a column of 200 g Al_2O_3 (activity 1·5), 16· g of the bromohydrine XII were separated. By elution with pet ether no more than 0·05 g were obtained, with benzene, 5· g of the substance, which, by distillation on a filled micro-column of 15 cm, gave 3 g of a liquid of camphor-like odour, b.p.$_{14}$ 52°, n_D^{20} 1,4656. According to the I.R.-spectra, the substance contains 35 ±10% of the *cis*-isomer, the residue representing the *trans*-isomer, which is easily volatile with all organic solvents.

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[10] M. T. Bogert and E. M. Slocum, *J. Amer. Chem. Soc.* 46, 765 (1924).