2-(o-Chlorophenyl)cyclohexanone. Reaction of 25 g. of 2-(*o*-chlorophenyl)nitrocyclohexane under the conditions described for the *para* isomer, without the sodium bisulfite, gave a white precipitate in the acid mixture. Filtration and recrystallization from ethanol gave 6 g. of crystalline material (A) m.p. 215–216°. Work-up of the remaining reaction mixture in the usual way gave 4 g. of the desired ketone (B) m.p. 70–71°. A was shown to be the oxime of 2-(*o*-chlorophenyl)cyclohexanone. A and B gave identical 2,4-dinitrophenylhydrazones, m.p. 171.5–172.5° (no depression of mixed melting point). Hydrolysis of A by refluxing in 20% sulfuric acid yielded B. The oxime prepared from B is identical to A.

Anal. of ketone. Calcd. for $C_{12}H_{13}ClO$: C, 69.06; H, 6.28; Cl, 16.99. Found: C, 68.83; H, 6.45; Cl, 16.87.

Anal of oxime. Calcd. for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; Cl, 15.85; N, 6.26. Found: C, 64.78; H, 6.64; Cl, 15.81; N, 6.64.

About the same ratio of oxime and ketone was obtained when sodium bisulfite was used, but the over-all yield was increased. Ten grams of the nitro compound yielded 3.4 g. of purified oxime and 2.1 g. of purified ketone when sodium bisulfite was used.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF KANSAS AND THE UNIVERSITY OF WISCONSIN]

Stereoaspects of the Prins Reaction of Anethole[1]

PHILIP S. PORTOGHESE AND EDWARD E. SMISSMAN

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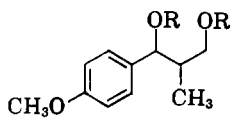
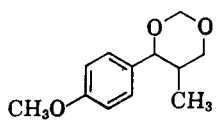
The stereochemistry of 1-anisyl-2-methyl-1,3-diacetoxypropane diasteromers (Ia, Ib) which arise from the condensation of formaldehyde with anethole has been assigned by the use of conformational principles and intramolecular hydrogen bonding studies. The formation of the above compounds and 4-anisyl-5-methyl-1,3-dioxane (III) are rationalized as proceeding through a classical carbonium ion intermediate.

The mineral acid-catalyzed condensation of formaldehyde with olefins, commonly known as the Prins reaction,[2] is useful in the preparation of 1,3-glycols and their derivatives.[3] An investigation of the stereochemistry of the Prins reaction employing cyclohexene,[4,5] demonstrated the condensation to proceed entirely with *trans* addition. Moreover, a recent study[6] on the conformational analysis of the Prins reaction illustrated the *trans* product to arise only by diaxial addition. It was of interest, therefore, to investigate further the Prins reaction in order to determine if this condensation is stereospecific in all cases.



Ia and Ib. R = Ac
IIa and IIb. R = H



III

When anethole was refluxed with paraformaldehyde in glacial acetic acid for five hours, a mixture of 25.6 mole percent 4-anisyl-5-methyl-1,3-dioxane (III)[2,7] and 56.6 mole percent of two diastereomers of 1-anisyl-2-methyl-1,3-diacetoxypropane (Ia and Ib) was obtained. The facility of the condensation in the absence of mineral acid catalyst is due to the activating influence of the anisyl group, as under similar conditions an unactivated olefin yielded no product.[8] If the reaction is conducted in the presence of a trace of sulfuric acid catalyst, a considerable quantity of polymeric material is formed in addition to I and III. Separation of diastereomer Ia and Ib was accomplished by fractional crystallization from benzene-petroleum ether (b.p. 63–70°). Diacetate Ia crystallized in the form of prisms, m.p. 70–71°, and Ib as sheaths, m.p. 64–65°. Infrared analysis of the diacetate mixture indicated the composition to be 25% Ia and 75% Ib. Saponification of Ia and Ib affords the corresponding glycols, IIa, m.p. 62–63°, and IIb, m.p. 87–89°, which can be reconverted to the diacetates by treatment with acetic anhydride in the presence of anhydrous sodium acetate. It was observed that diol IIb was converted to a mixture of diastereomeric diacetates (Ia and Ib) when refluxed in glacial acetic acid. Significantly, the product contained an odor characteristic of anethole. When subjected to identical conditions, the *m*-dioxane, III, was partially transformed to the diacetates Ia and Ib and formaldehyde. A quantitative determination in both of the above instances revealed the presence of 25% Ia and 75% Ib. The presence of anethole in the transformation of IIb to the diacetate mixture is probably due to the escape of a small amount of formaldehyde during the cleavage process, thus

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society at the 140th Meeting, Chicago, Ill., September 1961.

(2) H. J. Prins, *Chem. Weekblad*, **16**, 1510 (1919).

(3) E. Arundale and L. A. Mikeska, *Chem. Revs.*, **51**, 505 (1952).

(4) E. E. Smissman and R. A. Mode, *J. Am. Chem. Soc.*, **79**, 3447 (1957).

(5) A. T. Bloomquist and J. Wolinsky, *J. Am. Chem. Soc.*, **79**, 6025 (1957).

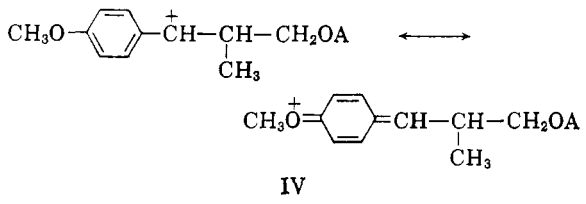
(6) E. E. Smissman and D. T. Witiak, *J. Org. Chem.*, **25**, 471 (1960).

(7) E. A. Drukker and M. G. J. Beets, *Rec. trav. Chem.*, **70**, 29 (1951).

(8) D. T. Witiak, Ph.D. thesis, 1961, University of Wisconsin.

preventing total conversion of the anethole intermediate to the diacetate. Similar cleavage reactions of 1,3-ditertiary diols and 1,3-secondary, tertiary diols have been reported[9] to yield olefinic products under strongly acidic conditions. When Ia was refluxed in glacial acetic acid, an equilibrium mixture resulted which consisted of 25% Ia and 75% Ib. As described above a diacetate mixture of identical composition was formed from the Prins reaction of anethole and the conversion of the *m*-dioxane, III, to the diacetates.

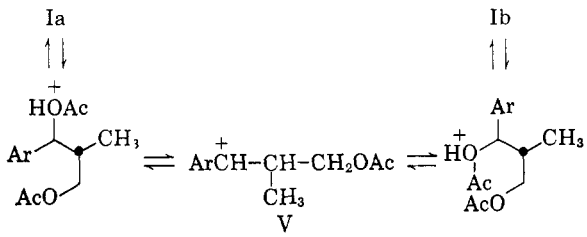
The preceding observations are in accord with a classical carbonium ion intermediate (IV) which is highly stabilized by resonance participation of the anisyl group. Such an intermediate would result



IV

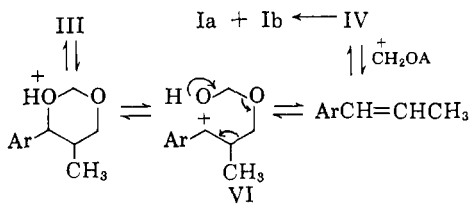
from attack of solvated formaldehyde (C^+H_2OA) on anethole. Subsequent nucleophilic attack by acetic acid or another molecule of formaldehyde should lead to the diacetates Ia and Ib and the *m*-dioxane III, respectively.

The first step in the equilibration of Ia can be viewed as the protonation of solvation of the benzylic oxygen, as heating pure Ia or Ib in toluene for eighteen hours in the absence of acetic acid produced no isomerization. Subsequent elimination of the benzylic acetoxy function would result in the formation of carbonium ion intermediate V, which can be converted to either Ia or Ib. The *m*-dioxane, III, can be transformed to the isomeric



V

diacetates *via* a similar primary protonation or solvation step to give a species capable of ionizing to carbonium ion intermediate VI. Elimination of two molecules of formaldehyde from VI gives

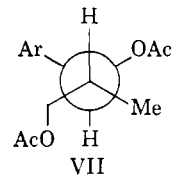


VI

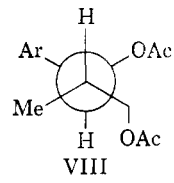
(9) T. E. Maggio and J. English, Jr., *J. Am. Chem. Soc.*, **83**, 968 (1961).

anethole and can be converted ultimately to Ia and Ib. The transformation to the diacetates is a slow process, as only about 25% *m*-dioxane III is converted to Ia and Ib after treatment with acetic acid for nineteen hours. The conversion of diol IIb to Ia and Ib can be rationalized by a similar mechanism.

In view of the stability of carbonium ion intermediates IV and V, it is expected that operation of thermodynamic control in the Prins reaction of anethole should result in the formation of a preponderance of the thermodynamically more stable diacetate product. An examination of the Newman projection formulas, VII and VIII, suggests diastereomer VIII to possess fewer nonbonded interactions; anisyl and acetoxymethylene are considered large groups, methyl and acetoxy to be medium groups, and hydrogen to be a small group.[10] On this basis VIII should correspond to Ib which



VII



VIII

comprises 75% of the isomeric diacetate mixture. Further support for the preceding assignment was obtained through an infrared study of the 3200–3800-cm.$^{-1}$ region of diols IIa and IIb. Both were shown to possess the following features: (a) a concentration-dependent band at approximately 3375 cm.$^{-1}$ which is attributed to intermolecular bonding; (b) a concentration-independent band at 3543 cm.$^{-1}$ which can be assigned to an intramolecular bond; (c) and a band at 3628 cm.$^{-1}$ assigned to free OH and to primary and secondary OH which are acting as bases in intramolecular hydrogen bond formation.[11] A carbon tetrachloride solution of diols IIa and IIb was examined at 0.005*M*, at which concentration the intermolecular bonded absorption at 3375 cm.$^{-1}$ is absent. The 3628 cm.$^{-1}$ and 3543 cm.$^{-1}$ bands were measured and expressed as intensity ratios.[12] The intensity ratio for IIa was greater than that of IIb, the values being 1.38 and 1.17, respectively. The differences in these ratios can be interpreted as a measure of the relative amounts of intramolecularly bonded OH due to conformational differences between the diastereomeric glycols.[13] The most energetically favorable intramolecularly bonded conformations of IIa and IIb are illustrated by diagrams IXa and Xa. As a $\Delta\nu$ of 85 cm.$^{-1}$ corresponds to a hydrogen bond

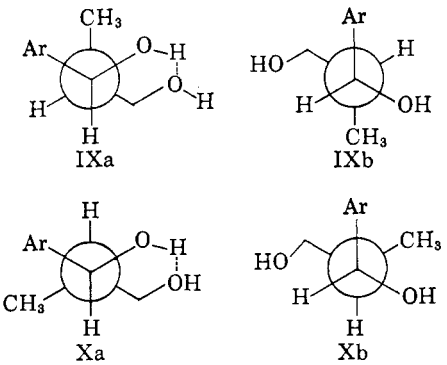
(10) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, 10, 44 (1956).

(11) R. West, J. J. Korst, and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960).

(12) The ratio of the absorption bands, free-OH/bonded-OH.

(13) P. V. R. Schleyer, *J. Am. Chem. Soc.*, **83**, 1368 (1961).

strength of approximately 2.5 kcal.,[14] it is considered that the unbonded forms of these conformations, in which the hydroxymethylene is rotated out of proximity with the benzylic hydroxyl group, are present only in minor amounts. The Newman projection formulas, IXb and Xb, represent conformations in which no hydrogen bonded hydroxyl



can exist. As IXa and Xa are most likely in equilibrium with IXb and Xb, respectively, it is expected that the thermodynamic stabilities of unbonded conformations IXb and Xb will govern the conformational equilibria. Conformation Xb possesses more nonbonded interactions than bonded conformation Xa, whereas IXb contains fewer nonbonded interactions than in IXa. This means the conformational equilibrium, IXa $\rightleftharpoons$ IXb, should be shifted further to the right than in the equilibrium, Xa $\rightleftharpoons$ Xb. It follows, therefore, that a structure corresponding to IX should have a greater population of free OH than in X. This is manifested by a higher intensity ratio for IX. On this basis glycols represented by IX and X correspond to IIa and IIb, respectively.

In view of the finding that thermodynamic control is operative in the Prins reaction of anethole, it is possible that the *m*-dioxane III is a mixture of *cis* and *trans* isomers and not a pure compound. The conversion of IIa and IIb to *m*-dioxane III when heated in aqueous formaldehyde supports this contention. As isomerization takes place under mild conditions, equilibration must certainly have occurred in the procedure normally employed[4] for preparation of III and similar dioxanes. Isothermal gas chromatographic analysis of III showed only a single peak. The stereochemistry of III is currently under investigation.

EXPERIMENTAL

Reaction of anethole with formaldehyde in glacial acetic acid. A mixture of 500 ml. of glacial acetic acid, 100 g. (0.675 mole) of anethole, and 30 g. (1.0 mole) of paraformaldehyde was refluxed 5 hr. in an atmosphere of nitrogen. The acetic acid was removed *in vacuo* and distillation of the remaining liquid gave the following fractions: A, 8 g., 85–130° (0.7 mm.), n^{22} 1.5470; B, 35 g., 130–143° (0.7 mm.), n^{22} 1.5202; C, 105 g., 143–146° (0.7 mm.), n^{23} 1.5005. The composition of the fractions are as follows: A, 5 g. of anethole, 3 g. of 4-anisyl-5-methyl-1,3-dioxane (III); B, 26 g. of III, 9 g. of 1-anisyl-2-methyl-1,3-diacetoxypropane (Ia and Ib); C, 7 g. of III, 98 g. of Ia and Ib. The total quantity of III is 36 g. (25.6% yield) and the total yield of Ia and Ib is 107 g. (56.6%). The dioxane III, obtained on redistillation of B, was identical in all respects to the compound prepared by Beets.[7] After redistillation of fraction C the boiling point and refractive index are as follows: 144–146° (0.7 mm.), n^{26} 1.4976.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 64.26; H, 7.19. Found: C, 64.42; H, 7.19.

On standing the mixture of Ia and Ib solidified to a crystalline mass, m.p. 44–57°. Three recrystallizations from benzene–petroleum ether (b.p. 63–70°) gave diacetate Ia as large prisms, m.p. 70–71°. On cooling, the mother liquor afforded the isomeric diacetate (Ib) as sheathlike crystals which after several recrystallizations melted at 64–65°. The infrared spectra were very similar, 5.75 μ (ester).

The relative amount of Ia and Ib obtained from fraction C was determined from a quantitative infrared analysis using the 10.11-μ band in Ib and the 10.26-μ band in Ia and Ib. Expressed as a ratio, 10.26-μ band/10.11-μ band, values were obtained which corresponded to 25% Ia and 75% Ib. The accuracy of the preceding method was corroborated by identical percentages obtained from a eutectic diagram of different mole fractions of Ia and Ib.

1-Anisyl-2-methyl-1,3-propanediol (IIa *and* IIb). The diacetate mixture (85 g., 0.318 mole) obtained from fraction C was refluxed in 500 ml. of 2*N* sodium hydroxide for 2 hr. The mixture was concentrated *in vacuo*, diluted with water, and extracted with several portions of ether. After drying over anhydrous magnesium sulfate, the ether extract was evaporated to a viscous oil which solidified, m.p. 55–66° (58.7 g., 97.8% yield). Crystallization from benzene produced crude IIb, m.p. 67–75°. On dissolving this material in boiling water and allowing the solution to cool, pure IIb, m.p. 87–89°, was obtained.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.21. Found: C, 67.10; H, 8.10.

The benzene was removed from the mother liquor *in vacuo*. The oil which solidified on standing could not be purified by fractional crystallization. The isomeric glycol (IIa) was obtained in pure form by refluxing 2.0 g. (0.01 mole) of pure Ia in 40 ml. methanolic in sodium hydroxide for 3 hr. The solution was concentrated *in vacuo*, diluted with water, and extracted with ether. After drying the ether extract over anhydrous magnesium sulfate, it was evaporated to an oil which crystallized when the last trace of ether was removed under reduced pressure to give the glycol, m.p. 62–63°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.21. Found: C, 67.72; H, 8.09.

The infrared spectra of IIa and IIb in chloroform displayed bands at 2.75 μ (unbonded OH) and 2.89 μ (bonded OH).

Acetylation of 1-anisyl-2-methyl-1,3-propanediol (IIa *and* IIb). The glycol (1.0 g., 0.5 mmole) was heated on a steam bath for 2 hr. in the presence of 3 ml. of acetic anhydride and 1 g. of anhydrous sodium acetate. A 5% sodium bicarbonate solution was added to decompose the acetic anhydride, after which the mixture was extracted with ether and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation the resulting oil crystallized. Glycol IIa produced 1.10 g. Ia, m.p. 70–71° whereas IIb yielded 1.06 g. Ib, m.p. 64–65°.

Conversion of 1-anisyl-2-methyl-1,3-propanediol (IIb) *to 1-anisyl-2-methyl-1,3-diacetoxypropane* (Ia *and* Ib). Diol IIb (0.50 g., 0.25 mmole) was refluxed in 25 ml. glacial acetic acid for 14 hr. The acetic acid was neutralized with sodium bicarbonate solution. After extraction with ether and drying over anhydrous magnesium sulfate, the solvent was removed. A quantitative infrared analysis indicated the presence of 24% Ia and 76% Ib. A trace of anethole odor was noted.

(14) R. M. Badger and S. H. Bauer, *J. Chem. Physics*, 5, 839 (1937).

Conversion of 4-anisyl-5-methyl-1,3-dioxane (III) *to 1-anisyl-2-methyl-1,3-diacetoxypropane* (Ia *and* Ib). A mixture of 40 g. (0.19 mole) III and 300 ml. glacial acetic acid was refluxed for 16 hr., after which time there was observed a deposit of paraformaldehyde in the reflux condenser. Removal of acetic acid *in vacuo* followed by fractional distillation gave two fractions. Fraction A, 30 g., 130–148° (1 mm.), consisted amost entirely of III. Fraction B, 11 g. 121–125° (0.08 mm.), n^{24} 1.4976, consisted entirely of the diacetate mixture. An infrared determination showed it to consist of 25% Ia and 75% Ib.

Equilibration of 1-anisyl-2-methyl-1,3-diacetoxypropane (Ia). A mixture of 1.0 g. of Ia and 25 ml. of glacial acetic acid was refluxed a total of 19 hr. The mixture was neutralized with aqueous sodium bicarbonate solution and extracted with ether. The ether extract was dried over magnesium sulfate and the solvent removed *in vacuo*. The remaining oil crystallized on standing. The mixture, when analyzed by infrared, contained 25% Ia and 75% Ib. On decreasing the refluxing time to 6 hr. the mixture consisted of 34% Ia and 66% Ib.

Conversion of 1-Anisyl-2-methyl-1,3-diol (IIa *and* IIb) *to 4-Anisyl-5-methyl-1,3-dioxane* (III). When subjected to the following conditions, both pure IIa and pure IIb afforded III. One gram of glycol on 30 ml. of 37% formaldehyde was heated on a steam bath for 24 hr. After extraction with ether, drying with magnesium sulfate, and removal of ether, the residual oil was found to be identical to the *m*-dioxane (III) obtained by the method of Beets.[7]

Infrared spectral procedure. The infrared spectra of diols IIa and IIb were determined in spectroquality carbon tetrachloride solution in the OH stretching region, 3200–3800 cm.$^{-1}$ A Perkin-Elmer Model 21 spectrophotometer was employed. The compounds were studied at 0.025*M* and 0.05*M* using a 0.5-mm. path length, and at 0.005*M* using a 1 cm. path length. Assignments are considered to be accurate to ±5 cm.$^{-1}$ for sharp bands.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation and the National Institutes of Health.

LAWRENCE, KAN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Conformational Analysis. XXIII. The 4-Cyclohepten-1-one System[1]

NORMAN L. ALLINGER AND WILLIAM SZKRYBALO

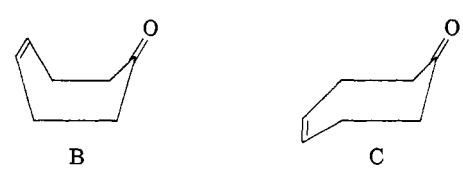
Received August 23, 1961

The conformation of the 4-cyclohepten-1-one system was investigated by studying the dipole moments of three compounds, 5,6,8,9-tetrahydro-7*H*-cycloheptabenzen-7-one (I), bicyclo[5.4.0]undecan-4-one (II), and 6,7,8,9-tetrahydro-5*H*-cycloheptabenzene (III). It was concluded that an equilibrium mixture of chair and boat forms existed in which the former predominated to the extent of about 92%. This result was interpreted as being primarily due to van der Waals repulsion forces which destabilize the boat form.

While the six-membered ring system has been studied intensively from the conformational viewpoint,[2] relatively little is known about the seven-membered ring. Some detailed calculations have been carried out regarding the geometry of cycloheptane,[3–5] some more approximate ones regarding cycloheptene[5] and cycloheptanone,[4] and there is a variety of evidence available[6] which indicates the flexibility of the ring. The reason for the contrast in our knowledge regarding six- and seven-membered rings is that while simple cyclohexane derivatives exist as a mixture of two chair forms separated by a large energy barrier, the corresponding cycloheptane exists (in general) as a mixture of fourteen chair forms and a similar number of boat forms, separated for the most part by small barriers.

In the present work the goal was to determine the exact conformation of a seven-membered ring. The 4-cyclohepten-1-one system has been examined for a number of reasons, the two most important being that the double bond puts a rigidity into the system which reduces the number of possible conformations to two, and it presents a system in which we may gain some idea of the correctness of earlier assumptions made regarding the van der Waals' repulsion between the π electrons of sp^2 hybridized carbons.[7]

Examination of scale models showed that the compound has only two conformations (energy minima), which will be called the boat (B) and the chair (C). Because of the easier availability of the compounds, the benzenoid derivative (I) of the



B C

(1) Paper XXII, N. L. Allinger, and M. A. DaRooge, *Tetrahedron Letters*, 676 (1961).

(2) For recent reviews and leading references see: (a) E. L. Eliel, *J. Chem. Ed.*, **37**, 126 (1960). (b) H. H. Lau, *Angew. Chem.*, **73**, 423 (1961).

(3) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

(4) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

(5) R. Pauncz and D. Ginsburg, *Tetrahedron*, **9**, 40 (1960).

(6) *e.g.* Ref. 3, 4. Also see: J. Sicher, F. Sipos, and J. Jonas, *Czechoslov. Chem. Commun.*, **26**, 262 (1961); J. W. Huffman and J. E. Engle, *J. Org. Chem.*, **24**, 1844 (1959); N. L. Allinger and V. Zalkow, *J. Am. Chem. Soc.*, **83**, 1144 (1961); N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 232 (1959); H. J. E. Loewenthal and P. Rona, *J. Chem. Soc.*, 1429 (1961).

(7) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Am. Chem. Soc.*, **83**, 1974 (1960).