titrating the excess bromine.[10] To determine the bromide ion produced in the reaction the residue in the reaction flask was extracted repeatedly with water and dilute nitric acid until the extracts were free of halide ion. The combined extracts then were extracted with ether to remove unreacted starting material, after which the bromide ion content was determined by the Volhard method.

Identification of Products from the Reaction of 2-Bromocyclohexanols.—The general procedure above was followed except that 110 mmoles (19.7 g.) of bromohydrin, 300 ml. of ethanol and 75 g. of zinc-copper were used. After the olefin content of an aliquot (5%) of the reaction mixture had been determined, the remainder was distilled using a Todd column until most of the cyclohexene and ethanol was removed. The column was washed down with ether and the residues were extracted 3 times with ether; the combined extracts were washed with water, dilute nitric acid and sodium bicarbonate solution, and dried with sodium sulfate. Distillation of the ether left, from the *cis*-bromohydrin, 3.14 g. of light brown oil and, from the *trans*-isomer, 2.10 g. of light brown oil. The oil from the *cis*-bromohydrin was distilled and collected in 3 fractions. The first fraction was 0.90 g. of cyclohexanol; b.p. 154–166° at 630 mm., $n^{22}\text{D}$ 1.4581 (lit.[11] b.p. 160° at 760 mm.); 3,5-dinitrobenzoate, m.p. 107–110° (lit.[12] 112–113°). A mixture of the 3,5-dinitrobenzoate with authentic material had m.p. 110–112°. The second fraction, 0.38 g., had b.p. 166–184°. The third fraction was 0.10 g. of *trans*-2-ethoxycyclohexanol, b.p. 184–186° (630 mm.), $n^{21}\text{D}$ 1.4561 (lit.[13] b.p. 187° (760 mm.), $n^{20}\text{D}$ 1.4563); 3,5-dinitrobenzoate, m.p. 83.5–84.5° (lit.[14] m.p. 82–83°). A mixture of the 3,5-dinitrobenzoate with authentic material had m.p. 83–84°. The residue was 1.75 g. of black tarry material which did not distil at 245°.

The oil from the *trans*-bromohydrin was distilled and separated into two fractions, the first boiling at 174–186°, and a second boiling at 184–194° at 630 mm., $n^{21}\text{D}$ 1.4561; 3,5-dinitrobenzoate, m.p. 83.5–84.5°, mixed with the 3,5-dinitrobenzoate of *trans*-2-ethoxycyclohexanol, m.p. 82.5–84°. The first fraction gave a 3,5-dinitrobenzoate melting at 72–77°. This was recrystallized twice to give m.p. 80–82.5°, and mixed with the 3,5-dinitrobenzoate of *trans*-2-ethoxycyclohexanol, m.p. 81–83°. The mother liquors from the recrystallizations were combined and evaporated to dryness. The residue was taken up in Skellysolve F which was allowed to evaporate over a two-week period. The resulting crystals, m.p. 72–80°, were examined under a microscope; only one type, long needles, could be seen. Because of the high initial boiling point of the distillate and the above observations on the 3,5-dinitrobenzoate it was concluded that no appreciable amount of cyclohexanol was formed in the reaction.

BOULDER, COLO.

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[10] (a) A. W. Francis, *Ind. Eng. Chem.*, **18**, 821 (1926); (b) S. J. Green, *J. Inst. Petroleum*, **27**, 66 (1941).

[11] N. A. Lange, "Handbook of Chemistry," 6th edition, Handbook Publishers, Inc., Sandusky, Ohio, 1946.

[12] T. Reichstein, *Helv. Chim. Acta*, **9**, 799 (1926).

[13] M. Mousseron and R. Granger, *Compt. rend.*, **205**, 327 (1937).

[14] M. Mousseron, R. Jacquier and M. Mousseron-Canet, *ibid.*, **235**, 177 (1952).

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

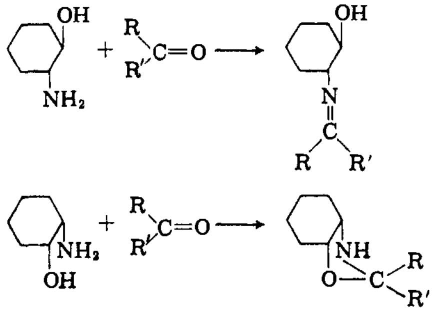
Condensation Products of the Epimeric 2-Aminocyclohexanols with Carbonyl Compounds

BY E. GIL-AV

RECEIVED SEPTEMBER 2, 1958

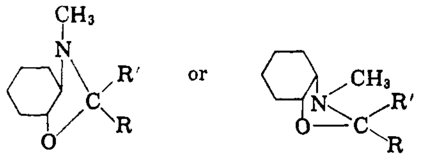
The condensation of the epimeric 2-aminocyclohexanols with certain carbonyl compounds, known to favor the formation of oxazolidines, was investigated. Products, having a correct analysis, could be isolated in three cases. The *trans* epimer forms Schiff bases with both acetophenone and *m*-nitroacetophenone. The *cis* epimer yields with acetone a product which is a mixture of an oxazolidine and a Schiff base.

In the course of studies on epimeric aminocyclanols, McCasland and Horswill[1] examined the possibility of differentiation between the *cis*- and the *trans*-2-aminocyclohexanols on the basis of their reaction with carbonyl compounds. In accordance with the behavior of such pairs of diastereoisomers toward other reagents, they expected to find differences in the nature of the products formed or in the rates of reaction. In particular, they anticipated that, whereas the *trans* compound would tend to form a Schiff base, the *cis* derivative might lead to an oxazolidine



Their experiments with benzaldehyde showed that both epimers give only Schiff bases with similar yields. They further examined the ultraviolet spectrum of the "oxazolidine" of M. Bergmann[2] and found that it is in fact a Schiff base, $CH_2OHCHOHCH_2N{=}CHC_6H_5$.

These findings demonstrated the lack of stability of oxazolidines capable of undergoing isomerization to Schiff bases, and further studies on the condensation of the epimeric aminocyclanols with carbonyl compounds therefore were abandoned. It it also of interest to mention that an attempt was made by the same authors to study the reaction of carbonyl compounds with the diastereoisomeric 2-methylaminocycohexanols which would be expected to lead to oxazolidines of unambiguous structure



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[1] G. E. McCasland and E. C. Horswill, THIS JOURNAL, **73**, 3923 (1951).

[2] M. Bergmann, E. Brand and F. Dreyer, *Ber.*, **54**, 936 (1921).

However, they found that no reaction occurred at all in these experiments and that the starting materials were recovered.[3]

Since the publication of the paper by McCasland and Horswill,[1] structural factors influencing the stability of the oxazolidines have been studied, particularly by Bergmann, Zimkin and co-workers.[4]

These authors found that aromatic aldehydes, which can form a conjugated system of double bonds with the C=N group of the Schiff base, favor the latter structure. If resonance is, however, interfered with by steric hindrance to the attainment of coplanarity, as, for instance, by the methyl group in the condensation products of acetophenone and *m*-nitroacetophenone,[5] formation of the oxazolidine structure is found to be relatively more probable than in the products from benzaldehyde.

On the other hand, aliphatic aldehydes and ketones, as well as cyclic ketones such as cyclohexanone, lead to condensation products of predominantly oxazolidinic structure.

From a consideration of these results, it was concluded that the condensation of 2-aminocyclohexanols with carbonyl compounds, having a stronger tendency to form oxazolidines than benzaldehyde, could possibly lead to a differentiation between the two epimers. Work carried out on these lines is reported in the present paper.

Procedure.—The condensation of the carbonyl compounds with the epimeric aminocyclanols was effected in benzene solution and the water formed in the reaction was distilled off azeotropically, a trace of iodine being added as a catalyst in some instances. The reaction was stopped when no more water came over. After the solvent had been removed, the product was worked up by distillation or crystallization. The structure of the products was then examined by infrared spectroscopy and in some cases also by molecular refraction and ultraviolet absorption measurements.

It has to be pointed out that, since the work on the oxazolidines had shown that the condensation products of primary β-aminoalcohols with carbonyl compounds were, in general, mixtures of Schiff bases and oxazolidines, one had to expect different proportions of the two isomers in the condensation product of the respective epimers, rather than exclusively one of the isomers.

The identification and semi-quantitative estimation of Schiff bases and oxazolidines, in each other's presence, can be carried out by the physical methods mentioned above.[4] Infrared spectroscopy, in particular, is very useful. It permits identification of the Schiff bases by the characteristic absorption of the C=N and the OH groups, and of the oxazolidine ring by a system of three bands[6] at 1086–1118, 1116–1139 and 1149–1185 cm.$^{-1}$. One has, however, to take guard against possible interference by other structural groups in the interpretation of the spectrum in the latter region.

Results and Discussion

Condensation Products of *trans*-2-Aminocyclohexanol.—The condensation products of *trans*-2-aminocyclohexanol were examined first. (The following carbonyl compounds were used in these experiments: (a) aliphatic aldehydes and ketones: formaldehyde, propionaldehyde, isovaleraldehyde, caprylaldehyde, acetone, methyl ethyl ketone, methyl isobutyl ketone, 3-heptanone and 2-octanone; (b) cyclohexanone; (c) aromatic carbonyl compounds: hydrocinnamic aldehyde, hydratropic aldehyde, acetophenone, *m*-nitroacetophenone and phenylacetone.) It was found that, though reaction occurred quite readily, it was difficult to purify the resulting products. Fractional distillation *in vacuo* and chromatography over alumina or silica gel were unsuccessful due to the instability of the products. It was further observed that the products changed on standing, even when dissolved in non-polar liquids. Recrystallization gave pure products in two cases, but care had to be taken to limit the duration of the procedure to a minimum.

With the exception of formaldehyde, all these carbonyl compounds yielded fractions the composition of which approached that expected for 1:1 condensation products. Formaldehyde gave only a relatively high molecular weight solid (mol. wt. (in benzene), about 300) which did not show any C=N or O—C—N absorption and was not further investigated.

Pure products, giving satisfactory analyses, were obtained from acetophenone and *m*-nitroacetophenone. They are solids and were purified by recrystallization from benzene. Both derivatives were found to be Schiff bases, that is, *trans*-2-(α-methylbenzylidene)-aminocyclohexanol (I) and *trans*-2-(α-methyl-*m*-nitrobenzylidene)-aminocyclohexanol (II), respectively. Their infrared spectra showed strong bands characteristic of the C=N and the OH groups. Compound I also was examined in the ultraviolet region and was found to absorb at 243 mμ (log ϵ 4, 12) (in isoöctane). The hypsochromic shift of this band, as compared with the absorption of the condensation product of benzaldehyde with the 2-aminocyclohexanols (λ_{max} 247 mμ, log ϵ 4,25), is in accordance with similar observations on the effect of the methyl group in the condensation product of cyclohexylamine and acetophenone.[7]

On the other hand, no evidence for the presence of oxazolidine structure was found; I has only

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[3] Recently. K. Bláha and J. Kovář. *Chem. Listy*. **52**, 77. 283 (1958). however. succeeded in carrying out this reaction. They also condensed the epimeric 2-aminocyclohexanols with *p*-nitrobenzaldehyde and concluded on the basis of the infrared spectra that mixtures of oxazolidines and Schiff bases were formed. Whereas there is clear evidence for the Schiff bases (bands in the C=N and OH regions), the conclusion as to the presence of the oxazolidines is not warranted. No triplet (see procedure) was found in the O–C–N region. but only two bands at about 1130 and 1110 cm.$^{-1}$. of which the latter is to be ascribed to the *p*-substituted phenyl group (*cf.* *p*-nitrobenzylidene-2-aminoethanol.[6] absorption band at 1110 cm.$^{-1}$).

[4] (a) E. D. Bergmann. E. Zimkin (Gil-Av) and co-workers. *Rec. trav. chim.*, **71**, 168 (1952): (b) **71**, 229 (1952): E. D. Bergmann, E. Gil-Av and S. Pinchas. THIS JOURNAL, **75**, 68 (1953): (c) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953) (see there for additional references).

[5] Available data[4(c)] on the influence of ring substituents on the nature of the condensation products from aromatic carbonyl compounds. show that the *m*-nitro group should further favor the formation of the oxazolidine structure.

[6] E. D. Bergmann. E. Zimkin (Gil-Av) and S. Pinchas. *Rec. trav. chim.*. **71**, 168 (1952).

[7] E. D. Bergman. Y. Hirschberg. S. Pinchas and E. Zimkin (Gil-Av). *ibid.*. **71**, 195 (1952).

two very weak absorptions in the 1100–1200 cm.$^{-1}$ region, namely, at 1114, and 1182 cm.$^{-1}$, whereas the oxazolidine formed from acetophenone and 3-amino-2-methyl-2-butanol has three well developed bands,[6] situated at 1078, 1136 and 1173 cm.$^{-1}$.

The case of II is more complicated, due to the presence of the *m*-nitro group. The spectrum in the 1100–1200 cm.$^{-1}$ region shows absorption bands at 1113 cm.$^{-1}$ (weak), 1139 cm.$^{-1}$ (shoulder) and 1161 cm.$^{-1}$ (strong), but they seem to be due essentially to the *m*-nitroacetophenone moiety (*m*-nitroacetophenone absorbs at 1139 and 1161 cm.$^{-1}$). In contradistinction, the condensation product of *m*-nitroacetophenone and ethanolamine,[6] which is mainly in the oxazolidine form, shows bands not only at 1143 and 1161 cm.$^{-1}$, but also at 1101 and 1128 cm.$^{-1}$.

The purity of the products from the other carbonyl compounds was estimated at 50–80% on the basis of their titration equivalents. The spectra of these impure mixtures also were examined. Certain conclusions can be drawn from these data, though they are necessarily of limited significance. All the spectra had a strong band at 1630–1670 cm.$^{-1}$, which is characteristic of the C=N double bond, as well as absorption in the OH region. Acetone, for instance, yielded a product (III) which had an equiv. wt. of 145 (calcd. for the 1:1 condensation product, 155). Its infrared spectrum showed a strong absorption at 1667 and 3300 cm.$^{-1}$ (hydrogen bonded OH). In the 1100–1200 cm.$^{-1}$ region only one peak at 1120 cm.$^{-1}$ was found. The possible presence of an oxazolidine structure in derivatives of the *trans* epimer was detected only in the condensation product of methyl propyl ketone, of about 75% estimated purity (equiv. wt., 167; calcd., 183), which showed a weakly developed triplet at 1110, 1125 and 1185 cm.$^{-1}$.

Thus the evidence for the structure of the pure products isolated from the reaction mixtures of carbonyl compounds with *trans*-2-amino-cyclohexanol, as well as the indications gained from the spectra of the impure products, permit the conclusion that the *trans* epimer does not form oxazolidines at all, or only to a very limited extent, even with those carbonyl compounds which are known to favor the stability of the oxazolidine ring.

Condensation of *cis*-2-Aminocyclohexanol.—In view of the difficulties experienced in the *trans* series, due to the instability of the reaction products, the carbonyl compounds for condensation with the *cis* epimer were chosen, either so as to make the formation of solid compounds more likely, or else to lead to relatively volatile derivatives. Accordingly, the following substances were used: acetophenone, *m*-nitroacetophenone, phenylacetone and acetone.

The first three carbonyl compounds did not, however, lead to solid products, as expected, but to relatively high-boiling liquids which could not be purified satisfactorily. Acetophenone gave a fraction which approached the expected 1:1 condensation product (equiv. wt., 208; calcd., 217). Its spectrum showed a strong C=N band and also a slight absorption in the 1100–1200 cm.$^{-1}$ region. In the latter region bands were observed at 1088, 1135 and 1178 cm.$^{-1}$ and are ascribed to the presence of some oxazolidine in the product. In the similar case of the condensation product of acetophenone and 3-amino-2-methyl-2-butanol, which was found to have essentially an oxazolidine structure,[6] the characteristic oxazolidine bands were found at the nearby frequencies 1078, 1136 and 1173 cm.$^{-1}$.

The spectra of the impure products from the other two aromatic ketones showed strong C=N absorption but none in the 1100–1200 cm.$^{-1}$ which could be ascribed to an oxazolidine ring.

Finally, acetone gave a product which could be fractionated by distillation *in vacuo* without change and gave a practically pure material (IV). This substance had mainly an oxazolidine structure according to its molecular refraction, its infrared spectrum, and its relative stability. Immediately after redistillation, the molecular refraction of the product was 44.06 (calcd. for the oxazolidine, 44.60; for the Schiff base, 46.1).[8] The infrared spectrum showed a triplet[9] characteristic of the oxazolidine ring at 1100, 1155 and 1190 cm.$^{-1}$, but no absorption in the C=N and the OH regions.

On standing, however, there is a change in the refractive index of IV and after a number of days the molecular refraction stabilizes at 44.60 (measured after 8 days). Correspondingly, there is an increase in the intensity of the absorption at 1667 cm.$^{-1}$ and in the OH region. This behavior is similar to that observed by Cope and Hancock[10] in the case of the condensation product of ethanolamine and methyl propyl ketone.

A comparison of the infrared spectra at equal concentration of IV (after standing) with that of the condensation product of acetone and the *trans* epimer is shown in Fig. 1. The appearance of the triplet, due to the oxazolidine, is clearly seen in the 1100–1200 cm.$^{-1}$ region; also the relatively smaller intensities of the OH and the C=N bands are fully in accord with the assignment of a predominant oxazolidine structure to IV.

Conclusions.—The influence of the nature of the aminoalcohol and of the carbonyl compound on the structure of their condensation products has been shown in previous studies.[4] The present data, in agreement with the observations of McCasland and Horswill,[1] show that the 2-aminocyclohexanols do not favor the formation of oxazolidines. In fact, among the carbonyl compounds tried, only the condensation of acetone with the *cis* epimer led to definite evidence for the formation of the oxazolidine structure, and even in this case the oxazolidine was in equilibrium with its Schiff base isomer.

On the other hand, the experiment with acetone confirms the view that formation of an oxazolidine ring can be brought about by a suitable choice of

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[8] The different values for the molecular refraction of the two forms are essentially due to the difference between the atomic refraction of the secondary amino nitrogen (2.50) and that of the azomethine (4.10).[4,10]

[9] A band at 1120 cm.$^{-1}$ appears in the products formed both from the *cis* and the *trans* epimer. Since the latter does not show another band in the 1100–1200 cm.$^{-1}$ region, the 1120 cm.$^{-1}$ absorption is not to be ascribed to an oxazolidine ring.

[10] A. C. Cope and E. M. Hancock, This Journal, **64**, 1503 (1942).

the carbonyl compound even with a structurally unfavorable aminoalcohol.

In this latter case there is, as expected, a clear difference between the behavior of the *cis* and the *trans* epimer, no oxazolidine structure being detectable in the reaction products from the *trans* epimer.

The instability of the condensation products of the carbonyl compounds with the aminocyclohexanols makes them unsuitable for differentiation between the epimers. However, the observations reported in this paper might be of some interest in the study of the aminodeoxyinositols,[11] where condensation with acetone is used for the determination of the configuration of the hydroxyl groups.

Experimental

Preparation of Compounds. *trans*-2-Aminocyclohexanol.—Cyclohexene was converted into *trans*-2-chlorocyclohexanol,[12] which was then aminated by treatment with aqueous ammonia,[13,14] according to Wilson and Read.

***cis*-2-Aminocyclohexanol** was prepared in two different ways: (a) by catalytic hydrogenation of 2-acetoaminophenol, followed by splitting off of the acetyl group[14]; (b) by inversion of *trans*-2-benzamidocyclohexanol (I) through reaction with thionyl chloride followed by hydrolysis, according to Johnson and Schubert.[15]

***trans*-(α-Methylbenzylidene)-2-aminocyclohexanol (I).**—*trans*-2-Aminocyclohexanol (5.75 g.) and 6.0 g. of acetophenone were dissolved in benzene and refluxed in a flask provided with a Dean and Stark adapter for the separation of the water formed. A trace of iodine, added to the solution, acted as a catalyst. After 3.5 hours the reaction was terminated, 0.8 cc. (calcd. 0.9 cc.) of water having been formed. On standing, 3.5 g. of product crystallized. Another gram of raw product was obtained on concentrating the benzene solution. The raw product was recrystallized from benzene, m.p. 115–116°, λ_{max} 243 mμ (log ε 4.12). The infrared spectrum shows absorption bands at 1114-(weak), 1630 and 3370 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45; active H, 0.46; mol. wt., 217.3; equiv. wt., 217.3. Found: C, 77.06; H, 8.53; N, 6.63; active H (Zerewitinoff), 0.46; mol. wt. in 2% benzene, 239; equiv. wt., 216.

Though this compound could be prepared in a pure state, it was not very stable. It was observed that, on standing for several days in a solvent such as benzene–heptane, complex condensation reaction occurred, with the formation of a precipitate and the appearance of a new band in the infrared spectrum, situated at 1685 cm.$^{-1}$, possibly due to acetophenone (see below, III).

***trans*-(α-Methyl-*m*-nitrobenzylidene)-2-aminocyclohexanol (II).**—*trans*-2-Aminocyclohexanol (5.75 g.) and 8.25 g. of *m*-nitroacetophenone were treated as above, but without addition of iodine; the theoretical amount of water separated after one hour and 8 g. (65% yield) of raw product was obtained. After three recrystallizations from benzene the m.p. was 101.5–102°. The infrared spectrum shows absorption bands at 1113(weak), 1139(shoulder), 1161, 1642 and 3460 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.91; N, 10.68. Found: C, 64.38; H, 6.77; N, 10.84.

Condensation Product of *trans*-2-Aminocyclohexanol and Acetone (III).—*trans*-2-Aminocyclohexanol (5.75 g.) and 2.9 g. of acetone were treated in the usual way without addition of a catalyst. After 0.7 hour, 0.7 cc. (calcd. 0.9 cc.) of water had separated. Addition of iodine, or of a drop of glacial acetic acid and of excess acetone, did not increase the extent of the reaction. On distillation of the reaction mixture, 5.95 g. (78% yield) of material, distilling at 70–80° (0.25 mm.), was obtained. The product had an equiv. wt. which corresponded almost to the theoretical value (found 153, calcd. 155.2). However, attempts to prove the homogeneity of the material were unsuccessful. Fractional distillation *in vacuo* on a Piros–Glover spinning band column led to partial decomposition, and the best fraction obtained had a titration equivalent of only 145.

On standing, the product crystallized but, again, it was found that there occurred partial decomposition on recrystallization. Similarly to what had been observed in the case of I, there appeared, on standing, a new line in the infrared spectrum of the mother liquid, which corresponded to the C=O frequency (1720 cm.$^{-1}$) of the carbonyl compound used. As would be expected for the volatile acetone, this line persisted in the spectrum of the solvent (heptane) on the removal of the latter from the mother liquid by simple distillation. The infrared spectrum (Fig. 1) was measured on the best cut obtained by fractional distillation. It shows bands at 1120, 1667 and 3300 cm.$^{-1}$, and in addition slight absorption at 1720 cm.$^{-1}$.

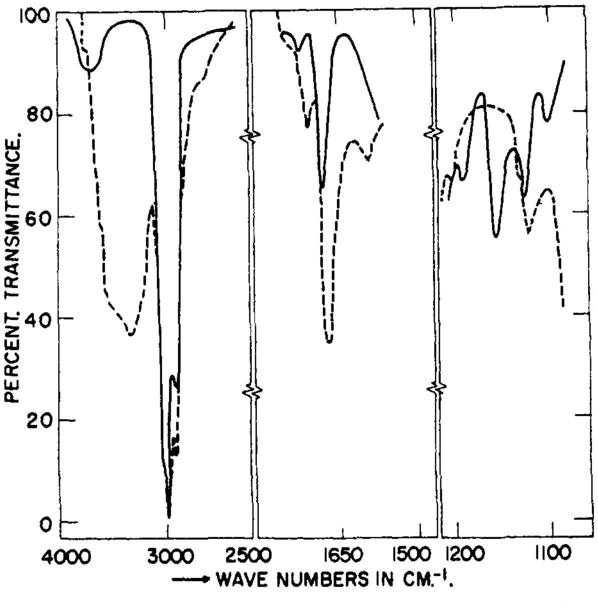

Fig. 1.—Infrared absorption spectra of the condensation products of acetone with *trans*-1,2-aminocyclohexanol (III) (dashed curve) and *cis*-1,2-aminocyclohexanol (IV) (solid curve), in about 10% chloroform solution.

Condensation Product of *cis*-2-Aminocyclohexanol and Acetone (IV).—*cis*-2-Aminocyclohexanol (9.4 g.) and 4.75 g. of acetone were dissolved in benzene and treated as above, without addition of a catalyst. After one hour 1.0 cc. (calcd. 1.47 cc.) of water had separated. On addition of an excess of 2 cc. of acetone, and again heating for one hour, another 0.3 cc. of water came over. The reaction mixture was first submitted to simple distillation, and 9.23 g. (73% yield) of product, distilling at 80–90° (3–6 mm.), was obtained; 8 g. of the raw product was then fractionally distilled on a Piros–Glover spinning band column. In contrast to III no decomposition seemed to occur. The distillates had the typical odor of oxazolidines. The heart fraction (about 2 g.), boiling at 75° (5 mm.) and having a titration equivalent of 159 (calcd. 155.2), was taken for the determination of the chemical and physical properties. The following values were found immediately after fractionation: $n^{24.7}$D 1.46725, $d_{24.7}$ 0.987, *MR* 44.06 (calcd. for the oxazolidine, 44.60; for the Schiff base, 46.10). After 8 days standing, the *MR* had increased to a value of 44.60. The infrared spectrum shows absorption bands at 1100, 1124, 1155, 1186, 1671 and 3450 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.31; H, 11.25; N, 8.10.

Compound IV was the most stable of the compounds examined, in accordance with its partial oxazolidine structure. Yet even in this case, complete purification could

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[11] S. J. Angyal, *Quart. Revs.* (*London*), **11**, 218 (1957).

[12] G. H. Coleman and H. F. Johnstone, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1932, p. 158.

[13] N. A. B. Wilson and J. Read, *J. Chem. Soc.*, 1269 (1935).

[14] G. E. McCasland, R. K. Clark and H. E. Carter, THIS JOURNAL, **71**, 640 (1949).

[15] W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2189 (1950).

not be obtained by fractional distillation, as evidenced by the somewhat low N value, the correspondingly high titration equivalent, and the presence of a small amount of carbonyl absorption at 1720 cm.$^{-1}$ (see Fig. 1).

The experiments with the other carbonyl compounds, mentioned in this paper, were carried out essentially in the same manner as described in the four examples given above. Titration equivalents were determined by neutralization with 0.1 N HCl in aqueous medium, using methyl orange as the indicator. The infrared spectra were measured in chloroform solution (usually about 10%) on a Perkin-Elmer model 12C or a Baird double beam spectrophotometer.

Acknowledgment.—Thanks are due to Dr. S. Pinchas, the Weizmann Institute of Science, for the measurement of the infrared spectra and help in their interpretation, and to Mr. C. Greener and Mrs. A. Jacob for valuable laboratory assistance. The analyses were carried out in our microanalytical laboratory, under the direction of Mr. E. Meier.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Shifts in Nuclear Magnetic Resonance Absorption Due to Steric Effects. II. Polysubstituted Cyclohexanes

BY S. BROWNSTEIN

RECEIVED JUNE 3, 1958

The ring protons in a polysubstituted cyclohexane are shifted toward lower field when they are adjacent to a more bulky substituent. The extent of the shift is proportional to the number and proximity of the substituents. For hexasubstituted cyclohexanes of identical stereochemistry the spectra are the same if the substituent is chlorine or hydroxyl.

Introduction

The stereochemistry of most isomers of the inositols, the hexachloro- and the heptachlorocyclohexanes have been established.[1,2] Therefore the arrangement of substituents with respect to the ring protons is known. When the ring interconverts from one chair conformation to another, protons which were in an equatorial position become axial and *vice versa*. However, this interconversion will only occur to an appreciable extent if both conformations have the same number of substituents opposing each other in axial positions, since otherwise there is an appreciable energy difference between the two forms. Isomers having three axial substituents might be expected to interconvert readily.[3] If this interconversion is rapid the magnetic environment of the ring protons, as observed by proton magnetic resonance spectroscopy, would be the average of that in the two conformations.[4] For those isomers which do not contain three axial substituents the ring protons will be in a constant environment.

Inductive effects on the bonding electrons of all the ring protons will be identical in 1,2,3,4,5,6-hexasubstituted cyclohexanes since the protons are attached to carbon atoms which are similarly substituted. Any departure of the proton resonance spectra from a single sharp peak will therefore be due to long range magnetic shielding effects. In principle this shielding is calculable from magnetic anisotropies but would be very difficult to determine.[5] The change in magnetic shielding is empirically correlated with the proximity of substituents and will therefore be treated as a steric effect although the actual mechanism of the shielding may arise from another cause. The interpretation of the spectra in terms of steric effects are done with this reservation. Except for a constant displacement, the spectra of equivalent stereoisomers should be identical provided the size of the different substituents is similar.

Experimental

The proton magnetic resonance spectra were obtained as previously described.[6] Saturated methylene chloride solutions of the hexa- and heptachlorocyclohexanes were used and the peak due to the solvent protons was used as an internal standard. Since the solvent is chemically similar to the solute, no account was taken of possible chemical shifts due to concentration effects or association.[7] Saturated carbon tetrachloride solutions of the heptachlorocyclohexanes were also used since some of the isomers absorbed at a similar field to the protons of the methylene chloride.

The hydroxyl hydrogens of the inositols were twice exchanged with a tenfold excess of 99% deuterium oxide and the spectra obtained in deuterium oxide as solvent. The concentrations were either 1.8 molar or saturated, whichever was more dilute. Methylene chloride was used as an external standard in an annular cell.[8]

The separation between the absorption due to the residual protons in the deuterium oxide and the protons of the external standard was the same for every sample. This was taken as an indication that any changes in concentration between these samples did *not* affect the chemical shift.

Results

Table I lists the results which were obtained. To facilitate comparison the chemical shift due to a difference in substituents, which is 34 cycles, has been subtracted from the observed values for the inositols, and the modified values listed in the third column of the table. The corresponding stereoisomers of the inositols and hexachlorocyclohexanes are listed in the same row. The details of the spectra for the γ- and ϵ-isomers of heptachlorocyclohexane are shown in Fig. 1, and that for *epi*-inositol in Fig. 2. The spectra were obtained at 40 Mc. and the observed shift is in cycles/sec. toward higher field from the signal due to the protons in methylene chloride. The spectra of the hexa-

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