

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

Acyl Migration O→N in the Diastereomeric 2-Aminocyclohexyl Benzoates

BY GÁBOR FODOR AND J. KISS

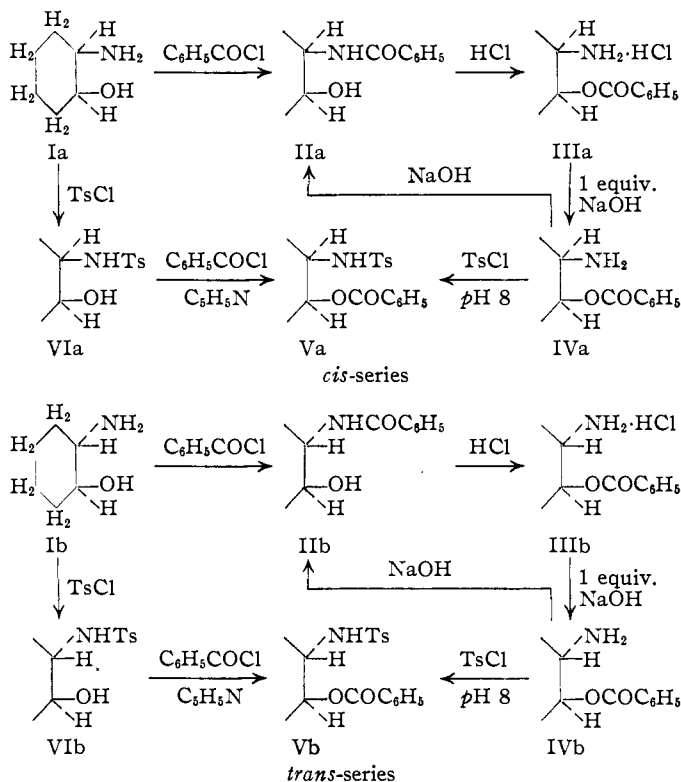
A recent communication concerns the N→O migration of the benzoyl group which results from

IVa' underwent the O→N acyl shift to yield *cis*-2-benzamidocyclohexanol, IIa. However, when an excess of 0.3–0.4 equivalent of alkali was added to the system containing the oily ester base, IVa, complete solution of the oil took place and was followed in one-half minute by precipitation of IIa.³

The combined hydrogen chloride of *trans*-2-aminocyclohexyl benzoate hydrochloride (IIIb) like that of its *cis*-isomer, could be titrated with alkali. Titration was accompanied by the deposition of oily *trans*-2-aminocyclohexyl benzoate (IVb) identifiable by virtue of its yielding on tosylation *trans*-2-tosylamidocyclohexyl benzoate (Vb) identical with the product obtained by treating *trans*-2-tosylamidocyclohexanol (VIb) with benzoyl chloride in pyridine. The ester base, IVb, yielded no hydroxyamide, IIB, when shaken thirty minutes with the aqueous phase at pH 8. However, dropwise addition of an excess of 0.6–1.0 mole of alkali caused IVb to dissolve, and, after about five minutes, deposition of IIB began.

The tendency of the oily aminoesters to dissolve in alkali is considered as experimental evidence indicating the formation of a cyclic ortho-acid derivative⁴ as an intermediate in the rearrangement, which may conceivably occur by the following mechanism.⁵

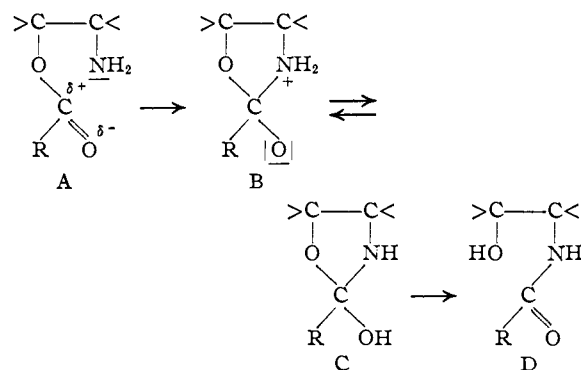
In the aminoester, A, which is formed as a result of adding alkali to the ammonium salt,



the action of hydrogen chloride on *cis*- and *trans*-2-benzamidocyclohexanol, IIa and IIb.¹ The work presently reported is related to the reverse (O→N) migration, which occurs when the diastereomeric 2-aminocyclohexylbenzoate hydrochlorides are treated with alkali.

Aqueous solutions of *cis*-2-aminocyclohexyl benzoate hydrochloride, IIIa,² and its *trans*-isomer, IIIb, showed a pH of 5.5–6.0. The combined hydrogen chloride of a 1% solution of IIIa could be titrated with 0.1 *N* sodium hydroxide to a sharp end-point in the presence of phenolphthalein. During the addition of one equivalent of alkali an oil gradually separated; it was identified as *cis*-2-aminocyclohexyl benzoate, IVa, since, when immediately tosylated at pH 8, it yielded a product identical with *cis*-2-tosylamidocyclohexyl benzoate (Va) prepared by benzoylating *cis*-2-tosylamidocyclohexanol (VIa) in pyridine.

On adding one equivalent of alkali to an aqueous solution of IIIa and stirring the mixture for five minutes at pH 8, a portion of the precipitated



(3) Welsh, *THIS JOURNAL*, **69**, 128 (1947), and Phillips and Baltzly, *ibid.*, **69**, 200 (1947), have reported that a rise in pH increases the speed of the O→N shift in esters of other 2-aminoalcohols.

(4) The formation of cyclic intermediates of similar structure has been assumed previously by Bell, *J. Chem. Soc.*, 2966 (1931), in rearrangements of acylated aminophenols, and by Phillips and Baltzly, *ref.* (3).

(5) After this paper was submitted for publication, Welsh, *THIS JOURNAL*, **71**, 3500 (1949), suggested a very similar mechanism for the rearrangement.

(1) Fodor and Kiss, *Nature*, **164**, 917 (1949).

(2) All compounds used in this work were racemic substances.

polarization of the carbonyl group results in the attraction of the unshared electrons of the nitrogen atom to carbonyl carbon. In the *cis*-compound, space relationships should be more favorable than in the *trans* for the mutual approach of these two atoms and the formation of a cyclic dipolar ion, B; the greater speed of rearrangement of the *cis*-derivative may be attributed to this circumstance. Shift of a proton from nitrogen to carbonyl oxygen gives the unstable, cyclic, alkali-soluble ortho-acid derivative, C. Rupture of the ester bond, perhaps by hydrolysis, yields the alkali-insoluble hydroxyamide, D.

Future work in this Laboratory will include efforts to demonstrate the presence of an intermediate of structure C by isolating it in the form of a stable derivative.

Experimental

cis-2-Benzamidocyclohexanol was prepared by hydrogenating 2-acetamidophenol,⁶ deacetylating the *cis*-2-acetamidocyclohexanol thus formed, and benzoylating the resulting aminoalcohol under Schotten-Baumann conditions.

trans-2-Benzamidocyclohexanol was obtained by ammonolysis of 2-chlorocyclohexanol⁷ and subsequent benzoylation of the resulting aminoalcohol.

Preparation of 2-Aminocyclohexyl Benzoate Hydrochlorides (IIIa and IIIb).—*cis*-2-Benzamidocyclohexanol (IIa) (2.5 g., 11.4 millimoles), m. p. 189°, was dissolved in 8.7 cc. of absolute ethanol, and 5 cc. (25 millimoles) of 5 *N* absolute ethanolic hydrogen chloride was added. The mixture was heated in a sealed tube at 100° for two hours and then cooled to -1°. The unreacted IIa which separated was filtered off, and the filtrate was evaporated at 20° under diminished pressure to remove solvent and excess acid. The residue was treated with 10-15 volumes of water to dissolve the *cis*-2-aminocyclohexyl benzoate hydrochloride (IIIa) and the undissolved IIa was filtered off. The two crops of unreacted IIa amounted to 46%. On cautiously evaporating the aqueous filtrate to dryness, 1.32 g. (45%) of IIIa was obtained. The product, which is easily soluble in water and in ethanol, was obtained as needles, m. p. 228°, on recrystallizing from ethanol-ether.

Anal. Calcd. for C₁₃H₁₉ClNO: C, 61.0; H, 7.1. Found: C, 61.4; H, 7.0.

trans-2-Benzamidocyclohexanol (IIb) (7.3 g., 33 millimoles), m. p. 174°, in 24 cc. of absolute ethanol was heated with 14.6 cc. (73 millimoles) of ethanolic hydrogen chloride as in the rearrangement of the *cis*-isomer. On cooling to -1°, crystals of *trans*-2-aminocyclohexyl benzoate hydrochloride (IIIb) deposited and were filtered off. The filtrate was evaporated to dryness and the residue of water-soluble IIIb and water-insoluble IIb was worked up as described in the preceding paragraph. Recovered IIb amounted to 3.15 g. (43%). The yield of IIIb was 4.22 g. (49%). The substance dissolves easily in hot ethanol, and but slightly in the cold solvent; needles, m. p. 274°.

Anal. Calcd. for C₁₃H₁₉ClNO: C, 61.0; H, 7.1. Found: C, 61.1; H, 7.2.

Acyl Migration O→N. **A.**—To a solution of 0.220 g. (8.5 millimoles) of IIIa in 20 cc. of water, *N* sodium hydroxide was added dropwise in the presence of phenolphthalein. After 0.3 cc. of alkali had been consumed, oily IVa began to deposit and gradually increased in amount until 0.85 cc. had been added; at this point the solution assumed a rose color. After scratching the oil for five minutes, it partly crystallized. Addition of excess alkali yielded more crystalline material. The yield was 0.173 g., m. p. 188°, not depressed by authentic IIa.

B.—A solution of 0.220 g. (8.5 millimoles) of IIIb, showing a pH of 5.5, on titration consumed 0.9 cc. of *N* sodium hydroxide. The oily precipitate of IVb did not crystallize during thirty minutes of shaking after inoculation with IIb. However, on adding an additional 0.6 cc. of alkali the oil dissolved, and, after a few minutes, 0.120 g. of IIb deposited from the solution; m. p. 174°.

C.—A solution (pH 6) of 0.220 g. of IIIa in 20 cc. of water was titrated with 0.1 *N* sodium hydroxide. Separation of the oily IVa was complete after the addition of 8.5 cc. of alkali. After 3.5 cc. more had been added, the solution was homogeneous, and in thirty seconds IIa began to deposit; yield 0.185 g., m. p. 188°.

D.—To the oil, IVb, obtained during titration of 0.220 g. of IIIb in 20 cc. of water, excess 0.1 *N* sodium hydroxide was added until the system was homogeneous; 6 cc. of alkali was required. Only after an interval of five minutes did crystals of IIb deposit; yield 0.102 g., m. p. 172°.

Identification of IVa and IVb. **A.**—To a solution of 0.180 g. (0.7 millimole) of IIIa in 3 cc. of water, 0.7 cc. of *N* sodium hydroxide was added in one portion. A solution of 0.134 g. (0.7 millimole) of *p*-toluenesulfonyl chloride in 5 cc. of benzene was then added to the system containing IVa, and, as the reaction proceeded, the mixture was maintained slightly alkaline to phenolphthalein by stirring and the dropwise addition of *N* sodium hydroxide. The crude product which separated (0.2203 g., m. p. 165-180°) on recrystallization from 5 cc. of ethanol yielded 0.085 g. of *cis*-2-tosylamidocyclohexyl benzoate (Va); needles, m. p. 180°, undepressed by authentic Va prepared as described below.

Anal. Calcd. for C₂₀H₂₃NO₄S: N, 3.75. Found: N, 3.8.

To a solution of 0.691 g. of *cis*-2-aminocyclohexanol hydrochloride, Ia·HCl, in 10 cc. of water was added 0.8 g. of *p*-toluenesulfonyl chloride in 3 cc. of benzene. On stirring the mixture with excess alkali, 0.786 g. of *cis*-2-tosylamidocyclohexanol (VIa) was obtained; m. p. 152-154°.

Anal. Calcd. for C₁₃H₁₉NO₃S: N, 5.2. Found: N, 5.32.

To 0.380 g. of VIa in 0.8 cc. of pyridine 0.2 g. of benzoyl chloride was added, and the mixture was allowed to stand for twenty-four hours. A yield of 0.193 g. of Va, m. p. 176°, was obtained after recrystallization from ethanol.

Anal. Calcd. for C₂₀H₂₃NO₄S: N, 3.75. Found: N, 3.79.

B.—To a solution of 1.125 g. (4.4 millimoles) of IIIb in 20 cc. of water the equivalent amount of *N* sodium hydroxide was added in order to liberate IVb. Tosylation was effected as described for IVa by adding *N* alkali and a solution of 0.9 g. (4.5 millimoles) of *p*-toluenesulfonyl chloride in 5 cc. of benzene. The crude *trans*-2-tosylamidocyclohexyl benzoate, Vb (1.578 g., 90%, m. p. 155-161°) which precipitated was recrystallized from 25 cc. of ethanol to yield 0.9 g. of needles; m. p. 168-170°, undepressed by authentic Vb prepared as described below.

Anal. Calcd. for C₂₀H₂₃NO₄S: N, 3.75. Found: N, 3.97.

***trans*-2-Tosylamidocyclohexanol (VIb)** was prepared essentially as described for VIa. From 15.5 g. of *trans*-2-aminocyclohexanol hydrochloride, Ib·HCl, was obtained 25 g. of VIb; m. p. 128° after recrystallization from dilute ethanol.

Anal. Calcd. for C₁₃H₁₉NO₃S: N, 5.2. Found: N, 5.4.

Benzoylation of 9.5 g. of VIb in 20 cc. of pyridine by means of benzoyl chloride yielded 9.2 g. of Vb, m. p. 165-166°, after recrystallization from 250 cc. of ethanol.

Anal. Calcd. for C₂₀H₂₃NO₄S: N, 3.75. Found: N, 3.82.

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(6) British Patent 454,032 (1936).

(7) Osterberg and Kendall, THIS JOURNAL, 42, 2616 (1920).

Summary

1. *cis*- and *trans*-2-aminocyclohexyl benzoate hydrochlorides on treatment with one equivalent of alkali yielded the corresponding oily 2-aminocyclohexylbenzoates which were identified by their conversion to crystalline tosyl derivatives.

2. The presence of alkali greatly facilitated the rearrangement of the diastereomeric 2-amino-

cyclohexyl benzoates to the corresponding benzamidocyclohexanols. Prior to the appearance of rearrangement product, transitory solution of the aminoester occurred; the phenomenon is attributed to the formation of an alkali-soluble ortho-acid derivative.

3. A mechanism for the O→N acyl migration has been presented.

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The Examination of a System Carbon and Hydrogen in the Temperature Range 1100-2600°

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Introduction

Since the beginning of our century the equilibrium between carbon and hydrogen has been the subject of numerous investigations. Pring and Hutton¹ heated a carbon bar electrically in a hydrogen atmosphere. Their experimental values scattered markedly. Other authors (Mayer, Bone, etc.),² also could not obtain more accurate data. Later Pring and his co-workers³ again investigated this methane equilibrium, especially the role of the catalyst in respect to the site of the equilibrium. Wartenberg, Wedensky, etc.,⁴ worked out the theoretical side of this problem.

The work of these authors was characterized by a comparatively primitive experimental technique and by defective, even incorrect, thermodynamic considerations. During the glowing, the carbon bar easily becomes inactive and reacts afterward very slowly. The temporarily constant values have been considered as equilibrium values. But when these values changed in the presence of certain catalysts, some authors^{3a,b} advocated the point of view that the equilibria could be changed by a catalyst, which would be equivalent to the realization of the perpetuum mobile of second kind. The wall effect has been also neglected, although this circumstance has a great influence on the concentration.

Our aim has been to investigate the system of carbon and hydrogen by modern experimental technique.

Carbon has been glowed electrically in pure hydrogen atmosphere, the carbon only being at a high but well-defined temperature. The reaction

(1) Pring and Hutton, *J. Chem. Soc. (London)*, **89**, 1591 (1906).

(2) Mayer and Altmayer, *Ber.*, **40**, 2134 (1907); Bone and Coward, *J. Chem. Soc. (London)*, **93**, 1197, 1975 (1908); *ibid.*, **97**, 1219 (1910); Coward and Wilson, *J. Chem. Soc. Industry*, **40**, 445 (1912).

(3) (a) Pring, *J. Chem. Soc. (London)*, **97**, 498 (1910); (b) Pring and Fairlie, *ibid.*, **99**, 1796 (1911); **101**, 91 (1912).

(4) (a) Berl and Bemman, *Z. physik. Chem.*, **A162**, 71 (1932); (b) Morris Travers, *Trans. Faraday Soc.*, **34**, 580 (1938); (c) Wartenberg, *Z. physik. Chem.*, **61**, 366 (1907); (d) Wedensky-Frost, *Chem. Zentr.*, **104**, II, 1928 (1933).

products have been immediately frozen out after leaving the zone of high temperature (see the discussion of the reaction space below). Moreover, we endeavored to employ accurate analytical methods.

Experimental and Analysis

The carbon was arc lamp carbon 7 mm. in diameter with a free length of 70 mm. which was heated between water-cooled electrodes in a 5-liter glass bulb, or in a cylindrical steel vessel of the same volume by current from a low-voltage transformer. The pressure of hydrogen, except for the low pressure experiments, was atmospheric. The temperature of the glowing carbon was measured by means of an optical pyrometer, with an accuracy of $\pm 3-5^\circ$. The samples for the analysis were taken into a gas analytical buret during the glowing. The experiments were made at a constant volume.

At very high temperatures special care must be taken with the fastening of the carbon bar, in order to preserve the contact and to allow free dilation and contraction. Therefore both ends of the carbon bar were set into precisely bored copper bars as seen in Fig. 1. One of these was fixed in a water-cooled, copper block; the other could slide in the bore hole of another copper block, also cooled by water. By this arrangement the carbon bar has sufficient mobility. The electrical contact and the cooling were also quite satisfactory.

For analysis, samples of 90-100 ml. of gas were collected. Because of the large volume of the vessel, the pressure did not change considerably during the sampling. Below 1700° the formation of only methane and carbon monoxide was observed, the latter from impurities containing oxygen; but its amount never exceeded a few hundredths of 1%. We have found that the final methane concentration is not influenced by varying carbon monoxide amounts, as was also found by Pring.^{3a} For the determination or for the removal of carbon monoxide a neutral solution of cuprous chloride was employed according to Bayer.⁵ The methane was measured through explosion.

Above 1700° acetylene and ethylene also form. The temperature limit of the formation of these gases was determined to be 1750° in special experiments. Still higher temperatures showed the CN-group too. In this case the sample was treated with alkali. The acetylene was determined with mercuric cyanide solution. It is indispensable that the sample for analysis be taken during the glowing; otherwise, the selective

(5) Bayer, "Gasanalyse," Stuttgart, 1941.