Summary

1. Chlorine and bromine as substituents in vanillin oxime cause no appreciable hindrance in the formation of the acetoxynitriles.

2. The acetoxynitriles may be hydrolyzed by caustic potash solution to give high yields of the corresponding acids, unless both ortho positions are substituted. When the 2,6-dibromo compound was used no acid was obtained but 87% of the nitrile was recovered. So far as examined, the chlorine derivatives are more reactive than the bromine compounds.

3. Each of the four 5,6-dihalogenated vanillic acids studied crystallized from water with half a molecular proportion of solvent of crystallization.

4. Further work is in progress.

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The Resolution of β-Ethoxyamines

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In an earlier paper[1] a method has been described for the synthesis of β-ethoxyamines. The present paper describes the complete resolution of β-ethoxyhexylamine and β-ethoxy-β-phenylethylamine and the partial resolution of β-ethoxybutylamine and β-ethoxyamylamine. The resolution of these amines proved to be extremely difficult. There appeared to be no marked difference in the solubility of the acid tartrate or camphor sulfonate salts of the *d*- and *l*-amines, and in addition there was a tendency to form gels which could not be filtered. In certain of the cases studied, more than twenty fractional crystallizations failed to yield a salt of constant rotation. In other cases a salt of constant rotation was obtained in two or three recrystallizations, and although fifteen to twenty additional crystallizations failed to change its rotation, the activity of the amine recovered from the mother liquor and the complete resolution of the amine by other resolving agents showed that only a partial resolution had been effected.

Considerable doubt may exist as to the completeness of a resolution if a statement indicating the constancy of the rotation of the salt or even the specific rotation of the salt is omitted. If the maximum rotation of the final pure salt were included, the repetition of the resolution by others would be greatly facilitated. A second consideration that is often overlooked in the resolution of asymmetric compounds is a determination of the rotation of the active compound that may be obtained by the hydrolysis of mother liquors which contain the more soluble fraction. In the case of the attempted resolution of β-ethoxy-β-phenylethylamine

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[1] Wernert and Brode, THIS JOURNAL, **54**, 4365 (1932).

as described in this paper, the resolution was apparently complete, in that the less soluble fraction had reached a constant rotation which was not altered by more than ten additional crystallizations, yet the more soluble fraction from the mother liquors gave an amine with a rotation of +16.2°, while the amine obtained from the supposedly pure crystals of constant rotation had an activity of only −4.3°. An incomplete examination of the literature shows that, while in most cases no mention is made of the rotation of the active compound obtained from the mother liquors, there are a few cases[2,3,4] reported in which the rotation of the asymmetric compound from the mother liquor was actually reported as higher than that of the supposedly pure material obtained from the less soluble fraction. The existence of these known cases, together with the absence of data on the activity of the mother liquor or more soluble compound, would tend to leave some uncertainty with regard to the completeness of some resolutions.

Experimental and Discussion

Partial Resolution of β-Ethoxybutylamine.—This resolution was first attempted with *d*-tartaric acid: 35.8 g. of amine was dissolved in 275 cc. of absolute alcohol and added to 47.2 g. (5% excess) of *d*-tartaric acid dissolved in 300 cc. of absolute alcohol. On cooling to 0°, the mass congealed and it was necessary to centrifuge in order to separate the solid matter from the alcohol solution. The separation of the two forms by fractional crystallization was so slow that there was no evident approach to a constant rotation. After more than 20 fractionations 4 g. of product having a specific rotation of +34.5° was obtained. On the opposite end of the series 17 g. of crystals was obtained from the mother liquors of the most soluble fractions which gave a specific rotation of +10.1°. Evidently a separation of the optical antipodes was taking place but the failure to obtain a constant rotation in the less soluble fraction indicated that only a partial resolution had been effected. The resolution was then undertaken with *d*-camphorsulfonic acid as the resolving agent; 109.3 g. of *d*-camphorsulfonic acid was added to 52.6 g. of β-ethoxybutylamine dissolved in 200 cc. of ethyl acetate. The first crystals which separated out on cooling had a specific rotation of +16.4°. After eight recrystallizations the less soluble fraction had a rotation of +19.7°. Three additional fractionations gave salts with rotations of +20.5, +19.3 and +19.6°, respectively. The material having a specific rotation of +19.6° amounted to 48.5 g. The free amine was prepared from this fraction by treatment with an excess of a concentrated sodium hydroxide solution and extraction with ether. The ethereal extract was dried over solid sodium hydroxide and on distillation yielded 10.5 g. of amine, b. p. 137.5–138.5°; 0.5738 g. of the amine in 25 cc. of absolute alcohol gave $[\alpha]^{25}_{D}$ +7.9°. The gum-like mass which resulted upon concentration of the most soluble fractions was decomposed with sodium hydroxide in the same manner as the less soluble salt. Eleven grams of the amine was obtained, b. p. 62.5–63.5° at 48 mm.; 0.4850 g. of the amine in 25 cc. of absolute alcohol gave $[\alpha]^{25}_{D}$ −11.3°. The greater activity of the more soluble fraction would indicate that only a partial resolution had been effected.

Partial Resolution of β-Ethoxyamylamine.—*d*-Camphorsulfonic acid did not form a well-defined crystalline salt with this amine so that *d*-tartaric acid was the only resolv-

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(2) Fischer and Scheibler, *Ann.*, **383**, 344 (1911).

(3) Pierre and Billon, *Ann. chim.*, **7**, 350 (1927).

(4) Fujisi, *Sci. Papers Inst. Phys.-Chem. Research* (*Tokyo*), **8**, 161 (1928).

ing agent used in an attempt to separate the isomeric forms of this base; 250 g. of β-ethoxyamylamine in 500 cc. of 95% ethyl alcohol was added to 286 g. of *d*-tartaric acid dissolved in a solution of 500 cc. of 95% alcohol and 50 cc. of water. On cooling the amine acid tartrate separated out in a solid unfilterable mass. Dilution with alcohol to a total volume of 3.5 liters still gave a solidified gel-like form which had to be centrifuged to separate the solid from the solvent. Recrystallization and centrifuging again gave 149 g. of a salt, $[\alpha]^{25}_{D}$ +15.7°. Eight recrystallizations produced a salt with a rotation of +28.6°, each fraction having a product of higher rotation than that of the preceding fraction. Examination of the end fractions of the more soluble salt showed salts of +11.6 and +9.6° for the last two fractions. In view of the fact that at no time during the fractionation were well-defined crystals formed and that the amount of the end fractions were rather small, with no indication of a constant rotation, it was not possible to carry the fractionation to completion.

Resolution of β-Ethoxyhexylamine.—This amine did not form a well-defined crystalline salt with *d*-camphorsulfonic acid, so the resolution was attempted only with *d*-tartaric acid. The *d*-acid tartrate was formed by the reaction of 335 g. of β-ethoxyhexylamine in 500 cc. of 95% alcohol with 346 g. of *d*-tartaric acid dissolved in 500 cc. of 75% alcohol. The solution was made up to a volume of 1.5 liters by the addition of 50% alcohol and on cooling deposited 280 g. of salt which was separated by centrifuging, $[\alpha]^{25}_{D}$ +8.4°. Subsequent recrystallization from 95% alcohol gave rotations of +1.01, −2.8, −4.5 and −5.8° for the second, fourth, sixth and eleventh recrystallizations. The less soluble middle fractions were then worked up until they gave a rotation of −5.9° and combined with this latter fraction. A yield of 102 g. of this salt was obtained; it formed short thick needles, m. p. 119.5–120.5°. The free amine was obtained by treatment with sodium hydroxide in the manner previously described. Sixteen grams of amine was obtained from 35 g. of salt, b. p. 70.5–70.7° (at 14 mm.); 0.5288 g. made up to 25 cc. in 95% alcohol gave $[\alpha]^{25}_{D}$ −24.6°. After the removal of several intermediate fractions from the mother liquor, the liquid residue was cooled to 0°. An amorphous residue was obtained which was centrifuged, washed with alcohol and finally recrystallized from 95% alcohol; 100 g. of this material was obtained, $[\alpha]^{25}_{D}$ +14.6°. After six recrystallizations a rotation of $[\alpha]^{25}_{D}$ +24.2° was obtained, which was not increased by two additional recrystallizations. Forty grams of this salt was decomposed with saturated sodium hydroxide solution as previously described. A yield of 16 g. of amine, b. p. 70.8–71.2° (at 15 mm.) was obtained. 0.6242 g. in 25 cc. of 95% ethyl alcohol gave $[\alpha]^{25}_{D}$ +8.6°.

Resolution of β-Ethoxy-β-phenylethylamine.—One hundred grams of β-ethoxy-β-phenylethylamine was dissolved in 300 cc. of ether and 147 g. (5% excess) *d*-camphorsulfonic acid was added to the solution in small portions, together with 450 cc. of ethyl acetate. The solution was heated during this process and upon cooling 130 g. of short well-defined crystals separated; 0.2270 g. of these crystals in 10 cc. of water gave $[\alpha]^{25}_{D}$ +13.2°. Recrystallization of this salt six times from ethyl acetate produced little change in the rotation. A final yield of 63 g. of salt was obtained which had a rotation of $[\alpha]^{25}_{D}$ +11.4° (m. p. 139–40°). Treatment of this salt with an excess of concentrated sodium hydroxide solution and extraction yielded the amine, b. p. 102–103° (at 10 mm.); 0.7003 g. in 25 cc. of ethyl alcohol gave $[\alpha]^{25}_{D}$ −4.3°. After separation of several intermediate fractions, the mother liquors were evaporated to dryness and the gum-like residue which could not be crystallized was hydrolyzed with sodium hydroxide and extracted with ether. An amine, b. p. 102–103° at 10 mm., was obtained, 0.7493 g. of which in 25 cc. of 95% ethyl alcohol gave $[\alpha]^{25}_{D}$ +11.8°.

Since over half of the camphorsulfonate salt had a nearly constant rotation, and the rotation of the recovered amine from the more soluble fraction was considerably higher than the amine from the less soluble fraction, the entire resolution was again repeated.

In the second resolution results were obtained which were identical with those of the first resolution. This *d*-camphorsulfonate salt ($[\alpha]^{25}_{D}$ +11.0°) was recrystallized from a number of organic solvents such as acetone, xylene, cyclohexane, diethyl ether, etc. Within the limits of observational error there was no change in the rotation of these recrystallized salts. The failure to effect a resolution, although a salt of constant rotation was obtained, would argue for the existence of some form of racemic compound which resists fractional crystallization. Such an effect has been noted in the resolution of other organic compounds.[5,6,7]

With the failure of the *d*-camphorsulfonate method of resolution the *d*-acid tartrate was tried. The crystals obtained from the *d*-acid tartrate salts were not as well defined as those from the *d*-camphorsulfonate salts, and the earlier fractionations gave distinct gels which could only be separated by centrifuging. Upon the gradual separation of the salts into the enantiomorphic forms the crystalline character improved and the final fractions were recrystallized with ease. Ninety grams of β-ethoxy-β-phenylethylamine was dissolved in 1200 cc. of alcohol to which was added 81.7 g. of *d*-tartaric acid. Fractional crystallization through seven series of fractionations caused only a slight rise in the rotation of the less soluble salt. On the eighth and ninth fractionations there was a distinct rise in the rotation of the less soluble fraction, together with a distinct decrease in the rotation of the central fractions, although the more soluble fraction had a rotation between these two. Further fractionation showed that compounds of different crystalline form were separated in the various intermediate fractions, those of a needle type being strongly dextrorotary while those of a plate type were levorotary. A careful separation of the fractions in accordance with the crystalline character of the salts showed an alternation between the two types. These were eventually concentrated into three series of needle fractions and three series of plate fractions. After some seven or eight fractionations a constant rotation of $[\alpha]^{25}_{D}$ +70.5° was reached in the less soluble (needle series), and a rotation of $[\alpha]^{25}_{D}$ −44.3–45.2° in the plate series.

Ingersoll[5] and Read, Campbell and Barker[8] have noted a similar anomaly in the resolution of *dl*-diphenylhydroxyethylamine, in that the first fraction of the *d*-camphorsulfonate gave on hydrolysis the pure *d*-base, while the second fraction on subsequent crystallization gave the *l*-base. It would appear that the solubility and rate of crystallization of the two acid tartrates were approximately the same, as would be evidenced by the slight resolution effected in the first seven fractionations. The fact that they were of markedly different crystalline character, however, might permit the possibility of one form separating from a supersaturated solution without the other form coming out of solution. Once having obtained a relatively pure form it would be a simple matter to complete the purification by fractional crystallization. In order to prove this a saturated solution was made from a mixture of equal parts of the two active salts ($[\alpha]^{25}_{D}$ +71° and −45°). It was found possible to induce the crystallization of either form by the addition of the appropriate seeding crystal. This would substantiate the suggestion of Stewart[9] that resolution is more a function of rate of crystal formation than of solubility. Ingersoll[5] and Read and Reid[10] have noted a similar effect in the inoculation of a racemic solution with a crystal of either of the isomeric forms (*d*A*d*B or *d*A*l*B) to induce the crystallization of that form from solution.

Thirteen grams of the *d*-salt ($[\alpha]^{25}_{D}$ +70.8°, m. p. 170.0–170.5°) was dissolved in water and treated with a saturated solution of sodium hydroxide. The liberated amine was extracted with ether and distilled; 0.5609 g. of the amine in 25 cc. of ethyl alcohol

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(5) Ingersoll, THIS JOURNAL, **47**, 1168 (1925); **50**, 2264 (1928); **54**, 274 (1932).

(6) Reed and Steel, *J. Chem. Soc.*, 910 (1927).

(7) Colles and Gibson, *ibid.*, 100 (1928).

(8) Read, Campbell and Barker, *ibid.*, 2310 (1929).

(9) Stewart and Allen, THIS JOURNAL, **54**, 4027 (1932).

(10) Read and Reid, *J. Soc. Chem. Ind.*, **47**, 9 (1928).

gave $\alpha = +4.70$ or $[\alpha]^{25}_{D}$ +104.5°. Ten grams of the *l*-salt ($[\alpha]^{25}_{D}$ −45.0°, m. p. 168.5–169°) was converted into the free amine in a similar manner; 0.5031 g. of this amine in 25 cc. of ethyl alcohol gave $\alpha = -4.19$ or $[\alpha]^{25}_{D}$ −104.2°.

Summary

A number of β-ethoxyamines have been partially or completely resolved. A study has been made of the procedure of resolution of these amines with *d*-camphorsulfonic acid and *d*-tartaric acid. It has been shown that it is possible to recrystallize a less soluble salt until a constant rotation is obtained and still not have effected a complete resolution. It is also possible that a salt may be recrystallized twenty or more times without reaching a constant rotation. If the salts of the enantiomorphic forms have a markedly different crystalline form, it is possible to crystallize either from a saturated solution of the active salt of the racemic compound (such as *d*A-*dl*B) by seeding with the pure active salt of the active compound (such as *d*A*d*B or *d*A*l*B).

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The Action of Chlorine on *p*-Toluenearsonic Acid under the Influence of Ultraviolet Light and its Chlorination with Hypochlorous Acid

BY CLIFF S. HAMILTON AND WILLIAM N. KING

It has been shown that the presence of phosphorus trichloride, phosphorus pentachloride[1] or ultraviolet light[2] greatly increases the rate of substitution of chlorine into the side chain of an aromatic hydrocarbon, when treated with chlorine. Book and Eggert[3] found that at a temperature of −80° it was possible to obtain a sixty to seventy per cent. yield of benzyl chloride if the reacting mixture was irradiated with ultraviolet light. *p*-Nitrotoluene has been chlorinated in the side chain, by passing the chlorine into the substance heated to 185–190°.[4]

Since toluene and especially *p*-nitrotoluene can be chlorinated in the side chain, it was thought that the analogous *p*-toluenearsonic acid, converted into the corresponding dichloroarsine by means of phosphorus trichloride and dissolved in a suitable solvent such as carbon tetrachloride, could likewise be chlorinated, the idea being to introduce one, two or three chlorine atoms into the side chain, and then by hydrolysis to obtain the corresponding alcohol, aldehyde and acid. In none of the experiments

(1) F. Berlstein, *Ann.*, **116**, 336 (1860).

(2) Sabatier and Reid, "Catalysis in Organic Chemistry," D. Van Nostrand Co., New York, 1922, p. 105.

(3) Book and Eggert, *Z. Elektrochem.*, **29**, 521 (1923).

(4) Wachendorff, *Ann.*, **185**, 271 (1877).