[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO]

THE PREPARATION OF OPTICALLY ACTIVE HYDRAZINES. III PARA-"ACTIVE-AMYL"-PHENYLHYDRAZINES[1]

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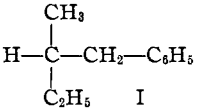
Efforts are now being made in this Laboratory[2] to synthesize and resolve some of the saccharinic acids. It was in the hope of facilitating this research by making available an optically active hydrazine for resolving purposes, that the work reported below was undertaken as a continuation of previous efforts along this line.[3]

In the present work the method of attack was the same as that used in the work reported in the previous papers of this series, namely, the preparation of the racemic amine corresponding to the desired hydrazine, its resolution, and the conversion of the active amines into the hydrazines. Both optically active forms of the hydrazine were obtained but further work is needed to show conclusively that the hydrazines were pure.

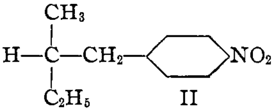
The preparation of the compounds studied is discussed below, in the order of preparation. In order to permit the use of simple names of compounds without ambiguity, a list of certain names used in the text, together with the structural formulas, is given below. The formulas will, then, serve as definitions of the names as used in this paper.

The compounds are benzylbutane (I), nitrobenzylbutane (II), aminobenzylbutane (III), benzoylaminobenzylbutane (IV), active-amylphenylhydrazine (V).



$$\mathrm{H{-}\overset{\displaystyle CH_3}{\underset{\displaystyle C_2H_5}{C}}{-}CH_2{-}C_6H_5}$$

I



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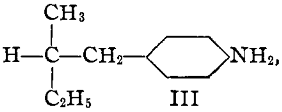

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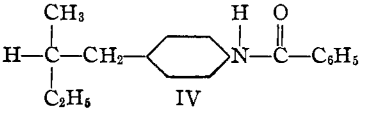
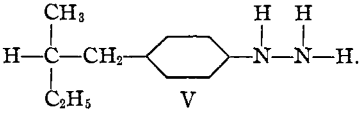


IV



V

Experimental Part

Benzylbutane.—This hydrocarbon has been isolated by Dumesnil[4]

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[1] The dissertation of which this paper is a condensation was presented by Charles N. Cameron, in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago.

[2] Glattfeld and Miller, THIS JOURNAL, **42**, 2314 (1920). Glattfeld and Sander, *ibid.*, **43**, 2675 (1921). Glattfeld and Sherman, *ibid.*, **47**, 1742 (1925).

[3] Glattfeld and Milligan, *ibid.*, **42**, 2322 (1920). Glattfeld and Wertheim, *ibid.*, **43**, 2682 (1921).

[4] Dumesnil, *Ann. chim. phys*, [9] **8**, 91 (1917).

as a by-product. Tafel and Hahl[5] and Tafel and Jürgens[6] obtained a compound which they considered to be benzylbutane. Later, however, Tafel[7] came to the conclsuion that the substance was not benzylbutane and this conclusion is concurred in by Braun and Deutsch.[8] No other references to this compound were found in the literature. Apparently, the work reported below constitutes the first direct attempt to prepare it.

Benzylbutane was prepared by five different methods, all of which yielded a product of the same boiling point, approximately 192° at atmospheric pressure.[9] This fact, together with the results of the analysis of a sample of the product and the nature of the methods of preparation, should leave little doubt that the substance prepared was actually benzylbutane.

1. **From Ethylmethylbenzylcarbinol,** $C_2H_5.CH_3.COH.CH_2C_6H_5$.—This carbinol has been prepared by Konowaloff[10] and by Davies and Kipping.[11] The carbinol was prepared in the present work by the Grignard method; from 100 g. of benzyl chloride, 50 g. (calcd., 56.9) of ethylmethylketone, and 20 g. of magnesium, there was obtained 86.8 g. of crude carbinol; b. p., 129–137°, at 30 mm.; av. yield in ten runs, 83%, calculated from the ketone used. The crude carbinol was dried and twice fractionated; 79 g. of pure product, b. p. 133–134° at 30 mm., was thus obtained.

Anal. Subs., 0.1342, 0.1403: H_2O, 0.1184, 0.1241; CO_2, 0.3954, 0.4136. Calcd. for $C_{11}H_{16}O$: C, 80.48; H, 9.75. Found: C, 80.35, 80.42; H, 9.87, 9.89.

Pure ethylmethylbenzylcarbinol is a colorless, mobile liquid, with a slightly sharp but pleasant odor. It is soluble in ligroin, alcohol and ether, but is insoluble in water. When heated to boiling at atmospheric pressure, it slowly loses water. The carbinol was reduced to benzylbutane by the method in which hydrogen iodide is used as the reducing agent and which has been found in previous work in this Laboratory to be satisfactory. Ninety-seven g. of the carbinol, b. p. 129–137° at 30 mm., 25 cc. of saturated hydrogen iodide solution, 20 g. of red phosphorus, and sufficient iodine, gave 70.9 g. of crude hydrocarbon; b. p., 190–198°, at atmospheric pressure. The yields of this fraction in ten runs averaged 80%, calculated from the carbinol used, and 67%, calculated from the ketone used at the start. Redistillation of the 70.9 g. of crude product gave 68 g. of pure hydrocarbon; b. p., 192–193°, at 715 mm.

Anal. Subs., 0.1520: CO_2, 0.4961; H_2O, 0.1491. Calcd. for $C_{11}H_{16}$: C, 89.16; H, 10.90. Found: C, 89.10; H, 10.90.

2. **From** *sec.*-**Butylphenylcarbinol,** $CH_3CH_2CH.CH_3.CHOH.C_6H_5$.—Dumesnil[12] found that this carbinol boiled at 120° at 13 mm. No other reference to it was found in the literature, but the intermediate magnesium-*sec.*-butyl bromide has been prepared.[13]

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[5] Tafel and Hahl, *Ber.*, **40**, 3317 (1907).

[6] Tafel and Jürgens, *Ber.*, **42**, 2556 (1909).

[7] Tafel, *Ber.*, **45**, 452 (1912).

[8] Braun and Deutsch, *Ber.*, **45**, 2180 (1912).

[9] "Atmospheric pressure," when used in connection with the report of original work in this paper, may be assumed to have been between 710 and 720 mm.

[10] Konowaloff, *Chem. Centr.*, **75** [I] 1496 (1904).

[11] Davies and Kipping, *J. Chem. Soc.*, **99**, 298 (1911).

[12] Ref. 4, p. 78.

[13] Freundler and Damond, *Compt. rend.*, **141**, 830 (1905); *Chem. Centr.*, **77** [I] 130 (1906).

From 38.6 g. of benzaldehyde, 50 g. of *sec.*-butyl bromide and 8.9 g. of magnesium, was obtained 36 g. of carbinol; b. p., 125–126°, at 15 mm.; yield, 60%. The carbinol was reduced by the hydrogen iodide method; 35 g. of carbinol gave 15 g. of hydrocarbon, presumably benzylbutane; b. p., 190–191°, at atmospheric pressure; yield, 47%, calculated from the carbinol.

3. **From *sec.*-Butyl Bromide, Benzyl Chloride and Sodium.**—The yield of benzylbutane by this method, calculated on the basis of the *sec.*-butyl bromide used, was 9.8%.

Fifty grams of *sec.*-butyl bromide, 46.2 g. of benzyl chloride, 16.8 g. of sodium and a few drops of ethyl acetate, in 85 cc. of ether, after refluxing on a water-bath at 60° for 30 hours, filtration, and fractionation of the filtrate at atmospheric pressure, gave 5.3 g. of material; b. p., 190–193°.

4. **From *sec.*-Butyl Bromide and Magnesiumbenzyl Chloride.**—The yield of benzylbutane, calculated on the basis of the *sec.*-butylbromide used, was 10%.

The "Grignard" formed from 50 g. of benzyl chloride in 200 cc. of ether and 9.5 g. of magnesium was refluxed for one hour and then cooled to room temperature. Addition of 46 g. of *sec.*-butyl bromide in 50 cc. of ether, refluxing at 60° for 50 hours, hydrolysis, extraction with ether, etc., followed by three fractionations at atmospheric pressure, gave 5 g. of material; b. p., 191–192°.

5. **From Benzyl Chloride and Magnesium *sec.*-Butyl Bromide.**—A yield of 18% of benzylbutane, calculated on the basis of the *sec.*-butyl bromide, was obtained in this experiment.

Fifty g. of *sec.*-butyl bromide, 8.5 g. of magnesium and 46 g. of benzyl chloride were used in this experiment. The quantities of solvent and all other details of procedure were the exact duplicate of those in the experiment just reported. There was finally obtained 9.8 g. of material; b. p., 191–192°, at atmospheric pressure.

***p*-Nitrobenzylbutane.**—The yield of nitro compound (obtained by the usual nitration procedure), b. p. 141° at 14 mm., in the experiment recorded below was 48% of that calculated from the benzylbutane used. This is fairly representative of the results usually obtained in this work.

Nitrobenzylbutane has a rather tenacious and penetrating, but not unpleasant, odor. It is soluble in ether, chloroform, acetone, methyl alcohol, ethyl alcohol and ligroin. It is colorless when freshly distilled, but rapidly turns yellow. The boiling point at 717 mm. is 257°, with rather extensive decomposition into black tarry products.

To 40 g. of benzylbutane, cooled to —5°, a cold mixture of 55 cc. of concd. nitric acid (d., 1.42) and 60 cc. of concd. sulfuric acid was added, in small portions. The temperature was maintained between 0° and —5°; under these conditions, the time of addition was 45 minutes. The temperature of the mixture was allowed to rise slowly to 35–40° and maintained for two hours. The mixture was cooled, diluted to 250 cc. and the nitro compound completely extracted with ligroin. The ligroin extract was washed and dried as usual. After removal of the ligroin at atmospheric pressure, the residue was fractionated at 14 mm. and yielded, after three fractionations, 25 g. of product; b. p., 141°.

Anal. Subs., 0.1645: CO_2, 0.4122; H_2O, 0.1161. Subs., 0.2042, 0.1829: N_2, 14.19 cc. (25°, 697.2 mm., corr.), 12.44 cc. (23°, 699.4 mm., corr.). Calcd. for $C_{11}H_{15}NO_2$: C, 68.38; H, 7.80; N, 7.29. Found: C, 68.34; H, 7.90; N, 7.30, 7.22.

The position of the nitro group was proved to be *para*. One g. of the nitro compound, 25 cc. of 5 *N* acetic acid and 10 g. of chromic acid gave, after refluxing for 26 hours followed by dilution with water, 0.81 g. of slightly yellow, fluffy crystals (calcd., 0.86 g.); m. p., 230–234°. The crystals, after purification by solution in sodium hydroxide and reprecipitation with hydrochloric acid, followed by a recrystallization from hot water, weighed 0.65 g. and melted sharply at 236°, which is the melting point of pure *p*-nitrobenzoic acid. A mixture of this material with a sample of pure *p*-nitrobenzoic acid also melted at 236°.

Aminobenzylbutane.—The average yield of crude amine, b. p. 133–140° at 15 mm., calculated on the basis of nitro compound, was 56.1%; calculated on the basis of the ethylmethylketone used at the start, the average yield in ten runs was 22%.

Pure aminobenzylbutane is a clear, colorless liquid when freshly distilled but rapidly takes on a yellow tint when exposed to the air. Its boiling point is 134–135° at 15 mm. It is very slightly soluble in water but quite soluble in ether, chloroform, ligroin, alcohol and acetone.

To a mixture of 41 g. of nitro compound and 72 g. of granulated tin, 135 cc. of hydrochloric acid (d., 1.18) was added, in portions. The mixture was refluxed for one hour and then subjected to steam distillation. The residue was made very faintly alkaline (an excess of alkali is to be avoided) and again subjected to steam distillation until the distillate was clear. This usually required two days. The distillate was extracted with ether, and the crude amine left after removal of the ether was fractionated twice. This process yielded 16.9 g. of material; b. p., 134–135°, at 15 mm.

Anal. Subs., 0.1900, 0.2308: N_2, 15.32 cc. (21°, 703.5 mm., corr.), 19.10 cc. (23°, 695.4 mm., corr.). Calcd. for $C_{11}H_{17}N$: N, 8.58. Found: 8.66, 8.73.

Benzoyl Derivative of Aminobenzylbutane.—The benzoyl derivative was prepared and found to melt at 118°.

Eight g. of aminobenzylbutane, 7 g. of benzoyl chloride and 10% sodium hydroxide, enough to make the mixture alkaline, were heated for 15 minutes; the crystals formed were washed first with sodium hydroxide and then with water. Two recrystallizations of the washed crystals from 60% alcohol yielded 6.8 g. of crystals; m. p., 118°. To effect the analysis of the product, samples were refluxed for eight hours with 0.5 *N* sodium hydroxide solution and the excess of sodium hydroxide was then determined by titration with 0.5 *N* hydrochloric acid.

Anal. Subs., 3.3376, 3.4150: 25.06, 25.68 cc. of 0.5 *N* NaOH. Calcd. for $C_{18}H_{21}NO$: 25.00 cc., 25.58 cc.

***dl*-Active-amylphenylhydrazine.**—This compound was prepared by the Fischer method. When freshly distilled it is a light yellow, rather viscous liquid which decomposes in the air, and also when distilled at 17 mm. At 8 mm. it boils without decomposition at 136–137°.

A solution of 20 g. of aminobenzylbutane in 36 cc. of hydrochloric acid (d., 1.18) and 60 cc. of water was diazotized with a solution of 9.5 g. of sodium nitrite. The diazotized solution was added, together with enough sodium hydroxide to keep the reaction mixture slightly alkaline, to a solution of freshly prepared sodium sulfite; this was acidified with 50% acetic acid, 14 g. of zinc dust was added and the mixture boiled for one hour in an open beaker. Filtration and cooling the filtrate yielded 24 g. of the sulfonate, a white, perfectly stable compound, crystallizing in plates. The hydrochloride was prepared as in previous work from the sulfonate (21 g. gave 14.5 g. of hydrochloride) and found to be a rather unstable substance when dissolved. A solution of 12 g. of the hydrochloride with alkali, extraction with ether and two fractionations of the residue at 8 mm. after removal of ether, etc. (air in all apparatus displaced by nitrogen during this work) gave 5.5 g. of hydrazine; b. p., 136–137°.

Anal. Subs., 0.2160, 0.2206: N_2, 30.98 (23°, 723.4 mm., corr.), 31.46 cc. (18°, 716 mm. corr.). Calcd. for $C_{11}H_{18}N_2$: N, 15.72. Found: 15.74, 15.76.

Resolution of *dl*-*p*-Aminobenzylbutane.—The resolution of the amine was accomplished by means of *d*-oxymethylenecamphor. The specific rotations of the amines obtained could not be pushed higher than +6.0° and —6.0° with this reagent.

The *d*-oxymethylenecamphor-*dl*-aminobenzylbutane was prepared by the same procedure as similar compounds previously reported, and was found to have a specific rotation in chloroform of about + 243°. A total of 468.8 g. of this compound was refluxed for two hours with seven parts of ligroin (b. p., 60–90°), the insoluble crystals were separated by filtration while hot (see Filtrate a, below) and washed with ligroin. This process yielded a total of 120.52 g. of crystalline material which was subjected to a process which included (a) two recrystallizations from methyl alcohol, followed by (b) three refluxings of the crystals so obtained in ligroin, followed by (c) a recrystallization of the crystals insoluble in hot ligroin from methyl alcohol. The crystals so obtained (wt., 62.2 g.) are called for purposes of reference "α-crystals"; m. p., 173°; $[\alpha]_D$ in chloroform, + 269°. Further recrystallizing from methyl alcohol and refluxing in ligroin, although often repeated, did not change these constants, and it was concluded that the crystals were pure.

The ligroin was completely removed from Filtrate a by distillation (finally at reduced pressure), the residue dissolved in methyl alcohol, and the solution cooled in ice. This procedure yielded a total of 94.4 g. of crystals, which were subjected to a process which included, in the order given: (a) recrystallization from methyl alcohol, (b) refluxing of the crystals so obtained with low-boiling ligroin and *rejection* of crystals left undissolved and (c) recrystallization of the crystals deposited by the ligroin, from methyl alcohol. The crystals thus obtained (wt., 42.4 g.) are called "β-crystals"; m. p., 122°; $[\alpha]_D$ in chloroform, + 251.0°. Efforts to change these constants by further repetitions of the process outlined above failed; they were apparently pure.

The oil obtained by the complete removal of solvent from the filtrate from the crude β-crystals (finally at reduced pressure) was freed of crystals by (a) filtration of the oil, (b) solution of the filtered oil in a small amount of methyl alcohol, and removal of solvent in a vacuum desiccator, (c) refiltration of the oil so obtained. This process was repeated until no crystals appeared in the oil; 110 g. of oil free from crystals was thus obtained.

_d-p_-Aminobenzylbutane.—Hydrolysis of both α- and β-crystals yielded the same aniline, which shows them to be isomeric forms of the same compound.

The usual process of hydrolysis was followed; 30 g. of α-crystals and 40 g. of β-crystals yielded, respectively, after two fractionations of the crude product, 6.2 g. of oil, b. p. 136° at 15 mm., and 8.5 g. of oil, b. p. 142–143° at 27 mm. Both oils had a specific rotation of + 6. 0°; each oil in a 0.5-dcm. tube, without solvent, gave α = + 3.0, (density assumed to be 1).

_l-p_-Aminobenzylbutane.—One hundred and ten g. of the non-crystalline *d*-oxymethylenecamphor amino compound yielded, on fractionation of the crude oil obtained by hydrolysis, 21.9 g. of oil; b. p., 140–141°, at 26 mm. A portion of this material in a 0.5-dcm. tube, without solvent, gave $\alpha = -3.04°$, whence $[\alpha]_D^{20}$ = approximately —6.0°.

Derivatives of the Active Aminobenzylbutanes.—The benzoyl derivatives of the two active anilines were prepared; that of the *d*-aniline was found to melt at 116° and to have a specific rotation, in chloroform, of + 6.66°; that of the *l*-aniline to melt at the same point and to have a specific rotation, in chloroform, of —6.98°. Both could be recrystallized, and thus purified, from 60% alcohol.

_d-p_-Active-amylphenylhydrazine.—This compound was prepared from the corresponding *d*-aniline by the Fischer method. The *d*-hydrazine sodium sulfonate was isolated as pure, white plates and converted into the hydrochloride. From 13 g. of *d*-aniline, 12 g. of vacuum-dry crystals of the hydrazine hydrochloride was finally obtained. The free hydrazine was obtained from the hydrochloride by hydrolysis with 20% sodium hydroxide. From 10 g. of the hydrochloride 4.6 g. of hydrazine, b. p. 139–140° at 9 mm., was finally obtained.

The *d-p*-active-amylphenylhydrazine is a viscous, light yellow oil when freshly distilled but turns brown rather rapidly. In an atmosphere of hydrogen or nitrogen it keeps its original color and so, presumably, is stable under these conditions. The specific rotation in ligroin was + 6.86°; that is, 2.1865 g. of substance, made up to 50 cc. with ligroin (b. p., 40–60°), gave $\alpha = +0.15$ in 0.5-dcm. tube.

***l-p*-Active-amylphenylhydrazine.**—Eighteen g. of *l-p*-aminobenzylbutane yielded 17.2 g. of the hydrazine hydrochloride. Thirteen g. of the hydrochloride yielded finally 5.2 g. of hydrazine; b. p., 139–140°, at 9 mm. A portion of this material had a specific rotation, in ligroin, of —6.42°; that is, 2.0231 of substance, made up to 50 cc. with ligroin (40–60°), gave $\alpha = -0.13°$ in 0.5-dcm. tube.

Summary

The object of the work reported in this paper was the preparation of an optically active hydrazine to be used for resolving purposes with the C_4-saccharinic acids which are being prepared and studied in this Laboratory. Two active hydrazines were prepared, but time in which to study their resolving power was lacking. This will be done as soon as opportunity offers.

The paper describes the preparation of *dl-p*-active-amylphenylhydrazine, $CH_3.C_2H_5.CH.CH_2.C_6H_4.NH.NH_2$, of its *dextro* and *levo* components and of the compounds isolated during the series of reactions necessary to produce the hydrazines. This series of reactions involved, in turn, the preparation of ethylmethylbenzylcarbinol, benzylbutane, nitrobenzylbutane, *dl*-aminobenzylbutane, and the resolution of the *dl*-amine. All of the compounds with the exception of ethylmethylbenzylcarbinol and benzylbutane are, so far as the authors are aware, new to the literature.

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