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

THE PREPARATION OF OPTICALLY ACTIVE HYDRAZINES.

I. THE PREPARATION OF *dl-p*-TRIMETHYLETHYL-PHENYLHYDRAZINE. THE ISOLATION OF PURE *d-p*-TRIMETHYLETHYL-ANILINE.

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In connection with the preparation of the optically-active C_4-saccharinic acids undertaken in this laboratory it was found that success depended in each case on the ability to resolve the *dl*-acid into the components by means of optically-active alkaloids. Such separations are usually very tedious, require many recrystallizations, and sometimes leave one in doubt as to whether a complete separation has actually been effected. It has seemed highly desirable, therefore, to make available other reagents than the alkaloids for such work.

Phenylhydrazine is known to form with many oxy acids easily crystallizable compounds, the phenylhydrazids. Some of the homologs such as tolyl-hydrazine form at times even more easily crystallizable compounds. It was thought, therefore, that an optically-active phenylhydrazine might be a possible substitute for the alkaloids when the latter do not give good results or when there is any doubt as to the completeness of the resolutions.

A search in the literature of optically-active hydrazines disclosed the fact that only 3 such compounds have been prepared, namely, *d*-α-optically-active amyl-phenylhydrazine;[2] *l*-α-ethyl-menthylhydrazine,[3] and *l*-menthylhydrazine.[4] The few known derivatives of these substances indicated that they might be very helpful in work with the oxyacids.

None of the hydrazines mentioned above was available, however, and it was decided to attempt the preparation of a number of racemic phenylhydrazines, and the resolution of these into active isomers in the hope that in this work some fairly easily-prepared active hydrazine would be discovered which could be used as a reagent in the separation of the saccharinic acids to supplement the alkaloids.

The present paper is the report of an attempt to prepare the first pair of these hydrazines decided upon, namely, the active trimethylethylphenylhydrazines. The hydrazine in its *dl* form was prepared, but all

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[1] The dissertation of which this paper is a condensation was presented by C. H. Milligan as part fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago. The original dissertation is on file in the University library.

[2] *Ber.*, **38**, 867 (1905).

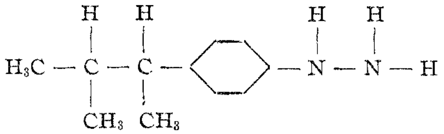
[3] *J. Russ. Phys. Chem. Soc.*, **27**, 534 (1896).

[4] *J. prakt. Chem.*, II, **52**, 425 (1895).

attempts to resolve it into the components failed, due largely, we think, to the instability of the free hydrazine in the air under ordinary conditions. The instability of the *dl* form suggested that the active components would also be very unstable and thus be useless as reagents. On the other hand, some of the derivatives of the *dl* form (see below) are perfectly stable compounds, and it was thought possible that the derivatives of the active forms would also be stable. We therefore decided to proceed with attempts to obtain the active forms. After much experimentation one of the amines, *d*-*p*-trimethylethyl-aniline, was obtained in the pure condition. It was intended to prepare from this the corresponding active phenylhydrazine by diazotization and reduction but time was lacking to complete this. This work will be continued, however, as soon as opportunity offers and attempts will be made to prepare other active phenylhydrazines.

Experimental Part.

This paper is a report on the preparation of *dl*-*p*-trimethylethyl-phenylhydrazine.



In order to prepare this substance, it was necessary first to prepare, in turn, the following corresponding compounds: (1)trimethylphenyl-ethylene; (2) trimethylethyl-benzene; (3) *p*-trimethylethyl-nitrobenzene; (4)*p*-trimethylethyl-aniline.

Only the second of these compounds is mentioned in the literature, under the name of *secondary*-amyl-benzene.[1] It seems probable in the light of our experiments, however, that the compound there discussed was *tertiary*-amyl-benzene.

For purposes of report, the work done and results obtained, will possibly be most easily followed if we discuss, in the order in which they are listed above, the preparation of the necessary compounds.

1. **Trimethylphenyl-ethylene.**—This compound was prepared from magnesium *iso*-propyl iodide and acetophenone by a modification of the method used by Klages[2] devised by Grignard.[3] The magnesium *iso*-propyl iodide was made in the usual way with all ordinary precautions by carefully dropping *iso*-propyl iodide into ether containing magnesium turnings. The ether was stirred constantly by a mechanical stirrer and kept cold. At the end of the reaction the solution was allowed to come to the temperature of the room and was then forced away from the re-

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[1] *Ann. Chim. phys.*, [6] 1, 434 (1884); *Monatsh.*, 9, 622 (1888).

[2] Klages, *Ber.*, 35, 2641 (1902); 33, 439 (1900).

[3] Grignard, *Compt. rend.*, 130, 1322 (1900).

maining magnesium turnings and into another flask properly fitted up and protected against moisture, etc.

Acetophenone was then carefully dropped into the solution with stirring. The end of the reaction was reached when the heat of reaction was not sufficient to keep the solution boiling. We found this condition to prevail after about $^1/_2$ the theoretical amount of acetophenone had been added. It had been found in preliminary experiments that further addition of acetophenone did not increase the yield and could be recovered unchanged. The mixture was then kept at the boiling temperature, with stirrer operating, for from 2 to 3 hours. The ether was then distilled off, after which the thick pasty residue was heated on the boiling water-bath for from 4 to 6 hours. The mass was then allowed to cool, the stirrer started and water carefully added from the dropping funnel. When all the mass had been completely hydrolyzed, the mixture was extracted 3 or 4 times with ether. The ether solution was dried with sodium sulfate and fractionated. The part which boiled between 175–200° was collected. This fraction weighed 125 g. when 100 g. of acetophenone was used.

In order to isolate the hydrocarbon in a pure state, this fraction (175–200°) was refractionated and the part which boiled at 187–188° collected. This fraction, in alcohol, was treated with phenylhydrazine, and the hydrazone of acetophenone, formed on standing, was removed by filtration. The filtrate was fractionated at 18 mm. pressure and the fraction of boiling range 75–95° was dissolved in a little dry ether and treated with dry hydrogen chloride to remove phenylhydrazine. The filtrate from the phenylhydrazine hydrochloride was subjected to repeated fractionation and gave finally 5.6 g. of a colorless liquid which boiled at 187–188°. The analysis of samples of this liquid showed that the compound thus prepared was not methyl-*iso*-propyl-phenyl-carbinol, but trimethyl-phenyl-ethylene.

Subs., 0.1167, 0.1217: CO_2, 0.3871, 0.3982; H_2O, 0.0989, 0.1032.

Calc. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.60, 90.70; H, 9.40, 9.44.

2. **Trimethylethyl-benzene.**—The next step was to reduce the unsaturated hydrocarbon to the saturated one. One hundred and twenty-five g. of the crude trimethyl-phenyl-ethylene (boiling range 175–200°) was treated, in a flask fitted with a wide reflux condenser, with 30 g. of red phosphorus and 50 cc. of a saturated solution of hydrogen iodide. The reaction mixture was heated to boiling and iodine added carefully in small portions through the condenser until fumes due to escaping hydrogen iodide were visible at the top of the condenser. The mixture was kept boiling until the color due to iodine in the hydrocarbon disappeared. The reaction mixture was now subjected to distillation. The distillate formed 2 layers of almost equal volume of which the lower was hydriodic acid, the upper almost pure hydrocarbon. The layers were separated, the hydriodic acid

returned to the reaction flask, and again distilled. This process was repeated as long as any hydrocarbon separated in the distillate.

The hydrocarbon was then washed with water and dil. sodium hydroxide solution and dried first by calcium chloride and finally over melted sodium which removed also the last trace of iodine, and then fractionated. That portion (40 g.) boiling at 180–190° was used for the subsequent preparations, a part being refractionated a number of times in order to get a pure product. The fraction boiling at 186–188° was considered pure.

Analysis of a sample of this product (186–188°) gave the following results:

Subs., 0.1688: CO_2, 0.5503; H_2O, 0.1602.

Calc. for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.9; H, 10.69.

3. ***p*-Trimethylethyl-nitrobenzene.**—Forty g. of trimethylethyl-benzene boiling at 180–190° was dissolved in 24 g. of glacial acetic acid and added dropwise to a constantly stirred mixture of 40 g. of glacial acetic acid[1] and 88 g. of fuming nitric acid kept at 35–40°. After the addition, the contents of the flask were kept at 50° for 3 hours, cooled and poured into twice the volume of cold water. The nitro compound thus obtained was extracted with low-boiling ligroin, and the ligroin extract repeatedly shaken with water and finally with a small amount of sodium carbonate solution and then dried over sodium sulfate and fractionated. A yield of 46 g. of nitro compound, boiling range 140–155° at 20 mm. pressure, was obtained.[2] After a number of fractionations, this gave 30 g. boiling at 152–154° under 20 mm. pressure. This fraction was considered pure substance and was used for analysis and for the determination of the position of the nitro group.

Subs., 0.2147: CO_2, 0.5423; H_2O, 0.1508.

Subs., 0.2557, 0.2835: N_2, 18.2 cc. (29° and 737.4 mm.), 19.1 cc. (25° and 736.9 mm.).

Calc. for $C_{11}H_{15}NO_2$: C, 68.38; H, 7.80; N, 7.29. Found: C, 68.37; H, 7.8; N, 7.51, 7.44.

Position of the Nitro Group.—One g. of the compound was treated in the usual way[3] with 10 g. of chromic acid dissolved in 25 cc. of 5 *N* acetic acid. This mixture was allowed to stand for 24 hours on a steam-bath, and gave, after filtration, solution in sodium hydroxide and reprecipitation with hydrochloric acid, 0.7 g. of crude substance with melting range 228–230°. After recrystallization from water, the crystals had a

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[1] *Ann.*, 327, 224 (1903).

[2] From the fraction which had the boiling range 130–132° there was obtained a small amount of white crystalline solid which had a melting point of 114–115°. In repetitions of the nitration crystals of the same melting point were usually obtained from this fraction. The almost invariable production of this compound led to the conclusion that it was the *o*-nitro-compound,

[3] Weyl, "Die Methoden der Organischen Chemie," **1909**, Vol. I, 518.

sharp melting point of 236°. A sample of *p*-nitrobenzoic acid at hand melted sharply at 236°. Furthermore a mixed melting-point determination proved the two to be identical. The compound oxidized, therefore, had the nitro group in the *para* position to the trimethylethyl group.

4. ***p*-Trimethylethyl-aniline.**—A mixture of 23 g. of the nitro compound, 36 g. of tin and 75 cc. of conc. hydrochloric acid was warmed to 100°, kept near this temperature, and very frequently shaken until the odor of the nitro compound had almost entirely disappeared. The remaining nitro compound was removed by steam distillation. The residue was made alkaline with sodium hydroxide, although a large excess of alkali is to be avoided. The aniline was extracted with low-boiling ligroin, dried over anhydrous sodium carbonate, and fractionated repeatedly at 18 mm. pressure. There was obtained finally 16 g. of a colorless oil of boiling range 129–131° at 18 mm. pressure.

That the substance was the pure aniline was proved by the analysis of samples for nitrogen.

Subs., 0.1853, 0.2225 g.: N_2, 14.5 cc. (22° and 736.6 mm.), 17.46 cc. (19° and 731.3 mm.).

Calc. for $C_{11}H_{17}N$: N, 8.57. Found: 8.76, 8.75.

5. ***dl-p*-Trimethylethyl-phenylhydrazine.**—This compound was made by a modification of the method of Fischer.[1] Fifteen g. of the aniline was diazotized, forming a gelatinous mass which was added in small amounts to a cold solution of sodium sulfite. A light yellow crystalline solid was obtained. The cold reaction mixture was treated with zinc dust and acetic acid until the yellow color had disappeared. The sulfonate thus obtained was filtered off, together with the excess of zinc dust, etc., and purified by crystallization from hot water, giving 19 g. of white plates which decomposed when heated to 190°.

The hydrochloride of the hydrazine was prepared by dissolving the sulfonate in a small amount of boiling water and passing hydrogen chloride into this hot solution. As the solution cooled, the hydrochloride crystallized out in rosets of fine white needles which were perfectly stable when dry.

The hydrochloride was dissolved in water and treated with sodium hydroxide. The solution was extracted with ether and the ether removed by distillation. The hydrazine separated out in fine needles as the residue cooled. This residue was subjected to distillation at 9 mm. pressure in an atmosphere of hydrogen. There was thus obtained 9 g. of a slightly yellow compound of boiling range 147–150° at 9 mm. which soon entirely solidified. The solid had a melting point of about 60°, and was soluble in alcohol, ligroin, benzene but less soluble in ether than in any of these. In contact with the air a part of this solid soon turned red and in the

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[1] *Ann.*, **190**, 78 (1877).

course of a few hours liquefied. When this substance is kept in an atmosphere of hydrogen, decomposition takes place very slowly, if at all.

Samples of this solid were quickly weighed and analyzed, with the following results:

Subs., 0.2085, 0.0698 g.: N_2, 28 cc. (19° and 735.2 mm.), 14.9 cc. (28° and 730.25 mm.).

Calc. for $C_{11}H_{18}N_2$: N, 15.78. Found: 15.62, 15.66.

As stated above, it was found impossible to resolve the hydrazine into the optical components. Several attempts were made to do this and some data have been accumulated. It was shown, for instance, that the hydrazine reacts with the sugars to form hydrazones or osazones and that it reacts with oxyacids such as *l*-erythronic, *d*-mannonic and *d*-gluconic acids. From the study of these derivatives, however, it did not seem likely that the racemic hydrazine could be resolved completely by the use of such compounds although some evidence of resolution was obtained. The hydrazine forms a particularly stable and well-crystallizing compound, m. p. 160–163°, presumably the hydrazid, with *d*-galactonic lactone.

The Resolution of *dl-p*-Trimethylethyl-aniline.

The resolution was finally accomplished by the use of *d*-oxymethylene camphor[1] according to the method of Pope and Read,[2] as follows.

Sixteen and five-tenths g. of the aniline was dissolved in 25 cc. of 30% acetic acid and added slowly and with shaking to a solution of 17.5 g. of *d*-oxymethylene camphor in 70 cc. of methyl alcohol. The yellow oil which separated out as a lower layer was shaken a number of times with water, then dissolved in as small a quantity of boiling alcohol as possible and reprecipitated from the cold solution with water. The liquid was decanted after the pasty mass had settled out completely. The latter was stirred thoroughly with dil. sodium hydroxide solution then with water and finally taken up in a little alcohol, and placed in a vacuum desiccator over sulfuric acid. After having stood for 2 days, the residue was a semicrystalline mass weighing 30.9 g. The specific rotation of this—presumably a mixture of equal parts of the isomers—was found to be +257.5°.

Subs., 0.6922 in 15.68 g. of 95% alcohol gave in a 2 dcm. tube α +17.82.

The mass was now treated with ligroin until most of the gummy material was removed and there remained a slightly yellow solid, which, after having been thoroughly air-dried, weighed 18.9 g. and which had a melting range of 156–158°. This product was twice recrystallized from boiling alcohol, and was then perfectly white. It weighed 8.2 g. A portion of it was dissolved in 95% alcohol. The specific rotation of this solution was determined as +300°.

Subs., 0.6540 in 20 cc. of 95% alcohol gave in a 2 dcm. tube α +19.69° at 25–26°.

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[1] *Ann.*, **281**, 333 (1894).

[2] Pope and Read, *J. Chem. Soc.*, **95**, 171 (1909).

This product was recrystallized 3 times from alcohol. The specific rotation was taken after each recrystallization and always found to be +300°, indicating that the compound was pure. The product now melted sharply at 168°.

Pure *d-p*-**Trimethylethyl-aniline.**—Forty g. of the product obtained as indicated above was heated at boiling for 30 hours with 225 cc. of conc. hydrochloric acid and then cooled. The liquid was decanted from the solid and evaporated to dryness on a steam-bath. The total solid thus obtained was treated with 200 cc. of strong sodium hydroxide solution and subjected to steam distillation as long as any oil came over. The distillate was made acid and evaporated on the steam-bath, the aniline set free again and distilled with steam, this process being repeated several times in order to purify the aniline. There was finally obtained 11.6 g. of the hydrochloride. This was treated with an excess of sodium hydroxide solution, the aniline thoroughly extracted with low-boiling ligroin and the ligroin solution dried with sodium carbonate. The ligroin was removed by distillation and the residue distilled at 24 mm. pressure. The distillate had a boiling range of 139–140° and weighed 8.6 g. When placed in a one dcm. tube, this oil gave α +0.96°. The hydrochloride was prepared by dissolving the aniline in ligroin and passing in hydrogen chloride. An air-dry sample of the hydrochloride thus prepared had a specific rotation of +0.974.

Subs., 1.0294 in 20 cc. of water containing 3 drops of conc. hydrochloric acid, gave in a 2 dcm. tube α + 0.10.

l-p-**Trimethylethyl-aniline.**—We were unable to obtain the more soluble derivatives of the aniline with *d*-oxymethylene camphor in the crystalline condition. When the filtrates from the crystalline derivative were evaporated to dryness and dried over sulfuric acid *in vacuo*, a few more crystals of the less soluble isomer separated. These were removed by treatment of the mass with ligroin, in which the crystals did not dissolve. A gum was finally obtained which did not deposit crystals on standing in a vacuum over sulfuric acid for 10 days, $[\alpha]_D^{20}$ +229, in 95% alcohol. The aniline from this, obtained as above, boiled at 139–140° and gave α +0.76 when placed in a one dcm. tube. The hydrochloride gave $[\alpha]_D^{20}$ +0.565. These figures show that the aniline was not perfectly pure.

Summary.

dl-p-Trimethylethyl-phenylhydrazine, and *dl-p*-trimethylethyl-aniline have been prepared, some of their properties determined and the latter partly resolved into the two optical isomers. The hydrazine was prepared from acetophenone and magnesium-isopropyl-iodide and making, successively, trimethyl-phenyl-ethylene, trimethylethyl-benzene, *p*-trimethylethyl-nitrobenzene, *p*-trimethylethyl-aniline.

CHICAGO, ILLINOIS.