5.0; OCH_3 11.0.) The product was acetylated in the usual manner to yield on crystallization from alcohol and ether **3(or 2)-acetyl-4,6-benzylidene-2(or 3)-acetamido-α-methylidoside** (55% yield); m. p. 188°; $[\alpha]^{12}D$ +43.4° (*c* 1.3, chloroform) (Found: N, 3.8. $C_{18}H_{23}O_7N$ requires N, 3.9) and **3(or 2)-acetyl-4,6-benzylidene-2(or 3)-acetamido-α-methylgalactoside** (8% yield; m. p. 260°; $[\alpha]^{12}D$ +70.3° (*c* 0.8, chloroform). Found: N, 3.9).

Partial Hydrolysis of 3(or 2)-Acetyl-4,6-benzylidene-2-(or 3)-acetamido-α-methylidoside.—The material was treated with warm hydrochloric acid, heating being continued for two hours, to give an 81% yield of **3(or 2)-acetyl 2(or 3)-acetamido-α-methylidoside** (sirup, $[\alpha]^{16}D$ −36.0° (*c* 3.3, methyl alcohol). (Found: N, 4.9. $C_{11}H_{19}O_7N$ requires N, 5.0.)

Summary

A number of new amino sugar derivatives have been prepared by action of aqueous ammonia on the 2,3-anhydro ring of allose, mannose and gulose (or talose) derivatives. In each case, two *trans* isomers were formed, the altroside configuration greatly predominating in reactions with the first two compounds.

WILMINGTON, DEL. RECEIVED OCTOBER 2, 1942

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Synthesis of Polyenes. III. A New Synthesis of Diethylstilbestrol

BY M. S. KHARASCH AND MORTON KLEIMAN[1]

The *trans*-4,4′-dihydroxy-α,α′-diethylstilbene, now commonly referred to as diethylstilbestrol, was first synthesized in 1938 by Dodds and coworkers[2] by the following series of reactions

$$\text{Anisaldehyde} \xrightarrow{\text{KCN}} \text{Anisoin} \xrightarrow[\text{acetic acid, } 100^\circ\text{, 24 hr.}]{\text{Zn dust}}$$

$$\text{Desoxyanisoin} \xrightarrow[\text{EtI}]{\text{EtONa}} \text{Ethyl desoxyanisoin} \xrightarrow{\text{EtMgBr}}$$

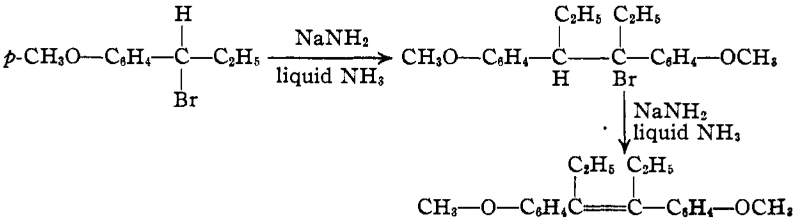
$$\text{3,4-Bis-(}p\text{-anisyl)-3-hexanol} \xrightarrow[\text{or } KHSO_4]{PBr_3}$$

$$\text{Diethylstilbestrol dimethyl ether} \xrightarrow[\text{alcohol, } 205^\circ]{\text{KOH}} \text{Diethylstilbestrol}$$

Numerous workers[3] have since attempted to improve upon this method of preparation; however, all the other suggested syntheses are equally laborious and, in our estimation, inferior to Dodds' method from a practical standpoint (availability of raw materials, etc.).

In this Laboratory, the condensation of allyl chloride and β-methylallyl chloride to hexatriene[4a] and 2,5-dimethylhexatriene,[4b] respectively, under the influence of sodamide in liquid ammonia has been studied exhaustively. The hypothesis evolved to account for these reactions suggested that a molecule such as anethole hydrobromide should react with sodamide or potassium amide to yield the products shown below.

Because of the possibility of side reactions, it was considered desirable to establish first the validity of the general method by the syntheses of the α,α′-dimethyl- and α,α′-diethylstilbenes from α-chloroethylbenzene and α-chloropropylbenzene, respectively.



$$p\text{-}CH_3O\text{—}C_6H_4\text{—}\overset{H}{\underset{Br}{C}}\text{—}C_2H_5 \xrightarrow[\text{liquid } NH_3]{NaNH_2} CH_3O\text{—}C_6H_4\text{—}\overset{C_2H_5}{\underset{H}{C}}\text{——}\overset{C_2H_5}{\underset{Br}{C}}\text{—}C_6H_4\text{—}OCH_3$$

$$\xrightarrow[\text{liquid } NH_3]{NaNH_2} CH_3\text{—}O\text{—}C_6H_4\overset{C_2H_5}{C}\text{==}\overset{C_2H_5}{C}\text{—}C_6H_4\text{—}OCH_3$$

trans and *cis* forms

α-Chloroethylbenzene, obtained by the addition of dry hydrogen chloride to styrene at low temperature, was treated with sodamide in liquid ammonia solution. When the sodamide was present in large excess, as was the case when the organic reactant was slowly added to the suspension of sodamide in liquid ammonia, a 40% yield of *cis*-dimethylstilbene was isolated. High boiling oils, the products of side reactions and poly-

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(1) This paper is part of a dissertation submitted by Morton Kleiman to the Faculty of the Division of the Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy, March, 1942.

(2) Dodds, Goldberg, Lawson and Robinson, *Nature*, **141**, 247 (1938).

(3) (a) Kerschbaum, Kleedorfer, Prillinger, Wessely and Zajic, *Naturwiss.*, **27**, 131 (1939); (b) Wessely and Kleedorfer, *ibid.*, **27**, 567 (1939); (c) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940); (d) Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 93 (1940); (e) Kuwada, Sasagawa and Nisikawa, *ibid.*, **60**, 553 (1940); (f) Peteri, *J. Chem. Soc.*, 833 (1940).

(4) (a) Kharasch and Sternfeld, THIS JOURNAL, **61**, 2318 (1939); (b) Kharasch, Nudenberg and Sternfeld, *ibid.*, **62**, 2034 (1940).

TABLE I

The conclusions of the petrographer[8] are that substances I and II are distinct from one another and from substances III and III′. Substances III and III′ are probably identical.

Substance	Crystallographic data	Optical data				
		Optical character	$2V$	Np	Ng	Remarks
I	Orthorhombic	Biaxial	Near 70° (+)	>1.54, near 1.59	>1.73	
II	Monoclinic	Biaxial	Small, near 15° (+)	. . .	. . .	Perfectly centered acute bisectrix figures, $Z = b$
III	Monoclinic, twinning common, crystals acicular	Biaxial	Very large, near 80–90°	<1.54, >1.52	>1.69	
III′	Monoclinic, twinning common, crystals tabular	Biaxial	Very large, near 80–90°	<1.54	Near >1.65	

merization, were also obtained. No *trans*-dimethylstilbene was found among the products. When the order of addition was reversed, *i. e.*, when the sodamide was added to a solution of the organic reactant in liquid ammonia, 2-chloro-2,3-diphenylbutane was found in the reaction product, indicating the removal of only one molecule of hydrogen chloride. This substance, upon repeated distillation, lost a molecule of hydrogen chloride and was partially converted to *trans*-α,α'-dimethylstilbene. Analysis for halogen and conversion of the substance into 2,3-diphenylbutane by reduction with sodium in liquid ammonia established the identity of the intermediate chloro compound.

The synthesis of α,α'-diethylstilbene was attempted by the same method, namely, by treating α-chloropropylbenzene with sodamide in liquid ammonia. The addition of sodamide to a liquid ammonia solution of α-chloropropylbenzene yielded only a small amount of the intermediate 3-chloro-3,4-diphenylhexane and a large quantity of an unidentified oil. The presence of the small amount of 3-chloro-3,4-diphenylhexane was established by reducing the compound to diphenylhexane with sodium in liquid ammonia.

With the reverse order of addition, *i. e.*, when the α-chloropropylbenzene was added to an excess of sodamide in liquid ammonia, the reaction product contained not only the intermediate 3-chloro-3,4-diphenylhexane, but also an unsaturated oil at first believed to be diethylstilbene.

These observations indicated that, by reaction of α-chloropropylbenzene with sodamide in liquid ammonia, a condensation similar to that which occurs with α-chloroethylbenzene had taken place. The exact structure of the unsaturated oil formed was not ascertained,[4a] however, because the substance could not readily be separated from the 3-chloro-3,4-diphenylhexane also formed in the reaction. Moreover, there is no agreement in the literature as to the physical constants of diethylstilbene,[5,6,7] nor have its *cis* and *trans* forms been differentiated and characterized. Hence, it was also impossible to know whether the dibromo derivative obtained was the racemic or *meso* compound. Subsequent detailed study of the unsaturated reaction product obtained by similar condensation of anethole hydrobromide shed more light upon these questions of structure.

Anethole hydrobromide rather than the hydrochloride was used for condensations with sodamide in liquid ammonia because anethole is readily polymerized when treated with dry hydrogen chloride, even at low temperatures. When anethole hydrobromide was treated with an excess of sodamide in liquid ammonia, an unsaturated product (I) containing no halogen was isolated in 40% yield. This compound, after careful purification, melted at 120.5°. The *cis* form of diethylstilbestrol dimethyl ether is an oil. Addition of the *trans* form (II) (m. p. 124°) to (I) caused a significant lowering of the melting point of the latter. The non-identity of the two substances is confirmed by the comparison of their absorption spectra (Fig. 1) and their crystal forms (Table I). But when compound (I) was hydrogenated, the calculated amount of hydrogen was consumed, and a practically quantitative yield of dihydrodiethylstilbestrol dimethyl ether (III) (m. p. 142°) was obtained. This substance did not lower the

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[4a] The possibility discussed in connection with formula (C) for compound (I), of a cyclic rather than an olefinic structure, may well be considered. The same applies to some of the supposed diethylstilbenes reported in references 5, 6 and 7. This problem is being further investigated.

(5) Rising and Zee, THIS JOURNAL, **50**, 1706 (1928), described diethylstilbene as a solid, m. p. 89–90°, and its dibromide as a solid, m. p. 122–123°. The dibromo derivative obtained in this study melted at 166.5°.

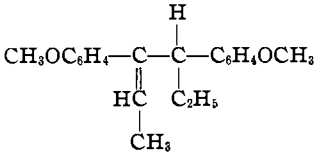
(6) Ramart-Lucas and Anagnostopoulas, *Bull. soc. chim.*, [4] **43**, 1356 (1928), report that diethylstilbene is an oil, b. p. 168° (14 mm.).

(7) Carlisle and Crawfoot, *J. Chem. Soc.*, 6 (1941), give the melting point of diethylstilbene as 70–71°.

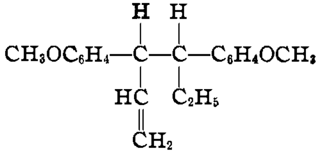
(8) Dr. F. J. Pettijohn (Department of Geology, University of Chicago) to whom sincere thanks are here expressed.

melting point of a known sample (III′) of dihydrodiethylstilbestrol dimethyl ether.

Since substance (I) is not diethylstilbestrol dimethyl ether, but gives dihydrodiethylstilbestrol dimethyl ether when hydrogenated, its formula must be

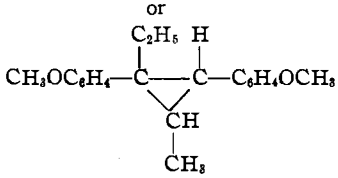


Two racemic pairs
cis and *trans* (A)



Two racemic pairs (B)
3,4-di-(*p*-methoxyphenyl)-hexene-1

or



(C) 1-methyl-2,3-di-(*p*-methoxyphenyl)-3-ethylcyclopropane

Both the *cis* and *trans* racemic forms of (A) have been described:[3b] one is an oil; the other, a solid melting at 50°. Formula (B) or (C) is therefore assigned to (I). A compound of either formula should have an absorption spectrum very much like that of dihydrodiethylstilbestrol dimethyl ether. Figure 1 shows this to be the fact.

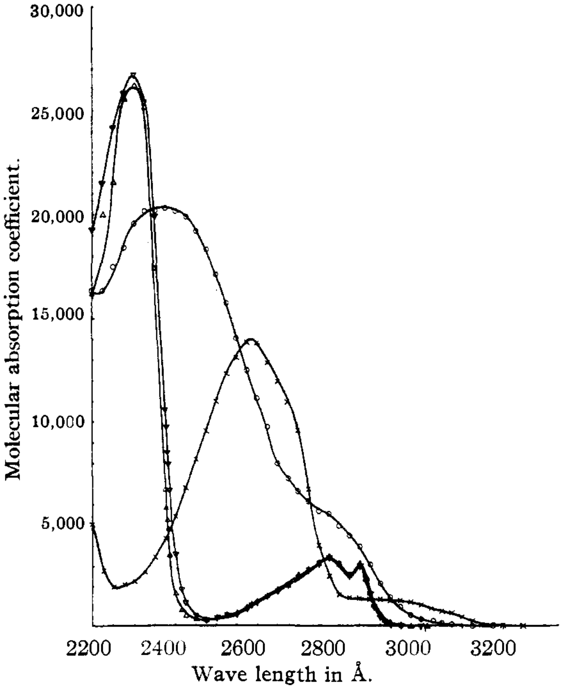


Fig. 1.—Absorption spectra: Δ, dihydrostilbestrol dimethyl ether; ∇, (Compound (I)); O, diethylstilbestrol dimethyl ether; X, anethole.

Two hydrogenation products of (C) are geometrically possible, but energetic effects of substituents would probably favor one over the other.

Demethylation of (I) by potassium hydroxide in glycol at 225° gave two products, a solid and an oil. The solid was identified as the 4,4′-dihydroxy-α,α'-diethylstilbene (diethylstilbestrol). When it was mixed with an authentic sample of this substance, its melting point was not depressed, nor was there any depression in the melting points of mixtures of the diacetate and the dibenzoate of this substance with authentic samples of diethylstilbestrol diacetate and dibenzoate, respectively. As a further confirmation, the absorption spectrum of the diethylstilbestrol derived from (I) was found to be identical with that of an authentic sample of diethylstilbestrol (Fig. 2).

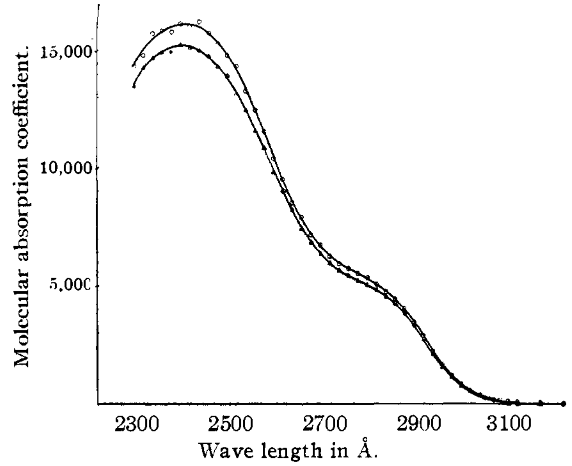


Fig. 2.—Absorption spectra: ⊙, highly purified sample of diethylstilbestrol; ◬, sample of diethylstilbestrol obtained from demethylation of compound (I).

These results suggest that in the conversion of (II) to diethylstilbestrol, rearrangement of the double bond or cleavage of the cyclopropane ring and demethylation occurred simultaneously.

When two moles of anethole hydrobromide in liquid ammonia was treated with one mole of sodamide, followed by one mole of sodium, an 80% yield of the corresponding amine (1-amino-1-[*p*-methoxyphenyl]-propane) was obtained.

Experimental

Preparation of α-Chloroethylbenzene.—Fifty grams of redistilled styrene (b. p. 40° (12–13 mm.)) was cooled to

−80° and dry hydrogen chloride was passed in until the gain in weight was 28 g. The reaction mixture was warmed slowly to room temperature and was then distilled at 11 mm. pressure (b. p. 73°). The yield of α-chloroethylbenzene was 48.5 g. (68%).

Preparation of 2-Chloro-2,3-diphenylbutane.—Ten grams of α-chloroethylbenzene (0.07 mole) was dissolved in liquid ammonia, and 4 g. of sodamide[9] (0.1 mole) added in portions. The reaction mixture was vigorously agitated. At the end of one and one-half hours, the ammonia was removed; the residue was taken up in water and extracted several times with ether. The combined ether extracts were dried over calcium chloride and, after removal of the ether, distilled at low pressure. After several distillations, a fraction boiling at 147–148° (11 mm.) was obtained. This oil was shown to contain 2-chloro-2,3-diphenylbutane by analysis for halogen and by the fact that when treated with sodium in liquid ammonia, it gave 2,3-diphenylbutane (m. p. 124°).

A portion of the above oil lost hydrogen chloride after repeated distillation *in vacuo*, and upon standing, deposited crystals of *trans*-dimethylstilbene. The latter, after crystallization from methyl alcohol, melted at 105°.

Preparation of *cis*-Dimethylstilbene.—Twenty grams of α-chloroethylbenzene, diluted with an equal volume of toluene, was added slowly to a vigorously agitated suspension of 24 g. of sodamide[9] in liquid ammonia. When the first portion of organic reactant was added, a deep red color developed; this color was discharged by each subsequent portion, and each time gradually reappeared in the reaction mixture. At the end of two hours, the ammonia was removed; the residual reaction mixture was first treated with water and then extracted several times with toluene. The extract was dried over calcium chloride, filtered, and fractionated at 10 mm. pressure. The fraction boiling at 135–156° was crystallized from methanol; it yielded 6 g. (40%) of *cis*-dimethylstilbene, m. p. 66–67°.

Preparation of α-Chloropropylbenzene.—Phenylethylcarbinol was prepared (according to Meisenheimer[10]) from ethylmagnesium bromide and benzaldehyde. The carbinol thus obtained was treated with dry hydrogen chloride at 0° for one hour and allowed to stand at room temperature for twenty-four hours. The layer of water formed in the reaction was then separated. The oil was dried over calcium chloride and twice distilled, b. p. 85–87° (15 mm.). The yield of the chloropropylbenzene (based upon the amount of carbinol used) was 55%.

Reaction of α-Chloropropylbenzene with Sodamide in Liquid Ammonia.—To a vigorously stirred suspension of 0.3 mole of sodamide in liquid ammonia was added drop by drop 15 g. (0.1 mole) of α-chloropropylbenzene diluted with an equal volume of toluene. During the addition, there was developed a light purple color which gradually became darker, finally changing to a deep orange-red. The stirring was continued for one-half hour after the addition of the organic reactant had been completed; then the ammonia was removed by evaporation. The reaction mixture was treated with small portions of water, chilled in an ice-salt bath, and acidified. The toluene layer was next separated. Several extractions with toluene were made, and the combined toluene extracts were dried over calcium chloride. The toluene was removed at reduced pressure, and the residue distilled at 12 mm. Small amounts at the beginning and at the end of the distillation were discarded. Most of the material distilled at 162–164°. Eleven grams of product was obtained.

When a portion of this material was dissolved in carbon tetrachloride and treated with a solution of bromine in the same solvent, the bromine was rapidly decolorized. Evaporation of the solvent left a solid residue which was crystallized several times from high-boiling ligroin. The compound thus obtained melted at 166.5°.

Anal. Calcd. fo $C_{18}H_{20}Br_2$: Br, 40.36. Found: Br, 40.66.

Hydrogenation of a second portion of the reaction product in ethyl alcohol over platinum black yielded a 3,4-diphenylhexane, m. p. 88.5–89°. Treatment of a third portion of the reaction product with sodium in liquid ammonia also yielded 3,4-diphenylhexane. The reaction product was thus shown to contain an unsaturated compound, supposedly diethylstilbene, and the intermediate diphenylchlorohexane.

Synthesis of Compound (I).—Fifty grams of redistilled anethole, diluted with an equal volume of toluene and kept at −80°, was allowed to absorb 27.5 g. of dry hydrogen bromide (one to one mole ratio). Some of the anethole crystallized, but soon redissolved. To remove any excess hydrogen bromide, the reaction vessel was first evacuated by a water pump, then a stream of dry carbon dioxide was passed through the mixture maintained at −80°. The toluene solution of anethole hydrobromide was then added in small portions to a suspension of 40 g. of amide in about 700 cc. of liquid ammonia (contained in an unsilvered Dewar flask). The mixture was stirred vigorously. The following color changes were observed: the mixture was yellowish-green after the first addition, but became deep red in a few minutes; each subsequent addition discharged the color, and the same sequence of color changes again took place. After all the organic reactant had been added and the reaction mixture had stood for fifteen minutes, the ammonia was removed; the residue was taken up in water. The well-cooled water solution was acidified and extracted four times with ethyl acetate. After the combined extracts had been dried over calcium chloride, the drying agent was removed by filtration. The solvents were distilled from the filtrate at reduced pressure, and the remaining oil was dissolved in hot methyl alcohol. Upon cooling, a crystalline material (17 g.) was obtained. This amount corresponds to 34% of the calculated yield. Higher yields, up to 40%, were obtained in some experiments. The melting point of the material was 118°. After repeated recrystallization from methanol, the substance melted at 120.5°. The residual products of this reaction were polymerized anethole and a high-boiling oil. In one experiment, ether was added to this residue, and 3.3 g. of a crystalline substance was obtained. This substance (m. p. 209–210°; mol. wt. 870) is probably a polymer containing six molecules of anethole.

Hydrogenation of Compound (I).—One-half gram of compound (I) dissolved in methyl alcohol was hydrogenated with the aid of platinum black catalyst. The calculated amount of hydrogen was absorbed, and recovery

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(9) Vaughn, Vogt and Nieuwland, This Journal, **56**, 2120 (1934).

(10) Meisenheimer, *Ann.*, **446**, 80 (1926).

of the hydrogenated product was practically quantitative. After crystallization from methanol, 0.45 g. of material was obtained, m. p. 142°.

Demethylation of Compound (I): Preparation of Diethylstilbestrol.—Two grams of compound (I), 5 g. of potassium hydroxide, and 30 cc. of ethylene glycol were sealed in a heavy Pyrex bomb tube at 10^{-5} mm. pressure, and heated at 224° for eighteen hours. After cooling and opening the bomb tube, the reaction mixture was diluted with water, filtered to remove silica, acidified with dilute hydrochloric acid, digested for a short time on the steam-bath, and finally cooled to 0°. The solid which separated was collected on a filter. This crude product was crystallized several times from benzene. By these operations it was separated into a solid and an oil. The solid melted at 165–166°. Its identity with diethylstilbestrol was established by the following criteria: (1) the preparation of the diacetate; (2) the preparation of the dibenzoate; (3) the fact that no depression in melting point was observed when the solid was added to an authentic sample of diethylstilbestrol. The diacetate of this material (crystallized from high-boiling ligroin) melted at 120°. The dibenzoate (crystallized from a mixture of high-boiling ligroin and benzene) melted at 209–211°.

When the residual oil (from the bomb tube reaction) was treated in a sealed tube at 224° with 1.5 g. of potassium hydroxide in 8 cc. of ethylene glycol (as in the first operation), it gave an additional amount of diethylstilbestrol. The total yield of the latter was 1.1 g., or 55.5% of the amount calculated from the weight of compound (I) used.

Preparation of 1-Amino-1-(*p*-methoxyphenyl)-propane.—Anethole hydrobromide (prepared from 20 g. of redistilled anethole according to the directions already described) was poured into liquid ammonia contained in an unsilvered Dewar flask; 2.7 g. of sodamide was then added. After stirring for two hours, a slight excess of sodium was added in small portions. When the excess sodium had reacted with the liquid ammonia (as evidenced by the disappearance of the characteristic blue color), the ammonia was removed by evaporation. The reaction mixture was taken up in water; the solution was made acid and extracted with toluene. Only a minute amount of brown oil was obtained by evaporation of the toluene; this was discarded. The acid aqueous solution was made alkaline with sodium hydroxide and extracted several times with toluene. The combined toluene extracts were dried with a small amount of "Drierite." After the drying agent had been removed by filtration, dry hydrogen chloride was passed into the filtrate. The solid which separated was collected on a filter and purified by solution in absolute alcohol, addition of absolute ether to the solution, and cooling. A snow-white, crystalline material melting at 215° (with decomposition) was thus obtained. The benzoyl derivative of this substance was prepared by the Schotten–Baumann method. When crystallized from aqueous alcohol, it melted at 120°. The total yield of amine hydrochloride was 21 g., or 80% of the amount calculated.

Summary

1. The reactions of α-chloroethylbenzene and α-chloropropylbenzene with sodamide in liquid ammonia have been studied.

2. The preparation of a compound (I) believed to be either 3,4-di-(*p*-methoxyphenyl)-hexene-1 or 1-methyl-2,3-di-(*p*-methoxyphenyl)-3-ethylcyclopropane in 40% yield is described.

3. The preparation of diethyl stilbestrol from (I) has been accomplished.

4. The preparation of 1-amino-1-(*p*-methoxyphenyl)-propane is given.

CHICAGO, ILLINOIS RECEIVED AUGUST 31, 1942

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Reactions of Atoms and Free Radicals in Solution. IV. Decomposition of Acetyl Peroxide in Aliphatic Acids—A New Synthesis of Succinic Acid and its Substitution Derivatives

BY M. S. KHARASCH AND MATTHEW T. GLADSTONE

Continuation of previously reported work on the relative reactivities of organic free radicals in solution[1] has led to investigation of the reactions which free radicals formed by decomposition of acetyl peroxide undergo with a number of organic solvents.[2] This paper describes the results obtained when acetyl peroxide is decomposed in liquid aliphatic acids.

When acetyl peroxide, dissolved in glacial acetic acid, is dropped slowly into glacial acetic acid maintained at 95–100°, a rapid evolution of gas indicates that decomposition has set in. This gas was identified as a mixture of methane and carbon dioxide. No hydrogen or unsaturated gases were found. From the reaction mixture, after removal of the acetic acid, there was obtained a residue which, after crystallization from water, was identified as succinic acid by analysis,

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[1] Kharasch, Kane and Brown, THIS JOURNAL, **64**, 1621 (1942).

[2] The decomposition of acetyl peroxide in the following solvents has been investigated: (a) diethyl and diisopropyl ethers by Kharasch, Fineman and Brown (unpublished work); (b) carbon tetrachloride and ether chlorinated hydrocarbons by Kharasch, Kane and Brown, THIS JOURNAL, **63**, 526 (1941); (c) acid chlorides by Kharasch and Jensen (unpublished work). The decomposition of other peroxides in the solvents mentioned and in ethers was also investigated.