

quinolinates have been described. None of the esters possessed marked activity as a local

anesthetic.

ANN ARBOR, MICHIGAN

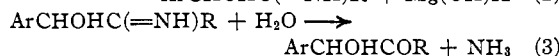
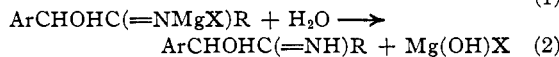
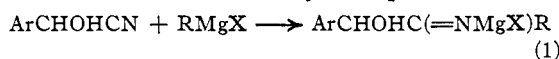
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[COMMUNICATION No. 853 FROM THE KODAK RESEARCH LABORATORIES]

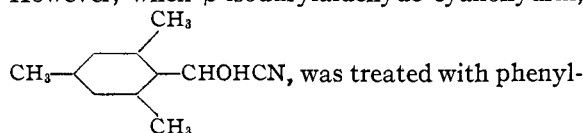
The Reaction of β -Isodurylaldehyde Cyanohydrin with Phenylmagnesium Bromide¹

BY A. WEISSBERGER AND DUDLEY B. GLASS

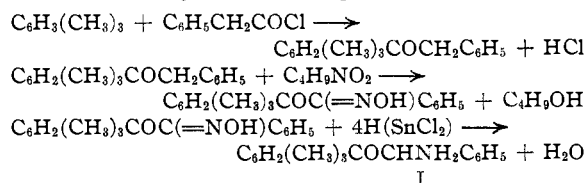
Benzoin and a number of substituted benzoin and other acyloins have been prepared by the reaction of aryl- or alkylmagnesium halides with the cyanohydrins of aryl aldehydes.^{2,3} Omitting the reaction of the Grignard reagent with the active hydrogen of the cyanohydrin, and the acid used in decomposing the magnesium complex, the course of the reaction may be represented as



The yields vary considerably, but no total failure of the reaction is reported in the literature. However, when β -isodurylaldehyde cyanohydrin,



was treated with phenylmagnesium bromide in an attempt to prepare 2,4,6-trimethylbenzoin for a study of its oxidation rate, the compound expected was not obtained. Instead, the product of the reaction was a nitrogen-containing substance with the properties of an α -aminoketone; the compound is a monohydric base, is oxidized by Fehling solution and by nitrosobenzene to 2,4,6-trimethylbenzil, and autoxidizes in alkaline solution.⁴ The same substance was obtained by the following series of reactions



(1) This investigation was started in the Dyson-Perrins Laboratory, Oxford. I wish to express thanks to Sir R. Robinson for his hospitality and to Imperial Chemical Industries, Ltd. for financial assistance.—A. W.

(2) Gauthier, *Compt. rend.*, **152**, 1100, 1259 (1911); Tiffeneau and Levy, *Bull. soc. chim.*, **37**, 1247 (1925); Asahina and Terasaka, *J. Pharm. Soc. (Japan)*, **494**, 219 (1923).

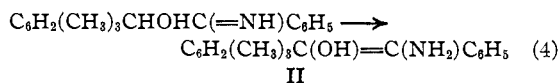
(3) Weissberger, Strasser, Mainz and Schwarze, *Ann.*, **478**, 112 (1930).

(4) Cf. James and Weissberger, *This Journal*, **59**, 2040 (1937).

This synthesis establishes the position of the oxygen and nitrogen atoms in respect to the mesitylene and benzene nuclei and identifies the compound as 2,4,6-trimethyldeacylamine (I) or its tautomer (II).

If one considers the work of Kohler⁵ and of Fuson,⁶ who have shown that in compounds of the types $\text{C}_6\text{H}_2(\text{CH}_3)_3\text{COCH=}$ and $\text{C}_6\text{H}_2(\text{CH}_3)_3\text{CH-OHC}\equiv$ the mesitylene residue promotes the formation and enhances the stability of the enolic form $\text{C}_6\text{H}_2(\text{CH}_3)_3\text{C=C<}$, the anomalous course of

the reaction of β -isodurylaldehyde cyanohydrin with phenylmagnesium bromide can be understood. With the mesitylene derivative, the imino compound, which ordinarily undergoes acid hydrolysis, eq. 3, is transformed by enolization into the amino compound II, eq. 4, which resists hydrolysis. This or the tautomeric amine I separates from the acid solution as the hydrochloride.



The phase in the sequence of reactions in which the enolization occurs is indicated by the reaction of β -isoduraldehyde cyanohydrin with methylmagnesium iodide.⁷ β -Isoduraldehyde cyanohydrin consumes two moles of the Grignard reagent and evolves one mole of methane. This agrees with the structure of the resulting complex as that of the imino derivative $\text{ArCH(OMgBr)C(=N-MgBr)R}$. The tautomeric enamino compound $\text{ArC(OMgBr)=C(NHMgBr)-R}$ should evolve another mole of methane. Hence, the amino compound is not formed before the hydrolysis of the Grignard complex.

The explanation of the anomalous reaction of β -isoduraldehyde cyanohydrin with phenylmag-

(5) Kohler and co-workers, *ibid.*, **57**, 2517 (1935); **58**, 2166 (1936); **59**, 887 (1937).

(6) Fuson and co-workers, *ibid.*, **58**, 1233 (1936), and succeeding papers.

(7) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927); Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930). We wish to thank Dr. Alan Bell of these laboratories for the "Grignard Machine" analyses.

nesium bromide as given above is corroborated by the results of the hydrolysis of desylamine and of 2,4,6-trimethyl-desylamine by heating with dilute hydrochloric acid. Under conditions that yield 40% of benzoin from desylamine, the 2,4,6-trimethyl-desylamine remains unchanged. Under more drastic conditions a quantitative yield of benzoin is obtained while only about 20% of the 2,4,6-trimethyl-desylamine is affected. Such results would be expected if the reaction mixture of the desylamine contains appreciable quantities of the imino compound, while the reaction mixture of the 2,4,6-trimethyl-desylamine is composed almost exclusively of the enamine and/or the aminoketone.

On acetylation, trimethyl-desylamine gives a monoacetate, and under very vigorous conditions, a triacetate. Formulation of these compounds as $(\text{CH}_3)_3\text{C}_6\text{H}_2\text{C}(\text{OH})=\text{C}(\text{NHCOCH}_3)\text{C}_6\text{H}_5$ and $(\text{CH}_3)_3\text{C}_6\text{H}_2\text{C}(\text{OCOCH}_3)=\text{CN}(\text{COCH}_3)_2\text{C}_6\text{H}_5$ is in agreement with the solubility of the monoacetate in dilute and in concentrated hydrochloric acid, and the results of the "Grignard Machine" analysis. The monoacetate dissolves in a 1:1 mixture of alcohol and concentrated hydrochloric acid. Upon addition of more concentrated hydrochloric acid no precipitation occurs, while upon addition of water the acetate precipitates. The monoacetate shows two active hydrogen atoms and does not add methylmagnesium iodide. As in acetanilide, the acetyl group in the monoacetate is too tightly bound to be eliminated under the conditions of this analysis. The triacetate has no active hydrogen and uses up four moles of methylmagnesium iodide in splitting off two of the acetyl groups; from the reaction mixture the monoacetate can be recovered. The monoacetate of desylamine on the other hand reacts as $\text{C}_6\text{H}_5\text{COCH}(\text{NHCOCH}_3)\text{C}_6\text{H}_5$, showing only one active hydrogen, and using up one mole of methylmagnesium iodide, presumably in an addition to the carbonyl group. These results again demonstrate the difference between the derivative of benzene and of mesitylene, and the enolizing effect of the mesityl group.

The oxidation of trimethyl-desylamine with molecular oxygen at a pH of 12.8 is about ten times faster than that of desylamine⁸ under the same conditions. Since the reactive species of the α -aminoketone in this reaction is the enolate

(8) We are indebted to Mr. D. S. Thomas of these laboratories for the determination of the autoxidation rates.

ion,⁴ this result again indicates the higher tendency for enolization of the mesitylene derivative.

The reasons for this higher degree of enolization may be tentatively discussed. The stability of the enolic double bond depends on the degree of resonance between this double bond and the aromatic system. Several conditions might favor this resonance. A steric factor comes first to mind in connection with a compound of the marked stereochemical characteristics of mesitylene. For maximum degeneracy the resonating system must lie in one plane. It might, therefore, be suggested that the stability of the enolic double bond in mesitylene derivatives is increased because the double bond is forced into the plane formed by the aromatic system. However, a repulsion between the two methyl groups in the ortho positions and a group on the α -carbon atom would not produce such an effect. An attraction between the methyl groups and a group on the α -carbon atom would serve the purpose, but is, in itself, not likely to occur. A more probable reason for the increased stability of the aromatic-olefinic conjugated system in mesitylene derivatives lies in the high electron density in the mesitylene nucleus. The latter is indicated by the direction of the dipole moments of toluene and of *m*-xylene, and by the great reactivity of mesitylene with anionotropic reagents. It appears that the electron distribution of mesitylene, as compared with that of benzene, increases the degeneracy of the enolic-aromatic conjugation, and stabilizes the enolic double bond.

Experimental

β -Isodurylaldehyde was prepared from mesitylene, zinc cyanide, and hydrogen chloride by the method of Hinkel, Ayling and Morgan.⁹ The yield of aldehyde was 75%. The aldehyde was purified by conversion to the anil, distillation and crystallization of the anil and, after hydrolysis of the anil, redistillation of the aldehyde. The yield of pure aldehyde was 60%, b. p. 113–115° (11 mm.), n_{20}^D 1.5505.

β -Isodurylaldehyde Cyanohydrin.—A solution of 44.4 g. (0.3 mole) of β -isodurylaldehyde in 240 cc. of petroleum ether was shaken vigorously for fifteen minutes with a solution of 52 g. (0.8 mole) of potassium cyanide and 44.4 g. (0.83 mole) of ammonium chloride in 135 cc. of water. The flask was closed tightly during the agitation. The resulting crystals were removed by filtration, washed with water and then petroleum ether, and dried in a vacuum desiccator over calcium chloride. There resulted 48 g. (91%) of cyanohydrin which melted at 106–107° (sealed tube) after recrystallization from two volumes of benzene.

(9) Hinkel, Ayling and Morgan, *J. Chem. Soc.*, 2793 (1932).

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.30; H, 7.50; N, 8.00.

2,4,6-Trimethyl-desylamine Hydrochloride from β -Isodurylaldehyde Cyanohydrin and Phenylmagnesium Bromide.—To a Grignard solution prepared from one-half molar quantities of magnesium and bromobenzene in 375 cc. of ether, was added with stirring a solution of 17.5 g. (0.1 mole) of β -isodurylaldehyde cyanohydrin in 200 cc. of dry ether during a period of five minutes. The reaction mixture was heated under reflux on a steam-bath for fifteen minutes and then was poured onto a mixture of 1 kg. of ice and 200 cc. of concentrated hydrochloric acid. The mixture was stirred for a minute, the layers were separated, and the aqueous layer was extracted immediately with 200 cc. of ether and filtered. Then 200 cc. of concentrated hydrochloric was added. The flask was stoppered and allowed to stand for two days at $25 \pm 5^\circ$. The precipitate was removed by filtration, washed with water and ether, and dried in air. The yield was 16 g. (55%) of hydrochloride which melted at $287\text{--}289^\circ$ (sealed tube). The substance was brought to analytical purity by dissolving in 150 cc. of 70% aqueous alcohol, filtering the solution and precipitating the hydrochloride with 300 cc. of concentrated hydrochloric acid. After cooling to around 15° , the hydrochloride was collected on a filter and recrystallized from 70% alcohol to which had been added 1% of hydrochloric acid; m. p. $290\text{--}291^\circ$ (sealed tube).

Anal. Calcd. for $C_{17}H_{20}ONCl$: C, 70.45; H, 6.96; N, 4.83. Found: C, 70.10; H, 6.70; N, 4.88.

2,4,6-Trimethyl-desoxybenzoin was prepared from mesitylene, phenylacetyl chloride and aluminum chloride in petroleum ether by the method of Klages.¹⁰ There was obtained an 88% yield of ketone which boiled at $136\text{--}137^\circ$ (0.5 mm.).

Isonitroso-2,4,6-trimethyl-desoxybenzoin.—The 2,4,6-trimethyl-desoxybenzoin was converted into the isonitroso derivative by a method similar to that used by Hartung and Munch¹¹ for the preparation of isonitrosopropiophenone. A solution of 88 g. (0.37 mole) of 2,4,6-trimethyl-desoxybenzoin and 42 g. (0.41 mole) of redistilled butyl nitrite (b. p. $78\text{--}79^\circ$) in 275 cc. of ether was stirred, and dry hydrogen chloride was introduced at the rate of four to five bubbles per second for two and one-half hours. At the end of this time the flask was stoppered and allowed to stand overnight. Ether (300 cc.) was added and the oxime was extracted from the ethereal solution with one 450-cc. portion of 5% sodium hydroxide solution, and three 150-cc. portions of 3% sodium hydroxide solution. The alkaline extracts were combined, filtered and run into a mixture of ice and excess concentrated hydrochloric acid. The precipitate was removed by filtration and dried in air; yield 75 g. (76%); m. p. $152\text{--}153.5^\circ$. A sample recrystallized from alcohol melted at $156\text{--}156.5^\circ$.

2,4,6-Trimethyl-desylamine Hydrochloride by the Reduction of Isonitroso-2,4,6-trimethyl-desoxybenzoin.—A solution of 225 g. (1.0 mole) of stannous chloride in 500 cc. of concentrated hydrochloric acid was added rapidly to a solution of 53.4 g. (0.2 mole) of isonitroso-2,4,6-trimethyl-desoxybenzoin in 500 cc. of alcohol. The reaction mixture was then heated under reflux on the steam-bath for one

and one-half hours. After standing overnight at room temperature, the precipitate was removed by filtration and dried in air; yield 50 g. (86%). A sample was recrystallized from 60% alcohol to which had been added a little hydrochloric acid; m. p. $289\text{--}290^\circ$ (sealed tube).

Anal. Calcd. for $C_{17}H_{20}ONCl$: N, 4.83. Found: N, 4.74.

Acetates of 2,4,6-Trimethyl-desylamine: Monoacetate.—Ten grams of 2,4,6-trimethyl-desylamine hydrochloride prepared by the Grignard method was added to a mixture of 100 cc. of acetic anhydride and 20 cc. of pyridine and the mixture was heated on the steam-bath for ten minutes. At the end of this time, the reaction mixture was poured onto ice and stirred until the anhydride had decomposed. The product was removed by filtration and crystallized from a benzene-ligroin mixture (1:2); m. p. $174.5\text{--}175^\circ$.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74; mol. wt., 295. Found: C, 77.50; H, 7.03; N, 4.76; mol. wt. (in benzene), 296, 300.

The 2,4,6-trimethyl-desylamine hydrochloride prepared by the reduction method was carried through the same procedure. It acted in all ways identically with the amine hydrochloride prepared by the Grignard method. The acetates gave no depression in a mixed melting point test.

Triacetate.—Five grams of 2,4,6-trimethyl-desylamine hydrochloride prepared by the Grignard method was added to a mixture of 50 cc. of acetic anhydride and 10 cc. of pyridine and the mixture was heated for seven hours on the steam-bath under a reflux condenser closed by a calcium chloride tube. After standing overnight, the reaction mixture was diluted with 250 cc. of warm (*ca.* 50°) water and stirred until the anhydride had decomposed. The precipitate was ground in a mortar with water and then recrystallized from 15 cc. of alcohol; m. p. $125\text{--}126^\circ$.

Anal. Calcd. for $C_{23}H_{25}O_3N$: C, 72.80; H, 6.64; N, 3.69; mol. wt., 379. Found: C, 73.01; H, 6.65; N, 3.71; mol. wt. (in benzene), 373, 368.

The 2,4,6-trimethyl-desylamine hydrochloride prepared by reduction behaved identically with that prepared by the Grignard method. The triacetates gave no depression in a mixed melting point test.

Hydrolysis of Triacetate to Monoacetate.—One gram of triacetate was dissolved in 15 cc. of warm alcohol and 5 cc. of concentrated hydrochloric acid was added. The solution was boiled on the steam-bath for ten minutes, cooled and diluted with 50 cc. of water. The precipitate was removed by filtration and recrystallized from ligroin; m. p. $173\text{--}174^\circ$. On addition of known monoacetate, the melting point was unchanged.

Hydrolysis of Triacetate to Amine.—One gram of triacetate was added to a mixture of 10 cc. of alcohol and 10 cc. of concentrated hydrochloric acid and the solution boiled for five hours under reflux. The solution was cooled and allowed to stand in the ice box for two hours. The precipitate of 2,4,6-trimethyl-desylamine hydrochloride was removed by filtration, washed with alcohol and dried in air; m. p. $283\text{--}285^\circ$ (sealed tube). A small sample of the product was dissolved in 70% alcohol and allowed to stand in an unstoppered test-tube for one week. The precipitate was removed by filtration and dried in air; m. p. $134\text{--}135^\circ$. A mixed melting point with a known sample of 2,4,6-trimethylbenzil showed no depression.

(10) Klages, *Ber.*, **32**, 1564 (1899).

(11) Hartung and Munch, *This Journal*, **51**, 2262 (1929).

Acetates of Desylamine. Monoacetate.—The monoacetate of desylamine¹² was prepared by the method used for the preparation of the monoacetate of 2,4,6-trimethyl-desylamine; m. p. 135–136°.

Anal. Calcd. for C₁₈H₁₉O₂N: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.12; H, 5.89; N, 5.51.

Triacetate.—Five grams of desylamine hydrochloride was heated on a steam-bath for eight hours with 50 cc. of acetic anhydride and 10 cc. of dry pyridine. At the end of this time 200 cc. of water was added and the mixture was stirred until the anhydride had decomposed. The aqueous portion was decanted and the gummy residue was washed with water. The gum was dissolved in 125 cc. of ligroin, and the solution was treated with Norit and filtered. After standing for twenty hours, the precipitate was collected on a filter and recrystallized from four volumes of methanol; m. p. 130–131°.

Anal. Calcd. for C₂₀H₁₉O₄N: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.20; H, 5.62; N, 4.05.

RESULTS OF THE "GRIGNARD MACHINE" ANALYSES⁷

Compound	Reaction time	Active hydrogen	Addition
2,4,6-Trimethyl-desylamine hydrochloride	10 min. ^a	3	0
2,4,6-Trimethyl-desylamine monoacetate	1 hr.	2	0
2,4,6-Trimethyl-desylamine triacetate ^b	1 hr.	0	4
β -Isodurylaldehyde cyanohydrin	10 min.	1	1
Desylamine monoacetate	1 hr.	1	1

^a Upon prolonged heating the value of the active hydrogen approached 4. ^b The reaction mixture yielded the monoacetate upon being worked up.

(12) Davidson, Weiss and Jelling, *J. Org. Chem.*, **2**, 319 (1937).

Hydrolysis of 2,4,6-Trimethyl-desylamine and of Desylamine.—(a) A mixture of 1 g. of the amine hydrochloride, 5 cc. of water, 5 cc. of concentrated hydrochloric acid, and 10 cc. of ethanol was heated at 95° in a sealed tube under nitrogen for twenty hours. Benzoin in a 40% yield separated and was collected on the filter. Under the same conditions 2,4,6-trimethyl-desylamine was unaffected.

(b) Same as (a) except heated at 130° for twenty-four hours. Desylamine gave a quantitative yield of benzoin. 2,4,6-Trimethyl-desylamine yielded 20% of a mixture of 2,4,6-trimethylbenzoin and 2,4,6-trimethylbenzil.

Summary

1. 2,4,6-Trimethyl-desylamine has been prepared by the reaction of phenylmagnesium bromide with β -isodurylaldehyde cyanohydrin and also by the reduction of isonitroso-2,4,6-trimethyl-desoxybenzoin.

2. The reactions of 2,4,6-trimethyl-desylamine and desylamine with dilute hydrochloric acid were compared.

3. The autoxidation rate of 2,4,6-trimethyl-desylamine was compared with that of desylamine.

4. The mono- and triacetate of 2,4,6-trimethyl-desylamine were prepared and their reactions with dilute hydrochloric acid and with methylmagnesium iodide were studied.

5. The results obtained were ascribed to the propensity toward enolization shown by acetomesitylene derivatives.

ROCHESTER, NEW YORK

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Tri-*o*-tolyltin and the Instability of Organo-metallic Free Radicals

BY HUMBERT MORRIS, WARD BYERLY AND P. W. SELWOOD

Previous magnetic measurements on triphenylgermanium,¹ triphenyllead,² trimethyltin³ and tricyclohexyllead³ have shown that all these compounds exist in the diamagnetic or dimeric state. Molecular weight measurements by others have, on the contrary, consistently indicated partial or complete dissociation to the free radical. These results raise two questions: first, why do these compounds not exist as free radicals and, second, why do the magnetic measurements contradict the molecular weight measurements?

A possible answer to the first question is to be

(1) Selwood, *THIS JOURNAL*, **61**, 3168 (1939).

(2) Preckel and Selwood, *ibid.*, **62**, 2765 (1940).

(3) Morris and Selwood, *ibid.*, **63**, 2509 (1941).

found in the much larger radius of the metal atoms as compared with carbon, as in triphenylmethyl. It has been suggested³ that the increased radius leads to a much greater number of effective collisions leading to formation of the dimer, and that a compound such as tri-*o*-tolyltin, in which steric effects are large, might exist as a free radical. This hypothesis is tested in the work reported here.

An effort to answer the second question by repeating ebulliometric measurements on trimethyltin and on triphenyllead is also reported.

Experimental Part

Magnetic Measurements.—The magnetic susceptibilities were measured on the Gouy balance previously de-