cipitate within 5 minutes. After standing overnight the mixture was poured into 6 *M* hydrochloric acid. The secondary amine (which does not form a hydrochloride in aqueous solution) was filtered, sucked dry and taken up in ether. Some of the solid, presumably benzhydrylamine hydrochloride, did not dissolve and was discarded. The solvent was removed, and the residue washed with methanol and recrystallized twice from acetone–methanol to yield 22.3 g. (49%) of dibenzhydrylamine, m.p. 138–139°, reported 136°.[42] Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_{26}H_{23}N$: C, 89.35; H, 6.63; N, 4.01. Found: C, 89.75; H, 6.77; N, 3.92.

The picrate recrystallized from ethanol melted at 206–207° dec., reported 212°.[42]

Anal. Calcd. for $C_{32}H_{26}N_4O_6$: N, 9.68. Found: N, 9.60.

(42) S. Goldschmidt and L. Reichel, *Ann. Chem. Justus Liebigs*, **456**, 152 (1927).

Reaction of XV with Potassium Amide.—Dibenzhydrylamine (7.98 g., 0.02 mole) and potassium amide (0.06 mole) in 300 ml. of liquid ammonia and 300 ml. of dry ether was stirred for 30 minutes (red-orange color) and ammonia was then removed on the steam-bath as 300 ml. of dry ether was added. Powdered Dry Ice was added, and after stirring for 30 minutes, water was added and the layers separated. The aqueous layer was acidified to precipitate diphenylacetic acid, which after recrystallization from methanol and water melted at 147–148°. A mixed melting point was the same, yield 3.2 g. (80%). The ethereal layer was extracted with 6 *M* hydrochloric acid and the acid solution warmed on the steam-bath for one hour to hydrolyze the imine hydrochloride. The resulting ketone was taken up in ether, recovered from this solvent and crystallized from 30–60° petroleum ether to give 2.65 g. (73%) of benzophenone, m.p. and mixed m.p. 47.5–48.5°.

DURHAM, NORTH CAROLINA

[CONTRIBUTION NO. 185 FROM THE JACKSON LABORATORY, E. I. DU PONT DE NEMOURS & CO.]

Relative Reactivity of the Isocyanate Groups in Toluene-2,4-diisocyanate

BY DONALD M. SIMONS AND ROBERT G. ARNOLD

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The greater reactivity of the *p*-isocyanate group in toluene-2,4-diisocyanate is demonstrated. 4-Methyl-3-nitro-, 2-methyl-5-nitro-, 3-amino-4-methyl- and 5-amino-2-methylcarbanilide have been prepared.

During the course of some work in this Laboratory it became desirable to demonstrate unequivocally which isocyanate group in toluene-2,4-diisocyanate (TDI) is the more reactive. Bayer[1] and Siefkin[2] state that an alkyl or alkoxy group *ortho* to an isocyanate exerts a rate-retarding effect but cite no experimental evidence.

Rate studies performed on *o*- and *p*-tolyl isocyanate–amine systems showed that *p*-tolyl isocyanate is the more reactive and one would be justified in suspecting that this is also true for the *p*-isocyanate group in TDI. However, to demonstrate the absence of any anomalous effects in TDI itself, the greater reactivity of the *p*-isocyanate group was demonstrated by the following procedure. TDI (one mole) was treated with aniline (one mole) in tetrahydrofuran solution and the residual isocyanate group then hydrolyzed with hydrochloric acid. Fractional recrystallization of the product gave 68% of theory of a compound which proved to be identical with an authentic sample of 3-amino-4-methylcarbanilide as judged by melting point, mixed-melting point and infrared spectra.

Experimental

Reaction of TDI and Aniline.—TDI (0.2018 mole) in one liter of anhydrous tetrahydrofuran was cooled to −25° and a solution of aniline (0.2017 mole) in 500 ml. of tetrahydrofuran (also cooled to −25°) added slowly with stirring. After the addition was complete the mixture was warmed to room temperature and allowed to stand overnight. The mixture was then poured into one liter of 6 *N* hydrochloric acid with sufficient cooling to keep the temperature at 25–30°. After standing for 3 hours the mixture was neutralized with potassium carbonate and the organic layer separated. (The potassium chloride concentration is high enough to salt out the tetrahydrofuran.) Removal of the solvent *in vacuo* gave 51.0 g. of solid. Repeated fractional recrystallization of this product from ethanol gave eventually two fractions of sufficient purity to identify.

	M.p., °C.	Mixed melting point[a]	Wt., g.	Nitrogen, %
Fract. A	198–199.5	197.5–198.5	22.7	17.5
Fract. B	193–195	193–195	10.3	17.1

[a] With an authentic sample of 3-amino-4-methylcarbanilide, m.p. 200–201°.

The infrared spectra of the two fractions were identical with that of an authentic sample of 3-amino-4-methylcarbanilide and were different from that of the isomeric 5-amino-2-methylcarbanilide. The combined weight of the two fractions represented a yield of 68%. The remaining 32% of the material consisted predominantly of a mixture of the two isomeric carbanilides which could not be separated readily.

3-Amino-4-methylcarbanilide and 5-Amino-2-methylcarbanilide.—These substances were prepared from the corresponding nitrotoluidines and phenyl isocyanate followed by hydrogenation.

The appropriate nitrotoluidine (0.20 mole) was dissolved in 300 ml. of dry dioxane, and phenyl isocyanate (0.20 mole) in 50 ml. of dioxane added. The solution was refluxed about 30 minutes, cooled and the product filtered off and recrystallized from alcohol–tetrahydrofuran. The nitro group was reduced by dissolving the carbanilide (15 g.) in 700 ml. of hot alcohol–tetrahydrofuran and hydrogenating at 60° with 200 lb. of hydrogen and about 5 g. of Raney nickel. After removal of the catalyst the product was obtained by evaporating part of the solvent *in vacuo* and cooling the residue in an ice-bath.

TABLE I

Carbanilide	Formula	Nitrogen, % Calcd.	Found	M.p., °C.
4-Methyl-3-nitro-	$C_{14}H_{13}O_3N_3$	15.5	15.4	218–219
2-Methyl-5-nitro-	$C_{14}H_{13}O_3N_3$	15.5	15.7	[a]
3-Amino-4-methyl-	$C_{14}H_{15}ON_3$	17.4	17.3	200–201
5-Amino-2-methyl-	$C_{14}H_{15}ON_3$	17.4	17.0	>200[a]

[a] M.p. dependent upon rate of heating.

(1) O. Bayer, *Angew. Chem.*, **59**, 257 (1947).

(2) W. Siefkin, *Ann.*, **562**, 75 (1949).

The carbanilides with substituents in the 2 and 5 positions were markedly more insoluble than the corresponding 3,4-substituted compounds. The amino-substituted carbanilides require prolonged drying under vacuum since they retain solvent tenaciously.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Synthesis of Dihydroxyacetone Phosphate

BY CLINTON E. BALLOU AND HERMANN O. L. FISCHER

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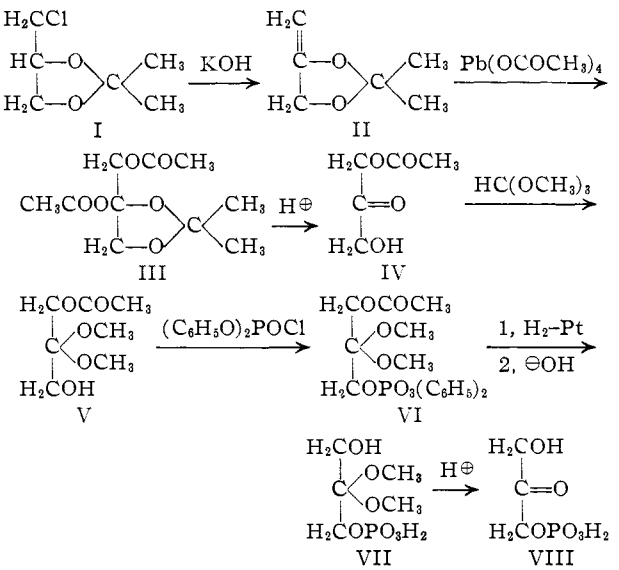
A new method for the synthesis of dihydroxyacetone phosphate, as its stable dimethyl or diethyl ketal, is described. The ketal can be converted in a 95% yield to the free compound by mild acid hydrolysis. This synthesis, which makes this important glycolytic intermediate readily available as a pure substance for the first time, should facilitate future studies on the role of this substrate in carbohydrate metabolism.

Although the Embden–Meyerhof glycolytic scheme is one of the most completely investigated metabolic pathways, until recently at least half of the intermediates were known chemically only as impure, poorly defined substances. We have undertaken the preparation of a number of these intermediates, and have recently described syntheses of D-glyceric acid 2-phosphate,[1] D-glyceric acid[2] 3-phosphate, and D-glyceraldehyde 3-phosphate.[3] The latter, normally an unstable substance, was prepared as the dimethyl acetal, which, although perfectly stable as its cyclohexylamine salt, hydrolyzed readily in dilute acid to give the free aldehyde in high yield. The success of this approach has led us to the new synthesis of dihydroxyacetone phosphate outlined below.



The starting material for this synthesis was prepared, with some modifications, according to published procedures.[4] Isopropylidene glycerol monochlorohydrin (isopropylidene 3-chloro-1,2-propanediol) (I)[5] was dehydrohalogenated, and the resulting isopropylidene 2-propen-1,2-diol (II) was oxidized with lead tetraacetate. Acid hydrolysis of the product III gave acetyl dihydroxyacetone (1-acetoxy-3-hydroxy-2-propanone) (IV)[4] which was then converted to its dimethyl ketal (1-acetoxy-2,2-dimethoxy-3-propanol) (V). Phosphorylation of the ketal V, with diphenyl phosphorochloridate gave the phosphorylated intermediate 1-acetoxy-2,2-dimethoxy-3-diphenylphosphonyloxypropane (VI), from which the phenyl groups were removed by hydrogenolysis and the acetyl group by saponification. The dihydroxyacetone phosphate dimethyl ketal (2,2-dimethoxy-1,3-propanediol phosphate) (VII) was isolated as a crystalline cyclohexylammonium salt. The ketal, as its free acid in aqueous solution, undergoes ready hydrolysis (4 hours at 40°) to give a 95% yield of dihydroxyacetone phosphate (VIII). This synthesis has been used in the preparation of 5–15 gram quantities of the product without modification.

The corresponding diethyl ketal of dihydroxyacetone phosphate (IX) also was prepared, and the rates of hydrolysis of the ketal structures in the two substances are compared in Fig. 1.

The dihydroxyacetone phosphate prepared by this definitive method has been characterized by the acid and alkali lability of the phosphate group; by its reduction in the presence of glycerol phosphate dehydrogenase and reduced diphosphopyridine nucleotide[6]; and by its oxidation in the presence of triose phosphate isomerase, glyceraldehyde phosphate dehydrogenase and diphosphopyridine nucleotide.[7] All tests applied gave results that were qualitatively and quantitatively those expected for dihydroxyacetone phosphate.

Other methods for the preparation of dihydroxyacetone phosphate involve the enzymatic dismutation of D-fructose 1,6-diphosphate,[8] and the indiscriminate phosphorylation of dihydroxyacetone with phosphorous oxychloride.[9] The synthesis

(1) C. E. Ballou and H. O. L. Fischer, THIS JOURNAL, **76**, 3188 (1954).

(2) C. E. Ballou and H. O. L. Fischer, Abstracts of Papers, 126th Meeting, American Chemical Society, 7D (1954).

(3) C. E. Ballou and H. O. L. Fischer, THIS JOURNAL, **77**, 3329 (1955).

(4) H. O. L. Fischer, E. Baer and L. Feldman, *Ber.*, **63**, 1732 (1930); H. O. L. Fischer and E. Baer, *ibid.*, **65**, 345 (1932).

(5) E. Fischer and B. Pfähler, *ibid.*, **53**, 1608 (1920).

(6) G. Beisenherz, T. Bücher and K.-H. Garbade, in "Methods in Enzymology," Vol. I, edited by S. P. Colowick and N. O. Kaplan, Academic Press, Inc., New York, N. Y., 1955.

(7) As described by G. Cori, M. Slein and C. Cori, *J. Biol. Chem.*, **173**, 605 (1948), for D-glyceraldehyde 3-phosphate, except that triose phosphate isomerase was also added.

(8) O. Meyerhof and K. Lohmann, *Biochem. Z.*, **271**, 89 (1934).

(9) W. Kiessling, *Ber.*, **67**, 869 (1934).