[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Preparation of Certain Nitrogen-Substituted Sulfonanilides

BY GEORGE H. YOUNG

In connection with certain crystallographic studies being carried out in this Laboratory we have had occasion to prepare a number of nitrogen-substituted sulfonamides. The Hinsberg reaction[1] between "primary" sulfonamides and alkyl halides has been successfully applied to the synthesis of the *n*-propyl, isopropyl, and *s*-butyl N-substituted *p*-toluene sulfonanilides, three compounds which have not heretofore been described in the literature.

Molar quantities of the sulfonanilide and the appropriate alkyl bromide were caused to react in the presence of potassium hydroxide. The products were recrystallized from methanol, from which they deposited in the form of thick, colorless, monoclinic plates or tablets. Yields of 78–86% were obtained based on the crude air-dried product.

The pure compounds are in general insoluble in water, sparingly soluble in ether and ethyl acetate, and quite soluble in boiling methanol from which they are reprecipitated on cooling. They exhibit increased solubility in ethanol, acetic acid and acetone, and are very soluble in the higher alcohols and other conventional solvents. All are stable in air and melt sharply without decomposition.

The melting points and analytical data for these compounds are given in the table.

TABLE I

p-Toluene-sulfon-N-anilide		*n*-Propyl	Isopropyl[a]	*s*-Butyl
M. p., °C.		56	99.5–100	75.5
Formula		$C_{16}H_{19}O_2NS$	$C_{16}H_{19}O_2NS$	$C_{17}H_{21}O_2NS$
N	Calcd.	4.84	4.84	4.62
	Found	4.79	4.96	4.60
S	Calcd.	11.07	11.07	10.56
	Found	10.98	11.09	10.44

[a] Recrystallized first from 1:1 ethanol–ethyl acetate, then from methanol.

The writer gratefully acknowledges the advice and assistance of Dr. Walter J. Keith, who suggested this research.

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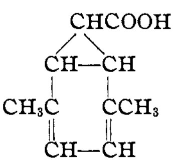
(1) Hinsberg, *Ann.*, **265**, 178–192 (1891).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

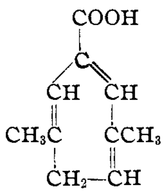
Studies on the Polymethylbenzenes. IX. Addition of Ethyl Diazoacetate to Durene[1,2]

BY LEE IRVIN SMITH AND PLINY O. TAWNEY

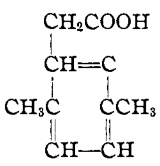
The action of diazoacetic ester upon aromatic hydrocarbons has been investigated by Buchner and his students,[3] who showed that the primary product of the reaction was the ester of a norcaradiene acid (I). These esters are characterized by a tendency to rearrange, especially at high temperatures, into derivatives of cycloheptatriene (II), phenylacetic acid (III), and β-phenylpropionic acid (IV), the latter rearrangement, of course, taking place only when the initial aromatic hydrocarbon contains one or more methyl groups.



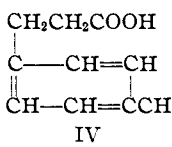
I



II



III



IV

In all the cases studied by Buchner, the addition proceeded in such a way that a norcaradiene con-

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(1) Abstracted from a thesis by Pliny O. Tawney, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science, July, 1934.

(2) Presented at the 88th meeting of the American Chemical Society held at Cleveland, Ohio, September, 1934.

(3) (a) Buchner, *et al.*, *Ber.*, **18**, 2377 (1885); (b) *ibid.*, **34**, 982 (1901); (c) *ibid.*, **36**, 3502, 3509 (1903); (d) *Ann.*, **358**, 1 (1908); (e) *ibid.*, **377**, 259 (1910); (f) *Ber.*, **53**, 865 (1920).

taining a quaternary carbon atom was never produced, and when mesitylene was used,[3f] in which a quaternary carbon atom is unavoidable in the primary addition product, no bicyclic system was formed. Instead, the product consisted chiefly of the trimethylcycloheptatriene, together with smaller amounts of 3,5-dimethylhydrocinnamic acid and mesitylacetic acid.

Since the work of Meyer,[4] as well as work done in this Laboratory,[5] indicated that the accumulation of methyl groups on an aromatic hydrocarbon promoted the coupling with aromatic diazonium salts, we desired to investigate this effect using aliphatic diazo compounds and to extend the reaction of Buchner to various polymethylbenzenes. We were particularly interested in the mechanism of the formation of β-phenylpropionic acid derivatives, and therefore we chose durene as the first hydrocarbon to be investigated since it seemed likely that this hydrocarbon would give the largest yields of products resulting from the introduction of an acetic acid residue into a side chain methyl group.

When diazoacetic ester is heated with an excess of durene, there is a slow reaction at 135° which becomes fairly rapid at 140°. After removing the excess durene from the reaction mixture, there remains an oil which yields, as the only homogeneous product, the ethyl ester of 2,4,5-trimethylhydrocinnamic acid. This was identified by hydrolysis to the acid, and comparison of the acid with a specimen synthesized in another way.[6]

The yield of the hydrocinnamic acid derivative is about 30%, based upon the diazoacetic ester used. Considerable amounts of tarry materials are formed, and not all of the diazoacetic ester reacts, even though there is present a great excess of the hydrocarbon. When first distilled from the reaction product, the hydrocinnamic ester is contaminated with small amounts of an unsaturated substance, for it slowly reduces permanganate, and gives colors with sulfuric acid,[3f] indicating the presence of cycloheptatriene derivatives. In one case we succeeded in isolating an impure solid cycloheptatriene amide by treating the reaction product with ammonia, but a complete purification was impossible with the small amount of material isolated. This is not surprising, for there are seven cycloheptatrienes possible in this reaction, differing in the positions of the double bonds. We tried treating the crude reaction product (after removing the excess durene) with maleic anhydride, as well as with cyclopentadiene, hoping in this way to obtain derivatives more suitable for separation, but there was no reaction with either reagent.

Experimental Part

Methyleneaminoacetonitrile was prepared in 53% yield by the method of Adams and Langley.[7]

Glycine ester hydrochloride was prepared in 77% yield by the method of Klages.[8]

Ethyl diazoacetate was prepared in 56% yield by the method of Bergstrom and Wood.[9]

Action of Ethyl Diazoacetate upon Durene.—The apparatus consisted of a 500-cc. three-necked flask equipped with a thermometer, reflux condenser and small dropping funnel. The top of the condenser carried a two-holed stopper, one opening of which was connected to a calibrated Mariotte flask for collecting the nitrogen; the other opening was connected to the top of the dropping funnel, acting as a pressure equalizer. The reaction flask was immersed in an oil-bath. Durene (115 g., 0.85 mole) was placed in the flask, and the inside temperature brought to 140–145°. Over a period of about five hours, 10 g. (0.087 mole) of ethyl diazoacetate was added from the dropping funnel, with occasional shaking. No nitrogen was evolved during the first thirty minutes; about 100 cc. during the second thirty minutes, and the amount gradually increased until the fifth hour, when 600 cc. was collected. At the end of seven hours, practically no more nitrogen was evolved. The excess durene was removed from the reaction mixture by vacuum distillation, leaving 13.5 g. of crude product. The combined crude products from five such condensations (amounting to 54 g.) were fractionated under 4 mm. pressure, and separated into three parts: (a) 4 g., b. p. up to 125°, consisting of durene and ethyl fumarate; (b) 29.5 g., b. p. 130–136°; (c) 18 g. of dark, tarry, undistillable residue from which no solids could be obtained.

Fraction (b) consisted chiefly of the ethyl ester of 2,4,5-trimethylhydrocinnamic acid. It was contaminated with small amounts of an unsaturated substance, since it slowly reduced cold permanganate, and gave with sulfuric acid an orange red color, changing to blue in a few moments. On refractionation there was obtained a product inert to permanganate and giving no color with sulfuric acid.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.38; H, 9.09. Found: C, 76.2; H, 9.2.

The ester is very resistant to hydrolysis, especially by acids.

2,4,5-Trimethylhydrocinnamic Acid.—Ten grams of the ester was refluxed for eight hours with a solution of 5.7 g. of potassium hydroxide in 57 g. of methyl alcohol.

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[4] Meyer, *Ber.*, **47**, 1711 (1914); **52**, 1468 (1919); **54**, 2283 (1921).

[5] Smith and Paden, THIS JOURNAL, **56**, 2169 (1934).

[6] Willgerodt, *J. prakt. Chem.*, [2] **81**, 390 (1910).

[7] "Organic Syntheses," J. Wiley & Sons, Inc., New York, 1932, Coll. Vol. I, p. 347.

[8] Klages, *Ber.*, **36**, 1506 (1903).

[9] Private communication from Dr. Wood, whom we wish to thank for sending us a copy of the procedure used.

The alcohol was distilled off, the residue taken up in 100 cc. of water and the solution extracted with ether, removing about 0.5 g. of unchanged ester. The aqueous layer, carefully acidified with 4 *N* sulfuric acid, gave a white gummy precipitate which was taken up in ether and dried over anhydrous sodium sulfate. From this solution there was obtained a slightly yellow oil which solidified on cooling. Recrystallized from 30% alcohol (after decolorizing with Norite) there was obtained a colorless solid, m. p. 96–97°.[10]

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.3. Found: C, 74.7; H, 8.3.

2,4,5-Trimethylhydrocinnamic Amide.—One gram of the acid was treated with phosphorus pentachloride and, without isolating the chloride, the reaction mixture was poured into iced ammonia; colorless needles, m. p. 152–154° when crystallized from 35% alcohol.

Anal. Calcd. for $C_{12}H_{17}ON$: C, 75.5; H, 8.91. Found: C, 75.3; H, 9.05.

Synthesis of 2,4,5-Trimethylhydrocinnamic Acid

I. **Dural malonic ester** $(CH_3)_3C_6H_2CH{=}C(COOC_2H_5)_2$ was prepared in 42% yield from 3.5 g. of durylic aldehyde, and 3.8 g. of malonic ester by heating them together on the steam-bath for eleven hours, adding initially two drops of piperidine and then one drop each hour. The reaction product was purified in the usual way, yielding 3 g. of ester, b. p. 182–186 at 11 mm. It was not analyzed.

II. **Dural Malonic Acid** $(CH_3)_3C_6H_2CH{=}C(COOH)_2$.—The ester was hydrolyzed by boiling it with an excess of aqueous 15% sodium hydroxide for three and one-half hours, adding water occasionally to keep the salt in solution. The cooled solution was extracted with ether, then acidified with 4 *N* sulfuric acid, and kept in the ice box overnight. The solid was recrystallized twice from 85% alcohol, giving 1.6 g. of fine colorless crystals of m. p. 183–185° with dec.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 5.98. Found: C, 66.5; H, 5.95.

III. **2,4,5-Trimethylcinnamic Acid.**—Dural malonic acid (1.2 g.) was heated to 190–200° until the evolution of carbon dioxide ceased. Recrystallized from dilute alcohol, there resulted 0.7 g. of colorless plates, m. p. 154–155°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.9; H, 7.36. Found: C, 76.1; H, 7.23.

IV. **2,4,5-Trimethylhydrocinnamic Acid.**—The unsaturated acid (170 mg.) was dissolved in 20 cc. of 95% alcohol and reduced by the method of Adams and Voorhees;[11] 25 mg. of platinum oxide was used as the catalyst, and the reduction required forty-five minutes. The catalyst was filtered off, the alcohol removed *in vacuo*, and the residue, a colorless oil, solidified on cooling. A single crystallization from 40% alcohol yielded 0.15 g. of the hydrocinnamic acid, melting point, and mixed melting point with the acid obtained from the reaction of ethyl diazoacetate on durene, 96–97°.

Summary

1. Ethyl diazoacetate has been added to durene. The only homogeneous product obtained was 2,4,5-trimethylhydrocinnamic acid, the reaction resulting in the introduction of an acetic ester residue into one of the methyl groups.

2. A synthesis of 2,4,5-trimethylhydrocinnamic acid from durylic aldehyde is described.

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[10] Willgerodt, *J. prakt. Chem.*, [2] **81**, 390 (1910), gives the m. p. as 92°.

[11] "Organic Syntheses," J. Wiley & Sons, Inc., New York, 1928, Vol. VIII, p. 10.

MINNEAPOLIS, MINNESOTA RECEIVED JULY 27, 1934

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Studies on the Polymethylbenzenes. X. Reaction with Aromatic Diazonium Compounds[1]

BY LEE IRVIN SMITH AND JOSEPH H. PADEN

Meyer and Schoeller[2] were the first to couple diazotized amines with hydrocarbons, obtaining crystalline azo compounds by coupling diazotized *p*-nitraniline and 2,4-di-nitroaniline with butadiene and some of its derivatives. The reaction failed, however, when applied to such hydrocarbons as mesitylene and anthracene, although the solutions showed colors which indicated some formation of azo compounds. In 1920 Misslin[3] succeeded in diazotizing picramide, and with this diazonium compound available, Meyer and Tochterman[4] succeeded in coupling it with mesitylene, obtaining a beautifully crystalline azo compound. With toluene and *m*-xylene no product could be isolated, although the solutions showed colors indicating the formation of some azo compounds, while with benzene there was not even the development of any color.

These experiments of Meyer indicated that the coupling of diazonium compounds with aromatic hydrocarbons was promoted by negative groups in the diazotized amine and by methyl groups in

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[1] Abstracted from a thesis by Joseph H. Paden, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science, July, 1933.

[2] Meyer and Schoeller, *Ber.*, **47**, 1711 (1914); *ibid.*, **52**, 1468 (1919).

[3] Misslin, *Helv. Chim. Acta*, **3**, 626 (1920).

[4] Meyer and Tochterman, *Ber.*, **54**, 2283 (1921).