g. of *l*-tyrosine in 139 ml. of water and 28 ml. of 6 *N* sodium hydroxide, the temperature of the reaction mixture being maintained at 30–40°. The clear yellow solution was kept at 40° for four hours and then 98% of the theoretical amount of 6 *N* sulfuric acid was added to the solution. The sirupy residue obtained upon evaporation of the solvent[14] was taken up in 200 ml. of absolute ethanol, the solution filtered, evaporated, the residue dissolved in 200 ml. of absolute ethanol and the solution again evaporated. The residue was then dissolved in 100 ml. of absolute ethanol, the solution saturated with anhydrous hydrogen chloride and refluxed for two hours. The reaction mixture was evaporated *in vacuo* to a thick sirup which upon treatment with *M* sodium carbonate crystallized to give, after washing and drying, 11.4 g. (55%) of XII, m. p. 130–132°. On recrystallization from water XII was obtained as well-defined colorless rhombic or hexagonal prisms, m. p. 133–134°. The recrystallized product was insoluble in dilute hydrochloric acid and in dilute sodium carbonate and soluble in dilute sodium hydroxide. It was optically inactive and gave a positive Folin–Denis reaction.

Anal. Calcd. for $C_{18}H_{17}O_4N$ (251): C, 62.1; H, 6.8; N, 5.6. Found: C, 62.4; H, 6.9; N, 5.7.

***dl*-α-Acetamido-β-[4-(2′,6′-diiodo-4′-nitrophenoxy)-phenyl]-propionic Acid Ethyl Ester (XIII).**—The procedure for the preparation of XIII was identical with that used for the preparation of IX. From 59 g. of XIII and 34 g. of 3,4,5-triiodonitrobenzene there was obtained, after one recrystallization from 70% acetic acid, 42.5 g. (58%) of XIII, m. p. 192–193°.

Anal. Calcd. for $C_{19}H_{19}O_6N_2I_2$ (624): C, 36.6; H, 2.9. Found: C, 36.6; H, 2.9.

***dl*-α-Acetamido-β-[4-(2′,6′-diiodo-4′-nitrophenoxy)-phenyl]-propionic Acid (XIV).**—The hydrolysis of 16 g. of XIV conducted as previously described for the preparation of X gave after recrystallization from Cellosolve 9.6 g. of XIV, m. p. 257° with decomposition.

Anal. Calcd. for $C_{17}H_{14}O_6N_2I_2$ (596): C, 34 3; H, 2.4. Found: C, 34.4; H, 2.5.

***dl*-α-Acetamido-β-[4-(2′,6′-diiodo-4′-aminophenoxy)-phenyl]-propionic Acid (XV).**—The procedure which proved to be successful for the preparation of IV failed to give satisfactory yields of XV nor was any other method found to be suitable. A sample of XV recrystallized from 70% acetic acid melted at 226° with decomposition.

Anal. Calcd. for $C_{17}H_{16}O_4N_2I_2$ (566): C, 36.1; H, 2.9. Found: C, 36.1; H, 2.9.

(14) See V. du Vigneaud and C. E. Meyer, *J. Biol. Chem.*, **98**, 295 (1932).

Summary

The synthesis of 2′,6′-diiodo-*dl*-thyronine and of N-acetyl-*dl*-tyrosine ethyl ester has been described.

PASADENA, CALIF. RECEIVED JULY 18, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

The Nitration of Brominated Fluorophenols by the Zincke Method[1]

BY L. CHAS. RAIFORD AND ARTHUR L. LEROSEN

In earlier work Raiford and Heyl[2] have shown that iodine or bromine, but not chlorine, atoms situated in *o*- or *p*-positions to the hydroxyl group of a phenol can be replaced by the nitro group in the Zincke method of nitration.[3] It was found that when two bromine atoms were present in *o*- and *p*-positions to the phenolic group, either could be removed, yielding isomeric nitrobromophenols. Later Raiford and Miller[4] studied chlorobromophenols and found that when both halogens occurred in the favorable positions mentioned, only the bromine was replaced.

The present work shows that when bromofluorophenols are treated with sodium nitrite in glacial acetic acid the fluorine is never displaced while, with one exception, any of the favorably situated bromine atoms was removed. Hodgson and Nixon[5] have found that the nitro group in 2-nitro-3-fluorophenol migrates to the 6-position during bromination of this compound and that on treatment with nitric acid the 6-bromine atom of 2,4,6-tribromo-3-fluorophenol is replaced by the nitro group. In agreement with this behavior we have found that the 2-bromine atom of the latter compound is in no case replaced in the Zincke procedure while the 4- and 6-bromine atoms react easily.

When 2,6-dibromo-4-fluorophenol was treated with sodium nitrite in glacial acetic acid, 2-bromo-4-fluoro-6-nitrophenol was the only product isolated. The isomeric 2-fluoro-4,6-dibromophenol gave both of the expected isomers, *viz.*, 2-fluoro-4-nitro-6-bromophenol, and 2-fluoro-4-bromo-6-nitrophenol. These compounds were separated on the basis of the greater solubility of the para compound in dilute acetic acid and its non-volatility with steam.[6] The *o*- and *p*-positions were assigned to the nitro group in these compounds on the basis of their color, melting points, volatility with steam, and their solubility.

Experimental[7]

Starting Materials.—The preparation of the three fluorobromophenols used for this study will be described later.[8]

(1) From a thesis submitted by Arthur L. LeRosen in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Graduate College of the State University of Iowa, June, 1940.

(2) L. C. Raiford and F. W. Heyl, *Am. Chem. J.*, **43**, 393 (1910); **44**, 209 (1911).

(3) T. Zincke, *J. prakt. Chem.*, [2] **61**, 563 (1900), first used nitrous acid to replace a bromine atom by the nitro group in bromine substituted phenols.

(4) L. C. Raiford and G. R. Miller, THIS JOURNAL, **55**, 2125 (1933).

(5) H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 273 (1932).

(6) L. C. Raiford, *Am. Chem. J.*, **46**, 417 (1911); THIS JOURNAL, **44**, 158 (1922); Sidgwick, "The Electronic Theory of Valency," Oxford University Press, London, 1929, p. 148.

(7) Melting points are uncorrected. Samples for analyses were decomposed in the Parr bomb and the bromine was determined by the Volhard method.

(8) L. C. Raiford and A. L. LeRosen, submitted for publication.

Nitration of 2,6-Dibromo-4-fluorophenol.—Three grams of sodium nitrate was added during forty-five minutes, with stirring, to a solution of 5.9 g. of 2,6-dibromo-4-fluorophenol in 50 ml. of glacial acetic acid at 14–18°. After fifteen minutes the mixture was poured into water; then the precipitate was removed by filtration and dried. A yield of 72% was obtained. Recrystallization from chloroform gave yellow needles melting at 67°.

Anal. Calcd. for $C_6H_3O_3NBrF$: Br, 33.85. Found: Br, 34.07.

Nitration of 2-Fluoro-4,6-dibromophenol.—Two grams of sodium nitrate was added during an hour to 5.17 g. of this compound in constantly stirred glacial acetic acid solution. Fifteen minutes after the addition was complete the reaction mixture was poured into water. The precipitated solid was filtered off and steam-distilled to give 1.34 g. (32%) of the bright yellow *o*-nitro derivative, *viz.*, 2-fluoro-4-bromo-6-nitrophenol, m. p. 62°.

Anal. Calcd. for $C_6H_2O_3NBrF$: Br, 33.85. Found: Br, 34.19.

The solution from which the *o*-nitro compound had been precipitated was evaporated to a small volume and the residue concentrated further *in vacuo*. On dilution of the residue with a little water and cooling the para compound was precipitated. After crystallization from chloroform 1.03 g. (25%) of colorless granular crystals, m. p. 101°, was obtained.

Anal. Calcd. for $C_6H_2O_3NBrF$: Br, 33.85. Found: Br, 34.23.

Nitration of 2,4,6-Tribromo-3-fluorophenol.—A solution of 34.9 g. of this compound in 300 ml. of glacial acetic acid at 18° was treated with 10.5 g. of sodium nitrate which was added during the period of one hour. The reaction mixture was poured into water and steam-distilled as long as volatile material was carried over. The solid volatile product was collected and recrystallized several times from dilute alcohol to yield 20 g. (63%) of yellow needles melting at 76°.[5] Some starting material, 2.6 g. (7%), was recovered from the mother liquor.

Anal. Calcd. for $C_6H_2O_3NBr_2F$: Br, 50.74. Found: Br, 50.87.

The residue from the steam distillation was evaporated *in vacuo* to a small volume then diluted with a little water and cooled in an ice-bath. In this way a precipitate was obtained. After drying, the precipitate was extracted with chloroform. This extract yielded 2.5 g. (8%) of colorless granules melting at 122° with decomposition. These properties indicate the presence of the *p*-nitro isomer, *viz.*, 2,6-dibromo-3-fluoro-4-nitrophenol.

Anal. Calcd. for $C_6H_2O_3NBr_2F$: Br, 50.74. Found: Br, 50.57.

The bright yellow chloroform-insoluble residue (6.4 g., 17%) was found to be the hydrated sodium salt of the 4-nitro derivative.

Anal. Calcd. for $C_6HO_3NBr_2Na\cdot 2.5H_2O$: Br, 41.84; wt. loss at 110°, 11.78. Found: Br, 41.68; wt. loss, 11.08.

Nitration of 3-Fluoro-4,6-dibromophenol.—Thirty grams of the phenol in 60 ml. of glacial acetic acid was treated with 150 ml. of concd. nitric acid containing 6 ml. of concd. sulfuric acid. After an hour the reaction mixture was poured into water. After drying 35 g. (100%) of the product was obtained. It melted at 75.5°[5] and showed a depression of 10° when mixed with the 2,4-dibromo-3-fluoro-6-nitrophenol (see above).

Anal. Calcd. for $C_6H_2O_3Br_2NF$: Br, 50.74. Found: Br, 50.60.

Summary

When brominated by the Zincke method 2,4,6-tribromo-3-fluorophenol gives 2,4-dibromo-3-fluoro-6-nitrophenol and 2,6-dibromo-3-fluoro-4-nitrophenol; 2-fluoro-4,6-dibromophenol yields 2 fluoro-4-bromo-6-nitrophenol and 2-fluoro-4-nitro-6-bromophenol, and 2,6-dibromo-4-fluorophenol gives 2-bromo-4-fluoro-6-nitrophenol.

RECEIVED AUGUST 4, 1944

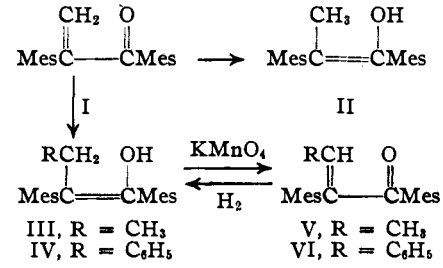
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Vinyl Alcohols. XIV.[1] Condensation of Grignard Reagents with α,β-Unsaturated Ketones

BY REYNOLD C. FUSON, D. J. BYERS,[2] STANLEY P. ROWLAND,[3] PHILIP L. SOUTHWICK[4] AND CARLETON A. SPERATI

The formation of stable propenols by the addition of hydrogen to the corresponding α,β-unsaturated ketones[5] ought to be capable of extension to the addition of other typical carbonyl reagents. In the present work it has been shown that the Grignard reagent can be used.

By the condensation of mesityl α-mesitylvinyl ketone (I), with methylmagnesium iodide, for example, 1,2-dimesityl-1-buten-1-ol (III) was produced. It was characterized by conversion to an acetate and by oxidation. Potassium permanganate produced the corresponding unsaturated ketone (V). Oxygen cleaved the enol, yielding mesitoic acid and propiomesitylene. Hydrogenation of the butenone (V) regenerated the butenol (III).



A similar series of observations was made when phenylmagnesium bromide was used. The enol (IV) in this case was much more stable than was the analogous propenol without the phenyl group (II). Attempts to ketonize the phenylpropenol

(1) For the preceding communication in this series see Fuson, Armstrong, Kneisley and Shenk, THIS JOURNAL, **66**, 1464 (1944).

(2) Du Pont Post-doctorate Research Fellow, 1940–1941.

(3) Du Pont Fellow in Chemistry, 1942–1943.

(4) Abbott Fellow, 1942–1943.

(5) (a) Fuson, Corse and McKeever, THIS JOURNAL, **62**, 3250 (1940); (b) Fuson and Sperati, *ibid.*, **63**, 2643 (1941).