

alga *Chlorella pyrenoidosa* with the known equilibrium constants for simple carboxylation reactions of this general type shows a difference in order of magnitude of something like 10^7 . It appears therefore that the primary reaction of carbon dioxide in photosynthesis does not consist solely of carboxylation but must be a more complex sequence of reactions.

A new formulation of the mechanism of photosynthesis is briefly presented which offers a plausible model for the fixation and reduction of carbon dioxide not only for green plant photosynthesis but also for carbon dioxide fixation and reduction by the many different chemosynthetic and heterotrophic organisms.

BERKELEY, CALIF.

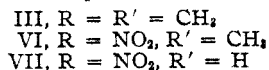
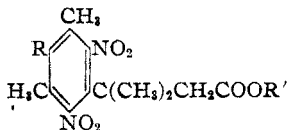
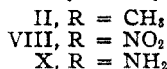
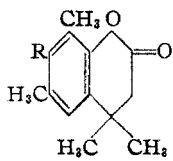
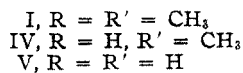
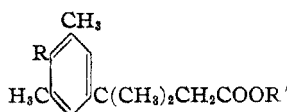
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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Nitration of β -Polyalkylphenylisovaleric Acids. II. β -[3,5-Dimethylphenyl]-isovaleric Acid¹

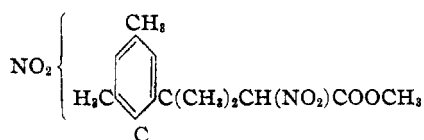
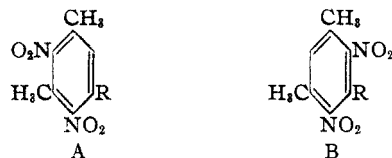
BY LEE IRVIN SMITH AND LEO J. SPILLANE²

Nitration of methyl β -[3,4,5-trimethylphenyl]-isovalerate I at low temperatures, by action of potassium nitrate and sulfuric acid in the presence of chloroform, has been shown to give two crystalline compounds in almost equal amounts. The structure of one of these was established as the nitrohydrocoumarin II; but the structure of the other was not established. This second sub-



stance gave analytical values well in accord with those required by III, the dinitro derivative of I, but the chemical behavior of the substance was so peculiar that structure III appeared rather unlikely.¹ In order to investigate further this peculiar reaction, and to gain more information concerning the structure of the compounds formed, a study has been made of the nitration of a lower homolog of I, methyl β -[3,5-dimethylphenyl]-isovalerate IV and the corresponding acid V.³

Nitration of a chloroform solution of the ester IV by action of potassium nitrate and sulfuric acid gave a mixture of two products. The major part (79%) consisted of an oily nitrosulfonic acid, and the remainder was a crystalline compound which had the composition C₁₄H₁₅O₅N₂, a dinitro derivative of IV.



When the ester IV was nitrated at room temperature by action of sulfuric acid and fuming nitric acid, an excellent yield of a crystalline trinitro ester (VI) was obtained, together with a small amount of a trinitro acid (VII). Further nitration of the dinitro ester produced VI; moreover, the trinitro ester VI could be hydrolyzed to the trinitro acid VII, and the latter could be reconverted into the ester VI by action of methanol and sulfuric acid. All of these nitro compounds, when warmed with alkali, gave cherry-red solutions.⁴ It appeared, therefore, that the structure of these dinitro compounds was most likely A or B, but in view of the very peculiar properties of the trinitro ester III, structure C also had to be considered.

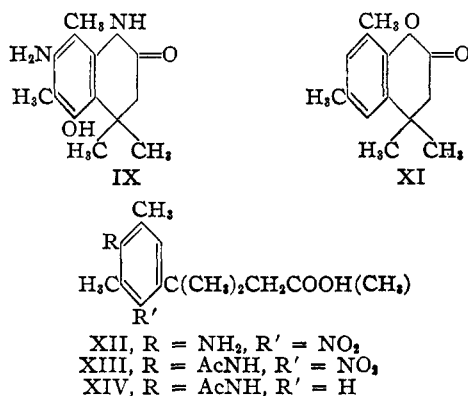
(4) Hoffman, *ibid.*, **51**, 2542 (1929), noted a similar behavior when the nitro derivative of methyl β -phenyl isobutyl ketone was dissolved in alkali.

(1) Paper I, THIS JOURNAL, **62**, 780 (1940).

(2) Abstracted from a thesis by L. J. Spillane, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1942.

(3) Smith and Spillane, THIS JOURNAL, **65**, 202 (1943).

When a solution of the trinitro acid VII in quinoline was heated with copper chromium oxide catalyst, much nitrogen oxides, together with some carbon dioxide, were evolved. The product was the dinitrohydrocoumarin VIII. This substance was insoluble in bicarbonate solution, but it gave a cherry-red solution in methanolic potassium hydroxide, from which it could be recovered unchanged on acidification. Reduction of VIII with zinc and acetic acid gave an unstable amphoteric compound which could not be isolated, but whose solution gave a strongly positive phenol



test (Folin). By analogy with the behavior of II, this phenolic substance was most likely the aminohydroxyhydrocarbostyryl IX. When VIII was reduced by action of ammonium sulfide, there resulted a yellow aminonitro compound, X, but this could not be purified sufficiently to give good analytical values. Since the results obtained by reduction of VIII were inconclusive in establishing the structure, VIII was synthesized from 2,4-dimethylphenol and β,β -dimethylacrylic acid. The two reagents reacted smoothly in the presence of aluminum chloride, and the product was the hydrocoumarin XI. This easy condensation of a phenol and this α,β -unsaturated acid to give a hydrocoumarin is to be contrasted with similar reactions between phenols and α,β -unsaturated ketones which, under the same conditions, give ill-defined, amorphous products.⁵ Nitration of the hydrocoumarin XI gave a dinitro derivative which was identical with VIII obtained from the trinitro acid VII. The synthesis of VIII by two independent methods showed that no rearrangement had occurred during the reaction between 2,4-dimethylphenol and β,β -dimethylacrylic acid; moreover, these reactions, together with the properties of the trinitro compounds VI

and VII, showed that all three of the nitro groups in VI and VII were attached to the ring. Therefore, structure C was eliminated for the dinitro compounds, and the possible structures for these were confined to A and B, both of which were nuclear dinitro compounds.

The dinitro ester was indifferent to the action of acetic anhydride and sulfuric acid; likewise, no reaction occurred when the dinitro ester was heated to 100° with hydrochloric acid. Reduction with zinc and acetic acid converted the dinitro ester into an unstable, amphoteric compound, probably an aminohydrocarbostyryl, but the product could not be isolated. Catalytic reduction converted the dinitro ester into a mixture of two solid products, but neither of these could be purified sufficiently to give analytical values which could be interpreted. The action of oxidizing agents either failed to attack the dinitro ester or else destroyed it completely. Action of sulfuric acid at room temperature converted the dinitro ester into the corresponding acid, and the acid could be esterified by action of methanol and sulfuric acid to give the original dinitro ester. Action of quinoline and a copper chromium oxide catalyst had little effect upon the dinitro acid and produced no hydrocoumarin; most of the acid was recovered unchanged, and only a very faint positive test for oxides of nitrogen (nitrite) was obtained. More strongly alkaline reagents either had no effect upon the acid, or converted it into brown amorphous materials.

Reduction of the dinitro ester by ammonium sulfide produced a yellow aminonitro ester XII. In analogy with the results of Baur-Thurgau on the structure and behavior of the nitration products of 3,5-dimethyl-*t*-butylbenzene,⁶ this aminonitro ester was assigned the structure indicated (XII). This amino ester XII formed an acetyl derivative (XIII), and it appeared likely that XIII could be synthesized by nitration of the acetamino acid (or ester) XIV, which in turn could be synthesized by condensation of 2,6-dimethylacetanilide with β,β -dimethylacrylic acid. However, attempts to bring about this condensa-

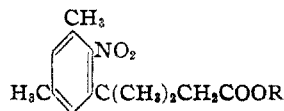
(6) Baur-Thurgau, *Ber.*, **33**, 2562 (1900). The results of Baur-Thurgau do not fix unequivocally the structures of the mono- and dinitro derivatives of this hydrocarbon. Although the results are consistent within themselves, the data agree equally well with either of two assumptions—that the first nitro group entered the 4-position and the second entered the 2-position or that the first nitro group entered the 2-position and the second entered the 4-position. Baur-Thurgau chose the first of these assumptions, and although he supplied no proof for the orientations of his compounds, his work did demonstrate that only nuclear nitration occurred.

(5) Smith and Prichard, *THIS JOURNAL*, **62**, 776 (1940).

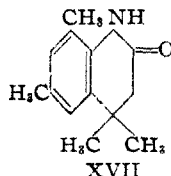
tion under a variety of conditions all resulted in failure. The nitroamino ester XII was hydrolyzed to the corresponding acid by action of hydrochloric acid; this nitroamino acid (XII) could also be prepared by action of ammonium sulfide upon the dinitro acid A but, when prepared this way, the acid XII was very difficult to purify.

The aminonitro acid XII was not converted into a nitrohydrocarbostyryl when it was boiled with mineral acid, or when its solution in alkali was acidified. It has been found that either of these conditions, when applied to amino acids of this series, results in an extremely stable hydrocarbostyryl whenever the amino group is located ortho to the acid side chain. It followed, therefore, that the amino group in XII could not occupy a position ortho to the acid side chain but must have been in the para position to this group. With this fact established, the only possible structures for the dinitro compounds—ester and acid—are represented by A.

Fortunately, it was possible to obtain evidence which confirmed this conclusion. Nitration of the ester or acid A by action of fuming nitric acid in acetic anhydride produced mononitro derivatives (XV and XVI) of each. The ester and the acid, XV and XVI, were interconvertible by hydrolysis or esterification, and when either the ester or the acid was reduced by action of zinc and acetic acid, there resulted the hydrocarbostyryl XVII. Formation of XVII definitely located the nitro group in XV and XVI in the ortho position to the acid side chain. Since it was shown that the nitro group in XV and XVI was in the ortho position, and the amino group of the aminonitro acid XII was in the para position, the



XV, R = CH₃
XVI, R = H



XVII

only possible structure for the dinitro compounds was A.

Further nitration of the mononitro ester XV under conditions identical with those used for formation of A from IV gave a mixture which was difficult to separate into pure compounds. But by allowing a solution of this product in methanol to crystallize slowly, it was possible to separate

the crystals manually and to obtain a considerable amount of the dinitro ester A. When the mononitro ester XV was nitrated by action of sulfuric and fuming nitric acids, the product was the trinitro ester VI.

All of the relationships discussed are consistent among themselves and they can lead only to these conclusions: under the conditions used in these experiments, nitration of β -[3,5-dimethylphenyl]-isovaleric acid V, or of its methyl ester IV, is entirely confined to the aromatic nucleus; the first nitro group enters the position ortho to the acid side chain; the second nitro group enters the para position and the dinitro derivatives must be represented by structure A; in the trinitro compounds, VI and VII, all three nitro groups are attached to the aromatic nucleus. It follows that the dinitro compound obtained by Smith and Prichard by nitration of methyl β -[3,4,5-trimethylphenyl]-isovalerate I must almost certainly have been the nuclear dinitro compound III. The very peculiar behavior of such nitro compounds as III, VI, XV, and A toward alkaline reagents and on reduction is, therefore, not due to the presence of aliphatic nitro groups in the side chains, but must be inherent in the nature of the aromatic nitro compounds themselves. This phase of the chemistry of these compounds is still under investigation; also to be investigated is the nature of the nitrosulfonic acid obtained when the ester IV is subjected to the action of potassium nitrate in sulfuric acid.

Experimental Part⁷

Methyl β -[3,5-Dimethyl-2,4-dinitrophenyl]-isovalerate (A).—A solution of the ester IV¹ (15.82 g.) in chloroform (55 cc.) was carefully poured over sulfuric acid (100 cc.). The mixture was kept below -15° in a bath of Dry-Ice, and to it was slowly (one and one-quarter hours) added, with vigorous stirring, a solution of potassium nitrate (24.1 g.) in sulfuric acid (45 cc.). The initial orange-red color faded to yellow when about a third of the nitrating solution had been added. After all the nitrating solution was added, the mixture was allowed to stand until the temperature reached 5° . It was then poured over a large quantity of ice, the chloroform layer was removed, and the aqueous layer was extracted with four 30-cc. portions of chloroform. The combined chloroform solutions were washed twice with water, once with bicarbonate (10%) and again with water, and the chloroform was removed by distillation under reduced pressure. The residue (4.6 g.) was a yellow oil which solidified when it was cooled and rubbed with a little methanol. After four recrystallizations from methanol, the substance formed white prisms which melted at $73.5\text{--}74^\circ$.

(7) Microanalyses by Stanley Rolfsen and E. E. Renfrew.

Anal. Calcd. for $C_{14}H_{19}O_3N_2$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.18; H, 5.91; N, 9.03.

When the aqueous residues were further diluted, a heavy oil precipitated. This oil was removed, and the aqueous solution was extracted with ether. The wet oil was only slightly soluble in ether, but it was fairly soluble in water and completely soluble in dilute sodium carbonate solution. The ethereal extracts were combined with the oil and the mixture was dried (sodium sulfate). As the water was removed, the oil became soluble in the ether. Removal of the ether left a viscous yellow oil (16 g.). This substance, apparently a nitrosulfonic acid, was not investigated further.

Much better yields of the ester A and much less of the nitrosulfonic acid were obtained as follows. A solution of potassium nitrate (10.1 g., 0.10 mole) in sulfuric acid (80 cc.) was added dropwise over a period of forty minutes to a well cooled (below 5°) and vigorously stirred solution of the ester IV (10.03 g., 0.00456 mole) in chloroform (35 cc.). Stirring was continued for twenty minutes after addition was complete, and then the cooling bath was removed and the mixture was allowed to reach a temperature of 10°. It was then poured over ice and processed as described above. The dinitro ester A, after one crystallization from methanol, weighed 9.17 g. (65%) and melted at 70–72°.

The dinitro ester A (0.08 g.) was refluxed for ten minutes with acetic anhydride (3 cc.) containing a drop of sulfuric acid. When the solution was poured into water, unchanged ester, m. p. and mixed m. p. 72–74°, was recovered. The ester also survived action of hydrochloric acid at 100° for thirty minutes.

The dinitro ester (0.153 g.) was shaken with a mixture of granulated tin (1.0 g.) and hydrochloric acid (1 cc.) containing a little methanol. The solution was decanted from the tin into water (10 cc.); a perfectly homogeneous solution resulted. This was made alkaline with potassium hydroxide (20%) and extracted with ether. No residue remained when the ether was evaporated. A portion of the aqueous layer was acidified with hydrochloric acid; it then gave a deep purple color when a few drops of alcoholic ferric chloride was added. Much the same results were obtained when the dinitro ester was reduced with zinc and 80% acetic acid. Catalytic reduction of the dinitro ester (0.247 g.) in methanol (10 cc.) under 38 lb. and with a platinum oxide catalyst had to be repeated twice before any change occurred. The solution had the odor of an aliphatic amine or ammonia, and the product was an oil which solidified after it was washed with water. The product (73 mg.) melted at 86.5–90° after recrystallization from methanol. It was apparently an amine, for it was soluble in dilute hydrochloric acid. Acetylation produced a solid which, after several crystallizations from aqueous methanol, melted at 138.5–139.5°. The acetyl derivative was analyzed, but the data did not agree with those required by any simple derivative of the dinitro ester.

Anal. Found: C, 59.6; H, 6.88.

Dilute nitric acid (1 cc., 2:1) and hydrogen peroxide (30%, 1 cc.) were added to a solution of the dinitro ester (0.1 g.) in acetic acid (3 cc.). The solution was heated to the boiling point, then cooled, poured into water and extracted with ether. The ether solution was extracted with sodium carbonate (10%). Removal of the ether left a

residue of impure ester (m. p. 58–67°); acidification of the carbonate solution produced no precipitate. The dinitro ester (0.15 g.) in acetic acid (7 cc.) was refluxed for twenty minutes with a solution of potassium permanganate (0.57 g.) in water (7 cc.). The sludge of manganese oxides was filtered, and the filtrate was made alkaline and again filtered. The colorless filtrate was acidified (litmus) with hydrochloric acid and evaporated until solid began to deposit. Water was added to the cooled mixture until the solid just dissolved; then saturated barium chloride (3 cc.) was added. No precipitate formed. A similar result was obtained when the dinitro ester was refluxed with an alkaline solution of potassium permanganate.

The dinitro ester (0.33 g.) was refluxed for thirty minutes with methanol (4 cc.) and sodium hydroxide (4 N, 4 cc.). The cooled cherry-red solution was added rapidly to cold dilute sulfuric acid (1:5, 24 cc.) in an apparatus arranged for collection of any evolved gases. No gas was evolved. The tan solid (0.316 g., m. p. 162–180°) was crystallized several times from aqueous methanol, but no pure material could be obtained. The crystallized solid melted at 194–202° with decomposition. It gave a deep greenish-blue color with alcoholic ferric chloride, and it was apparently not an acid for it was recovered unchanged when it was refluxed for an hour with methanol containing some sulfuric acid.

β -[3,5-Dimethyl-2,4-dinitrophenyl]-isovaleric Acid (A).—The ester (7.13 g.) was dissolved in sulfuric acid (90 cc.) and the solution was allowed to stand at room temperature for sixteen hours. The solution was poured over ice, and the solid was removed and crystallized first from aqueous acetic acid and then three times from a mixture (30 cc.) of benzene and petroleum ether (b. p. 60–68°). The acid (5.79 g.) then melted at 153–154.5°.

Anal. Calcd. for $C_{18}H_{21}O_5N_2$: C, 52.7; H, 5.46; N, 9.03. Found: C, 52.6; H, 5.63; N, 9.03.

The acid (0.04 g.) was refluxed for forty-five minutes in methanol (2 cc.) containing sulfuric acid (0.3 cc.). The product, isolated in the usual way, was the ester A (0.024 g.), m. p. and mixed m. p. 72–73°.

The acid (0.6 g.) was heated with quinoline (3 cc.) and a small amount of copper chromium oxide catalyst. Only a small amount of gas was evolved even when the mixture was heated at 225–235° for twenty minutes. The gas was passed through dilute sodium hydroxide solution, but only a faint test for nitrite could be obtained from the solution. The organic product was diluted with water, acidified with hydrochloric acid, and extracted thoroughly with ether. Removal of the ether left a small amount of a black oil from which no pure material could be obtained.

The acid (0.2 g.) was dissolved in 1 N sodium hydroxide (10 cc.) and the solution was refluxed for forty-five minutes. The initially colorless solution gradually became orange-red; acidification produced a tan precipitate which was impure acid. After crystallization from acetic acid, it melted at 152.5–154.5°. The dinitro acid (10.5 g.) was refluxed for one hour with a solution of sodium (0.12 g.) in dry methanol (5 cc.). The orange solution was diluted with water and acidified; the recovered acid melted at 146–152°. The filtrate from the acid contained no nitrite. As the concentration of the alkali was increased, less acid could be recovered. Finally, when the acid (about 0.2 g.)

was refluxed with a solution of sodium (1.2 g.) in methanol (10 cc.), or with a solution of aqueous potassium hydroxide (2 cc., 50%) in methanol (4 cc.), only brown amorphous products could be recovered, but still no nitrite could be detected in the solution.

Methyl β -[3,5-Dimethyl-2,4,6-trinitrophenyl]-isovalerate (VI).—The ester IV (10.35 g.) was slowly (one hour) added to a cooled (3°) and vigorously stirred mixture of fuming nitric acid (d. 1.5) and sulfuric acid (1:1.2, 60 cc.). The mixture was slowly (forty-five minutes) allowed to attain room temperature and was poured over crushed ice. The yellow solid was removed, dissolved in hot methanol (200 cc.) and the solution was set aside in the refrigerator. The trinitro ester (14.3 g., 86%) crystallized in long yellow needles which melted at 121–124°. The color was very difficult to remove, but after five crystallizations from 200-cc. portions of methanol, the substance was white and it melted at 127–127.5°.

Anal. Calcd. for $C_{14}H_{17}O_8N_3$: C, 47.32; H, 4.82; N, 11.82. Found: C, 47.69; H, 4.82; N, 11.73.

When the dinitro ester A (0.1 g.) was nitrated with the same nitrating mixture (2 cc.) and according to the above procedure, the product (0.098 g.) was the same trinitro compound, m. p. and mixed m. p. 126–127°.

The trinitro ester (0.495 g.) was added to a cold solution of sodium hydroxide (1 N, 20 cc. in 50% methanol). No change occurred until the mixture was boiled, when the ester dissolved giving a cherry-red solution. After the solution was boiled for five minutes, it was cooled and acidified (litmus) with acetic acid. A brown flocculent precipitate (90 mg.) was removed. This material melted at 190–225° to a dark red liquid, and it gave a deep purple color with alcoholic ferric chloride. The filtrate was acidified more strongly; more solid was obtained. This melted at 183–192° to a viscous red liquid; it was insoluble in sodium bicarbonate, but dissolved readily in potassium hydroxide solution. The initial, brown material was crystallized several times from aqueous methanol, using a little Norite each time, and was finally obtained as shiny yellow needles which melted at 234–244° with decomposition. It was analyzed, but no structure could be written to agree with the analytical values.

Anal. Found: C, 49.05; H, 4.44.

β -[3,5-Dimethyl-2,4,6-trinitrophenyl]-isovaleric Acid (VII).—A solution of this ester (1.82 g.) in sulfuric acid (30 cc.) was allowed to stand at room temperature for two days. It was poured over ice and the product was removed, washed with water, and crystallized twice from dilute acetic acid. The acid formed white needles which melted at 194–198.5° with evolution of gas and formation of a red liquid.

Anal. Calcd. for $C_{13}H_{16}O_8N_3$: C, 45.74; H, 4.43. Found: C, 45.92; H, 4.35.

When this acid (33 mg.) was refluxed for twenty minutes with methanol (2 cc.) and sulfuric acid (0.3 cc.), the white product (17 mg.) was the ester VI, m. p. and mixed m. p. 127–128°.

The trinitro acid was recovered unchanged after its solution in acetic acid was boiled for half an hour.

4,4,6,8-Tetramethyl-5,7-dinitrohydrocoumarin (VIII).—The trinitro acid VII (1.80 g.) was dissolved in quinoline

(freshly distilled, 5 cc.) in a distillation flask so arranged that a current of gas could be swept through the apparatus and into a solution for absorption of gases. Copper-chromium oxide catalyst (24 mg.) was added to the solution, and a current of pure dry nitrogen was passed through the apparatus while the flask was heated in a metal bath. Evolution of gas began at 140° and was quite rapid at 170°. The temperature was maintained at 170–175° until no further evolution of gas occurred. Part of the time the exit gases were passed through potassium hydroxide solution (20%), and part of the time they were passed through a saturated solution of barium hydroxide. A fairly heavy precipitate of barium carbonate was formed in the latter solution. The potassium hydroxide solution was acidified with acetic acid. This solution, when tested with concentrated aqueous ferrous sulfate, gave a strong, positive test for the nitrite ion.

The residue in the distilling flask was diluted with water, acidified with acetic acid, and extracted thoroughly with ether. The combined ether extracts were washed successively as follows: water, twice with hydrochloric acid (3 N), water, dilute bicarbonate, hydrochloric acid, water. The solvent was removed, the residue was dissolved in hot methanol (50 cc.), and the solution was set aside in the refrigerator. The solid (0.97 g.) was removed and crystallized several times from methanol, using Norite until the solution was nearly colorless. The white product then melted at 163.5–164°.

Anal. Calcd. for $C_{13}H_{16}O_6N_2$: C, 53.05; H, 4.79. Found: C, 53.1; H, 4.83.

The dinitrohydrocoumarin gave no reaction with Tollens reagent, nor any with a cold solution of potassium permanganate in acetone. The phenol test (Folin) was negative. The substance dissolved very slowly in cold 4 N sodium hydroxide; the cold solution was yellow, but became cherry-red when it was heated. Acidification of the alkaline solutions precipitated the nitrohydrocoumarin, m. p. and mixed m. p. 163–163.5°. Reduction of VIII (0.197 g.) by refluxing it with acetic acid (80%, 5 cc.) and zinc (0.5 g., 20-mesh), gave an initially deep orange solution the color of which gradually faded. When this mixture was poured over ice, no precipitate formed, nor did any result when the diluted solution was made alkaline. A portion of the alkaline solution was acidified with acetic acid and tested for phenols (Folin); the test was strongly positive.

4,4,6,8-Tetramethyl-5-nitro-7-aminohydrocoumarin (X).—The dinitro compound VIII (0.5 g.), concentrated ammonium hydroxide (0.6 cc.), and absolute alcohol (1.5 cc.) were placed in a heavy-walled test-tube and the mixture was saturated with hydrogen sulfide. The tube was sealed, wrapped in a towel and heated on the steam-bath for three days. The mixture was diluted with water, acidified with acetic acid and boiled to expel alcohol and hydrogen sulfide. The yellow solid was removed and extracted on the filter with hot alcohol. The chilled alcoholic solution deposited the amino compound (0.13 g.) as yellow needles melting at 172–194°. The solid was extracted with hydrochloric acid (6 N), and reprecipitated with ammonia. This process was repeated, and then the substance was recrystallized three times from aqueous ethanol. The substance was pale yellow, softened at

188°, and melted at 192–197°. It was, however, not pure, and concordant analyses could not be obtained.

4,4,6,8-Tetramethylhydrocoumarin (XI).—A mixture of 2,4-dimethylphenol (3.7 g., 0.03 mole) and dimethylacrylic acid (3.0 g., 0.03 mole) was vigorously stirred and cooled in an ice-salt bath for fifteen minutes, after which a rapid stream of dry hydrogen chloride was passed through the mixture for three minutes. Aluminum chloride (4.56 g., 0.034 mole) was then slowly (twenty-five minutes) added; the cherry-red complex formed immediately, and the mixture soon became quite viscous. Petroleum ether (2 cc., b. p. 90–100°) was added, stirring was continued for twenty minutes longer, and then the cooling bath was removed and the mixture was stirred for a further three and one-half hours at room temperature and for one hour on the steam-bath. Additional aluminum chloride (0.64 g.) was added, and the mixture was stirred for an hour on the steam-bath. The very viscous red material was decomposed by addition of hydrochloric acid (20 cc.) and a little ice. The mixture was allowed to stand at room temperature for fourteen hours and the small amount of solvent was removed by steam distillation. The residual green oil solidified on cooling. It was extracted with ether (three 25-cc. portions) and the combined extracts were washed with water. Unchanged phenol and dimethylacrylic acid were removed by extracting the ether solutions three times with potassium hydroxide (10%), after which the solution was washed with water and the ether was evaporated. The crystalline residue was dissolved in alcohol (25 cc.), the solution was decolorized with Norite and filtered through Hyflo. The filtrate was concentrated to about 15 cc. and the hot solution was diluted with water to incipient turbidity and cooled. The hydrocoumarin (2.93 g., 45%, m. p. 95–103°) was removed and crystallized twice from alcohol (20 cc.). It then melted at 104.5–105°. No XI was obtained when this condensation was carried out in carbon disulfide.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.42; H, 7.90. Found: C, 76.70; H, 7.82.

The hydrocoumarin XI (2.09 g.) was slowly (thirty-five minutes) added to a cooled and stirred mixture (15 cc., 1:1.2) of fuming nitric acid (d. 1.5), and sulfuric acid. After the mixture was stirred for twenty minutes longer it was poured over ice and the solid product was removed, washed, and crystallized, first from alcohol (30 cc.) and then from methanol. The product (2.55 g., 85%) was the dinitrohydrocoumarin VIII, m. p. and mixed m. p., 163–164°.

Methyl β -[3,5-Dimethyl-2-nitro-4-aminophenyl]-isovalerate (XII).—The dinitro ester A (2.94 g.) was dissolved in a mixture of ammonium hydroxide (29%, 2.4 g.) and methanol (11 cc.). The solution was saturated with hydrogen sulfide and was heated in a sealed tube at 100° for twenty-four hours. The solution was decanted from the sulfur, water was added, and the mixture was warmed on the steam-bath to remove the methanol and excess hydrogen sulfide. Addition of hydrochloric acid produced an oily solid which was filtered and washed with ether. The aqueous filtrate was extracted with ether (10 cc., extract discarded), combined with the solid and the suspension was made alkaline with sodium hydroxide (20%). The yellow solid was removed and crystallized twice from

aqueous methanol (15 cc.). The nitroamino ester (1.41 g.) formed bright yellow needles which melted at 91–92°.

Anal. Calcd. for $C_{14}H_{20}O_4N_2$: C, 59.99; H, 7.19. Found: C, 60.06; H, 6.82.

The acetyl derivative XIII (0.11 g.) was prepared from the ester (0.12 g.) in the usual way and crystallized twice from methanol (5 cc.). It was white and melted at 138.5–139°.

Anal. Calcd. for $C_{16}H_{22}O_5N_2$: C, 59.60; H, 6.88. Found: C, 59.96; H, 6.70.

β -[3,5-Dimethyl-2-nitro-4-aminophenyl]-isovaleric Acid (XII).—The above aminonitro ester (0.29 g.) was refluxed for one and one-quarter hours with hydrochloric acid (6 *N*, 3 cc.). The acid XII precipitated as the hydrolysis proceeded; the cooled suspension was made alkaline with ammonium hydroxide, filtered, and the filtrate was acidified with acetic acid. The solid was removed and crystallized from methanol. It formed yellow needles which melted at 176.5–179° with some decomposition.

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81. Found: C, 58.73; H, 6.49.

The above acid (1.44 g.) gave an acetyl derivative (1.0 g.) which melted at 187.5–188.5° (XIII). When the dinitro acid A was reduced by the procedure described above for the ester, the product was the aminonitro acid XII. But the crude product melted over a wide range (150–172°) and only after many crystallizations could a substance of proper melting point (175.5–178°, mixed m. p. 176–179°) be obtained. Even then, the substance was not analytically pure.

The acetyl derivative XIII (0.41 g.) of the acid XII was warmed with thionyl chloride (0.4 cc.). Excess thionyl chloride was removed by addition of solvent and evaporation of the solution under reduced pressure; this process was carried out three times with ether and once with carbon disulfide. Carbon disulfide (4 cc.) and aluminum chloride (0.12 g.) were added to the residue and the mixture was refluxed for four hours. Hydrogen chloride was evolved, but no hydrindone or any other solid product could be isolated from the black product.

2,6-Dimethylacetanilide (10.4 g.) was prepared from 2,6-xylydine (10.3 g.) in the usual way and crystallized from dilute alcohol. It melted at 179–180°; the recorded m. p. is 177°. This product (5.0 g.) and dimethylacrylic acid (3.07 g.) were dissolved in tetrachloroethane (25 cc.) and a rapid stream of hydrogen chloride was passed through the cooled (ice-salt) solution for ten minutes. Aluminum chloride (9.1 g.) was slowly (fifteen minutes) added to the cooled (5°) and stirred solution, and then the mixture was warmed on the steam-bath for a short time. Almost no hydrogen chloride was evolved, and the deep color of the mixture faded as the temperature was increased. A small sample of the reaction product was removed and steam distilled from hydrochloric acid. The residue contained only unchanged dimethylacetanilide. The remainder of the reaction mixture was saturated with hydrogen chloride, aluminum chloride (3.2 g.) was added, and heating on the steam-bath was continued for two hours. Nothing but a red oil could be isolated from this product.

(8) Hodgkinson and Limpach, *J. Chem. Soc.*, 77, 67 (1900).

Methyl β -Chloroisovalerate.—Sulfuryl chloride (66 g., 0.5 mole) and benzoyl peroxide (0.5 g.)⁹ were added to a solution of isovaleric acid (50 g., 0.5 mole) in carbon tetrachloride (75 g.). The mixture was refluxed until evolution of gases ceased (one and one-quarter hours). Methanol (300 cc.) and sulfuric acid (10 cc.) were added, and about 130 cc. of material was removed by distillation on the steam-bath. Methanol (50 cc.) was then added, the mixture was refluxed for two hours, and 150 cc. of liquid was removed by distillation. The residue was poured into water, extracted with ether, and the combined extracts were washed with water and dried (sodium sulfate). The solvent was removed and the residual oil was distilled under reduced pressure through a 6-in. packed column. The fraction boiling at 67–78° (17 mm.) was collected and re-fractionated. The ester (19.8 g., 28%) boiled at 69–72° (17 mm.).

Anal. Calcd. for $C_{10}H_{11}O_2Cl$: C, 47.85; H, 7.36. Found: C, 47.75; H, 7.35.

When refluxed with sodium hydroxide (5 cc., 25%) for forty minutes, the above ester (1.0 g.) gave the sodium salt of β , β -dimethylacrylic acid. The acid had a m. p. and mixed m. p. of 65–67.5°.

A solution of 2,6-dimethylacetanilide (3.0 g.) and methyl β -chloroisovalerate (2.77 g.) in nitrobenzene (8 cc.) was cooled (0°) and was vigorously stirred while aluminum chloride (5.32 g.) was added. No hydrogen chloride was evolved, even when the mixture was heated to 50°. More aluminum chloride (5 g.) was added and the mixture was stirred and heated at 50° for thirty minutes. No reaction occurred. When the temperature was raised to 67°, the mixture became black, but no hydrogen chloride was evolved and no condensation occurred.

Methyl β -[3,5-Dimethyl-2-nitrophenyl]-isovalerate (XV).—A solution of the ester IV (20.6 g., 0.093 mole) in acetic anhydride (10 g.) was cooled to 0° and to it was slowly (thirty minutes) added, with cooling (below 20°) and stirring, a solution of fuming nitric acid (d. 1.5, 5.3 g.) in acetic acid (3.36 g.) and acetic anhydride (3.36 g.). The mixture was allowed to stand at room temperature for two hours and then it was stirred and heated gradually to 50° on the steam-bath. After the temperature was held at 50° for ten minutes, the mixture was cooled, poured into water and extracted thoroughly with ether. The ether solution was washed with 5-cc. portions of sodium hydroxide (10%) until the washings remained alkaline (litmus), then with water, and the solvent was removed by distillation. After a small fore-run, the residual yellow oil boiled at 153–155° (5 mm.). The distillate was a viscous yellow oil which weighed 21.2 g. (87%).

Anal. Calcd. for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22. Found: C, 63.56; H, 7.23.

β -[3,5-Dimethyl-2-nitrophenyl]-isovaleric Acid (XVI).—The above ester XV (1.33 g.) was refluxed for one hour with sodium hydroxide (11 cc., 20%). Alcohol (5 cc.) was added and refluxing was continued for forty-five minutes. The cooled reaction mixture was acidified and the solid was removed and crystallized from dilute acetic acid. The pale yellow solid (0.25 g.) melted at 134–136°. The same acid XVI was also obtained by nitration of the acid V (1.0

g.) in acetic anhydride (2.0 cc.) with a solution of fuming nitric acid (0.3 cc.) in acetic acid (0.3 cc.) and acetic anhydride (0.3 cc.) by the procedure described above for nitration of the ester. The ether extracts containing the acid were extracted with sodium hydroxide (10%), and the alkaline extracts were acidified with hydrochloric acid. The solid was removed and crystallized several times from dilute methanol. It was then dissolved in benzene, the solution was decolorized with Norite and diluted with petroleum ether (b. p. 60–68°). The cooled solution deposited XVI as large rectangular prisms which melted at 135–136°.

Anal. Calcd. for $C_{13}H_{17}O_4N$: C, 62.13; H, 6.82. Found: C, 62.32; H, 6.77.

4,4,6,8-Tetramethylhydrocarbostyryl (XVII).—The mononitro ester XV (1.3 g.) was refluxed for three hours with zinc (1.3 g., 20 mesh) and acetic acid (80%, 15 cc.). The initial red color gradually faded to a light yellow. The mixture was poured over ice and the solid was removed and crystallized twice from dilute alcohol. The white product melted at 150–151°. The same product (5.12 g., m. p. 146–150°) was obtained by reduction of the crude mononitro ester XV (12.8 g.), or by reduction of the mononitro acid XVI. The hydrocarbostyryl XVII was insoluble in boiling sodium hydroxide (10%) and was recovered unchanged after it was refluxed for five minutes with acetic anhydride containing a little pyridine.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 76.80; H, 8.43. Found: C, 77.10; H, 8.15.

Nitration of the Mononitro Ester XV.—The ester XV (1.0 g.) was slowly added to a cooled (0°) and stirred mixture of fuming nitric acid (d. 1.5, 1.25 cc.) and sulfuric acid (1.75 cc.). The reaction mixture was allowed to stand at room temperature for twenty minutes and was then poured over ice. The solid was removed, washed with water and crystallized from methanol (30 cc.). It then weighed 0.7 g. and melted at 118–127°. This product was dissolved in ether and the solution was washed with saturated bicarbonate solution. The ether was removed and the residue was crystallized twice from methanol (15 cc.). The trinitro acid VII was then white, and had a m. p. and mixed m. p. of 127–128°. A solution of the mononitro ester XV (5.03 g.) in chloroform (17 cc.) was cooled (below 5°) and was vigorously stirred while a solution of potassium nitrate (1.9 g.) in sulfuric acid (16 cc.) was slowly (fifteen minutes) added. The mixture was stirred for fifteen minutes longer, the cooling bath was then removed and, when the temperature rose to 10°, the mixture was poured over ice. The chloroform layer was removed and the aqueous layer was extracted with three 15-cc. portions of ether. The combined organic solutions were washed successively with water, bicarbonate (10%) and again thoroughly with water, and the solvents were removed by distillation. The residual oil solidified when it was cooled and rubbed with a little methanol; the resulting white solid melted at 64–74°. The solid was dissolved in hot methanol and the solution was chilled. The first crop of crystals (m. p. 68–106°) was removed and the filtrate was set aside in the refrigerator for several hours. The second crop of crystals (m. p. 67–72°) was removed, and the filtrate was concentrated to about half the original volume and set aside in an unstoppered flask at room

(9) Kharasch and Brown, *THIS JOURNAL*, **62**, 925 (1940).

temperature overnight. Three different types of crystals resulted; these were separated manually. One type melted at 113–113.5°, another at 64–72°, and the third at 72–73.5°. The last was the dinitro ester A (mixed m. p. 72–74°). The bulk of the material was the mixture which melted at 64–72°, and no method was found whereby this mixture could be further separated into its components.

Nitration of the mononitro acid XII by the procedure described above also gave a mixture of nitro acids which could not be separated.

Summary

1. Nitration of methyl β -[3,5-dimethylphenyl]-isovalerate IV or the corresponding acid V in chloroform solution by action of potassium nitrate and sulfuric acid gives the 2,4-dinitro compounds. The ester also gave a sulfonic acid, but the structure of this has not been determined.

2. Action of ammonium sulfide converted one of the nitro groups in either the dinitro ester or dinitro acid to an amino group. The resulting aminonitro compounds could not be converted into hydrocarbostyrils; hence the amino group was not located in the 2-position, but must have been in the 4-position.

3. Nitration of the ester IV or of the acid V by fuming nitric acid in acetic anhydride gave the respective mononitro compounds; these products, on reduction, gave the same hydrocarbostyryl. Hence the nitro group must have entered the 2-position. This result and that outlined in (2)

above, show that the dinitro compounds have the nitro groups in the 2- and 4-positions.

4. Nitration of the ester IV or of the acid V by sulfuric and fuming nitric acids gave the respective 2,4,6-trinitro compounds. No hydrocoumarin was formed during the nitration, but action of copper-chromium oxide catalyst upon a quinoline solution of the trinitro acid converted it into 5,7-dinitro-4,4,6,8-tetramethylhydrocoumarin VIII.

5. Condensation of 2,4-dimethylphenol with β,β -dimethylacrylic acid gave 4,4,6,8-tetramethylhydrocoumarin. This reaction constitutes a convenient and practical method for synthesis of 4,4-dialkylhydrocoumarins. When the tetramethylhydrocoumarin was nitrated, the product was the dinitro derivative VIII.

6. In contrast to the alkylphenol, 2,6-dimethylacetanilide failed to condense with either β,β -dimethylacrylic acid or methyl β -chloroisovalerate.

7. The nitro groups of these nitro compounds, but particularly those of the trinitro compounds, were extremely sensitive to alkaline reagents.

8. The fact that only nuclear nitro compounds were obtained in this work indicates strongly that the dinitro compound obtained in previous work from methyl β -[3,4,5-trimethylphenyl]-isovalerate is a nuclear dinitro compound.

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

The Rearrangement of Phenyl Allyl Ethers. VIII. Ethyl p -(γ,γ -Dimethylallyloxy)-benzoate¹

BY WALTER M. LAUER AND OWEN MOE²

Earlier studies have shown that phenyl monoalkyl-substituted allyl ethers in which the γ -position of the allyl group remains unsubstituted rearrange with inversion in accordance with the pattern outlined by Claisen. However, in the case of phenyl γ -monoalkylallyl ethers, the rearrangement becomes more complex and products in addition to those predicted on the basis of the pattern of Claisen are formed.³ Very few pyrolysis studies have been carried out with γ,γ -dialkylallyl ethers: $\alpha,\alpha,\gamma,\gamma$ -tetramethylallyl

phenyl ether was shown by Hurd and Cohen⁴ to undergo cleavage to produce phenol and 2,4-dimethylpentadiene-1,3, but no substituted allyl phenol was obtained, and γ,γ -dimethylallyl phenyl ether was reported (but without experimental detail) by Claisen⁵ to yield the cleavage products, isoprene and phenol, and the normal rearrangement product when heated with sodium carbonate. With the exception of the report of Claisen, the aforementioned studies concerning the influence of substitution on the course of the rearrangement led to the expectation that cleav-

(1) Paper VII, *THIS JOURNAL*, **65**, 198 (1943).

(2) Abstract of Ph. D. thesis submitted in June, 1942.

(3) For an excellent discussion of the Claisen rearrangement, see D. Stanley Tarbell, *Chem. Rev.*, **27**, 495–546 (1940).

(4) Hurd and Cohen, *THIS JOURNAL*, **53**, 1917 (1931).

(5) Claisen and Tietze, *Ber.*, **59**, 2344 (1926).