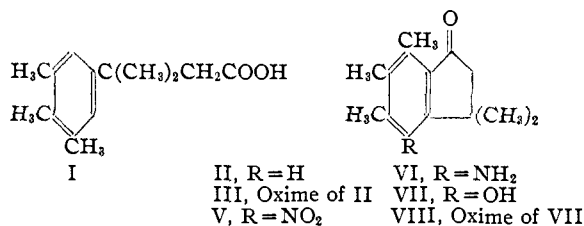


[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

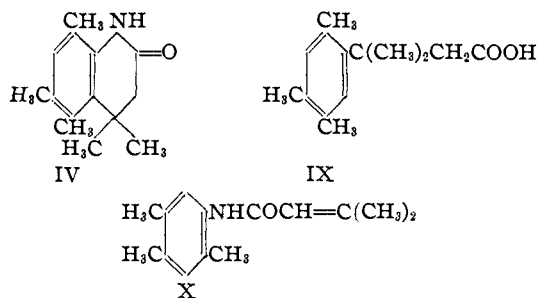
3,3,5,6,7-Pentamethylhydrindone and 4,4,5,6,8-Pentamethylhydrocarbostyryl

BY LEE IRVIN SMITH AND WILLIAM W. PRICHARD¹

In the preceding paper² there were outlined the general lines of attack by means of which 4,4-dialkyl-6-hydroxychromans might be prepared. The reactions chosen for this purpose failed to produce the proper intermediates, because when



pseudocumene was condensed with dimethylacrylic acid, rearrangement occurred and a derivative of hemimellitene (I) resulted. In the early stages of this work it was discovered that the acid I could be converted readily into a hydrindone.



Although not convertible to a 6-hydroxychroman, this hydrindone II was studied in some detail, and for comparison, the hydrocarbostyryl IV, although likewise not convertible to a 6-hydroxychroman, was synthesized.

The hydrindone II gave a good yield of the oxime III, but this oxime gave very unsatisfactory results when attempts were made to carry out a Beckmann rearrangement. Frequently a small amount of solid product was obtained, but this product was a mixture from which, in no case, could any pure substance be isolated. These results were surprising in view of the fact that the unsubstituted hydrindone oxime can be rearranged to a hydrocarbostyryl (although in poor yield) by refluxing it in ether with phosphorus

pentachloride,³ while fluorenone oxime gives a 90% yield of product when rearranged with phosphorus pentachloride in phosphorus oxychloride.⁴

Since no pure product could be obtained by rearrangement of the oxime III, it was decided to introduce the hydroxyl group into the hydrindone II and then attempt the Beckmann rearrangement of the phenolic oxime VIII. The hydrindone was readily nitrated to a mono nitro compound V which was reduced to the amino hydrindone VI. Replacement of the amino group by hydroxyl was accomplished by diazotization in the usual way. The phenolic hydrindone VII formed an oxime VIII, but this oxime could not be rearranged to a crystallizable product, either by the method of Kipping³ or by that of Huntress.⁴

In order to examine the properties of the hydrocarbostyryls which should result from the rearrangement of hydrindone oximes, the hydrocarbostyryl IV was synthesized from pseudocumidine-5 via the trimethyl anilide of dimethylacrylic acid (X). It was hoped also that this hydrocarbostyryl IV could be converted into the phenylisovaleric acid IX which would also have been the product had the condensation of dimethylacrylic acid with pseudocumene involved the 6-position of the hydrocarbon. The amide X was readily prepared, and in the presence of aluminum chloride this amide was converted into an excellent yield of the hydrocarbostyryl IV. This reaction is of interest, since Mayer, van Zütphen and Phillips⁵ found that the N-methylanilide of acrylic acid did not give the corresponding hydrocarbostyryl with aluminum chloride while several substituted anilides of β -chloropropionic and β -chlorobutyric acids gave excellent yields of hydrocarbostyryls. These authors concluded therefore that the ring closure occurred by loss of hydrogen chloride from the β -chloroanilides and that the α,β -unsaturated anilide was not involved. The easy cyclization of the unsaturated amide X apparently refutes this argument, but it is of course possible that cycliza-

(1) Abstracted from a thesis by W. W. Prichard, presented to the Graduate School of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, October, 1939.

(2) Smith and Prichard, *THIS JOURNAL*, **62**, 771 (1940).

(3) Kipping, *J. Chem. Soc.*, **65**, 490 (1894).

(4) Huntress, *THIS JOURNAL*, **49**, 2618 (1927).

(5) Mayer, van Zütphen and Phillips, *Ber.*, **60**, 858 (1927).

tion of X by aluminum chloride is preceded by the addition of hydrogen chloride to the double bond.

Mayer, Phillips, Ruppert and Schmitt⁶ succeeded in opening the heterocyclic ring of their hydrocarbostyryls by action of aqueous barium hydroxide at 150°. In this Laboratory, Mayer's method had been used with success in an analogous situation⁷ but all attempts to open the ring of the hydrocarbostyryl IV failed and it appears that when the anilides of α,β -unsaturated acids have two substituents in the β -position, ring closure to the hydrocarbostyryl is particularly easy and the heterocyclic compound, once formed, is particularly stable.

Experimental Part⁸

3,3,5,6,7-Pentamethylhydrindone, II, and its Oxime, III.—Preparation of these substances is described in the previous paper.²

Beckmann Rearrangement of Oxime III.—The oxime (0.34 g.) was dissolved in a mixture of phosphorus pentachloride (1.0 g.) and phosphorus oxychloride (5.0 g.). A vigorous reaction occurred, accompanied by evolution of hydrogen chloride. The mixture was refluxed for twenty minutes and then poured over ice. The product, a sticky brown material, was taken up in chloroform. Removal of the solvent left a brown gum, whose solution in dilute ethanol deposited a small amount of a somewhat gummy solid melting at about 85°. This substance could not be purified further. Repetitions of the experiment always gave products of the same gummy nature; on one occasion a small amount of crystalline product melting at 150–170° was obtained. This was a mixture which could not be separated.

3,3,5,6,7-Pentamethyl-4-nitrohydrindone, V.—The hydrindone II (3.0 g.) was dissolved in chloroform (20 cc.) and the solution was cooled (–5°) and stirred with sulfuric acid (50 cc.) while a solution of sodium nitrate (1.3 g.) in sulfuric acid (10 cc.) was slowly added. The solution was cooled and stirred for ten minutes longer and then poured on ice. The chloroform layer was removed and the acid layer was extracted thoroughly with chloroform. The combined chloroform solutions were washed with water, dilute carbonate and again with water. The solvent was removed at about 50° under reduced pressure, and the residual oil was crystallized from dilute methanol. The nitrohydrindone (1.14 g.) melted at 94–94.5°; the mother liquor, when concentrated, deposited a second crop (0.4 g.) melting at 92–93°. The remainder of the product was a red oil.

Anal. Calcd. for $C_{14}H_{17}O_3N$: C, 68.01; H, 6.88. Found: C, 68.74; H, 6.98.

3,3,5,6,7-Pentamethyl-4-aminohydrindone, VI.—The nitrohydrindone V (1.10 g.) was dissolved in acetic acid (10

cc., 60%) and the solution was warmed with zinc (20 mesh, 1.0 g.) for ten minutes after the initial vigorous reaction subsided. Dilution of the solution with ice precipitated the amine (0.90 g.) as a white solid which melted sharply at 81–82°. Two crystallizations from dilute methanol gave a product melting at 101–102°. Investigation showed that this compound had two melting points. A fairly large crystal of the substance was powdered and packed into two melting point capillary tubes. One of these was placed in a bath the temperature of which was raised at a moderate rate. This specimen was completely liquefied at 84°; it then re-solidified and melted again sharply at 101–102°. The other tube was placed in the bath at 70° and the temperature was raised very slowly. There was no evidence of softening until a temperature of 100° was reached; the sample then melted sharply at 101–102°. A similar dimorphism was shown by some of the other compounds in the series.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.42; H, 8.76. Found: C, 75.74; H, 8.89.

3,3,5,6,7-Pentamethyl-4-hydroxyhydrindone, VII.—The amino compound VI (0.46 g.) was dissolved in sulfuric acid (10%, 10 cc.) by warming. The solution was cooled to 0°, and to the resulting suspension there was slowly added a solution of sodium nitrite (0.15 g.) in water (2 cc.). The mixture was allowed to stand for thirty minutes. Copper sulfate (saturated solution, 5 cc.) and sulfuric acid (1 cc.) were added and the mixture was refluxed for twenty minutes. Nitrogen was evolved and a white solid (0.40 g.) separated. This was removed and crystallized from dilute methanol. The substance melted at 183–185° and was completely soluble in cold Claisen alkali.

Anal. Calcd. for $C_{14}H_{19}O_2$: C, 77.07; H, 8.26. Found: C, 77.02; H, 8.60.

Oxime, VIII.—The oxime was prepared from the hydrindone in dilute methanol in the usual way with hydroxylamine hydrochloride and sodium acetate. After crystallization from dilute methanol, it melted at 183–185° to a dark liquid. When mixed with the hydrindone VII (m. p. 183–185°) the substance melted at 165–170°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.10; H, 8.15. Found: C, 71.70; H, 8.90.

The oxime (0.1 g.) in ether (5 cc.) was refluxed with phosphorus pentachloride (0.5 g.) for four hours. The ether solution was washed with water and dilute carbonate and dried over Drierite. Removal of the solvent left a yellow oil containing chlorine. The oxime (0.15 g.) in phosphorus oxychloride (3 cc.) was refluxed with phosphorus pentachloride (0.5 g.) for one hour. Addition of water slowly precipitated an amorphous solid which could not be crystallized from dilute alcohol, although the expected hydrocarbostyryl (synthesized in another way; see next paper) crystallized readily from this solvent.

2,4,5-Trimethyl Anilide of Dimethylacrylic Acid, X.—Pseudocumidine-5 (11.1 g.) was dissolved in benzene (50 cc.) and a solution of dimethylacrylic acid chloride (4.85 g.) in benzene (15 cc.) was slowly added. The amine hydrochloride precipitated at once. The mixture was refluxed for thirty minutes and the suspended solid was filtered off. The benzene filtrate was extracted several

(6) Mayer, Phillips, Ruppert and Schmitt, *Ber.*, **61**, 1966 (1928).

(7) Smith and Denyes, *THIS JOURNAL*, **58**, 304 (1936).

(8) Microanalyses by J. W. Opie, H. H. Hoehn and C. O. Guss.

times with dilute hydrochloric acid, washed with water and then concentrated to about 40 cc. On cooling, a solid was deposited. Petroleum ether (100 cc., b. p. 28–35°) was added and the solid was filtered off. It weighed 7.1 g. (80%) and melted at 107.5–108°.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.42; H, 8.76. Found: C, 76.90; H, 9.08.

4,4,5,6,8-Pentamethylhydrocarbostyryl, IV.—The anilide X (3.0 g.) was mixed with aluminum chloride and the dry mixture was warmed on the water-bath for twenty-five minutes. Ice was added, and the nearly white solid (2.9 g.) which separated was removed. It melted at 207–209°. Crystallization from ethanol gave a slightly yellow product which melted at 209–210°.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.42; H, 8.76. Found: C, 77.18; H, 9.09.

One gram portions of the hydrocarbostyryl were heated to 150, 200 and 250° for fifteen, ten and eight hours, respectively, in a bomb with barium hydroxide (3.0 g.) and water (15 cc.). In each case the starting material

was recovered unchanged, and the alkaline solution contained no organic matter.

Summary

1. This paper contains a description of the conversion of 3,3,5,6,7-pentamethylhydrindone II to 3,3,5,6,7-pentamethyl-4-hydroxyhydrindone VII via the nitro compound and the amine.

2. Neither the oxime of II, nor that of VII, could be made to undergo a Beckmann rearrangement.

3. The 5-pseudocumidide of dimethylacrylic acid, X, is converted smoothly to 4,4,5,6,8-pentamethylhydrocarbostyryl IV by action of aluminum chloride. The heterocyclic ring in IV is extremely stable; it is not opened by treatment with barium hydroxide at 250°.

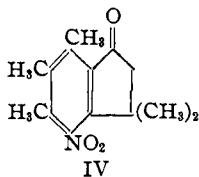
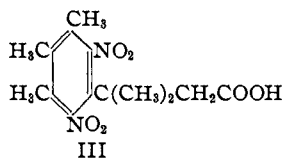
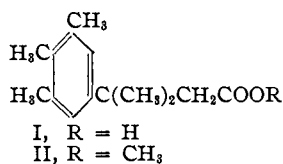
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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Nitration of β -[3,4,5-Trimethylphenyl]-isovaleric Acid and its Methyl Ester I. Formation of 4,4,6,7,8-Pentamethyl-5-nitrohydrocoumarin

BY LEE IRVIN SMITH AND WILLIAM W. PRICHARD¹

In the preceding papers² it was established that condensation of dimethylacrylic acid with pseudocumene was accompanied by rearrangement of the methyl groups and that the resulting β -[trimethylphenyl]-isovaleric acid had structure I, with the methyl groups in positions 3, 4 and 5.



The acid I, obtained in good yield, offered a suitable material for model researches on the conversion of such β -phenylisovaleric acids into 4,4-dimethylhydrocoumarins. Accordingly it was planned to carry out this transformation by the

series of reactions already used for this purpose³ which involved reduction of the nitro compound to the amine or hydrocarbostyryl, and conversion of the latter to the hydrocoumarin by the method of Mayer, Phillips, Ruppert and Schmitt.⁴

Astonishingly, nitration of the acid I by the method of Smith and Denyes³ produced neither the dinitro compound III nor the known nitrohydrindone IV^{2b} but the nitrohydrocoumarin V, $C_{14}H_{17}O_4N$, melting at 152.5–153°. The yield of this substance was very poor, but when the methyl ester II was nitrated by a solution of sodium nitrate in sulfuric acid there resulted in almost quantitative yield a mixture of two substances, one of which was the compound $C_{14}H_{17}O_4N$, m. p. 152.5–153°. These two nitration products crystallized well, but their solubilities were so nearly identical that the separation was very difficult and was effected only after repeated crystallization supplemented by manual separation of the two types of crystals. The nitrohydrocoumarin V was neutral, but dissolved in strong alkali after continued boiling, giving a bright cherry-red solution, and it was precipitated unchanged when this alkaline solution was satu-

(1) Abstracted from a thesis by W. W. Prichard, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, October, 1939.

(2) (a) Smith and Prichard, *THIS JOURNAL*, **62**, 771 (1940); (b) **62**, 778 (1940).

(3) Smith and Denyes, *ibid.*, **68**, 304 (1938).

(4) *Ber.*, **61**, 1966 (1928).