

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°.

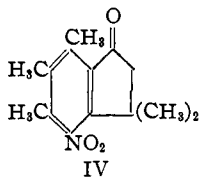
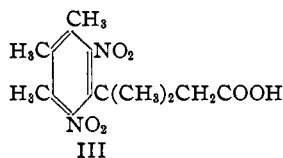
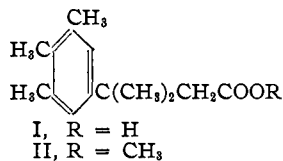
MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 15, 1939

[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

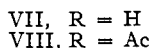
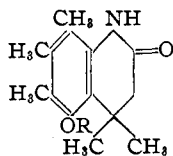
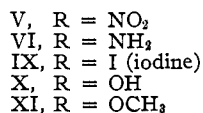
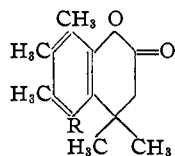
Astonishingly, nitration of the acid I by the method of Smith and Denyes³ produced neither the dinitro compound III nor the known nitrohydrindone IV^{2b} but the nitrohydrocoumarin V, $C_{14}H_{17}O_4N$, melting at 152.5–153°. The yield of this substance was very poor, but when the methyl ester II was 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 (1936).

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



rated with carbon dioxide. Reduction of V produced an amine VI which dissolved readily in hot dilute mineral acids, and which crystallized as the hydrochloride or sulfate when the solutions were cooled. The amine VI also dissolved readily in strong alkalis, but it could not be recovered from these solutions. When the solution of VI in alkali was saturated with carbon dioxide, there resulted an isomer of VI, the hydroxyhydrocarbostyryl VII. The hydroxyhydrocarbostyryl VII was soluble in alkali and was precipitated unchanged when the solution was acidified; it was insoluble in dilute acids, however, and formed no salts with them, but it could be converted into a monoacetyl derivative, VIII. While the amine VI was readily diazotized and coupled with naphthols to give colored azo compounds, the hydrocarbostyryl VII could not be diazotized. This hydroxyhydrocarbostyryl is the one which should result from a Beckmann rearrangement of the oxime of 4-hydroxy-3,3,5,6,7-pentamethylhydrindone^{2b} but unfortunately no crystalline material could be obtained from the rearrangement product of this oxime.

The diazonium salt from the amine VI reacted with potassium iodide to give the iodo compound IX which slowly dissolved in boiling alkali to give a red solution. This solution contained ionic iodine, but acidification gave no pure products. When the diazonium sulfate derived from VI was refluxed with a little copper sulfate, there resulted the hydroxyhydrocoumarin X. This substance dissolved readily in alkali and was recovered unchanged when the solution was acidified. Various attempts to convert X into a dimethoxy methyl ester by action of methyl sulfate and alkali invariably gave the monomethyl ether XI and no product resulting from opening of the hydrocoumarin ring could be obtained. However, this ether XI slowly dissolved in boiling alkali, indicating either that the ring had opened under these conditions, or else enolization of the carbonyl group had occurred. No benzoyl de-

rivative resulted when the alkaline solution of XI was shaken with benzoyl chloride, nor was it possible, by any means tried, to recover anything from the alkaline solutions except the ether XI.

Previous work on some similar hydrocoumarins without the two methyl groups in the 4-position⁵ has indicated that it is extremely difficult to open the rings in these compounds; introduction of the two methyl groups in position 4 adjacent to the benzene ring apparently results in rings of even greater stability. Solubility of many of these compounds in alkali indicates that although salts of open chain derivatives may be formed in alkaline solutions, these revert at once to the cyclic compounds as soon as the strong alkali is removed, even when the alkaline solutions are shaken with methyl sulfate. The easy conversion of the amino hydrocoumarin VI into the hydroxyhydrocarbostyryl VII must involve at least a momentary opening of the hydrocoumarin ring, although the reverse transformation, from VII to VI, cannot be brought about even partly. No compounds analogous to open chain derivatives of VI, VII or X are known with certainty. Niederl,⁶ who condensed mesityl oxide with phenol, oxidized the product and described the resulting substance as β -[*o*-hydroxyphenyl]-isovaleric acid, but he gave no properties nor analysis of his compound, and consequently exact information is lacking. John, Günther and Schmeil,⁷ who prepared 4,4,5,7,8-pentamethyl-6-hydroxyhydrocoumarin, did not give any discussion of the properties of this compound nor were any derivatives of it cited which resulted from reactions in which the ring was opened.

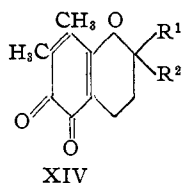
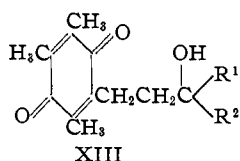
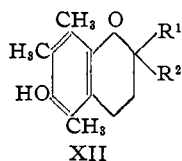
The surprising formation of the hydrocoumarin V by nitration of the acid I or its ester II and which involves the equivalent of hydroxylation at position 6, finds a parallel in a reaction discovered in connection with α -tocopherol, a 2,2-dialkyl-6-hydroxychroman (XII). When α -tocopherol is subjected to the action of any of a number of mild oxidizing agents, the first products formed are yellow *p*-quinones, such as XIII.⁸ When, however, certain silver salts, notably silver nitrate, are used and the action is prolonged, oxidation proceeds beyond the yellow stage and

(5) Smith and Tenenbaum, *THIS JOURNAL*, **59**, 667 (1937).

(6) Niederl, *ibid.*, **51**, 2426 (1929).

(7) John, Günther and Schmeil, *Ber.*, **71**, 2617 (1938).

(8) (a) John, Dietzel and Emte, *Z. physiol. Chem.*, **257**, 173 (1939); (b) Karrer, Fritzsche and Escher, *Helv. Chim. Acta*, **22**, 661 (1939).



brilliant red solutions result.^{8,9} These red solutions also result when nitric acid in ethanol is used as the oxidizing agent.^{8b,10} Crystalline red compounds have been isolated as nitric acid oxidation products of simple model substances having structure XII, and it has been shown that these red substances are *o*-quinone derivatives such as XIV.¹¹ The transformation of XII into XIV thus involves the equivalent of hydroxylation of the ring by nitric acid or a silver salt and it is comparable to the transformation of the acid I into the nitrohydrocoumarin V. There are considerable differences between the two cases, however. Formation of orthoquinones from coumarin and chroman compounds results only when the hydroxyl group para to the bridge oxygen is present; it takes place via the yellow *p*-quinone intermediate and is accompanied by elimination of the group adjacent to the carbon junction of the two rings. Moreover, 6-hydroxyhydrocoumarins do not give the reaction.¹¹ In the transformation of I into V, no group is eliminated, the reaction is accompanied by nitration, and the position para to the bridge oxygen is blocked by a methyl group. Whether or not the two series of reactions have a common mechanism remains to be decided.

As stated above, nitration of the ester II gave two products, one of which was V. The other product, melting at 125–125.5°, was a substance having the composition C₁₅H₂₀O₆N₂. This composition corresponds to that of the methyl ester of III; but the properties of the substance indicate quite clearly either that it does not have this structure, or, if it does, that the methyl ester of III is a most remarkable substance. Reduction of this substance results in the loss of two carbon

atoms and most of the oxygen, giving a compound C₁₃H₂₀ON₂. The structure and properties of this second nitration product are still under investigation and the results will form the subject of a later paper.

Experimental Part¹²

β-[3,4,5,-Trimethylphenyl]-isovaleric Acid, I, and its Methyl Ester, II.—The preparations of I, m. p. 111–112°, and of II, b. p., 130–130.5° under 6 mm., are described in a previous paper.^{2a}

4,4,6,7,8-Pentamethyl-5-nitrohydrocoumarin, V. A. By Nitration of the Ester II.—The ester (10.41 g., 0.045 mole) was dissolved in chloroform (30 cc.) and stirred with sulfuric acid (60 cc.) at –15°. A solution of potassium nitrate (10 g., 0.098 mole) in sulfuric acid (20 cc.) was added slowly (one hour and fifteen minutes). After 18 cc. of the nitrating mixture had been added, the dark red color of the mixture faded to light yellow. The cooling bath was removed and the mixture was allowed to warm to 5°. Ice was added, the chloroform layer was separated and the aqueous layer was extracted three times with chloroform (20 cc. each time). The combined chloroform solutions were washed with water, 10% carbonate, and again with water. Evaporation of the solvent at 50–60° under diminished pressure left an oil which solidified when rubbed with a little methanol. The product was taken up in methanol (75 cc.) and allowed to crystallize slowly. The first crop of crystals weighed 10.3 g.; a second crop (0.83 g.) was obtained by concentrating the mother liquor. This material, a mixture of two nitration products, was best separated by allowing the solution in methanol to crystallize very slowly at room temperature. Crystals of one of the compounds separated first and, by watching carefully, the first crystals of the other compound could be seen. At this point the solution was decanted from the crystals; the solution then deposited the other substance. Working in this way alternate crops of the two substances could be obtained. The solubilities of these two compounds were nearly the same in all solvents tried; seeding the solutions with one or the other compound was not effective as this often caused both substances to crystallize together. When the whole mixture was allowed to crystallize very slowly, the two substances could be separated manually. The hydrocoumarin V crystallized in stubby rods which melted at 152.5–153°. The other product formed long needles of square cross section, which melted at 125–125.5°. Using the method of manual separation, the first crop of the nitration product (10.3 g.) was separated with 4.56 g. (53%) of the hydrocoumarin V and 4.66 g. (45%) of the other product.

Anal. V. Calcd. for C₁₄H₁₇O₄N: C, 63.87; H, 6.46; N, 5.14. Found: C, 63.97; H, 6.63; N, 5.25. *Anal.* of second nitration product. Calcd. for C₁₅H₂₀O₆N₂: C, 55.55; H, 6.17; N, 8.64. Found: C, 55.35; H, 6.31; N, 8.72.

B. By Nitration of the Acid I.—A solution of acid I (0.5 g.) in acetic acid (5 cc.) was dropped slowly into

(9) (a) Evans, Emerson and Emerson, *Science*, **88**, 38 (1938); (b) John and Emte, *Z. physiol. Chem.*, **261**, 24 (1939); (c) Karrer, Escher and Rentschler, *Helv. Chim. Acta*, **22**, 1287 (1939).

(10) Furter and Meyer, *ibid.*, **22**, 240 (1939).

(11) Smith, Irwin and Ungnade, *THIS JOURNAL*, **61**, 2424 (1939).

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

fuming nitric acid (5 cc., d. 1.6). Each drop produced a dark color, which immediately faded. The mixture was stirred for fifteen minutes and then diluted with ice. The gummy yellow material was taken up in ether, dried, and the ether was removed. The product (V) was crystallized from dilute ethanol, when it melted at 146–148° alone or when mixed with a specimen of V prepared from the ester. The yield was about 20%. Several attempts to nitrate the acid at lower temperatures without using sulfuric acid failed; only starting material was recovered.

4,4,6,7,8-Pentamethyl-5-aminohydrocoumarin, VI.—Granulated zinc (1.0 g., 20-mesh) was added to a boiling solution of the nitro compound V (1.0 g.) in acetic acid (8 cc.) and water (3 cc.). The mixture was refluxed for ten minutes; the solution was then carefully decanted from the zinc onto ice. The solid was removed and crystallized from dilute methanol. The amine (0.8 g., 90%) crystallized in long needles melting at 125–125.5°. It dissolved readily in hot dilute acids or bases; the hydrochloride and sulfate were both fairly insoluble in cold water. Several attempts were made to reduce the nitro compound V catalytically under low pressures, but the starting material was always recovered in these cases.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.10; H, 8.15. Found: C, 71.88; H, 8.39.

4,4,6,7,8-Pentamethyl-5-hydroxyhydrocarbostyryl, VII.—When a solution of the amine VI in dilute sodium hydroxide was acidified with hydrochloric acid or saturated with carbon dioxide, the hydrocarbostyryl precipitated almost quantitatively. After crystallization from dilute ethanol it melted at 193–194°. The substance was soluble in 20% sodium hydroxide and was recovered unchanged when the solution was acidified. No color was produced when VII was subjected to the successive action of nitrous acid and β -naphthol.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.10; H, 8.15. Found: C, 71.43; H, 8.19.

Acetate, VIII.—The hydrocarbostyryl VII (0.1 g.) was refluxed for ten minutes in acetic anhydride (3 cc.) containing a drop of sulfuric acid. The mixture was poured into water and the solid was removed and crystallized from dilute methanol. It melted at 207–208°.

Anal. Calcd. for $C_{16}H_{21}O_3$: C, 69.82; H, 7.64. Found: C, 69.75; H, 7.56.

4,4,6,7,8-Pentamethyl-5-iodohydrocoumarin, IX.—The amino compound VI (0.50 g.) was warmed with sulfuric acid (10%, 5 cc.). The amine dissolved and, as the solution was cooled, the sulfate separated. To the cooled (0°) suspension of the sulfate a solution of sodium nitrite (0.152 g.) in water (2 cc.) was slowly added. The amine sulfate gradually dissolved and a finely divided, foamy solid appeared at the surface of the solution. The diazonium solution was allowed to stand at 0° for thirty minutes, and then a solution of potassium iodide (1.0 g.) in water (5 cc.) was added. After standing at room temperature for an hour, the mixture was warmed on the steam-bath for thirty minutes. The solution became dark and a black solid separated. Saturated thiosulfate solution (2 cc.) was added and the heating was continued. The dark color gradually disappeared and a light yellow solid then remained suspended in the liquid. The solid

was removed and crystallized from ethanol. It formed white plates (0.45 g.) which melted at 131.5–132.5°. The substance contained no nitrogen.

Anal. Calcd. for $C_{14}H_{17}O_2I$: C, 49.16; H, 5.12. Found: C, 48.83; H, 4.94.

The substance dissolved in boiling 20% potassium hydroxide, giving a crimson solution. Acidification of this solution by nitric acid produced a small amount of a solid melting at 150–180°; the aqueous solution gave a heavy precipitate of silver iodide when silver nitrate was added.

4,4,6,7,8-Pentamethyl-5-hydroxyhydrocoumarin, X.—When the diazonium solution prepared from the amine VI (0.50 g.) was refluxed with copper sulfate (saturated solution, 2 cc.) and sulfuric acid (3 cc.), a vigorous evolution of nitrogen occurred and a white solid separated. After crystallization from methanol, this substance (0.40 g.) formed square plates melting at 207–208°. The phenol dissolved readily in Claisen's alkali, giving a red solution, from which the phenol was recovered unchanged when the solution was acidified with hydrochloric acid or saturated with carbon dioxide.

Anal. Calcd. for $C_{14}H_{19}O_3$: C, 71.79; H, 7.69. Found: C, 71.38; H, 8.04.

4,4,6,7,8-Pentamethyl-5-methoxyhydrocoumarin, XI.—The phenol X (0.343 g.) was dissolved in methyl sulfate (1.66 g.) and methanol (2 cc.). To the boiling solution potassium hydroxide (0.75 g.) in methanol (3 cc.) was added slowly. The mixture was refluxed for fifteen minutes and then diluted with water. The product separated readily and after crystallization from dilute methanol it formed long, flat needles (0.340 g.), melting at 132–132.5°. The substance was soluble in dilute alkali, giving a faintly pink solution. Acidification of this solution regenerated the ether XI. Several attempts were made to methylate this compound further in order to open the hydrocoumarin ring, but repeated action of methyl sulfate and 20% potassium hydroxide was without any effect. Likewise the action of benzoyl chloride and 20% potassium hydroxide was without effect; in all cases the ether XI was recovered practically quantitatively and in a pure state.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.57; H, 8.06. Found: C, 72.59; H, 8.25.

Summary

1. Nitration of β -[3,4,5-trimethylphenyl]-isovaleric acid (I) results in the formation of 4,4,6,7,8-pentamethyl-5-nitrohydrocoumarin (V). Nitration of the methyl ester of this acid produces the nitrohydrocoumarin and a second product $C_{15}H_{20}O_6N_2$ in about equal amounts. The structure of this second product has not yet been established.

2. Several transformations of the nitrohydrocoumarin V are described. In particular, the aminohydrocoumarin VI rearranges readily into the isomeric hydroxyhydrocarbostyryl VII when its solution in alkali is acidified.

3. It was not possible to open the heterocyclic

rings of any of the derivatives of the hydrocoumarin or of the hydrocarbostyryl.

4. The formation of the hydrocoumarin V by nitration of the ester II is paralleled by a similar reaction in connection with the tocopherols and

compounds related to them. Here also the action of nitric acid is equivalent to hydroxylation of a ring at one of the stages of the reaction.

MINNEAPOLIS, MINNESOTA

RECEIVED NOVEMBER 15, 1939

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

Chloromethylation of Aryl Ketones

BY REYNOLD C. FUSON AND C. H. MCKEEVER¹

The chloromethylation of methyl aryl ketones was undertaken in the hope of obtaining a useful synthesis of β -chloropropiophenones. The success of Colonge² in chloromethylating aliphatic ketones by treatment with formalin in the presence of hydrogen chloride and zinc chloride suggested that a similar procedure might prove effective in the aromatic series. We therefore attempted to adapt his method to serve our purpose. In order to minimize the amount of water present, and thus enhance the solubility of the ketones, paraformaldehyde was used in place of formalin. Preliminary experiments on acetomesitylene showed that zinc chloride was not necessary to bring about the reaction. However, the product was not the expected β -chloropropiomesitylene

a method for nuclear chloromethylation similar to that developed by Blanc³ for aromatic hydrocarbons and extended by others, notably Quelet,⁴ to other types of aromatic compounds.

Experiments with other aromatic ketones have substantiated this surmise. The method appears to be general for ketones in which the aryl radical carries two or more alkyl groups. Acetophenone and benzophenone failed to react under these conditions.

The reaction provides an indirect method of methylation; this is shown by the fact that acetosodurene and pentamethylacetophenone were obtained in 80 and 90% yields, respectively, by reducing the corresponding chloromethyl derivatives according to the method of v. Braun and Nelles.⁵

TABLE OF RESULTS

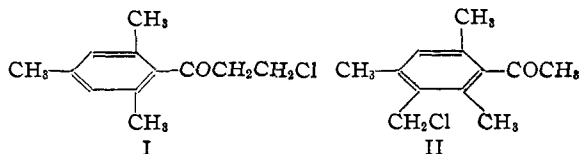
Compound	Time, hr.	Yield, %	M. p., °C.	Carbon, %		Hydrogen, %		Chlorine, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
5-Chloromethyl-2,4-dimethylacetophenone ^a	41	50	68.5-69	67.17	67.03	6.66	6.75	18.02	17.94
3-Chloromethylacetomesitylene ^b	12	80	74.5-75.5	68.42	68.55	7.18	7.04		
3-Chloromethylacetosodurene ^b	12	75	88.5-90	69.48	69.14	7.62	7.81		
3-Chloromethylpropiomesitylene	15	88	75-76	69.48	69.50	7.62	7.75	15.78	15.73
3-Chloromethylisobutyromesitylene ^c	36	78		70.43	70.23	8.02	8.09		
3-Chloromethylpivalylmesitylene ^{b,d}	15	25	54-55	71.27	71.11	8.37	8.34	14.02	14.29
3-Chloromethylbenzoylmesitylene ^b	150	35	90-91	74.85	74.87	6.28	6.20		
3-Chloromethyl-2,4,6-triethylacetophenone	60	57	57-58	71.27	71.41	8.37	8.27	14.02	14.29

^a The reaction mixture was kept at 80°. The position of the chloromethyl group in this compound was not proved.

^b The yield here is calculated on the original amount of ketone, in all other cases on the amount of ketone that reacted.

^c This compound is a liquid, b. p. 140° (2 mm.); n_D^{20} 1.5395; d_4^{20} 1.0785. ^d Pivalylmesitylene is a new compound. It was prepared from mesitylene and pivalyl chloride by the Friedel-Crafts method; b. p. 97-97.5° (2.5 mm.); n_D^{20} 1.5093; d_4^{20} 0.9531. *Anal.* Calcd. for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.33; H, 9.83.

(I) but a chloroacetosodurene (II). The chloro-



methyl group had entered the ring instead of the side-chain. In other words, we appeared to have

Procedure.—A mixture of 0.1 mole of the ketone, 0.11 mole of paraformaldehyde and 100 cc. of concentrated hydrochloric acid was shaken for fifteen to seventy-two hours at 25-85° depending upon the nature of the ketone. The solid which precipitated was removed by filtration, washed thoroughly and recrystallized from high-boiling petroleum ether or methyl alcohol.

In some cases the chloromethyl derivative did not sepa-

(3) Blanc, *ibid.*, **33**, 313 (1923).

(4) For a leading reference see Quelet and Allard, *Compt. rend.*, **206**, 238 (1937).

(5) v. Braun and Nelles, *Ber.*, **67**, 1094 (1934).

(1) Röhm and Haas Research Assistant.

(2) Colonge, *Bull. soc. chim.*, [5] **3**, 2116 (1936).