and 10 cc. of dry pyridine were mixed together and heated under reflux on a steam-bath for six hours. The ester crystallized out on cooling and the process was completed by keeping overnight in the refrigerator. The crystals were filtered, washed with acetone and dried in vacuum. The filtrate and the acetone washings were combined, evaporated to a small volume and, on the addition of iso-propanol, a second crop of crystals was obtained. The total yield was 3.58 g. (86.5%), m. p. 122–124°.

The ethyl ester was similarly prepared with a yield of 85–90%, by using an equivalent quantity of monoethyl malonate in the place of the methyl ester.

Methyl *p*-Dimethylaminocinnamate.—Three grams (0.02 mole) of *p*-dimethylaminobenzaldehyde, 4.8 cc. (*ca.* 0.04 mole) of monomethyl malonate, 0.25 cc. of piperidine and 10 cc. of dry pyridine were heated under reflux on the steam-bath for four hours. The pyridine was then distilled off *in vacuo* and the crystalline residue was taken up in 10–15 cc. of boiling acetone. To this solution, water was added slowly with stirring until the precipitation of the ester was complete. The crystals were filtered off, washed with acetone and dried at 90–100°; yield 3.9 g. (95%); m. p. 130–132°. One recrystallization from hot acetone gave a pure material melting at 134–136°. The same yield of the ethyl ester was obtained by using monoethyl malonate.

Ethyl Caffeate.—Two and eight-tenths grams (0.02 mole) of protocatechuic aldehyde, 4.5 cc. (*ca.* 0.04 mole) of monoethyl malonate, 0.25 cc. of piperidine and 10 cc. of dry pyridine were mixed together and allowed to stand overnight in a stoppered flask. The mixture was then heated under reflux for two hours on a steam-bath, the pyridine distilled off *in vacuo* and the mixture diluted with 2 cc. of alcohol. Five cc. of water was then added slowly with stirring and the mixture was made acid to congo red with hydrochloric acid. The ester separated as a granular crystalline mass which was filtered, washed with dilute alcohol and dried at 60–70°. The yield of the crude ethyl caffeate was 3.82 g. (92%), m. p. 140–142°. One recrystallization from dilute alcohol brought the melting point to 149–150°. By re-using the mother liquors in the subsequent runs to secure the maximum yield, an over-all yield of 90–91% of the pure ester was obtained.

Summary

A one-step method for converting aldehydes into the α,β-unsaturated esters is described. It consists of condensing an aldehyde with a half-ester of malonic acid under the conditions of the Doebner reaction. The new synthesis gives good yields and has a wider range of applicability than the Claisen or the Reformatsky reactions.

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[CONTRIBUTION FROM THE BUREAU OF PLANT INDUSTRY, SOILS AND AGRICULTURAL ENGINEERING, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

The Anomalous Reaction between Ammonia and 9-Chlorofluorene. Substitution of the Labile Hydrogen in Fluorene Derivatives

BY LOUIS A. PINCK AND GUIDO E. HILBERT[1]

Courtot and Petitcolas[2] in a note on the synthesis of 9-substituted aminofluorenes reported that the action of anhydrous ammonia on 9-chlorofluorene yields dibiphenylene-ethylene, 9,9′-difluorylamine and a trace of 9-aminofluorene. This reaction has now been reinvestigated, and the results obtained do not agree with those of the French workers.

9-Chlorofluorene[3] and liquid ammonia interact at room temperature to form dibiphenylene-ethylene in a yield approximately 45% of the theoretical. The nitrogenous products of the reaction are fluorylidene-imine, in fair yield, and traces of 9-aminofluorene. Any possibility of confusing 9,9′-difluorylamine with fluorylidene-imine is readily excluded by the wide difference in their melting points.[4] The formation of an unsaturated compound, such as the imine, obviously requires the simultaneous production of a fluorene derivative saturated presumably at the 9 position. This compound was isolated and found to be fluorene, the yield of which was comparable with that of the imine.

In the presence of a solvent, such as toluene, an additional nitrogenous compound, 1-aminodibiphenylene-ethane, is formed by the reactants. The structure of this compound was determined by the following reactions: (a) methylation with methyl iodide, yielding 1-methylaminodibiphenylene-ethane, and (b) treatment with nitrous acid, giving 1-hydroxydibiphenylene-ethane. These derivatives were found to be identical with specimens prepared by other procedures.[5,6]

The formation of the various compounds from the reactions of 9-chlorofluorene in ammonia may be expressed by the equations given on the next page. This theory of reaction mechanisms is advanced on the basis of experimental data reported in this paper and also on analogous reactions referred to in previous work. Reactions I and IV are analogous inasmuch as the lability of the hydrogen atom in the 9 position plays an important role in both cases. That 1-chlorodibiphenylene-ethane, the primary product of reaction I, was not found is not surprising since this compound is rapidly converted to dibiphenylene-ethylene in an alkaline

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(1) Present address: Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, Peoria, Illinois. Article not copyrighted.

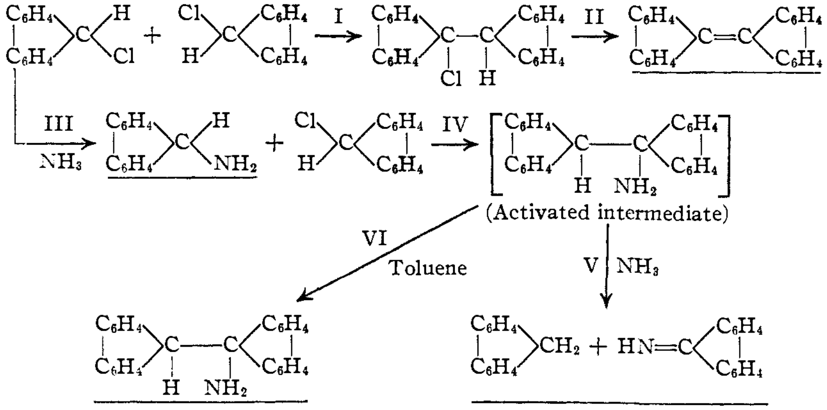
(2) Courtot and Petitcolas, *Compt. rend.*, **180**, 297 (1925).

(3) Thiele and Wanscheidt, *Ann.* **376**, 269 (1910); Bergmann and Hervey, *Ber.*, **62**, 893 (1929).

(4) The imine melts at 124°, whereas the melting point of difluorylamine according to Goldschmidt and Reichel [*Ann.*, **456**, 163 (1927)] is 198°.

(5) Pinck and Hilbert, THIS JOURNAL, **57**, 2398 (1935).

(6) Courtot, *Ann. chim.*, [9] **4**, 164 (1915).



(Underscored compounds were isolated).

medium. The formation of 1-aminodibiphenylene-ethane instead of 9,9′-difluorylamine indicates that the lability of the hydrogen atom at the 9 position in 9-aminofluorene is greater by far than that of the hydrogen atom in the amino group. Equivalent amounts of 9-aminofluorene and 9-chlorofluorene in ammonia–toluene yield 1-aminodibiphenylene-ethane, fluorylidene-imine and fluorene as the main products of the reaction, whereas only an insignificant amount of dibiphenylene-ethylene is formed (reactions IV, V, VI). The dismutation of 1-ethylaminodibiphenylene-ethane[5] in alcohol at 100° provides an analogy for the assumed reaction V, although the stability of 1-aminodibiphenylene-ethane in liquid ammonia under the conditions of the present experiments, excludes this material as a precursor of the fluorene and fluorylidene-imine except in the form of an activated intermediate,[7] which may be assumed to suffer dismutation on collision with ammonia (reaction V), but to yield the stabilized amino ethane on collision with toluene (reaction VI). The formation of the observed products could also conceivably be interpreted by assuming the intermediate formation of fluorylidene radicals. However, the observed formation of 9-phenylfluorene and fluorylidene-imine by interaction between 9-aminofluorene and 9-chloro-9-phenylfluorene demonstrates that reactions analogous to the over-all course of IV and V can proceed without the intermediation of such radicals.

Other compounds, containing weakly acidic hydrogen, combine with 9-chlorofluorene in liquid ammonia to yield 1-substituted dibiphenylene-ethane derivatives. 9-Dimethylaminofluorene reacts with 9-chlorofluorene, forming 1-dimethylaminodibiphenylene-ethane. The rate of reaction is slow and accordingly the yield of the ethane derivative is low. On the other hand, a practically quantitative yield of 1-carbethoxydibiphenylene-ethane is obtained in the interaction of 9-carbethoxyfluorene and 9-chlorofluorene. This is to be expected since 9-carbethoxyfluorene readily forms a sodium salt,[8] indicating the presence of a hydrogen atom, which is more acid than most members of the fluorene series. Consideration of these results suggests that the first step leading to the condensation (reaction I) is the ionization of the hydrogen atom in the 9 position.

9-Bromofluorene undergoes a series of reactions in liquid ammonia quite similar to those of 9-chlorofluorene. From the relative quantities of the reaction products, it appears that in 9-bromofluorene the halogen atom is more active and the hydrogen atom in the 9 position less labile than the corresponding atoms in 9-chlorofluorene.

Not all basic reagents interact with the halogeno fluorenes in a manner similar to ammonia. Thus, in hydrazine, 9-chlorofluorene yields fluorenone-hydrazone and in piperidine, 9-(N-piperidino)-fluorene.

We wish to express our appreciation to Mrs. M. S. Sherman for carrying out the microanalyses recorded in the experimental section.

Experimental

Reactions of 9-Chlorofluorene in Ammonia.—Two grams of 9-chlorofluorene and 10 cc. of anhydrous liquid ammonia were kept in a sealed tube at room temperature for twenty hours. The solution developed a yellow color, and red needles separated. Toward the end of the reaction the color changed to a faint greenish-blue. As the red solid adhered to the sides of the tube, separation from the ammonia solution was effected by cautious inversion of the tube, which was then cooled and opened. The red product was recrystallized and identified as **dibiphenylene-ethylene**; yield 0.65 g.; m. p. 187°.

The solid residue obtained after evaporation of the ammonia solution was triturated with ether. On treatment of the ether extract with hydrogen chloride, an orange-colored solid was precipitated. This salt was converted by water to ammonium chloride and fluorenone. Only a trace of **9-aminofluorene** was found in the aqueous filtrate. In another experiment the orange-colored salt was converted to the free base by dissolving in liquid ammonia. After removal of ammonia the residue was recrystallized from ligroin. Pale-yellow needles melting at 122° were obtained, and the product was identified as **fluorylidene-imine**. The melting point of a mixture of this substance with fluorylidene-imine[9] prepared by the action of ammonia on fluorenone was 123°.

Anal. Calcd. for $C_{13}H_9N$: N, 7.82. Found: N (Kjeldahl), 7.78; N (titration of ammonia liberated by hydrolysis with standard acid), 7.68.

The ether filtrate from the crude imine hydrochloride was washed with water and dried. Removal of the ether yielded a residue composed of **fluorene** and a small amount of dibiphenylene-ethylene. Fluorene (0.25 g.) was separated from the ethylene and purified by sublimation *in vacuo*.

The yields of the products of the reactions of 9-chlorofluorene in liquid ammonia were influenced considerably

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[7] Eyring, *J. Chem. Phys.*, **3**, 107 (1935); Wynne-Jones and Eyring, *ibid.*, **3**, 492 (1935); Evans and Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).

[8] Wislicenus and Mocker, *Ber.*, **46**, 2772 (1913).

[9] Pinck and Hilbert, This Journal, **56**, 490 (1934).

by the presence of 9-aminofluorene. A typical experiment is the following one. A solution of 9-chlorofluorene (0.5 g.) and 9-aminofluorene (2.5 g.) in liquid ammonia was kept at room temperature for an hour. A pale-yellow color developed, and the reaction appeared to be very rapid. The main products of the reaction were fluorylidene-imine (0.40 g.) and fluorene (0.25 g.). Only traces of dibiphenylene-ethylene were formed.

Reactions of 9-Chlorofluorene with Ammonia in Toluene. Formation of 1-Aminodibiphenylene-ethane.—Two grams of 9-chlorofluorene, 2.2 g. of 9-aminofluorene hydrochloride, 10 cc. of toluene and 15 cc. of liquid ammonia, a mixture forming two liquid phases, were shaken in a sealed tube at room temperature for four hours. After standing overnight the tube was opened, and the ammonia removed from the pale-green liquids. The precipitated ammonium chloride was separated by filtration, and the filtrate treated with hydrogen chloride. The orange-colored precipitate formed consisted of fluorylidene-imine (yielding 0.98 g. of fluorenone) and 9-aminofluorene hydrochlorides. Like the hydrochlorides of some other aminofluorene derivatives, that of 1-aminodibiphenylene-ethane is soluble in toluene. To recover this the toluene filtrate was concentrated by distillation at reduced pressure. The residue was treated with 200 cc. of 1% hydrochloric acid and heated to boiling. The insoluble material, fluorene, was removed by filtration, and the filtrate was made alkaline. The crude **1-aminodibiphenylene-ethane** that separated was collected (0.6–0.7 g.) and purified by crystallization from an alcohol–benzene solution. The colorless hexagonal crystals obtained melted at 181° (decomposition to a yellow melt); **hydrochloride**, m. p. 221°; 1-aminodibiphenylene-ethane was not affected over a period of a few days by liquid ammonia, or by boiling 10% hydrochloric acid.

Anal. Calcd. for $C_{26}H_{19}N$: C, 90.39; H, 5.55; N, 4.06. Found: C, 90.47; H, 5.69; N, 4.07.

For comparison, the results of an experiment in which no 9-aminofluorene was added to the reaction mixture are reported. Two grams of 9-chlorofluorene, 15 cc. of liquid ammonia and 5 cc. of toluene were kept at room temperature for two weeks. The procedure used for separating the products was similar to that used in the preceding experiment. The yield of 1-aminodibiphenylene-ethane was 0.22 g.

Although 1-aminodibiphenylene-ethane and 9,9′-difluorylamine have identical empirical formulas and melt at about the same temperature, they readily can be distinguished from each other. The former yields a yellow melt on fusing and a colorless solution in liquid ammonia, whereas the latter produces a dark-green melt and a deep-blue solution when dissolved in ammonia.

1-Hydroxydibiphenylene-ethane.—A solution of 1-aminodibiphenylene-ethane hydrochloride (0.10 g.) in acetic acid (a few cc.) was treated with an aqueous solution of sodium nitrite (0.03 g.). After thirty minutes the solution was diluted with water. The colorless 1-hydroxydibiphenylene-ethane which precipitated was crystallized from carbon tetrachloride; *m.* p. 197°; the melting point of a mixture with an authentic specimen synthesized according to the method of Courtot[6] was unchanged.

1-Methylaminodibiphenylene-ethane.—A solution of 0.5 g. of 1-aminodibiphenylene-ethane in 8 cc. of acetonitrile was treated with a few drops of methyl iodide. The methiodide, which separated in the form of pale yellow prisms melting at 196° (dec.), was collected and dissolved in alcohol, and the solution treated with alkali. The methylamino derivative was precipitated by the addition of water and purified by crystallizing several times from hexane. Colorless elongated prisms melting at 151° were obtained; a mixture of the product and 1-methylaminodibiphenylene-ethane[5] formed by the addition of methylamine to dibiphenylene-ethylene melted at 151°.

Reaction of 9-Bromofluorene in Ammonia.—A solution of 1.0 g. of 9-bromofluorene and about 10 cc. of liquid ammonia on standing at room temperature turned green. The products formed in the reaction were separated in the manner described in the analogous experiment with 9-chlorofluorene. The yields of dibiphenylene-ethylene, fluorene, fluorylidene-imine and 9-aminofluorene were 0.14, 0.10, 0.18 and 0.16 g., respectively.

1-Dimethylaminodibiphenylene Ethane.—To 2.0 g. of 9-chlorofluorene and 2.1 g. of 9-dimethylaminofluorene[10] in 10 cc. of toluene was added 15 cc. of liquid ammonia and the mixture was kept in a sealed tube at room temperature for twenty-four hours. After removal of ammonia the toluene solution was clarified and treated with hydrogen chloride. The orange-colored precipitate was collected and boiled in water. The insoluble material, after extraction with hexane, consisted essentially of crude **1-dimethylaminodibiphenylene-ethane** (0.1 g.). This was purified by crystallization from a solution of benzene and alcohol. Colorless prisms melting at 216° were obtained. The melting point of a mixture with an authentic specimen[5] was unchanged. This tertiary amine was found to be an extremely feeble base, its hydrochloride in water being hydrolyzed to the free amine. The other products isolated were those resulting from the interaction of 9-chlorofluorene and ammonia.

1-Carbethoxydibiphenylene Ethane.—A solution of 2.0 g. of 9-chlorofluorene and 2.4 g. of 9-carbethoxyfluorene in 10 cc. of toluene was mixed with 15 cc. of liquid ammonia. Within a few minutes a very bulky precipitate separated, and the reaction appeared to be complete. However, to ensure a complete reaction the mixture was allowed to stand overnight. The ammonia was evaporated and the organic substance dissolved in hot toluene. The filtrate was concentrated, and the ethane derivative precipitated by the addition of alcohol. 1-Carbethoxydibiphenylene-ethane crystallized from alcohol in the form of colorless prisms melting at 170°.

Anal. Calcd. for $C_{29}H_{22}O_2$: C, 86.53; H, 5.51. Found: C, 86.50; H, 5.68.

An attempt to convert the ester to the acid by heating in boiling alcoholic sodium hydroxide for eight hours yielded dibiphenylene-ethane melting at 247°.

Reaction of 9-Aminofluorene with 9-Chloro-9-phenylfluorene in Liquid Ammonia.—A liquid ammonia solution (*ca.* 10 cc.) containing 0.50 g. of 9-aminofluorene and 0.64 g. of 9-chloro-9-phenylfluorene, after standing at room temperature for five days, was fractionated. The basic and neutral products were separated by means of hydrogen chloride. In addition to 9-amino-9-phenylfluorene,[11] 9-phenylfluorene (0.25 g., m. p. 144–145°) and fluorylidene-imine (converted to fluorenone, 0.21 g.) were formed in this reaction.

Reaction of 1-Chlorodibiphenylene-ethane with Ammonia.—In liquid ammonia, 1-chlorodibiphenylene-ethane[6] is converted rapidly and practically quantitatively to dibiphenylene-ethylene, which separated as glistening red needles. Fluorylidene-imine and 1-aminodibiphenylene-ethane were not found even in traces.

Degradation of 1-Hydroxydibiphenylene-ethane in Ammonia.—One gram of the hydroxy compound was kept in liquid ammonia at room temperature for two days. After the ammonia was evaporated, the residue was dissolved in about 7 cc. of acetic acid, and the solution treated with hydrazine and boiled for thirty minutes to convert fluorenone to the more insoluble fluorylidene-azine. The ketazine separated as reddish-purple needles; yield, 0.42 g.; m. p. and mixed m. p. 269°. Dilution of the filtrate resulted in the precipitation of fluorene and unchanged 1-hydroxydibiphenylene-ethane (0.20 g.). Fluorene was separated by sublimation; yield 0.21 g.

Reaction of 9-Chlorofluorene with Hydrazine.—One gram of 9-chlorofluorene and 5 cc. of 90% hydrazine hydrate were heated on a steam-bath for several hours. A yellow solid gradually separated. After cooling, the solid was collected and was washed with water; yield 0.94 g. It crystallized from alcohol as pale-yellow needles melting at 149° and was found to be fluorenone-hydrazone[12];

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[10] Ingold and Jessop, *J. Chem. Soc.*, 2357 (1929).

[11] Pinck and Hilbert, THIS JOURNAL, **59**, 8 (1937).

[12] Wieland and Roseeu, *Ann.*, **381**, 231 (1911).

mixed melting point with fluorenone-hydrazone prepared by the interaction of fluorenone and hydrazine was unchanged; hydrochloride, deep yellow crystals melting at 268° (dec.).

Reaction of 9-Chlorofluorene with Piperidine.—Colorless needles were deposited from a solution of 0.5 g. of 9-chlorofluorene in 5 cc. of piperidine kept at room temperature for a few hours. The product, 9-(N-piperidino)-fluorene, was recrystallized from ethyl alcohol and melted at 99°.

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.69; H, 7.69. Found: C, 87.25; H, 8.04.

Summary

The reaction of 9-chlorofluorene in liquid ammonia at room temperature has been shown to produce dibiphenylene-ethylene, fluorene, fluorylidene-imine and a trace of 9-aminofluorene. In the presence of toluene there was also formed 1-aminodibiphenylene-ethane, the yield of which was increased significantly by supplementing the ammonia–toluene mixture with 9-aminofluorene. The complexity of the reaction can be accounted for by the presence of two labile substituents, namely hydrogen and chlorine, in the 9 position of the fluorene ring.

9-Bromofluorene in ammonia behaved essentially like the chloro analog. Of chief interest in a comparison of the dyiels of the products from the two halogen derivatives was the appreciably higher yield of 9-aminofluorene from 9-bromofluorene.

In confirmation of the view that intermolecular condensation plays an important part in these reactions, it was found that 9-chlorofluorene in liquid ammonia with 9-dimethylaminofluorene and 9-carbethoxyfluorene yielded 1-dimethylaminodibiphenylene-ethane and 1-carbethoxydibiphenylene-ethane, respectively. Reaction of 9-chloro-9-phenylfluorene with 9-aminofluorene in ammonia gave 9-phenylfluorene and fluorylideneimine.

9-Chlorofluorene with hydrazine formed fluorenone-hydrazone, and with piperidine, 9-(N-piperidino)-fluorene.

BELTSVILLE, MARYLAND RECEIVED[13] DECEMBER 12, 1945

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[13] Original manuscript received June 30, 1939.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

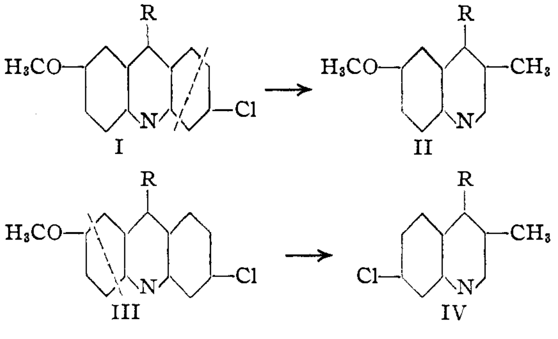
Quinolines. III. The Synthesis of 5- and 7-Chloro- and Bromo-3-methyl-4-dialkylaminoalkylaminoquinolines

BY EDGAR A. STECK, LOUIS L. HALLOCK AND ARNOLD J. HOLLAND

The investigations on compounds derived from 4-aminoquinoline as antimalarials have been reported in few detailed papers,[1,2,3,4] the greater number being mentioned in the patent literature.[5,6] Compounds containing a methyl group in position 3 have been the subject of detailed investigation in these laboratories[7,8] to determine their merits as schizontocides. The present paper deals with the details of preparation of certain 5- and 7-halo-3-methyl-4-dialkylaminoalkylaminoquinolines. Data relative to the screening and clinical testing of these compounds will be published elsewhere.

A relationship may be considered to exist between quinacrine and certain quinolines, as indicated by Gilman and Spatz[3] in their studies of "open models" of the acridine derivative. In these types, one of the benzenoid nuclei has been sheared from its attachment to the quinoline moiety of the acridine. The 6a and 7-substituted compounds of the 3-methyl type might also be visualized as products resulting from a scission of one or the other of the benzenoid cycles of the acridine as indicated (I to II and III to IV).

$R = NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$



I II III IV

The preparation of the 7-substituted quinolines of the desired type was accomplished by application of the Conrad–Limpach[9,10] synthesis to *m*-chloro- and *m*-bromoaniline. As shown in the equations below, the cyclization of ethyl α-(*m*-substituted-phenylimino)-β-methylsuccinates (V) can theoretically give rise to both 5- and 7-substituted quinolines (VI and VII). That such behavior was encountered was indicated by the unsharp melting point of the cyclization product and by the ultimate isolation and proof of structure of two compounds from each *m*-haloaniline. Each

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[1] Magidson and Rubtsov, *J. Gen. Chem., U.S.S.R.*, **7**, 1896 (1937).

[2] Holcomb and Hamilton, THIS JOURNAL, **64**, 1310 (1942).

[3] Gilman and Spatz, *ibid.*, **66**, 621 (1944).

[4] Van Arendonk and Shonle, *ibid.*, **66**, 1284 (1944).

[5] Andersag, Breitner and Jung, U. S. Patent 2,233,970; *C. A.*, **35**, 3771^7 (1941).

[6] Andersag, Breitner and Jung, German Patent 683,692; *C. A.*, **36**, 4973^8 (1942).

[7] Steck, Hallock and Holland, THIS JOURNAL, **68**, 129 (1946).

[8] Steck, Hallock and Holland, *ibid.*, **68**, 132 (1946).

[9] Conrad and Limpach, *Ber.*, **20**, 944 (1887).

[10] Limpach, *ibid.*, **64**, 969 (1931).