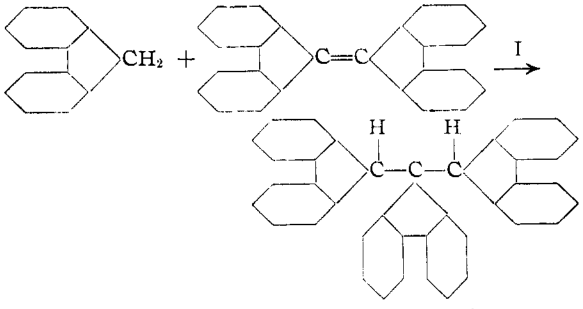
[CONTRIBUTION FROM THE BUREAU OF PLANT INDUSTRY, SOILS AND AGRICULTURAL ENGINEERING, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

The Michael Condensation of Fluorene with Unsaturated Compounds

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

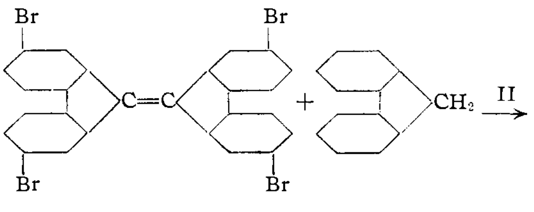
Heretofore the Michael condensation involved reactions in which both the acceptor and the addendum required the presence of such labilizing groups as —COOR, —COR, —CN, —$CONH_2$, —NO_2, —SO_2R and —CHO.[2] In the present study, condensations are reported with certain compounds which do not have any of the labilizing groups cited above. The novel acceptors are dibiphenylene-ethylene, 2,7,2′,7′-tetrabromodibiphenylene-ethylene and benzalfluorene. The common reactive grouping in these compounds is the fluorylidene nucleus. In a previous publication dealing with the reaction of amines with dibiphenylene-ethylene[3] it was inferred that the electronic configuration of the double bond in dibiphenylene-ethylene is more like that of the ethylenic linkage with an adjacent carbonyl group than that of the normal type in ethylene. The addenda used in the present study are fluorene and 2,7-dibromofluorene.[4] The lability of the hydrogen in the (9) position of fluorene derivatives has been emphasized in a previous publication[5] and conclusive evidence will be presented in this investigation showing the ionization of the fluorene molecule.

It has been found that fluorene condenses with dibiphenylene-ethylene in an alkaline medium to form tribiphenylene-propane as shown in the reaction.



This propane derivative was first obtained in a reaction of dibiphenylene-ethylene with liquid ammonia at a temperature of 65° for a period of three weeks.[3] Fluorene, one of the reactants, was formed in a reaction involving the dismutation of the unstable 1-aminodibiphenylene-ethane In this study we have found that the above reaction can be more easily obtained in such solvents as pyridine containing a small volume of aqueous sodium hydroxide and in an alcoholic solution of sodium ethylate. Evidence for the structure of tribiphenylene-propane is obtained in the carbon, hydrogen and molecular weight determinations. Since carbon and hydrogen determinations of a hydrocarbon are not crucial factors for establishing composition, other condensations were therefore obtained with organic compounds containing three elements. Condensations were therefore carried out with (1) dibiphenylene-ethylene and 2,7-dibromofluorene, (2) 2,7,2′,7′-tetrabromodibiphenylene-ethylene and fluorene, (3) 2,7,2′,7′-tetrabromodibiphenylene-ethylene and 2,7-dibromofluorene and (4) benzalacetophenone and fluorene. It was also found that benzalfluorene, which is considerably less reactive than dibiphenylene-ethylene, readily reacts with fluorene.

The most interesting reaction obtained in this study involves the condensation of 2,7,2′,7′-tetrabromodibiphenylene-ethylene with fluorene. The anticipated reaction product, 2,7,2′,7′-tetrabromotribiphenylene-propane, was not isolated in pure form. On the basis of the analytical data it appeared that the tetrabromo derivative was contaminated with a less halogenated product. When this experiment was repeated, the reaction mixture was heated for a longer period, this time yielding a product containing even less halogen than that occurring in 2,7-dibromotribiphenylene-propane. However, some 2,7-dibromofluorene was isolated from the reaction mixture. This experiment was therefore repeated for the third time using such conditions so as to obtain a complete reaction. Here the products formed were tribiphenylene-propane and 2,7-dibromofluorene. The final experiment clarified the apparent complexity of the involved reaction mechanisms. This last observation definitely indicates that 2,7,2′,7′-tetrabromotribiphenylene-propane dissociates into 2,7-dibromofluorene and the ethylene derivative which in turn is condensed with a fluorene molecule. The complete reaction, therefore, involves three condensations and two dismutations as shown by the equations



---

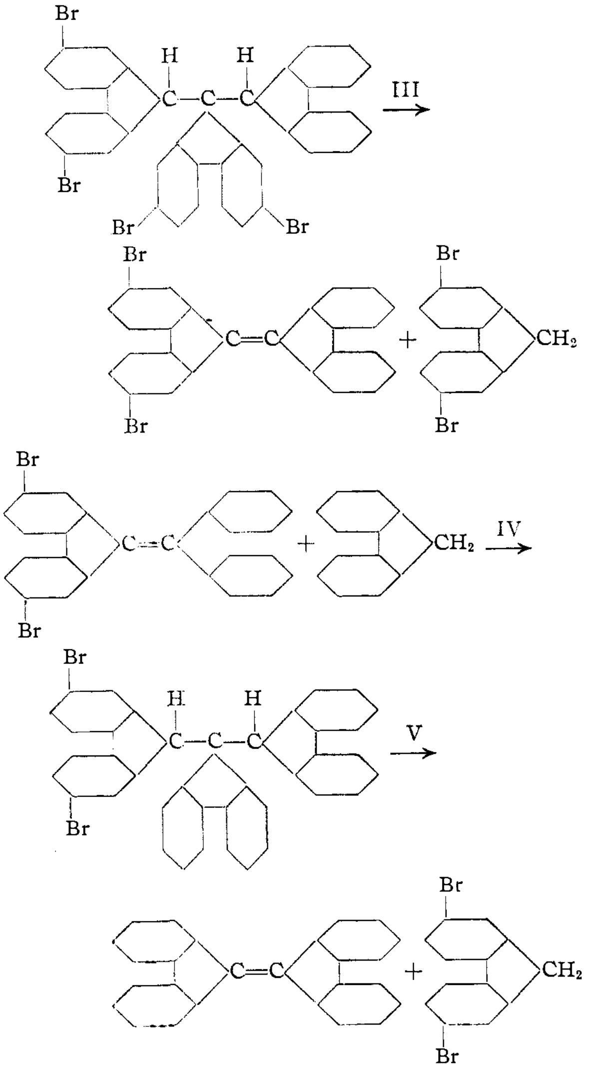
[1] Present address: Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, Peoria, Illinois.

[2] Connor and McClellan, *J. Org. Chem.*, **3**, 570 (1939).

[3] Pinck and Hilbert, THIS JOURNAL, **57**, 2398 (1935).

[4] While this work was in progress France, Maitland and Tucker (*J. Chem. Soc.*, 1739 (1937)) reported a Michael condensation of fluorene with mesityl oxide and after our experimental work had been completed Taylor and Connor (*J. Org. Chem.*, **6**, 696 (1941)) published a paper showing that fluorene and 2,7-dibromofluorene condense with benzalacetophenone, benzal-*p*-bromoacetophene and with benzalacetone.

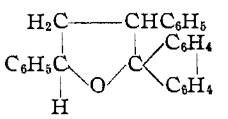
[5] Pinck and Hilbert, THIS JOURNAL, **68**, 377 (1946).



The final reaction is indicated by equation I.

The dissociation of the fluoryl nucleus was also observed in the synthesis of dibiphenylenephenylpropane, the compound dissociating into its original components, namely, fluorene and benzalfluorene. It is possible that this effect may be due to the electronegativity of the phenyl group.

The structural formula 1-biphenylene-2,4-phenylhydrofuran



$$\begin{array}{ccc} H_2C & \text{———} & CHC_6H_5 \\ C_6H_5\overset{|}{\underset{|}{C}} & \diagdown O \diagup & C\begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix} \\ H & & \end{array}$$

is assigned to the condensation product of benzalacetophenone and fluorene,[6] since this compound failed to form a phenylhydrazone and a carbazide and failed to show an OH absorption in the infra-red.

In conclusion it should be noted that all the Michael condensations reported in this paper are made possible through the dissociation of the fluorene molecule into a fluoryl ion and a proton. Furthermore the dismutation of dibiphenylenephenylpropane into benzalfluorene and fluorene probably involves the intermediation of the fluoryl ion. A similar intermediation probably also occurs in the interaction of the tetrabromotribiphenylenepropane with fluorene.

Acknowledgment.—We wish to express our appreciation to Mrs. M. S. Sherman for carrying out the recorded microanalyses.

Experimental

Tribiphenylene-propane was prepared by heating a solution of 1 g. of dibiphenylene-ethylene and 2 g. of fluorene in 15 cc. of pyridine and about 1 cc. of a saturated aqueous solution of sodium hydroxide in a sealed tube at 100° for one hour. The reaction mixture was obtained in two liquid phases with the aqueous layer at the bottom. The pyridine layer turned olive brown on heating and green upon cooling. The crystalline precipitate was removed and an additional crop was obtained by diluting the pyridine filtrate with an equal volume of alcohol, yield 1.23 g. (82%). Large glistening colorless tetragonal prisms were obtained by crystallization from either pyridine or ethyl acetate, m.p. 300° (red melt). It is very soluble in dioxane, soluble in benzene, less soluble in pyridine, ethyl acetate, acetic anhydride, acetic acid and acetone, practically insoluble in alcohol and ether and can be sublimed *in vacuo* at 220°.

Anal. Calcd. for $C_{39}H_{26}$: C, 94.70; H, 5.30; mol. wt., 494. Found: C, 94.64; H, 5.49; mol. wt., 485.

It is significant to note that pyridine alone is too weak a base to effect this condensation.

A practically quantitative yield (89%) was also obtained when the reaction was carried out in absolute alcohol containing sodium ethylate. Here, however, the compound was slightly colored regardless of the number of recrystallizations due to the contamination with a slight quantity of dibiphenylene-butadiene.[7]

Tribiphenylene-propane was obtained as one of the products in the interaction of dibiphenylene-ethylene with ammonia.[3] In the experiment previously published 1 g. of the ethylene yielded 0.50 g. of tribiphenylenepropane. In another experiment 1 g. of the ethylene in 15 cc. of liquid ammonia and 10 cc. of toluene yielded 0.10 g. of the hydrocarbon. A third experiment using the above reagents plus 0.5 g. of fluorene gave 0.37 g. of the hydrocarbon.

2,7-Dibromotribiphenylene-propane was obtained by heating an alcoholic solution of 2 g. of dibiphenylene-ethylene, 4 g. of 2,7-dibromofluorene (excess) and sodium ethylate in a sealed tube at 80° for eleven hours. The crude reaction product (4.06 g.) was purified by numerous recrystallizations from ethyl acetate and ether, yielding fine needles, which begin to decompose at 280° and melt at 290°.

Anal. Calcd. for $C_{30}H_{24}Br_2$: C, 71.78; H, 3.71; Br, 24.51. Found: C, 71.58; H, 4.06; Br, 24.01.

2,7-Dibromo-9-chlorofluorene[8] was obtained by heating for about forty minutes a mixture of 10 g. of 2,7-dibromo-9-fluorenol and 50 cc. of phosphorus oxychloride at such a temperature as to maintain a complete solution. The crude product (10 g., m.p. 159°) was purified by crystallization from benzene or by sublimation, clusters of fine colorless prisms, m.p. 170°.

Anal. Calcd. for $C_{13}H_7Br_2Cl$: C, 43.53; H, 1.97; Br, 44.60. Found: C, 43.37; H, 2.09; Br, 44.55.

---

(6) Taylor and Connor (ref. 4), however, considered this compound to be a "normal" type of condensation (Gardner and Rydon, *J. Chem. Soc.*, 48 (1938)) and assumed its structure to correspond to β-(9-fluorenyl)-β-phenylpropiophenone.

(7) Wislicenus, *Ber.*, **48**, 617 (1915).

(8) This compound was first prepared by Courtot (*Ann. Chim.*, [10] **14**, 103 (1930)) by a method not at all suitable for fair sized preparations. His product melted at 154–155°.

Preparation of 2,7,2′,7′-Tetrabromodibiphenylene-ethylene.—Various attempts to prepare the tetrabromodibiphenylene-ethane by the method of Schmidt and Wagner were unsuccessful.[9] Reactions were tried in boiling benzene, toluene and xylene with different types of copper including Schering–Kahlbaum Naturkupfer C. An impure ethylene was obtained by using a freshly prepared copper powder[10] in boiling xylene. The product, after several recrystallizations from bromobenzene, remained impure.

Anal. Calcd. for $C_{26}H_{12}Br_4$: C, 50.59; H, 2.12. Found: C, 48.46; H, 1.86.

The following procedure was finally developed. A solution of 2 g. of 2,7-dibromo-9-chlorofluorene in 20 cc. of nitromethane and 5 cc. of triethylamine was heated in a sealed tube at 100° for an hour. The red ethylene was precipitated as it was formed and the solution was dark green. The precipitate after being leached with the following hot solvents: 50% and 95% alcohol and benzene, weighed 1.63 g. It was then recrystallized from bromobenzene; no sign of melting at 370°.

Anal. Calcd. for $C_{26}H_{12}Br_4$: C, 48.46; H, 1.86; Br, 49.68. Found: C, 49.10; H, 2.22; Br, 48.82.

The preparation of the ethylene from the chloro compound in alcoholic sodium hydroxide or in isoamyl ether containing triethylamine was not satisfactory.

Reaction of 2,7,2′,7′-Tetrabromodibiphenylene-ethylene with Fluorene.—The mechanism of this reaction is established by the results obtained in the following experiments.

1. A solution of 1 g. of 2,7,2′,7′-tetrabromodibiphenylene-ethylene, 0.5 g. of fluorene and about 1 cc. of a saturated aqueous solution of sodium hydroxide in 20 cc. of pyridine was heated in a sealed tube at 100° for one and one-half hours. The reaction product upon recrystallization from benzene yielded 0.69 g. of colorless needles, m.p. 320° (red melt).)

Anal. Calcd. for $C_{39}H_{22}Br_4$: C, 57.79; H, 2.74; Br, 39.47. Found: C, 65.18; H, 3.32; Br, 29.85, 30.03.

2. The experiment was repeated using 1 g. of the ethylene and 5 g. of fluorene (large excess). The solution was heated at 75° for twenty-four hours. Acetic acid was added to the reaction mixture to neutralize the sodium hydroxide, and the mixture was subjected to steam distillation thereby effecting the removal of pyridine, excess acetic acid and fluorene (3.5 g.). The residue was triturated with hot alcohol and recrystallized first from benzene–alcohol and then from ethyl acetate; weight 0.47 g. Two types of crystals were noted, the bulk of which consisted of needles and the smaller quantity were diamond-shaped plates. Upon recrystallization the product melted at 296°.

Anal. Calcd. for $C_{33}H_{24}Br_2$: C, 71.78; H, 3.71; Br, 24.51. Found: C, 74.07; H, 4.12; Br, 21.01, 21.29.

The material soluble in the alcohol and benzene–alcohol was recrystallized from acetic acid and then further purified by sublimation, m.p. 163°, mixed m.p. with 2,7-dibromofluorene 165°.

3. The results of the second experiment seemed to indicate that equilibrium conditions were not attained and the experiment was again repeated, this time, however, the solution was heated at 100° for six days. After steam distillation the residue was subjected to sublimation thereby removing any residual fluorene and also 0.14 g. of 2,7-dibromofluorene whose identity was established by melting and mixed melting points. The residue (1.3 g.), fractionally crystallized from acetic acid, yielded 0.56 g. in the first two fractions (m.p. 285°; Beilstein test negative) which, after two recrystallizations from ethyl acetate, gave pure tribiphenylenepropane, melting at 299° and with a m.p. of 300°, when mixed with an authentic sample.

Anal. Calcd. for $C_{39}H_{26}$: C, 94.70; H, 5.30. Found: C, 94.84; H, 5.48.

The third fraction (0.23 g.) melted at 164°, mixed m.p. with 2,7-dibromofluorene 164°.

2,7,2′,7′,2″,7″-Hexabromotribiphenylene-propane was obtained by heating a pyridine solution of 1 g. of 2,7-dibromofluorene (excess) and 1 g. of 2,7,2′,7′-tetrabromodibiphenylene-ethylene containing 1–2 cc. of a concentrated aqueous solution of sodium hydroxide for one hour at 100°; yield 0.91 g.; colorless microcrystals from xylene; m. p. 332° with decomposition. In an attempt to crystallize the hexabromo derivative from pyridine it appeared to dissociate into its original components.

Anal. Calcd. for $C_{39}H_{20}Br_6$: C, 48.36; H, 2.08; Br, 49.55. Found: C, 48.69; H, 2.30; Br, 49.29.

Dibiphenylene-phenylpropane[11] was prepared in 70% yield by the interaction of 10 g. of benzalfluorene with 20 g. of fluorene in 80 cc. of pyridine and 5 cc. of a saturated aqueous solution of sodium hydroxide in a stoppered 100-cc. flask. The green colored solution was shaken intermittently and kept at room temperature for a week. The reaction mixture was acidified with acetic acid and steam distilled, thereby effecting the removal of the pyridine, excess acetic acid and the unreacted fluorene. The residue was triturated with about 400 cc. of hot alcohol leaving 12 g. of a white insoluble product, m. p. 230°, which when recrystallized from benzene yielded needle-like prisms, m. p. 239°.

Anal. Calcd. for $C_{33}H_{24}$: C, 94.24; H, 5.76; mol. wt., 420. Found: C, 94.28; H, 5.78; mol. wt., 400, 404.

In certain preliminary experiments very poor yields of the propane derivative were obtained when the reaction was carried out at an elevated temperature. The following experiment was therefore designed to determine the fate of the propane derivative when heated. A pyridine solution of 4 g. of dibiphenylene-phenylpropane and about 1 cc. of sodium hydroxide solution was heated at 105° for eighteen hours. The solution turned blue at room temperature and green when hot. The cooled contents of the tube were neutralized and then steam distilled. Alcohol, in 50-cc. aliquots, was added from time to time to hasten the distillation of the fluorene, weight 1.32 g. (79.4%). The unsublimed residue was triturated with hot alcohol leaving 0.3 g. (7.5%) of the insoluble propane. The alcoholic solution was concentrated to a small volume and upon cooling and scratching yielded 1.80 g. (76.9%) of benzalfluorene. The identity of the products was established by melting and mixed melting points.

Reaction of Fluorene with Benzalacetophenone.—Ten grams of fluorene, 7 g. of benzalacetophenone, 5 cc. of concentrated aqueous sodium hydroxide solution and approximately 85 cc. of pyridine were placed in a 100-cc. stoppered flask which was shaken intermittently and kept at room temperature for five days. The solution was diluted with about 6 volumes of water and acidified with hydrochloric acid. The solid which deposited was crystallized from 1:1 benzene-alcohol solution; yield practically quantitative; hexahedral prisms; m. p. 129°.

Anal. Calcd. for $C_{28}H_{22}O$: C, 89.80; H, 5.93. Found: C, 90.31; H, 5.90.

Summary

Michael condensations were effected using novel acceptors and addenda. Reactions of fluorene were obtained with dibiphenylene-ethylene, 2,7,2′,7′-tetrabromodibiphenylene-ethylene, benzalfluorene and benzalacetophenone. 2,7-Dibromofluorene was condensed with dibiphenylene-ethylene and 2,7,2′,7′-tetrabromodibiphenylene-ethylene. A number of experiments were performed with fluorene and 2,7,2′,7′-tetrabromodibiphenylene-ethylene, which clarified a rather involved series of reaction mechanisms. The dissociation of fluorene and its dibromo derivative

---

[9] Schmidt and Wagner, *Ann.*, **387**, 157 (1911).

[10] Ullmann and Bielecki, *Ber.*, **34**, 2175 (1901).

[11] This compound may be 1,3-dibiphenylene-2-phenylpropane or 1,2-dibiphenylene-3-phenylpropane.

were obtained from certain condensates. These studies presented evidence for the ionization of fluorene into a fluoryl ion and a proton.

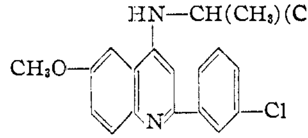
BELTSVILLE, MARYLAND RECEIVED MAY 9, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

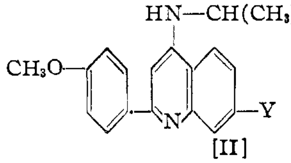
Some Methylquinolines Patterned as "Open Models" of Atebrin

BY HENRY GILMAN, J. LEWIS TOWLE AND SYDNEY M. SPATZ[1]

The initial[2,3] series of so-called open models of atebrin, designed primarily to incorporate the gametocidal activity of certain quinolines as well as the schizonticidal activity of certain acridines, was focused chiefly on 6-methoxy-2-(3'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline [I]. In [I] the chlorophenyl group replaces the fused chlorobenzo group of atebrin.



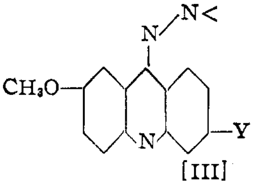
[I]



Y = Cl, CH₃

[II]

The acridine nucleus of atebrin may be "opened" at three other positions to yield quinolines of interest in antimalarial studies. For example, a consideration of atebrin as a methoxybenzo derivative of 7-chloro-4-substituted-aminoquinoline suggests the synthesis of [II] where Y is chlorine. Because of the relative inaccessibility of 7-chloroquinoline when this study was commenced a few years ago,[4] the synthesis of [II] where Y is the methyl group was attempted instead. In connection with the replacement of the chlorine atom by the methyl group, it should be noted that Mietzsch and Mauss[5] demonstrated the importance of either a chlorine atom or a methyl group in the 6-position of 2-methoxy-9-basically substituted acridines [III]. These findings, first demonstrated in malaria infected canaries,[6] were confirmed by other studies[7] on the sparrow. Later, a series of active quinolines with a dialkylaminoalkylamino chain in the 4-position and either a methyl group or preferably a chlorine atom in the 7-position was reported in the patent literature.[8]



Y = Cl, CH₃

[III]

The synthesis of the isomeric 6-methyl-2-(4'-methoxyphenyl)-4-([α-methyl-δ-diethylaminobutyl)-amino]-quinoline was carried out to study further[2,3] the effect of position isomerism on the thereapeutic activity of the open models. The first step in the two syntheses, involving the addition of the *p*-anisyllithium to the —N=C< linkage of the 6- and 7-methylquinolines, yielded, subsequent to hydrolysis, both the 1,2-dihydro compound and the dehydrogenated derivative. The syntheses are summarized in the equations presented below.

An unsuccessful attempt to prepare the isomer of [II] with the methyl group in the 8-position was due to the failure of the 8-methyl-2-(4'-methoxyphenyl)-quinoline to undergo N-oxidation. A similar phenomenon, possibly steric in origin, was observed in the case of the 8-methyl-2-(4'-chlorophenyl)-quinoline.[3]

The 2-(*p*-dimethylaminophenyl)-quinolines listed in Table I were prepared by the azomethine-addition reaction of *p*-dimethylaminophenyllithium with quinoline, 6-methyl-, 7-methyl-, 8-methyl-, 8-hydroxy- and 8-methoxyquinoline, respectively.

Of the several compounds described in this report, the only one which showed any activity in experimental avian malaria was 8-methyl-2-(*p*-dimethylaminophenyl)-quinoline.

Experimental

6-, 7- and 8-Methyl-2-(4'-methoxyphenyl)-quinolines and 6-, 7-Methyl-1,2-dihydro-2-(4'-methoxyphenyl)-quinolines.—Two-tenths of a mole[9] of *n*-butyllithium and 46.8 g. (0.25 mole) of *p*-bromoanisole in 350 cc. of ether were stirred at 0° for fifteen minutes. Without delay, a solution of 28.6 g. (0.2 mole) of the methylquinoline in 50 cc. of ether was added at 0° over a three-minute interval to the

---

[1] Present address: National Aniline Division, Allied Chemical and Dye Corp., Buffalo, N. Y.

[2] Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944).

[3] Gilman, Christian and Spatz, *ibid.*, **67**, 979 (1945).

[4] Syntheses of such types by R. A. Benkeser, starting with 4,7-dichloroquinoline, will be reported later.

[5] Mietzsch and Mauss, *Klin. Wochschr.*, **12**, 1276 (1933); German Patent 553,072 (1930) [*Chem. Zentr.*, **103**, II, 1201 (1932)], German Patent 571,449 (1930) [*Chem. Zentr.*, **104**, I, 3969 (1933)]; *Angew. Chem.*, **47**, 633 (1934); *Ber.*, **69B**, 641 (1936); U. S. Patent 2,077,249 (1937) [*C. A.*, **31**, 4060 (1937)].

[6] Mietzsch, in "Medicine in its Chemical Aspects," Vol. III, "Bayer," Germany, 1936.

[7] Feldman and Kopeliovich, *Arch. Pharm.*, **273**, 488 (1935).

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

[9] Estimated by the procedure of Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).