

curves were plotted against composition to give the phase diagram.

Since the weight of acids obtained by the cleavage of *o*-chlorodibenzoylmethane indicated a mixture falling near the eutectic point and since these mixtures are not suited to thermal analysis, the cleavage mixture was first diluted by the addition of five grams of pure *o*-chlorobenzoic acid. The cooling curve for the diluted mixture showed an initial halt at 115.8°, representing a mixture containing 0.640 mole fraction of *o*-chlorobenzoic acid. The original mixture of acids therefore contained 0.442 mole fraction of *o*-chlorobenzoic acid.

The following calculation indicates that a quantitative conversion of the diketone into the two acids had taken place. Cleavage in one direction only would have produced 7.04 g. of benzoic acid while cleavage in the other direction would have produced 9.02 g. of *o*-chlorobenzoic acid.

Calcd. wt. of benzoic acid = 0.558 × 7.04 g. = 3.93 g.

Calcd. wt of *o*-chlorobenzoic

acid = 0.442 × 9.02 g. = 3.99

Total 7.92

## Summary

The preparation and alkaline cleavage of *o*-chlorodibenzoylmethane are reported.

$\beta$ -Methoxy-*o*-chlorobenzalacetophenone, the precursor of the diketone, was easily isolated and proved to be much more stable than closely related compounds.

The evidence of cleavage does not support the conclusion of Bradley and Robinson that the direction of cleavage is determined by the strength of the two possible aryl acids, the stronger acid being formed in the larger proportion. In fact, no relationship between the strength of the acids and the direction of the cleavage can be established in the cases studied.

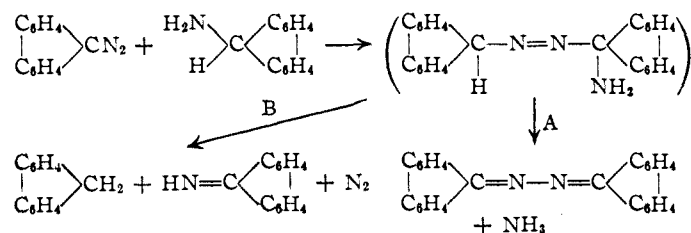
EXETER, NEW HAMPSHIRE RECEIVED JANUARY 5, 1946

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

## Reaction of Diazofluorene with 9-Substituted Fluorene Derivatives

BY LOUIS A. PINCK AND GUIDO E. HILBERT<sup>1</sup>

A reaction of diazofluorene with 9-aminofluorene in an alkaline medium, such as liquid ammonia, was obtained, yielding fluorenone ketazine in an amount corresponding to 65% of the theoretical, and small amounts of fluorylidene-imine and fluorene. The formation of these products may be interpreted by the formation of an unstable intermediate product involving a 1,3-addition. In liquid ammonia at room temperature, approximately two-thirds of the azo intermediate undergoes transformation by reaction A and the rest by reaction B. These transformations may be modified by altering the substituents of the addendum in the 9 position. Thus in the



reaction of diazofluorene with 9-anilino fluorene, A is augmented to a yield of 76% with a corresponding decrease in the yield of products resulting from B. By a proper choice of a suitable 9-substituted fluorene derivative in place of 9-aminofluorene, A or B can be eliminated. When diazofluorene reacts with 9-chlorofluorene the reaction is principally in the direction of A, and when 9-fluorenyl is

used A is entirely eliminated, the products formed are fluorene and fluorenone in accord with B. These reactions can also be obtained in an alcoholic solution of sodium ethylate.

With the possible exception of the ethylene formation by the pyrolysis of diazofluorene, the chemical properties of this compound are in general similar to those of other aliphatic diazo compounds and it is therefore postulated that other substituted diazomethane derivatives will undergo a 1,3-addition with 9-substituted fluorenes (substituents being amino, anilino, halogeno or hydroxy groups) to form either a mixed ketazine and/or other derivatives corresponding to B.

## Experimental

**Reaction of Diazofluorene with 9-Aminofluorene.**—When 0.500 g. of diazofluorene and 0.564 g. of 9-aminofluorene hydrochloride were treated with 10–15 cc. of liquid ammonia in a sealed tube at room temperature, a rapid deposition of a brick-red, amorphous precipitate was observed. After completion of the reaction, the contents of the tube were cooled to liquid ammonia temperature, transferred into a Dewar tube, and the ammonia was evaporated spontaneously through a tube containing calcium chloride to prevent the absorption of moisture. The dry residue was triturated with anhydrous ether. The ether-insoluble fraction was crystallized from xylene yielding 0.605 g. of fluorenone ketazine, melting and mixed m. p. 269° (65.3% of the theoretical).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{16}\text{N}_2$ : C, 87.60; H, 4.53; N, 7.87. Found: C, 87.26; H, 4.75; N, 8.07.

On treatment of the ether filtrate with dry hydrogen chloride a mixture of white and orange colored hydrochlorides (0.15 g.) precipitated simultaneously. The orange color is one of the characteristic properties of fluorylidene-imine hydrochloride. The formation of fluo-

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

rylidene-imine was confirmed by hydrolyzing the salt which yielded 0.09 g. of fluorenone (purified by crystallization from petroleum ether). The small quantity of the white hydrochloride was not identified but was presumed to be the salt of a trace of unreacted 9-fluorylamine. The ether-hydrochloric acid soluble fraction was purified by sublimation and identified as fluorene. All products identified in this and subsequent experiments were compared with authentic specimens.

This reaction was also effected in an alcoholic solution of sodium ethylate. Because of the ease with which the 9-amino and hydroxy derivatives are oxidized by air in an alkaline medium, this experiment as well as those involving fluorenol were performed in a flask containing an auxiliary tube through which a gentle stream of nitrogen was flushed throughout the run. Using 0.5 g. of diazofluorene and 1.15 g. of 9-aminofluorene in about 75 cc. of an alcoholic solution of sodium ethylate, the reaction was found to be rapid. The yields of reaction products were: 0.23 g. of fluorenone ketazine, 0.40 g. of fluorylidene-imine and 0.125 g. of fluorene.

**Reaction of Diazofluorene with 9-Anilino fluorene.**—The quantities of materials used were 0.375 g. of diazofluorene and 0.500 g. of 9-anilino fluorene in about 10 cc. of liquid ammonia. After removal of the ammonia the reaction products were extracted with petroleum ether and the insoluble fraction upon recrystallization yielded 0.55 g. of fluorenone ketazine (76% of the theoretical). The petroleum ether extract was concentrated and the aniline was distilled *in vacuo*. The latter was identified as the tribromo derivative.

**Reaction of Diazofluorene with 9-Chlorofluorene.**—A reaction which appeared to be complete in approximately fifteen minutes took place between 0.5 g. of diazofluorene and 0.522 g. of 9-chlorofluorene in 10–15 cc. of liquid ammonia at room temperature. The isolated reaction products were fluorenone ketazine (0.692 g. corresponding to 74.8% of the theoretical) and a trace of fluorylidene-imine.

**Reaction of Diazofluorene with 2,7-Dibromo-9-fluorenol.**—The reaction between 0.5 g. of diazofluorene and 0.9 g. of

2,7-dibromo-9-fluorenol in absolute ethanol containing sodium ethylate was complete within an hour at room temperature. During the course of the reaction there was gas evolution and a gradual deposition of the yellow needle-like precipitate of 2,7-dibromofluorenone. The mixture was acidified with acetic acid and the 2,7-dibromofluorenone (0.69 g.) was separated by filtration, m. p. 203°, mixed m. p. with an authentic specimen 205°. The alcoholic filtrate and washings were steam distilled whereby 0.35 g. of fluorene was obtained. The residue from the steam distillation after triturating with a small volume of alcohol yielded an additional 0.08 g. of 2,7-dibromofluorenone. The recovered yields of fluorene and dibromofluorenone corresponded to 81 and 87.5%, respectively.

**Reaction of Diazofluorene with 9-Fluorenol.**—This reaction was found to be sluggish and in order to obtain satisfactory results an excess of fluorenol was used and the alcoholic solution heated at 60–70° for seven hours. The formation of ketazine due to thermal decomposition of the diazo compound was negligible. The sodium silicate formed by the action of the alkali on the glass was readily removed after acidifying the solution. The fluorenone was separated from the fluorene and excess fluorenol by converting it to the difficultly soluble fluorenone ketazine<sup>2</sup> and the fluorene by steam distillation. From 0.5 g. of diazofluorene and 1 g. of 9-fluorenol were obtained 0.40 g. of ketazine and 0.35 g. of fluorene.

### Summary

Reactions were obtained in alkaline media, such as liquid ammonia and alcoholic sodium ethylate, between diazofluorene and 9-aminofluorene, anilino fluorene, 9-chlorofluorene and 9-fluorenol. The products formed were either fluorene and a fluorylidene derivative or fluorenone ketazine.

(2) Pinck and Hilbert, *THIS JOURNAL*, **57**, 2400 (1935).

BELTSVILLE, MARYLAND

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[CONTRIBUTION FROM THE NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

## Some Quaternary Ammonium Salts of Heterocyclic Bases<sup>1,2</sup>

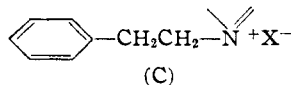
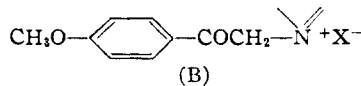
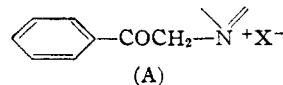
BY JONATHAN L. HARTWELL AND SYLVIA R. L. KORNBERG

The biological results obtained by our collaborators<sup>2</sup> with some of the  $\alpha,\beta$ -diphenylethylamines<sup>3</sup> made desirable the synthesis of several series of compounds which, while retaining certain features of the  $\alpha,\beta$ -diphenylethylamines, would have other features modified. Three series of compounds, A, B and C, were chosen for synthesis. Each of these resembled the  $\alpha,\beta$ -diphenylethylamines in possessing two aromatic rings separated by two carbon atoms on one of which was attached a nitrogen atom. They differed, however, in several respects that are obvious on comparison. The present paper reports the synthesis and properties of these three series of quaternary ammonium compounds formed by adding the elements of

(1) Paper XII in the series entitled "Chemical Treatment of Tumors." Paper XI in this series: Hartwell and Kornberg, *THIS JOURNAL*, **67**, 1606 (1945).

(2) Material contained in this paper was presented, in part, at the A. A. S., Gibson Island Conference on Cancer at Gibson Island, Maryland, on August 3, 1945.

(3) Paper XI.



phenacyl (series A), *p*-methoxyphenacyl (series B) and  $\beta$ -phenethyl (series C) halide to a number of tertiary heterocyclic bases of the pyridine, quinoline and isoquinoline groups. In addition, one member of the naphthalene series and several oximes were prepared. An attempt to prepare a styryl series by the addition of  $\beta$ -bromostyrene to the heterocyclic bases resulted in too small yields of products for the reaction to be preparatively useful.