[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE UTILIZATION OF ETHYL GAMMA-DIETHOXY-ACETO-ACETATE FOR THE SYNTHESIS OF DERIVATIVES OF GLYOXALINE. AN ATTEMPT TO SYNTHESIZE HISTAMINE BY A NEW METHOD

BY GEORGE W. PUCHER AND TREAT B. JOHNSON[1]

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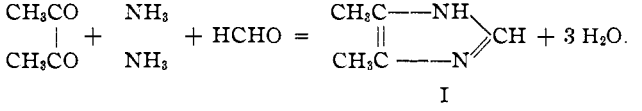
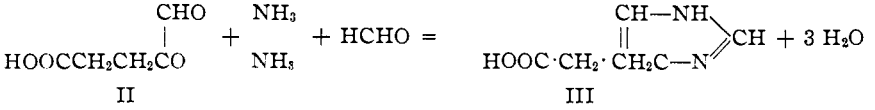
A fundamental reaction which has been applied successfully for the preparation of glyoxaline compounds is that involving the condensation of an *ortho*-diketonic compound with an aldehyde in the presence of ammonia. It was first utilized by Debus[2] for the synthesis of glyoxaline itself and the reaction has been used with success by several investigators since its discovery.[3] The interaction of diacetyl, for example, with ammonia and formaldehyde giving dimethylglyoxaline (I) is expressed by the following equation.



I

Windaus and Vogt[4] applied this type of reaction in one stage of their interesting synthesis of histidine and histamine, when they showed that the ketone-aldehyde (II) condenses normally with formaldehyde and ammonia with formation of β-imidazole-propionic acid (III), but outside



II III

of this work no plan of synthesis, so far as the writers are aware, has been developed which involves the application of their principle for glyoxaline constructions of the type of histamine.

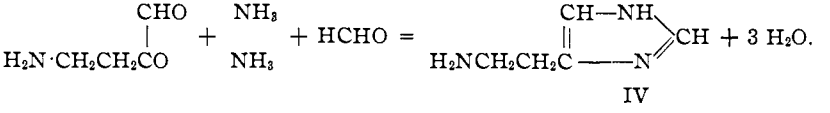
Analysis of the accepted structural formula of histamine (IV) reveals the fact that amino-ethyl-glyoxal, $H_2N.CH_2CH_2.CO.CHO$, is the *ortho*-ketone-aldehyde structure functionating in this cyclic molecule. In other words, this amine together with formaldehyde and ammonia theoretically have interacted in accordance with the principle outlined above giving a glyoxaline and the hypothetical synthesis of histamine (IV) may be expressed as follows.

[1] This paper is constructed from a dissertation presented by George Walter Pucher in June, 1920, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy. (T. B. J.)

[2] Debus, *Ann.*, **17**, 199 (1856).

[3] von Pechman, *Ber.*, **21**, 1417 (1888). Radziszewski, *ibid.*, **15**, 1493 (1882).

[4] Windaus and Vogt, *ibid.*, **40**, 3691 (1907).



IV

If we extend this series to the higher homologs it will be observed, for example, that the corresponding aminopropyl-glyoxal, $NH_2CH_2CH_2CH_2COCHO$, is the *ortho*-ketone-aldehyde which would be productive of the next higher homolog of histamine by condensation with ammonia and formaldehyde. In other words, a synthesis, which would permit of the formation of this series of glyoxal amines, theoretically would enable us to synthesize by a new method a series of glyoxaline bases related to histamine.

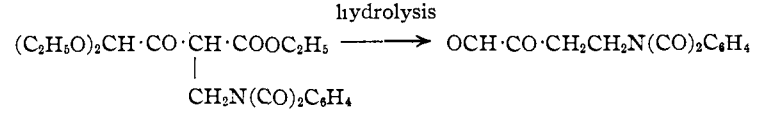
This analysis of the histamine molecule together with the fact that at present we have very scanty knowledge of aminoglyoxaline combinations of the above type created a renewed interest in the study of new methods of synthesis in this interesting biochemical field. Such a method of synthesis applicable to histamine alone would have many advantages over those that already have been applied. It would be a more direct method of approach and involve a smaller number of intermediate reactions.

An organic reagent which is now available, but has never been utilized in the development of glyoxaline syntheses, is the very reactive β-ketone ester, namely, ethyl γ-diethoxy-aceto-acetate (V) which is obtained easily in a pure state by condensation of ethyl diethoxy-acetate[5] with ethyl acetate. Not only does it contain an acetal structure which is extremely susceptible to hydrolysis in acid solution, but it also contains a reactive methylene group which permits of the carrying out of fundamental reactions characteristic of a normal β-ketone ester.

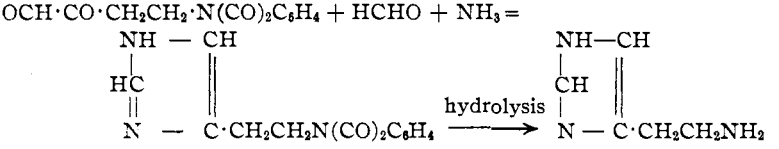
$$(C_2H_5O)_2CHCOOC_2H_5 + CH_3COOC_2H_5 = (C_2H_5O)_2CH\cdot COCH_2COOC_2H_5 + C_2H_5OH.$$

V

The synthesis which we attempted to develop by use of this reagent is expressed in its different stages by the formulas given below and, as will be readily seen by inspection, its successful application depends primarily on a normal and smooth interaction between the sodium salt of the β-ketone ester and bromomethyl-phthalimide. So far as the writers



[5] Dakin and Dudley, *J. Chem. Soc.*, **105**, 2453 (1914). Johnson and Cretcher, THIS JOURNAL, **37**, 2144 (1915).



are aware, no one has even utilized this primary halide in an alkylation experiment, while it is well known that the higher homolog bromo-ethyl-phthalimide, $C_6H_4(CO)_2NCH_2CH_2Br$, and bromopropyl-phthalimide, $C_6H_4(CO)_2N.CH_2CH_2CH_2Br$, react normally in such transformation. The phthalimido combinations were selected for this work for two reasons, first to offer protection to the amino group so as to avoid intramolecular condensation after formation of the alkylation product, and second to increase the molecular weight so as to insure the possibility of obtaining crystalline reaction products.

Thus far we have not been successful in bringing about the change representing the first stage of this new synthesis of histamine, namely, the interaction of bromomethyl-phthalimide with the ketone ester. The reaction has been applied under the normal conditions generally employed for reactions of this type, namely, by operating with the sodium salt of the ketone ester in alcohol solution, and also by alkylation of the sodium salt in anhydrous benzene, but with this ketone ester and also with ethyl aceto-acetate we obtained no evidence of the formation of alkylation products containing nitrogen.

Bromomethyl-phthalimide interacts with the sodium salts of these respective ketone esters with formation of sodium bromide, organic compounds which contain no nitrogen and *phthalimide*. Ethyl aceto-acetate is much more reactive towards this halide than is ethyl γ-diethoxy-aceto-acetate, but in both cases we were able to isolate over 80% of the calculated yield of phthalimide. In other words, bromomethyl-phthalimide interacts as though it had an entirely different constitution from that of a primary halide, $R.CH_2Br$. While this halide reacts in a quite unexpected manner we find that its next higher homolog bromo-ethyl-phthalimide interacts smoothly with the β-ketone esters with the formation, respectively, of normal alkyl derivatives. We obtained no evidence in this case of the formation of phthalimide. A full description of these reactions and the characteristics of the products of reaction are given in the experimental part of this paper.[6]

The method of preparing bromomethyl-phthalimide has been greatly

[6] We are now engaged in the study of the mechanism of this quite abnormal reaction, but the work has been delayed much since the departure of Mr. Pucher from this laboratory. This research will involve not only a study of the action of these halogenated alkyl derivatives of phthalimide, but we shall also incorporate into our work an investigation of the action of halogenated ethers, $ClCH_2·O·C·H_5$, on ethyl γ-diethoxy-aceto-acetate. Very promising results have already been obtained by my colleague Professor A. J. Hill, who is extending the research into the pyrimidine series. (T. B. J.)

improved so that this reagent is now made available in any quantity desired. The compound has received hitherto very little attention, and in the experimental part are described several derivatives whose preparation illustrates its pronounced activity. This research will be continued in this laboratory.

Experimental Part

Phthalimide, $C_6H_4(CO)_2NH$.—Dunlop[7] prepared this reagent by heating phthalic anhydride with urea. Herzog[8] later applied the same reaction and showed that these reagents interact nearly quantitatively at 135° and that the reaction is strongly exothermic. Noyes and Cass[9] showed that ammonium carbonate can be substituted successfully for urea in this preparation. The yield of phthalimide by both procedures is good, but it has been our experience that the method of operating as recommended by Kuhara[10] is just as satisfactory and convenient. All of the reagent used in our research was made according to this method. The process is as follows. One hundred g. of phthalic anhydride is placed in a liter flask which is connected with an ammonia generator through a wash-bottle containing a strong solution of sodium hydroxide and a series of drying tubes charged with granulated calcium oxide. The flask containing the anhydride is heated in an oil-bath to 140° and when the anhydride has melted a moderately rapid stream of ammonia gas is passed over the surface of the liquid. There is immediately a rapid absorption of gas, and the temperature of the bath is finally raised to 160° where it is held until the reaction, which lasts about 2 hours is complete. The phthalimide solidifies in the flask and is easily purified by crystallization from hot water.

Condensation of Phthalimide with Formaldehyde. The Formation of Hydroxymethyl-phthalimide, $C_6H_4(CO)_2N \cdot CH_2OH$

Sachs[11] states that this primary alcohol is formed when phthalimide (10 g.) is heated with 10% formaldehyde solution (25 cc.) in a sealed tube at 100° but no statement is made regarding the yield obtained. It was found by experiment that heating under pressure is unnecessary and that phthalimide is converted almost quantitatively (90–93%) into hydroxymethyl-phthalimide when digested under a reflux condenser with an excess of 10–15% formaldehyde solution. Cautious evaporation of the filtrate after the reaction is complete, as reported by Sachs, is not necessary as the hydroxymethyl-phthalimide is very insoluble in cold, dil. formaldehyde solution. The alcohol is obtained easily in pure condition in the following manner. The finely pulverized phthalimide obtained from 100 g. of phthalic anhydride is suspended in a solution of 80 cc. of 40% formaldehyde, 200 cc. of water is added, and this then heated under a reflux condenser at 103–108° for 4 hours. when practically all of the phthalimide will have dissolved and the reaction is practically complete. The hot solution is then filtered if necessary and allowed to cool when the hydroxymethyl-phthalimide crystallizes in beautiful, colorless glistening plates melting at 141–142°. It crystallizes from hot benzene and melts after purification from this solvent at 140° which is the melting point recorded by Sachs. The yield of alcohol is 90 g.

Bromomethyl-phthalimide, $C_6H_4(CO)_2N \cdot CH_2Br$.—This compound is easily prepared by the action of hydrobromic acid on hydroxymethyl-phthalimide. Gabriel[12]

[7] Dunlop, *Am. Chem. J.*, **18,** 332 (1896).

[8] Herzog, *Z. angew. Chem.*, **32,** 301 (1919).

[9] Noyes and Cass, THIS JOURNAL, **42,** 1282 (1920).

[10] Kuhara, *Am. Chem. J.*, **3,** 27 (1881).

[11] Sachs, *Ber.*, **31,** 3230 (1898).

[12] Gabriel, *ibid.*, **41,** 242 (1908).

used fuming hydrobromic acid to bring about the change, and it has been our experience that the alcohol reacts incompletely with a weaker acid. On the other hand, if sulfuric[13] acid is added along with hydrobromic acid the reactivity is greatly accelerated and the bromide is formed smoothly with a more dilute hydrobromic acid. Our method of preparing the halide is as follows. Eighty g. of hydroxymethyl-phthalimide is digested for 2 hours at 50–60° with 150 cc. of hydrobromic acid (48%) and 45 cc. of conc. sulfuric acid. The reaction proceeds smoothly and is productive of a thick magma of the bromide crystals, which are separated by filtration and washed first with water and finally with dil. aqueous ammonia to remove all acid present and then dried at 80°. The yield is about 75 g.; m. p. 146–147°. Recrystallization of the halide from acetone gives a product melting at 148° or at the same temperature as assigned by Sachs.[11]

Analyses. Calc. for $C_9H_6O_2NBr$: N, 5.83; Br, 33.3. Found: N, 5.97, 5.98; Br, 33.4.

When prepared according to the above method bromomethyl-phthalimide is obtained as a colorless crystalline powder which has a slightly irritating action on the eyes. It gradually decomposes on standing at ordinary temperature in moist air with the liberation of bromine and discoloration of the product. It is decomposed easily by water with formation of the corresponding alcohol. Bromine is given off when the compound is exposed to ultra-violet light and it also suffers decomposition when warmed with nitric acid. The bromide can be crystallized from hot glacial acetic acid, but long heating leads to its destruction with the liberation of bromine.

Sachs[11] prepared this halide by direct bromination of methyl-phthalimide, $C_6H_4(CO)_2N\cdot CH_3$, at 160°. While this method enables one to obtain the compound it is, however, an extremely tedious process and the yields are very unsatisfactory. Furthermore, the quality of the product is poor. An attempt was made to improve the method by introducing iron as a catalyst, but the bromination was not accomplished successfully under such conditions.

The Action of Ethyl Alcohol on Bromomethyl-phthalimide

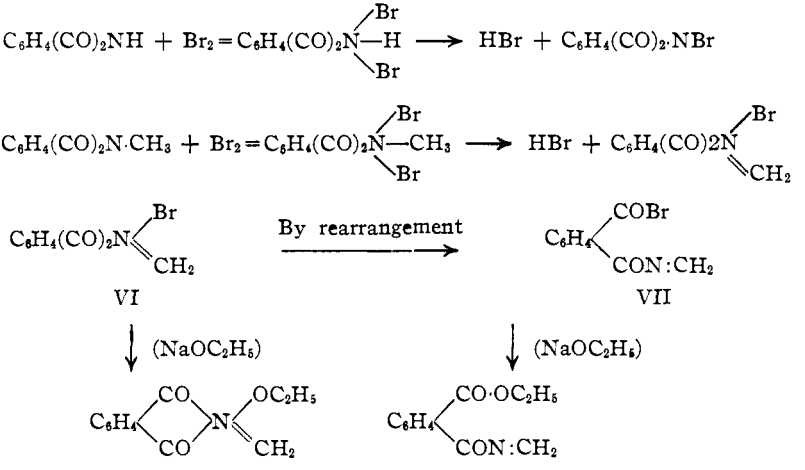
Phthalimido Methylethyl Ether, $C_6H_4(CO)_2\cdot N\cdot CH_2\cdot OC_2H_5$.—Sachs[11] prepared this ether by the action of potassium cyanide or potassium iodide on bromo-methyl-phthalimide in alcohol solution. The introduction of potassium salts is absolutely unnecessary here and the compound is formed smoothly by simply warming the bromide with alcohol. Two g. of the bromide was digested with 20 cc. of absolute alcohol for 3 hours. After evaporation of the solvent and recrystallization of the reaction product from acetone the ether was obtained in the form of long needles melting at 86°. This corresponds to the melting point assigned by Sachs. This same ether is also obtained by treatment of the bromide in alcohol solution at ordinary temperature with sodium ethylate. The change is not a quantitative one, however, and partial hydrolysis takes place leading to the formation of phthalic acid.

The Action of Chloromethylethyl Ether on the Potassium Salt of Phthalimide

The Formation of Phthalimido Methylethyl Ether, $C_6H_4(CO)_2N\cdot CH_2OC_2H_5$.—In the bromination of methyl-phthalimide Sachs[11] represents the substitution of halogen as taking place in the methyl group giving a primary halide, $C_6H_4(CO)_2N\cdot CH_2Br$. The possibility that an isomeric compound of entirely different structure might be formed here was not considered by him. If one assumes that both phthalimide and its methyl derivative interact with bromine in an analogous manner, namely, by addition of halogen to nitrogen with formation primarily of pentavalent compounds, it is conceivable that this monobromo derivative of methyl-phthalimide may have an entirely

[13] Kamm and Adams, THIS JOURNAL, **42**, 299 (1920).

different constitution from that assigned to it by Sachs and Gabriel. Theoretically, the addition product might dissociate with formation of an unsaturated derivative such as is represented below in Formula VI. If such a combination, or its rearrangement product (Formula VII), is formed the constitution would not be revealed necessarily by reaction with sodium ethylate. The interaction might be expected to lead to the formation of an ethoxy derivative having an entirely different constitution from that assigned to the ethyl ether described above, but such data should be accepted with caution as it has already been shown that phthalimido derivatives[14] are very susceptible to isomeric change in the presence of sodium ethylate and also that intramolecular rearrangements can be brought about easily in organic combinations containing the grouping $-N=CH_2$.[15]



In the light of these considerations it was important, therefore, to establish the structure of the ethyl ether by direct synthesis. This is easily accomplished by allowing the potassium salt of phthalimide to react with chloromethylethyl ether $ClCH_2OC_2H_5$. Fifteen g. of the potassium salt and 10 g. of the chloro ether dissolved in 50 cc. of dry benzene were digested on a steam-bath for 5 hours. The potassium salt slowly disappeared and potassium chloride separated. On evaporating the solvent the ethyl ether was obtained in the form of an oil which solidified immediately on cooling. After recrystallization from alcohol it melted sharply at 86°, and proved to be identical with the ether described above. The yield was practically that calculated.

Phthalimidomethyl Thiocyanate, $C_6H_4(CO)_2N\cdot CH_2\cdot SCN$.—The fact that bromomethyl-phthalimide reacts like an acid halide and is easily decomposed by warming with alcohol with formation of hydrobromic acid suggested that it would interact also with potassium thiocyanate to form an isothiocyanate or a mustard oil. We now find that the reaction proceeds in the reverse order and is productive of a rhodanide or normal thiocyanate. This compound is obtained easily by interaction of potassium thiocyanate with bromomethyl-phthalimide in acetone. Alcohol cannot be used as a solvent on account of its reactivity towards the bromide. Ten g. of the bromide was dissolved in 50 cc. of dry acetone and 4 g. of potassium thiocyanate added to the solution. There was an immediate reaction with precipitation of potassium bromide. After heating for 2 hours on a water-bath and then filtering hot to separate undissolved potassium

[14] Gabriel and Colman, *Ber.*, **33**, 981 (1900).

[15] Unpublished data (T. B. J.).

bromide and potassium thiocyanate the acetone solution was concentrated by evaporation and finally cooled when the thiocyanate separated in the form of glistening plates. These were separated by filtration and the compound recrystallized from acetone when it melted at 147–148°. The substance gave a strong test for sulfur.

Analyses. Calc. for $C_{10}H_6O_2N_2S$: N, 12.85. Found: 12.85, 12.6.

This new thiocyanate crystallizes from acetone in yellow plates and its vapor is extremely irritating to the eyes, causing a burning sensation and inflammation of the eyeballs. That the compound has not the structure of an isothiocyanate is shown by its failure to react with aniline or ammonia to form thio-urea combinations. The compound is also not desulfurized by action of aqueous lead acetate.

The Action of Potassium Cyanide on Bromomethyl-phthalimide in Acetone Solution

Sachs investigated the action of potassium cyanide on this halide and applied the reaction in alcohol solution without success. Instead of obtaining the corresponding nitrile the ethyl ether was formed by interaction of the bromide with alcohol. In order to avoid this action of alcohol we applied the reaction with potassium cyanide in acetone, but here again, to our surprise, we obtained only abnormal results. For example, a mixture of 5 g. of bromomethyl-phthalimide and 2 g. of finely pulverized potassium cyanide was added to 25 cc. of acetone; the mixture was digested for 8 hours on a steam-bath and finally allowed to cool. The insoluble material was then separated by filtration and triturated with cold water to remove inorganic salts when 1.5 g. of a crystalline organic product was obtained which proved to be phthalimide. More of this same reagent was found in the acetone filtrate and when crystallized from alcohol melted at 228-230°. We obtained no evidence of the formation of a nitrile. Exactly the same result was obtained when potassium iodide was incorporated with potassium cyanide as a catalyst.

Analyses. Calc. for $C_8H_5O_2N$: N, 9.52. Found: 9.60, 9.4.

Iodomethylphthalimide, $C_6H_4(CO)_2N{\cdot}CH_2I$.—Gabriel states[12] that this iodide can be prepared by dissolving the corresponding alcohol in strong hydriodic acid. Sachs[11] failed to obtain the compound by allowing potassium iodide to act on bromomethyl-phthalimide in alcohol, the corresponding ether being formed instead. This latter reaction can be brought about successfully when acetone is used as a solvent in place of alcohol. Ten g. of the bromide and 7 g. of potassium iodide interacted in acetone solution completely after warming on the steam-bath for 2 hours. On concentrating the acetone solution and cooling, the iodide separated in a crystalline condition and after crystallization from ethyl acetate melted at 150°. This halide is a colorless crystalline substance which slowly decomposes at ordinary temperature and assumes a dark brown color due to separation of iodine. It is decomposed immediately by action of nitric acid at ordinary temperature with liberation of iodine.

Analysis. Calc. for $C_9H_6O_2NI$: N, 4.9. Found: 5.1.

Potassium cyanate and potassium nitrite failed to react with bromomethyl-phthalimide when heated with the latter reagent in acetone solution.

The Action of Bromomethyl-phthalimide on the Sodium Salt of Ethyl Aceto-acetate

In our preliminary study of this reaction we always operated with units of 11 g. of the β-ketone ester and 20 g. of the bromide. The reaction was also applied several times but for purposes of description the results of only one experiment will be recorded in detail. The method of operating was as follows. Two g. of sodium was dissolved in 70 cc. of absolute ethyl alcohol and the sodium salt of ethyl aceto-acetate prepared in the usual manner by dissolving 11 g. of the ketone ester in this alkaline solution. The alcohol solution of the sodium salt was then cooled to room temperature, 20 g. of finely

pulverized bromomethyl-phthalimide added to this at once, and the flask immersed immediately in ice water. There was an immediate reaction with evolution of heat and the bromomethyl-phthalimide gradually dissolved. Within a short time the alcohol acquired a turbid appearance and a crystalline precipitate began to deposit. The temperature of the solution did not rise above 60° throughout the operation and on standing the reaction was easily brought to completion, giving a solution perfectly neutral to litmus. The intensity and velocity of this reaction are revealed by reference to Table I.

TABLE I

Time of reaction Min.	Temperature °C.	Time of reaction Min.	Temperature °C.
Start	23	7	48
2	44	11	45
3	50	36	23
5	59		

When the reaction was complete the solid material was separated by filtration and after drying at 100° weighed 18 g. On triturating this with cold water we extracted 6 g. of sodium bromide while the calculated amount possible from the reaction would be 8.2 g. The colorless crystalline material insoluble in cold water (12 g.) was apparently a pure substance and was identified as phthalimide melting at 228–230°. The calculated yield of the imide would be 16 g.

Analysis. Calc. for $C_8H_5O_2N$: N, 9.53. Found: 9.4.

The alcohol filtrate above was heated under diminished pressure at 100° to remove all excess of ethyl alcohol when a dark colored oil was obtained which deposited on cooling more sodium bromide and phthalimide. About 1 g. of the imide was recovered in this manner bringing the total yield to 13 g. or 81.3% of the calculated amount. This oil was triturated with water to remove sodium bromide and finally extracted with ether. After drying and evaporation of the ether we obtained 10 g. of a dark viscous oil which gave only a slight coloration with ferric chloride solution, and could not be heated to its distillation temperature under diminished pressure without decompositon. That the oil did not contain an appreciable amount of unaltered ethyl aceto-acetate was evidenced by the fact that no trace of 2-thio-4-methyluracil was formed by digestion of a fraction of the oil with thio-urea and sodium ethylate in absolute alcohol.[16] This oil is apparently

$$CH_3COCH_2COOC_2H_5 + CS(NH_2)_2 = \begin{matrix} & & NH—CO \\ & & | \quad\quad | \\ SC & & CH \\ | & & \| \\ NH—C\cdot & & CH_3 \end{matrix} + H_2O + C_2H_5OH$$

a mixture of at least two products one of which is soluble in cold aqueous alkali and the other insoluble. All attempts to obtain a definite, constant-boiling product by distillation under diminished pressure were unsuccessful on account of decomposition below the temperature of distillation.

Application of the Reaction in Benzene.—Using exactly the same proportions of sodium, and ethyl aceto-acetate as described in the preceding experiment, the sodium salt of the ketone ester was prepared by interaction of these reagents in boiling benzene. When the formation of salt was complete the bromide (20 g.) was added and the reaction brought to completion by heating on the water-bath for 6 hours. The insoluble material was identified as a mixture of sodium bromide and phthalimide and the latter was obtained in practically the same amount as when the reaction was applied in alcohol

[16] Johnson and Heyl, *Am. Chem. J.*, **37**, 628 (1907).

solution. It melted at 228–230°. On evaporating the benzene an oil was obtained which exhibited the same behavior as the oil obtained in the previous experiment. It could not be distilled under diminished pressure without decomposition.

The Action of Bromomethyl-phthalimide on the Sodium Salt of Ethyl γ-Diethoxy-aceto-acetate, $(C_2H_5O)_2CHCOCH_2COOC_2H_5$

The following proportions were used in this experiment: 2 g. of sodium, 70 cc. of absolute ethyl alcohol and 19 g. of the β-ketone ester. The reaction was carried out under exactly the same conditions as when ethyl aceto-acetate was used but it was our experience that the change was much less vigorous. In fact, in order to bring the reaction to completion it was necessary to heat on the steam-bath for about 3 hours before the alcohol became neutral to litmus. The reaction product was worked up in the same manner as before and about 80% of the calculated amount of phthalimide isolated. In addition a viscous oil was obtained which decomposed when an attempt was made to purify it by distillation under diminished pressure. A fraction of 5 g. of this oil was digested with thio-urea and sodium ethylate in alcohol solution, but we obtained no evidence of the formation of a pyrimidine compound as would be expected if any unaltered β-ketone ester were present.

$$(C_2H_5O)_2CH\cdot COCH_2COOC_2H_5 + CS(NH_2)_2 = SC\begin{matrix}NH—CO\\ \\ NH—CCH(OC_2H_5)_2\end{matrix}CH + H_2O + C_2H_5OH.$$

The Action of Bromo-ethyl-phthalimide on the Sodium Salt of Ethyl γ-Diethoxy-aceto-acetate

The Formation of Ethyl α-Phthalimido-ethyl-γ-diethoxy-aceto-acetate.—Quite different was the behavior of this halide towards this sodium salt from that of the lower halide bromomethyl-phthalimide. The reaction was carried out in the usual way with 3.7 g. of sodium, 100 cc. of absolute alcohol and 20 g. of ethyl γ-diethoxy-aceto-acetate. The reaction was extremely sluggish and in order to hasten it 5 g. of potassium iodide was added to the solution. After heating on the steam-bath for 12 hours the solution finally became neutral to litmus and sodium bromide deposited, but there was no evidence of the separation of phthalimide as when bromomethyl-phthalimide was used. The alcohol was removed by distillation under diminished pressure and the oil finally extracted with ether, washed with water and dried over sodium sulfate. After removal of the ether we obtained 31 g. of a light red viscous oil which gave a strong test for nitrogen, and when subjected to distillation under diminished pressure decomposed with formation of a black, tarry mass. The crude oil was therefore carefully freed from the last traces of ether by heating in a high vacuum at 100° and then analyzed for nitrogen. The analysis gave results which indicated that the bromide had reacted normally with the sodium salt of the ketone ester giving the desired condensation product

$$(C_2H_5O)_2CH\cdot CO\cdot CH\cdot COOC_2H_5$$
$$|$$
$$H_2CCH_2\cdot N(CO)_2C_6H_4$$

Analysis. Calc. for $C_{20}H_{25}O_7N$: N, 3.56. Found: 3.24.

Summary

1. An improvement in the method of preparation of bromomethyl-phthalimide has been described, and a description given of several new derivatives of methyl-phthalimide.

2. An attempt has been made to use this halide for the alkylation of ethyl aceto-acetate and ethyl γ-diethoxy-aceto-acetate but without success. The halide reacts abnormally with the sodium salt of β-ketone esters with formation of phthalimide.

3. The higher homolog, bromo-ethyl-phthalimide, reacts normally with β-ketone esters with formation of alkylation products containing nitrogen.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

RESEARCHES ON THIAZOLES. I. DERIVATIVES OF 2-PHENYL-BENZOTHIAZOLE. SYNTHESIS OF AN ANALOG OF CINCHOPHEN (ATOPHAN)

BY MARSTON T. BOGERT AND EMANUEL M. ABRAHAMSON

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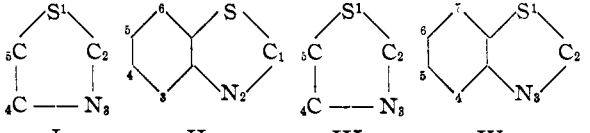
Introductory

The Organic Laboratory of Columbia University has had under way for some time a number of investigations in the thiazole field, the results of which it hopes to publish as rapidly as opportunity permits.

The plan adopted for numbering the positions on the thiazole and benzothiazole nuclei both in Richter's "Lexikon" and in the Decennial Index to *Chemical Abstracts* is as indicated in Formulas I and II. This lack of uniformity seems to us highly undesirable and confusing. Therefore, we have employed consistently throughout this paper the numbering given in Formulas III and IV, so that S is always in position 1 and N at 3, while the C at 2 occupies the μ-, or middle position. This is in agreement with the system adopted in the new (2nd) edition of Meyer-Jacobson's "Lehrbuch der organischen Chemie.[1]"



I II III IV

For the experiments described in this first paper, 2-phenyl-benzothiazole has served as initial material, and from this interesting substance various derivatives have been prepared and studied.

Of the many methods of preparing this compound already given in the literature,[2] we have found fusion of benzanilide or benzalaniline

[1] Vol. II, Part 3, Sec. 2, pp. 535 and 549.

[2] *Ber.*, **10**, 2135 (1877); **12**, 2360 (1879); **13**, 8, 17, 1223, 1236 (1880); **15**, 2033 (1882); **19**, 1068, 1069 (1886); **23**, 2476 (1890); **35**, 1946 (1902); **44**, 3037 (1911); **48**, 1244, 1251 (1915). *Ann.*, **259**, 301 (1890). *Am. Chem. J.*, **17**, 1401 (1895). Ger. pat. 51,172 and 55,222; *Friedländer*, **2**, 301, 302 (1891).