methyl-5-nitro-uracil.[1]—An attempt was made to bring about this reduction smoothly by subjecting the nitropyrimidine to the action of aluminum amalgam in dil. aqueous ammonia solution. The reaction was applied at a temperature of 40°. After complete reduction the aluminum hydroxide was filtered off and the filtrate then concentrated under diminished pressure. We obtained a syrupy residue which was extremely soluble in cold water and which only partially solidified after standing for a long time. The small amount of crystalline material was separated from the oil; washed with a small volume of cold alcohol in which solvent it was difficultly soluble and then recrystallized from water, when it separated on cooling in a crystalline condition and melted at 231–233°. The reduction of this nitropyrimidine is apparently not on easy operation and it was extremely difficult to obtain a sufficient amount of material by this method for an investigation. Due to the fact that Mr. Matsuo was obliged to discontinue his research, it was impossible to perfect the reaction by applying other methods of reduction and therefore the work was discontinued.

Summary.

5-Amino-uracil undergoes alkylation when its potassium salt is allowed to interact with methyl iodide and is converted into a dimethyl derivative. In this change the hydrogen atoms of the amino group are not replaced by methyl, but substitution takes place in the 1- and 3-positions of the pyrimidine ring with formation of 1,3-dimethyl-5-amino-uracil.

NEW HAVEN, CONN.

ORGANIC CHEMICAL REAGENTS. IV. THE PREPARATION OF ALKYL IODIDES.[2]

BY ROGER ADAMS AND V. VOORHEES.

Of the alkyl iodides, methyl and ethyl iodides are by far the most important and at least one of them is made by almost every student in elementary organic chemistry. The propyl, butyl and amyl iodides are in less demand but nevertheless are often needed in large amounts. For the production of 50 to 100 g. of these products, the usual procedure described in laboratory manuals of adding powdered iodine in small portions to a mixture of red phosphorus and the alcohol is quite suitable. As soon as the size of the preparation becomes larger, however, the method is quite tedious and considerable amounts of material are lost by volatilization, particularly if the lowest two alcohols are used.

[1] Lehmann, *Ann.*, 253, 77 (1889).

[2] For previous articles in this series see THIS JOURNAL, 40, 1281, 1950 (1918); 41, 276 (1919).

The reaction of alcohols with iodine and phosphorus may be greatly accelerated if yellow phosphorus is used in place of part of the red phosphorus. The contact of solid iodine directly with yellow phosphorus, however, causes so violent a reaction that the replacement of the red by the yellow in the ordinary procedure for making alkyl iodides is out of the question. In order to use yellow phosphorus and to be able to prepare quantities of 500 g. of methyl or ethyl iodide at a time, Walker[1] designed a special apparatus. The form of this apparatus is such that the alcohol and phosphorus are refluxed together and the condensed vapors are forced to flow back to the reaction flask through a container holding the iodine. The iodine is thus dissolved and carried in solution into the alcohol-phosphorus mixture. By regulating the temperature of the reaction mixture flask, the amount of alcohol flowing over the iodine is controlled and consequently the speed of reaction itself is controlled. The principle of the apparatus is excellent and the production of methyl and ethyl iodides in this way is far superior to the old method. Even this procedure, however, has its difficulties and limitations. If the temperature of the reaction flask happens for one reason or another to get a few degrees too high, the amount of liquid flowing back increases to such an extent that far too much iodine is dissolved and introduced into the reaction mixture at one time. This in turn causes the reaction to become more vigorous and the refluxing is liable to reach such a stage that unless very prompt cooling of the reaction flask is carried out, loss of material through the condenser occurs. Walker himself has pointed out that not more than 100 g. of iodine should be used at once on account of the possibility of this superheating and consequently the apparatus must be disconnected each time a subsequent addition of iodine is made. Moreover, to control the temperature in such a way that it does not endanger any loss of material, the product can not possibly be made in the time mentioned by Walker. A second disadvantage is that with alcohols of higher molecular weight than methyl or ethyl, the speed of the reaction is very difficult to regulate. For the preparation of a few hundred grams of methyl or ethyl iodides, however, the method is quite satisfactory. In an experiment to make these substances using 4 of the apparatus simultaneously, it was found that the constant attention of one man for a day was necessary in order to regulate the temperature and to add the iodine. Even under these conditions not more than about 5 or 6 pounds of unpurified methyl or ethyl iodides could be produced.

In order to make several kg. of an alkyl iodide at a time with the minimum amount of attention and in a few hours, a glass apparatus, which has given excellent results, was designed. The principle is the same as that involved in Walker's apparatus but has the advantage over his

[1] J. Chem. Soc., 61, 717 (1892).

of not requiring constant watching and control of temperature. Moreover, the production of propyl, butyl, and amyl iodides in the apparatus proceeds as smoothly as that of the methyl or ethyl iodide. The new features are, first, two glass stopcocks, one above the bulb holding the iodine to regulate the speed of liquid flowing over the iodine and one below as a safety cock; second, a special tube allowing for the return into the reaction flask of any excess liquid not needed for dissolving the iodine; third, additional iodine may be introduced in an extremely simple manner without disconnecting any part of the apparatus. With an iodine bulb that will hold 1.5 kg., it is possible in about 4 hours to produce over 3 kg. of crude alkyl iodide, an amount which requires a further 2 to 3 hours for complete purification. After the apparatus is set up, very little attention is necessary during the whole experiment, in fact it is possible for a man, without seriously interfering with his regular laboratory work, to prepare over 6 kg. of crude material a day by using a 12-liter round-bottom flask with enough phosphorus and alcohol to provide for 4 portions of iodine of 1.5 kg. each. Moreover, if it is desired to obtain a large quantity of either of these products a man by devoting his entire time to production can run with great ease 5 apparatus simultaneously, in which, during a day considerably over 30 kg. of crude product can be produced. On the next day while carrying out a second run of 30 kg., he can purify the yield of iodide already prepared. By using for this purification two 12-liter flasks, the time required for carrying out the process is very short.

There is no reason why a larger bulb holding double or triple the amount of iodine could not be used. The general principle of the apparatus moreover, could undoubtedly be applied to large scale work provided such quantities of these products might be desired. The yields are in every case between 90–100% of the theoretical amount. The apparatus may be recommended highly to any laboratory that may desire these alkyl iodides in considerable amounts. It is possible to make them for very slightly more than the actual cost of the chemicals involved while the market price of any of them is nearly double the actual cost of the necessary raw materials. Although the apparatus has been applied only to those alkyl iodides which are very common it undoubtedly could be used for any alkyl iodide which distills at atmospheric pressure without decomposition.

Walker stated that a mixture of yellow and red phosphorus gives much better results than either alone. The value of substituting yellow phosphorus for part of the red phosphorus should be pointed out particularly. The reaction under these conditions is instantaneous and the iodine color disappears immediately upon reaching the reaction flask. Experiments showed that when using red phosphorus alone with methyl alcohol or

ethyl alcohol, the time required for the addition of one kg. of iodine is about 3.5 hours and that a large amount of iodine is unreacted even after an additional hour of refluxing. Moreover, toward the end of the distillation of the product from the reaction flask, foaming may frequently occur. With butyl or amyl alcohols it seemed probable that the higher refluxing temperature would allow the use of red phosphorus, but the results were very little better than those with the methyl and ethyl alcohols. It takes twice as long to add the iodine, the reaction does not run smoothly and the iodine does not completely disappear for a considerable time after it is in the mixture. Moreover, the foaming already mentioned with the methyl and ethyl iodides is likely to occur during the last part of the distillation of the crude material. With the addition yellow phosphorus in the proportion used, the reaction is so very rapid that the iodine is used up as soon as it reaches the reaction flask and the distillate from the crude reaction mixture is generally completely colorless; it is never more than tinged with red. It is interesting to note that in spite of having less than $^1/_2$ yellow phosphorus, which is much less than the theoretical amount of phosphorus needed, a small amount of yellow phosphorus is always left behind at the end of the reaction. After the alkyl iodide has been distilled when the reaction is completed, a small amount of yellow phosphorus often collects between the neck of the flask and the condenser and flashes upon disconnecting the tube. This is so slight that no special precaution is necessary but care must be taken in disposing of the residues left in the distillation flask.

In text-books, it is invariably recommended that after the alkyl iodide has first been formed, then distilled from the crude reaction mixture, washed and dried, it should be redistilled. This last distillation is quite unnecessary with the iodides as made by this method. In every case all the material boils within two degrees.

Walker recommended that water be added to the crude reaction mixture before the halide is distilled, in order to destroy phosphonium compounds. It was found that in the preparations described no phosphonium compounds are produced so that addition of water is unnecessary.

Description of Apparatus.[1]

The length of the special apparatus from top to bottom is 67.5 cm. The upper end A, 2.5 cm. in diameter, is fitted with a rubber connector to an efficient reflux condenser. The inner tube of the condenser should be about the same size as the upper end of the apparatus. The condenser should be 180 cm. long or made up of 2 smaller ones which will amount to a condensing space of this length. The bottom end of the apparatus

[1] The apparatus may be purchased from Mr. Paul Anders, Chemistry Building, University of Illinois, Urbana, Illinois and can be had in any size desired by specifying the capacity of bulb E.

B should be of the same diameter as the top and connected to a round-bottom flask by means of a rubber stopper. Bulb C is of about 75 cc. capacity, narrowed at the bottom to a 6 mm. tube in which is sealed a glass stopcock D of 2 mm. bore. Bulb E is of about 1200 cc. capacity and is drawn down at the lower end to a 1 cm. tube holding Stopcock F of 5 mm. bore. Into the side of Bulb E is sealed tube G, which should be about 2.5 cm. in diameter, 5 to 7.5 cm. long and inclined at an angle of 60°. Through the tube G is inserted a platinum foil, H, perforated with holes approximately 2 mm. in diameter, which rests near the bottom of Bulb E as shown in the diagram. If such a foil is not available, glass wool may be substituted although this is not so satisfactory. Tube G is closed by means of a rubber stopper I through which is inserted a 6 mm. tube, J, drawn to a capillary at the inner end. Side arm K is a 12 mm. tube extending from B to a point in C above the entrance of Tube L. Tube L, 6 mm. in diameter, has at its lower end a goose-neck seal. Its upper end, as already mentioned, enters C below the entrance of K and at such a height above Stopcock D that a volume of 20 to 25 cc. exists between it and the stopcock.
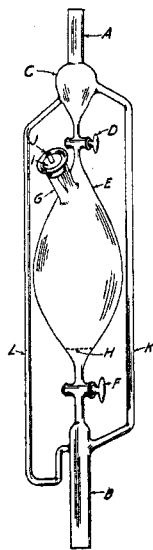
Discussion of Apparatus.

(a) The diameter of Tube A was selected arbitrarily as 2.5 cm. When the amounts of material such as those described in the experimental part of this paper are used, a tube of smaller diameter is insufficient to take care of the vapors and the liquid resulting from their condensation. A larger tube, however, may be used. The condenser attached to A should be very efficient. One of 180 cm. in length is none too large if the maximum speed in the preparation is desired. The inner tube should be about the same size as A so as to allow vigorous refluxing without danger of liquid filling the tube and being blown out through the condenser. An ordinary condenser with 12 mm. inner tube can not be used to advantage.

(b) The same diameter of 2.5 cm. was selected for the lower end B. This allows ample space for the simultaneous upflowing vapors and downflowing liquids. The round-bottom flask to which it is connected is set in an oil bath, heated best by a 3-heat electric hot plate if methyl or ethyl iodides, or by a free flame if the higher iodides are being produced.

(c) The size of C, provided it is more than 50 to 75 cc. is immaterial. It must be at least the size mentioned, however; first, so as to give 20 to 25 cc. reservoir space between the entrance of Tube L and Stopcock D and second, to serve as a good initial condensing place for the large amount of vapor before it reaches the condenser.

(*d*) Stopcock D regulates the flow of condensed liquid over iodine in bulb E. It is essential that the liquid which flows through D should not drop through Bulb E but simply run down the sides; otherwise a hole is dissolved in the mass of iodine and the reaction does not run smoothly. If the tube below Stopcock D gradually widens into Bulb E, as shown in the diagram, the liquid will flow in the correct way.

(*e*) The iodine container, Bulb E, may be made a size capable of holding the amount of iodine it is desired to run at one time.

(*f*) Stopcock F serves two purposes. After a preparation is started and the original amount of iodine in bulb E has been carried into the reaction flask, more may be added without stopping the heating. To do this, both Stopcocks D and F are closed and additional iodine introduced through G. The stopcock is also a safety cock as it may be closed if for any reason it is desirable to shut off instantly the entrance of iodine to the reaction flask. During the flow of the iodine solution from E to the flask, Stopcock F is in general left wide open and needs no regulation. Its bore is 5 mm. in diameter in order to prevent any possibility of clogging by small mechanical impurities which might be present in the iodine.

In case the reaction becomes too rapid due to the addition of too much iodine, it is necessary to regulate F. This too-rapid entrance of iodine may be caused either by D being left open more than is desirable or, sometimes when higher alcohols are used, by hot vapors ascending through Stopcock F into Bulb E and dissolving the iodine. Under either of these two circumstances, Stopcock F is first shut for a few moments to allow the reaction to slow down and is then opened gradually so that the liquid collected in E may run slowly into the reaction flask. It happens occasionally during this precautionary procedure, especially with butyl and amyl alcohols, which dissolve large amounts of iodine when hot, that while waiting for the reaction to slow down, the liquid resting on Stopcock F cools to such a temperature that iodine actually crystallizes out and prevents further flow through F when it is opened. This is easily remedied by closing Stopcock D to cut off the supply of hot alcohol, closing the outer end of the capillary Tube J with the finger to prevent entrance of air into E, and opening wide Stopcock F. Bulb E cools rapidly and the diminishing pressure due to the condensation of vapors within it draws up hot vapor from the reaction flask. This hot vapor in a few seconds dissolves the crystalline mass above F, and the reaction may then be continued in the usual way.

It sometimes happens when using propyl, butyl or amyl alcohols that the alcohol running through D at the very beginning becomes saturated with iodine and while flowing over the cold under part of Bulb E becomes cool so that iodine crystallizes and prevents the liquid from flowing through Stopcock F. This is also remedied very easily in the way just described.

(g) The side Tube G is made 2.5 cm. in diameter to allow the introduction of the platinum foil or glass wool and iodine and to facilitate the cleaning of the bulb.

(h) The round piece of platinum Foil H perforated with holes serves to hold the iodine in place.   Moreover, it holds back any mechanical impurities which may be present in the iodine.   Care should be taken in filling Bulb E with iodine not to allow it to get under H and clog Stopcock F.   Glass wool may be substituted for the platinum foil but is not so satisfactory as it sometimes tends to become matted.

(i) and (j) The glass Tube J drawn to a capillary on the inner end and passing through rubber Stopper I allows the pressure in Bulb E to adjust itself at any time during the reaction.   It happens that when the reaction has started Bulb E becomes warm and Stopcock D is so regulated that only a small stream of liquid is flowing through it.   Without capillary Tube J if a sudden draft occurs around the apparatus and cools the bulb, the condensation of the vapor present and consequent lowering of the pressure in E causes the stopping for a few moments of the regular flow of liquid through F till Bulb E has again become hot from the liquid entering through D.   Thus several cubic centimeters of liquid collect in E and, as soon as the temperature conditions have again become adjusted, run into the reaction flask all at once thus causing too violent ebullition and in some cases even loss of material through the top of the condenser, This is particularly noticeable in the preparation of the butyl and amyl iodides.   The capillary tube, however, prevents the diminution of pressure and consequently the collecting of liquid in E, thus assuring a continuous smooth reaction.

(k) The diameter of Tube K is made 12 mm. so as to accommodate easily large amounts of vapor from the flask.   It should enter C near the top or at least above the entrance of L so that the liquid returning from the condenser and not running through D will not return through K but through L.

(l) The tube L need be only 6 mm. in diameter and is inserted to take care of any excess liquid which is not needed to flow through D and dissolve the iodine.   There are two points concerning it to be emphasized. First, the entrance to C must be, as already mentioned, below the entrance of K and should be high enough in C to provide a space of 20 to 25 cc. between it and Stopcock D as a reservoir to allow a uniform flow of liquid through D.   The lower end has a goose-neck seal which immediately fills with liquid as soon as the reaction starts and prevents the ascending of vapors from the reaction flask.

Experimental.

Below is given a description of an individual run with each of the following alcohols: methyl, ethyl, N-propyl, N-butyl, and isoamyl.   No more

than 3 kg. of iodine was used in a single experiment because of the expense involved.   It was felt that successful results on this size run were sufficient indication that no difficulty would arise when still larger amounts should be used.

The temperature of the bath for heating the reaction flask in the case of methyl and ethyl iodides is best lowered after some alkyl iodide has formed.   This is a precautionary measure against loss of halide through the condenser because with the heat of reaction and the comparatively high temperature of the bath, the condensation of the volatile iodides may not be complete.   With propyl, butyl and amyl iodides, however, this precaution is unnecessary and a constant temperature of the bath may be held.

Due to the high temperature involved and to the greater solubility *of iodine when working with propyl, butyl, and amyl alcohols, the prep-* aration can be completed in considerably less time than with the methyl and ethyl alcohols.   Attention should again be brought to certain other irregularities, discussed under F, which occasionally occur when the higher alcohols are used.

In making methyl and ethyl iodides, excess of methyl or ethyl alcohols were used.   For the higher iodides, however, large excess of alcohol must be avoided partly on account of the expense but more particularly because of their decreased solubility in water which makes it more dif- ficult to wash them from the product formed.

Methyl Iodide.

In a 5-liter r. b. pyrex flask were placed 1200 g. of absolute methyl alcohol, 150 g. of yellow phosphorus and 180 g. of red phosphorus.   1.5 kg. of iodine was placed in Bulb E of the apparatus, care being taken that none got below platinum Foil H which might have clogged Stopcock F. Stopcocks D and F were left open and the electric hot plate was turned on and regulated to maintain the oil bath temperature at 90–100°.   The alcohol distilled, condensed and ran on the iodine for some time before it began to flow through F into the main reaction flask.   As soon as it did this, Stopcock D was partially closed so that only a small stream of liquid was continually flowing into the reaction flask, while Stopcock F was allowed to remain wide open during the whole reaction.   This stream should be as large as possible without causing the heat of reaction to produce too violent refluxing.   After 700 to 800 g. of the iodine had been carried into the flask, the speeding up of the reaction began to be noticeable due to the formation of methyl iodide which upon refluxing and flowing through the apparatus dissolved much more iodine than the corresponding amount of methyl alcohol.   In fact, so much methyl iodide was present in the reaction flask at this point that Stopcock D had

to be closed somewhat more, so that a smaller stream of liquid flowed through.

It was also advisable to allow the temperature of the oil bath to drop to about 70–75°. As soon as the 1.5 kg. was dissolved, the Stopcocks D and F were closed and a second 1.5 kg. of iodine introduced into Bulb E. Stopcock F was then opened wide and Stopcock D regulated as before. From the time the alcohol began to reflux until all of the 3 kg. of iodine had been added, about 4 hours elapsed. When all this iodine had been added, the flask was allowed to cool, was then fitted with an efficient condenser set for downward distillation and finally heated on a water bath to distill the product. The end of the condenser had an adapter tightly attached so that the methyl iodide as it distilled was collected under a slush of ice and water. When no more iodide came over, the distillate was placed in a separatory funnel, washed once with water, or with dil. sodium hydroxide if the product was discolored, then separated; after shaking the wet product for a few minutes with a little calcium chloride, it was filtered finally through glass wool. The material is satisfactory for most purposes without another distillation and any loss of product due to manipulation and volatility is avoided. In general, however, in this laboratory the product was again distilled. Practically all the product boils between 42–44° and weighs 3150 g. (93.8% theory).

Ethyl Iodide.

The production of ethyl iodide is very similar to that of methyl iodide. 1500 g. of absolute ethyl alcohol, 150 g. yellow phosphorus and 180 g. of red phosphorus were employed for every 3 kg. of iodine. The bath temperature during the addition of the first kg. of iodine was about 100–120° and after this about 90–100°. As with methyl iodide, about 3.5 to 4.5 hours elapsed from the time the alcohol started to boil until the 3 kg. of iodine had been added. The product was worked up just as was the methyl iodide, and after washing, drying and a final distillation, boiled at 71–73° and weighed 3400 g. (93% theory).

N-Propyl Iodide.

As only a small amount of propyl alcohol was available, no excess was used. The reaction was run with 175 g. propyl alcohol, 370 g. iodine, 30 g. red phosphorus and 30 g. yellow phosphorus. Within 20 minutes after the refluxing of the alcohol started, the iodine had been added and the reaction was complete. The oil bath was kept at about 130°. In distilling from the crude reaction mixture it was necessary to use an oil bath for heating, and unnecessary to use the extra condensing precautions described under methyl iodide. The yield of final product after washing drying and distilling amounted to 480 g. (96% theory). It boiled at 101–103°.

<center>N-Butyl Iodide.</center>

In an experimental run, 600 g. (theory calls for 582 g.) N-butyl alcohol, 50 g. of yellow phosphorus, 60 g. red phosphorus and one kg. iodine were allowed to react. After the alcohol started to boil, 40 minutes were required to complete the reaction. The oil bath temperature should be kept approximately at 175°. After purification as described under propyl iodide, the product boiled at 126–128° and weighed 1430 g. (98% yield).

<center>Isoamyl Iodide.</center>

Technical isoamyl alcohol was used in this experiment, consequently pure isoamyl iodide was not obtained. From 700 g. of isoamyl alcohol (theory calls for 693 g.) 50 g. yellow phosphorus, 60 g. red phosphorus and one kg. iodine, complete reaction occurred in 40 minutes after the alcohol refluxed. The oil bath temperature was about 190°. The yield of product purified as described under propyl iodide amounted to 1480 g. (94% theory). It boiled at 138–148°.

URBANA, ILLINOIS.

THE SYNTHESIS OF CERTAIN SUBSTITUTED PYROGALLOL ETHERS, INCLUDING A NEW ACETOPHENETIDE DERIVED FROM THE ETHYL ETHER OF SYRINGIC ACID.[1]

BY MARSTON TAYLOR BOGERT AND JACOB EHRLICH.

Introductory.

Chassevant and Garnier[2] have maintained that triatomic phenols as a class are less toxic than monotomic phenols, and there is already in the literature ample evidence to the effect that alkylation of a phenolic hydroxyl tends to reduce its poisonous action.

With these generalizations in mind, the thought suggested itself that a dialkyloxy derivative of the ordinary phenacetin of commerce might be synthesized which would retain the valuable antipyretic and analgesic properties of the latter and at the same time show reduced toxicity. It was with this end in view that the investigation described in the following pages was undertaken, and it constitutes a first step in the study of a problem which we hope to follow further as opportunity offers.

[1] The investigation described in this paper formed part of the work carried out by Mr. Ehrlich in fulfilment of the requirements for the degree of Doctor of Philosophy under the Faculty of Pure Science, Columbia University. It was completed in the spring of 1917, but its publication has been delayed by the war duties of the senior author.—M. T. B.

[2] *Compt. rend. soc. biol.*, 55, 1584 (1903), and *Arch. Pharmacodyn.*, 14, 93 (1905).