perature. By the next morning the crude amide had separated from the solution. This was collected, steam distilled to remove any unreacted ketone, and hydrolyzed as before. The yields varied from 40–60% of the theoretical based on the amount of ketone used. The individual compounds prepared are described in Table I.

Esterification of Glycolic Acids.—The substituted glycolic acids were esterified in the usual manner by refluxing with absolute ethyl alcohol saturated with dry hydrogen chloride. The approximate boiling points of these esters are given in Table I.

5-Methyl-2,4-oxazolidinedione.—To a cool solution of 11.5 g. (0.5 mole) of metallic sodium in 250 cc. of absolute alcohol was added 30 g. (0.5 mole) of dry urea and 56 g. (0.5 mole) of ethyl lactate. This mixture was refluxed on the steam-bath for fifteen hours, and as much alcohol as possible was removed under diminished pressure. The gummy residue was cooled and dissolved in 500 cc. of ice water. This aqueous solution was extracted with two 50-cc. portions of ether and acidified with hydrochloric acid. The product was taken up in ether and purified by distillation under reduced pressure. The fraction boiling at 147–148° at 5 mm. was collected and on standing crystallized to a colorless solid melting at 48–50° (cor.). The yield amounted to 44 g. (81%). This compound gave no lowering of the melting point of a sample of 5-methyl-2,4-oxazolidinedione prepared by the method of Traube and Ascher.[5]

Anal. Calcd. for $C_4H_5NO_3$: N, 12.17; neut. equiv., 115.1. Found: N, 12.05; neut. equiv., 115.0.

The dialkyl oxazolidinediones, with the two exceptions noted below, were prepared from the proper α-disubstituted glycolic acid ester by the same procedure as described above. The final products were purified either by distillation under reduced pressure or by recrystallization from petroleum ether or both. Yields averaging 80% were obtained. The physical characteristics of these compounds, together with their anesthetic activities and toxicities, are given in Table II.

5-*t*-Butyl-5-methyl-2,4-oxazolidinedione.—A mixture composed of 14.5 g. of α-*t*-butyl-α-methylglycolamide, 15 cc. of ethyl chlorocarbonate and 25 cc. of toluene was refluxed in an oil-bath for three hours, at which time the evolution of hydrogen chloride had nearly ceased. The condenser was arranged for downward distillation and the bath temperature raised slowly to 150°. After all the volatile material had distilled off, the reaction mixture was cooled and stirred with 100 cc. of a 10% solution of sodium carbonate. The small amount of oil remaining was extracted with ether and the aqueous portion acidified with hydrochloric acid. This precipitated the product as a colorless solid. The yield of pure material in this case amounted to 10 g. (65%) but was much lower when other amides were used. Diisopropyloxazolidinedione was prepared in 50% yield in the same way from α-diisopropylglycolamide.

Summary

A method has been developed for the preparation of 5-substituted-2,4-oxazolidinediones by the condensation of an α-hydroxy ester with urea in the presence of sodium ethylate. Nineteen new dialkyl derivatives have been prepared and characterized. These substances were found to exhibit hypnotic action, and their relative anesthetic activity in white mice has been evaluated.

NASHVILLE, TENNESSEE RECEIVED MAY 27, 1941

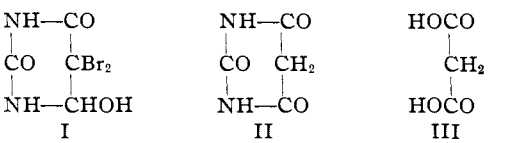
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Action of Dibromoxyhydrouracil on Malonic and Barbituric Acids[1]

BY TREAT B. JOHNSON[2] AND MARY G. WINTON

The two reactions, which the authors describe in this paper, serve to illustrate the dual reactivity inherent in the pyrimidine dibromoxyhydrouracil (I): namely, (1) its ability to donate bromine to an organic compound and (2), to serve as an oxidizing agent in aqueous and non-aqueous solutions. Experimentation with other representatives of this series of hydropyrimidines promises to be productive of results of equal interest to those brought about by interactions with the pyrimidine (I).

As is well known, malonic acid (III) and barbituric acid (II) are subject to several chemical reactions in common, due to the presence of the reactive methylene group (—CH_2—) functioning in their respective molecules. It was, therefore, of special interest to the authors to investigate the comparative behavior of these two reagents toward dibromoxyhydrouracil (I).

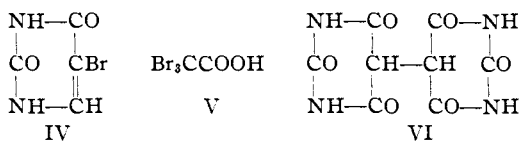


Malonic acid (III) and barbituric acid (II) both interact immediately when heated with dibromoxyhydrouracil (I) in aqueous solution with production of compounds already described in the literature. In both reactions the dihydro-

(1) Researches on Pyrimidines, CLXXIV.

(2) One unit of a research program partially supported by a grant from the George E. Sheffield Research Fund of the Sheffield Scientific School.

pyrimidine (I) undergoes degradation with formation of 5-bromouracil (IV), which is easily recovered. The malonic acid (III) is completely destroyed by the action of (I) with loss of carbon dioxide and the production of tribromoacetic acid (V) melting at 129–130°.[3] This result is entirely in accord with the observation made by Petriew,[4] who showed that malonic acid (III) interacts with bromine in aqueous solution (HOBr) to yield the same halogen acid (V).



Barbituric acid (II) reacts with the pyrimidine reagent (I) in an entirely different manner. In this case, the authors obtained no conclusive experimental evidence indicating the formation of either monobromo or dibromobarbituric acids resulting by direct bromination. On the other hand, the barbituric acid was converted by oxidation into the long known hydurilic acid (VI). Therefore, the pyrimidine (I) serves the same purpose here as potassium permanganate in alkaline solution, which oxidizes barbituric acid (II) in aqueous solution at 100° to the same dipyrimidine construction (VI).[5] Excessive oxidation of barbituric acid (II) with potassium permanganate leads to the formation of 5-oxyhydurilic acid.[5] Biltz and Hehn report also that barbituric acid (II) is not oxidized to hydurilic acid (VI) by potassium permanganate in acid solution (H_2SO_4).

New reactions of both the above types are now under investigation in this Laboratory.

Experimental Part

Interaction of Dibromoxyhydrouracil (I) with Malonic Acid. Formation of Tribromoacetic Acid, Br_3CCOOH.—A series of five oxidation experiments were conducted using in each case 2.0 g. of the dibromoxypyrimidine (1 mol), and varying proportions of malonic acid from 2 to 0.25 mol. The general procedure was to dissolve the reactants in 25 to 30 cc. of water and then digest at 100° until the aqueous solution failed to respond to the Wheeler and Johnson color test for uracil.[6] The time required varied in the series of experiments from eight to ten hours. Carbon dioxide was evolved during the digestion period and the quantities of gas generated from 2, 1, 0.5 and 0.25 mols of malonic acid were 0.2924, 0.1930, 0.1300 and 0.0593 g. of carbon dioxide, respectively. After the end of the digestion period the solution was cooled and filtered from undissolved monobromouracil resulting from dissociation of the hydropyrimidine. The clear aqueous filtrate containing hydrobromic acid was then evaporated in a vacuum leaving behind an oily residue which partially dissolved in ether. The material insoluble in ether proved to be monobromouracil and crystallized from boiling water in prismatic crystals melting at 298°. On allowing the ether solution to evaporate in the air, beautiful colorless, tabular crystals deposited on the sides of the evaporating dish. These gave a strong test for bromine; dissolved immediately in cold sodium hydroxide solution, and melted at 129–130° with no effervescence to a clear oil. A mixed melting point with a pure specimen in storage proved this compound to be *tribromoacetic acid*. On warming with water the tribromoacetic acid slowly underwent decomposition yielding an oily film having all the properties of bromoform, $CHBr_3$. After recovery of this organic acid there remained behind a small quantity of thick oil which partially solidified on cooling. This melted below 50°; dissolved in alkali and gave a strong test for bromine. It was apparently a mixture of mono- and dibromoacetic acids. We obtained no evidence of the formation of any succinic acid resulting by oxidation and decarboxylation of the malonic acid.

Interaction of Dibromoxyhydrouracil (I) with Barbituric Acid. Formation of Hydurilic Acid (VI).—This reaction was studied according to the same technique as described in the experiments with malonic acid. A series of seven experiments were conducted using one molecular proportion of the oxidizing agent to two of barbituric acid in five of the experiments and in the ratio of 2 to 1 and 1 to 1 in the remaining two. Five grams of the dibromoxyhydropyrimidine (I) and 60 cc. of water with the proportional amount of barbituric acid served as a practical experimental oxidation unit. The failure of the Wheeler and Johnson color test[6] for uracil was depended upon to indicate the end of the respective reaction. After completion of the oxidation the recovered monobromouracil was separated by filtration and the aqueous filtrate concentrated at 100°, when more of the same pyrimidine was recovered. Accompanying this pyrimidine two other products were identified, namely: unaltered barbituric acid and its oxidation product—*hydurilic acid* (VI). These were separated by fractional crystallization after concentration of the aqueous filtrate to a small volume. Unaltered barbituric acid was identified by its melting point and by formation of violuric acid. The hydurilic acid was successfully purified by crystallization from hot water. It did not respond to a test for bromine and showed, on heating, the characteristic behavior of this pyrimidine, beginning to darken at 295° and showing no melting point at 320°.[7]

Anal. Calcd. for $C_8H_6O_6N_4$: N, 22.04. Found: N, 22.3, 22.08.

In the experiment in which the proportion of oxidizing agent to barbituric acid was 2 to 1, practically no barbituric acid was recovered, and the hydurilic acid was easily separated and crystallized from water for analysis. In no experiment did we obtain any conclusive evidence of the formation of monobromo- or dibromobarbituric acids. The best yields obtained in any experimental unit by oxidation

(3) Schaefer, *Ber.*, **4**, 370 (1871); Sudborough, *J. Chem. Soc.*, **75**, 477 (1899); Biltz, *Ber.*, **35**, 1536 (1902).

(4) Petriew, *ibid.*, **8**, 730 (1875).

(5) Biltz and Hehn, *ibid.*, **52**, 1302 (1919).

(6) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

(7) Hamburger, *Ber.*, **49**, 657 (1916).

of barbituric acid with 5 g. of dibromoxyhydrouracil (I) was 0.8 g. of hydurilic acid (III).

Anal. Calcd. for $C_8H_6O_6N_4$: N, 22.04. Found: N, 21.78, 21.89.

It is interesting to note that carbon dioxide was evolved in small quantity during these oxidation reactions. That the pyrimidine ring in barbituric acid is partially ruptured by the oxidizing agent is also revealed by the presence of ammonium bromide which is easily identified in the aqueous filtrate after separation of the pyrimidines.

Summary

1. Malonic acid undergoes bromination with loss of carbon dioxide by interaction with dibromoxyhydrouracil giving tribromoacetic acid.

2. Barbituric acid is oxidized by interaction with dibromoxyhydrouracil giving hydurilic acid.

NEW HAVEN, CONNECTICUT RECEIVED JUNE 26, 1941

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Oxidation of Alcohols with Ketones

BY HOMER ADKINS AND RICHARD C. FRANKLIN[1]

Reactions of the type, $R_2CO + Al(OCHR'_2)_3 \longleftrightarrow Al(OCHR_2)_3 + R'_2CO$ have for many years been useful for the reduction of ketones.[2-5] More recently Oppenauer[6] utilized the reaction for the oxidation of an alcohol such as cholesterol. In order to avoid the necessity of treating aluminum with the alcohol to be oxidized, he added aluminum *t*-butoxide to the alcohol and so secured the desired alkoxide by interchange, *i. e.*, $3ROH + (t\text{-}C_4H_9O)_3Al \longleftrightarrow Al(OR)_3 + 3t\text{-}C_4H_9OH$.

The ideal oxidizing agent for this method would be a ketone which had a high oxidation potential,[7] reacted rapidly at a low temperature and was not readily condensed under the influence of aluminum alkoxides.[8] Other desirable characteristics for such a ketone would be a low molecular weight, a ready availability and a low cost.

Among the more accessible ketones are acetone, cyclohexanone, *p*-benzoquinone, benzil, methyl ethyl ketone, mesityl oxide, pinacolone, diacetone alcohol, phorone, isophorone and isobutyl methyl, diisobutyl and diisopropyl ketones. The effectiveness of these ketones has been tested against diphenylcarbinol, cholesterol, various cyclohexanols, neopentyl and other alcohols. In most instances oxidations were first made on a small scale and the rate and extent of reaction determined with a polarograph. Oxidations were then made on a preparational scale for those oxidizing agents that seemed attractive.

(1) Wisconsin Alumni Research Foundation Fellow, 1937-1939.
(2) Meerwein and Schmidt, *Ann.*, **444**, 221 (1925).
(3) Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926).
(4) Verley, *Bull. soc. chim.*, [4] **37**, 537, 871 (1925).
(5) Lund, *Ber.*, **70**, 1520 (1937).
(6) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).
(7) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).
(8) Wayne and Adkins, *ibid.*, **62**, 3401 (1940).

The studies by Cox,[9] Baker[7] and Wayne[8] in this Laboratory upon the oxidation potential and upon the susceptibility of ketones to undergo the mesityl oxide type of condensation, indicate certain general considerations to be followed in the choice of a ketone as an oxidizing agent. The oxidation potentials of *p*-benzoquinone (0.71 v.), cyclohexanone (0.195), acetone (0.162), benzophenone (0.163), and diisopropyl ketone (0.133) are such that there will be a very large difference between the concentrations at equilibrium depending upon the ketone selected as an oxidizing agent. For example, *p*-benzoquinone should oxidize diphenylcarbinol quantitatively to benzophenone if the quinone and the alcohol were mixed in equimolecular proportions. However, to attain even a 90% oxidation with diisopropyl ketone the latter would need to be used in the proportion of 80 moles to one mole of diphenylcarbinol. Nine moles of acetone or 1.4 moles of cyclohexanone should give a similar conversion.

The branched chain ketones, such as phorone, pinacolone, diisobutyl or diisopropyl ketone were very attractive as oxidizing agents for they are completely resistant to condensation and their

(9) In the early work the false assumption was made that since acetone and cyclohexanone did not show a depolarization potential at a dropping mercury electrode, these ketones would have a lower power as oxidizing agents than unsaturated ketones such as mesityl oxide and phorone [Cox and Adkins, *ibid.*, **60**, 1157 (1938)]. There appears to be little correlation between the depolarization potential of a ketone and its power as an oxidizing agent. Another regrettable feature of this paper is that the term "reduction potential" was used for the value which we now call a "depolarization potential." An alcohol, but not a ketone, has a "reduction potential," *i. e.*, it has power as a reducing agent. Since the strength of a ketone as an oxidizing agent is inseparably linked to the strength of the corresponding alcohol as a reducing agent, it has been customary, for example, to speak of the "oxidation–reduction potential of a quinone." It seems to us simpler and more accurate to refer to the oxidizing power of a ketone or quinone as its "oxidation potential."[7]