2-O-Benzyl-L-glyceric acid. Six grams of crystalline 2-*O*-benzyl-L-arabinose was dissolved in 100 ml. of water and the *p*H was adjusted to 10 with potassium hydroxide. Sodium borohydride (500 mg.) in about 2 ml. of water, adjusted to *p*H 10, was added and the solution was left for 10 hr. After treatment with Dowex 50 H^+ to remove the excess borohydride, the solution was nonreducing.

After concentration to a small volume, the borate was removed as the methyl ester by taking the product to dryness repeatedly from methanol. The final semicrystalline colorless sirup weighed 6 g. (100%) and was oxidized without further purification. For the oxidation 10.64 g. of sodium periodate was dissolved in 100 ml. of water and the solution was cooled in an ice bath. A concentrated aqueous solution of 6 g. of benzyl arabitol was then added slowly with rapid stirring, the addition being completed in about 30 min. Ten minutes later a couple of drops of glycerol were added and the reaction mixture was extracted three times with 100 ml. of ether. The dry ether solution was concentrated and gave 4.6 g. (100%) of a reducing, colorless sirup. This sirup (2-*O*-benzyl-L-glyceraldehyde) was dissolved in 100 ml. of water and a solution of 9.6 g. of iodine and 11.7 g. of potassium iodide in 15 ml. of water was added followed immediately by a solution of 8.9 g. of potassium carbonate and 6.9 g. of potassium bicarbonate in 80 ml. of water. After 2 hr. in the dark, the reaction mixture was acidified with 5*N* sulfuric acid, and the excess iodine was destroyed with thiosulfate. The product was extracted into ether, and after drying the ether solution over sodium sulfate, the ether was removed, yielding 2.7 g. (55%) of a colorless sirup, having a neutralization equivalent corresponding to that of 2-*O*-benzyl-glyceric acid. The cyclohexylammonium salt could be crystallized from absolute ethanol and gave a melting point of 156–157°.

L-Glyceric acid 2-phosphate. One and seven tenths grams of the above sirup of 2-*O*-benzyl-L-glyceric acid in 20 ml. of ether was treated with an excess of etheral diazomethane, and upon concentration 1.8 g. of the methyl ester was obtained as a sirup (100%). The sirup was dissolved in 15 ml. of dry pyridine, and 2 ml. of benzoyl chloride (10% excess) was added slowly to the ice cold pyridine solution. After 20 hr. at 4°, a few drops of water was added, followed by 50 ml. of chloroform. The chloroform phase was washed with 50 ml. portions of 1*N* hydrochloric acid, 1*M* potassium bicarbonate and water, and the pyridine free, neutral chloroform solution was dried over sodium sulfate. Upon removal of solvent (high vacuum at 50°), 2.8 g. of methyl 3-*O*-benzoyl-2-*O*-benzyl-L-glycerate (100%) was obtained as a sirup. The benzyl group was next removed by catalytic hydrogenation with palladium on carbon in ethanol solution. The theoretical uptake of hydrogen (210 ml.) was completed in 2 hr., and after removal of catalyst and solvent, 2 g. of a semicrystalline residue of methyl 3-*O*-benzoyl-L-glycerate was obtained (100%). This was phosphorylated directly in 20 ml. of dry pyridine with 2 g. of diphenyl phosphorochloridate at ice bath temperature. After 10 hr. at 4°, the reaction mixture was freed of pyridine hydrochloride and excess reagent as indicated in the benzoylation step, yielding finally 2.5 g. of a sirupy product (66%) of methyl 3-*O*-benzoyl-2-*O*-diphenyl phosphonyl-L-glycerate. The phenyl groups were removed by hydrogenation with 500 mg. of platinum oxide catalyst and the theoretical uptake of 1430 ml. of hydrogen was completed in 90 min. The ethanol solution was freed of catalyst and 20 ml. of 1*N* sodium hydroxide was added to saponify the methyl and benzoyl esters. The ethanol was removed and another 5 ml. of base was added to complete the saponification. Attempts to obtain the crystalline sodium salt of L-glyceric acid 2-phosphate failed, and the product was converted to the tricyclohexylammonium salt which crystallized from water-acetone. One and three tenths grams of crystals was collected (50%). The product was indistinguishable from authentic D-glyceric acid 2-phosphate[2] on paper chromatography in several solvents. After conversion to the free acid it titrated with 3 equivalents of base, and its optical rotation was numerically very similar to that of the D-isomer (Table I).

L-Glyceric acid 3-phosphate. One and eight tenths grams of methyl 2-*O*-benzyl-L-glycerate was phosphorylated as above with 1.9 ml. of diphenyl phosphorochloridate in 10 ml. of pyridine. The product after the workup (3.05 g. of methyl 2-*O*-benzyl-3-*O*-diphenylphosphonylglycerate) was reduced with palladium and hydrogen (170 ml. in 1 hr.) and platinum and hydrogen (1400 ml. in 2 hr.) and after saponification with 20 ml. of 1*M* sodium hydroxide, the tricyclohexylammonium salt of L-glyceric acid 3-phosphate (1.8 g., 71% yield) was collected. Again the product was indistinguishable from the authentic D-isomer by its titration and chromatographic properties, and numerically the optical rotation checked well with that of the D-isomer (Table I).

Acknowledgment. This work was supported by a U. S. Public Health Grant, RG-6370. Some of the experiments were done in the laboratory of Dr. C. E. Ballou, Department of Biochemistry, University of California, Berkeley, Calif.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CREIGHTON UNIVERSITY]

Long Carbon-Chain Sugars. Condensation of Diethyl Acetonedicarboxylate with Aldoses in Concentrated Hydrochloric Acid at 0°

PHILIPPOS E. PAPADAKIS

Received May 6, 1960

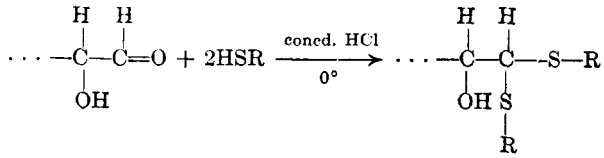
Diethyl acetonedicarboxylate condenses with D-glucose, L-arabinose, and D-xylose, respectively, in concentrated hydrochloric acid at 0°, producing carbethoxy derivatives of long chain unsaturated keto sugars.

The molar proportion of the ester to the aldose condensed was 1:1 or 1:2 depending on the relative concentration of the reagents and the reaction time.

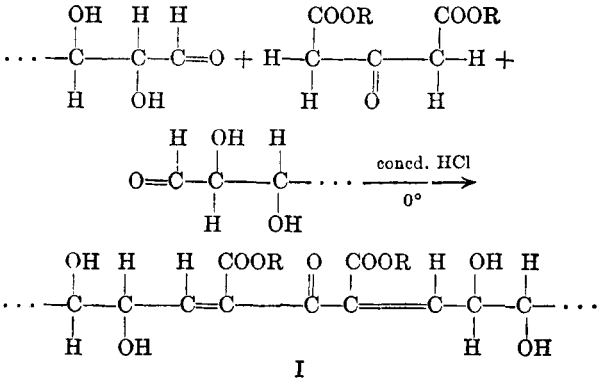
The products were converted and characterized as phenylhydrazine or 2,4-dinitrophenylhydrazine derivatives.

In a previous publication[1] the condensation of diethyl acetonedicarboxylate with 1,2-*O*-isopropylidene-D-xylopentadialdose, using piperidine as a catalyst was described. It was pointed out then, that this method favored the formation of long chain sugars. In view of the method used in the

(1) P. E. Papadakis, *J. Org. Chem.*, **20**, 630 (1955).



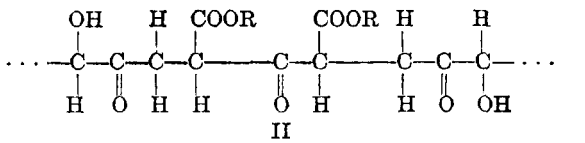
preparation of glucose diethyl thioacetal[2] it seemed reasonable that with similar reagents and conditions which apparently favored the aldehyde form of glucose, the latter may react with the methylene group of β-dicarbonyl compounds such as diethyl acetonedicarboxylate or other carbonyl compounds having *alpha* carbon hydrogens to produce derivatives of long carbon chain sugars.



I

Depending on the concentration of the reagents and on the time of the reaction at 0° one may expect that the product may be the result of a reaction of one aldose to one ester or of two aldoses to one ester. Such products, due to structural reasons, would be expected to be partially soluble in ethyl acetate and in water. The product of one aldose to one ester would be, relatively, more soluble in ethyl acetate than the product of the reaction of two aldoses to one ester and the latter more soluble in hot water.

Under alkaline conditions and with a reagent such as phenylhydrazine structure I by tautomerization of hydrogens may be converted to structure II which will react with a greater proportion of phenylhydrazine than compound I. Besides the

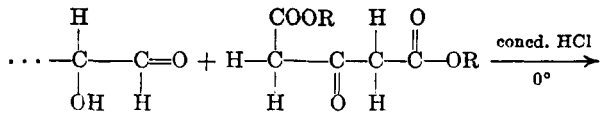


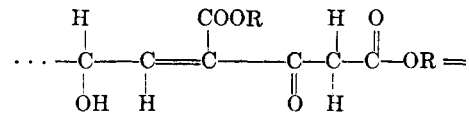
II

phenylhydrazone formation with each of the keto groups in formulas I and II, excess phenylhydrazine and a longer period of heating may produce phenylhydrazide derivatives with the ester groups. The experimental part furnishes evidence that such transformations take place.

In the present paper diethyl acetonedicarboxylate was treated with reducing sugars D-glucose, L-arabinose, and D-xylose in concentrated hydrochloric acid at 0°. In the preliminary experiments the reaction time period was three hours. In later experiments the time period was extended to three days as excess of the aldose and longer reaction time period favored the reaction of the molar proportion of two aldoses to one ester. After the reaction time period the hydrochloric acid was either neutralized with cold alkali solution or it was allowed to react with ether to remove any unchanged diethyl acetonedicarboxylate; thereafter the procedure was varied to suit the purpose of the respective experiments.

In an experiment with glucose (reaction time period three hours) after the ether extraction the mixture was extracted several times with ethyl acetate. After evaporation of the solvent the residue was processed with phenyl hydrazine. In another experiment the mixture without extracting with ethyl acetate was treated with phenylhydrazine. The derivative melts at 202°, and the carbon, hydrogen, and nitrogen analyses correspond to the formula $C_{29}H_{32}O_6N_6$, formula VI. This may be explained as follows:





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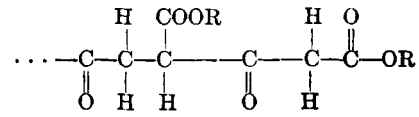

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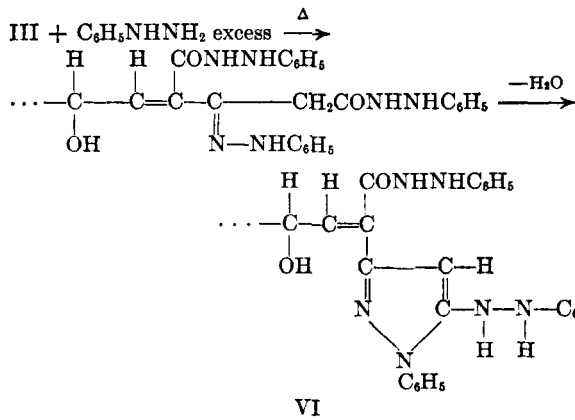
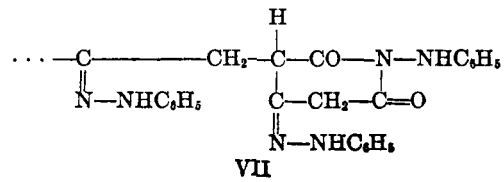


VI

Compound IV with phenyl hydrazine may form an isomeric compound VII.

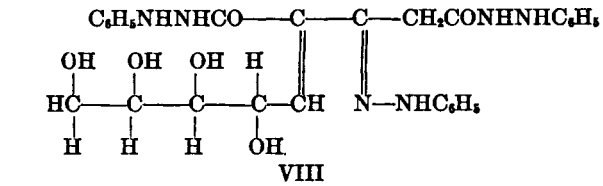


VII

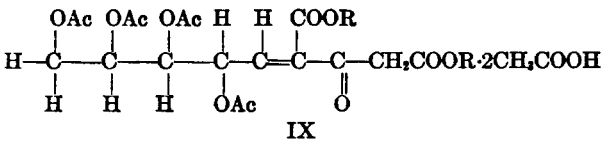
(2) E. Fischer, *Ber.*, 27, 673 (1894).

A similar experiment with L-arabinose (reaction time period three hours) rendered a phenylhydrazine derivative of the material extracted by ethyl acetate which may be represented by formula VIII. After the ethyl acetate extraction the water solution was evaporated and the residue was acetylated. The analysis of the acetylated product corresponded to formula IX. Part of the acetylated product was dissolved in methanol and treated with 2,4-dinitrophenylhydrazine according to the method described by Cheronis.[3]

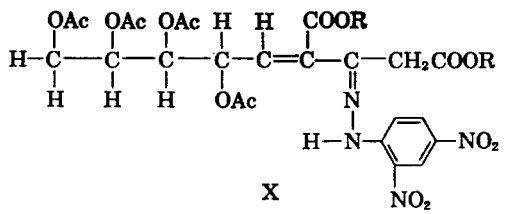
The product corresponds to formula X. With excess 2,4-dinitrophenylhydrazine and longer period of heating the analysis of the product obtained corresponds to formula XI.



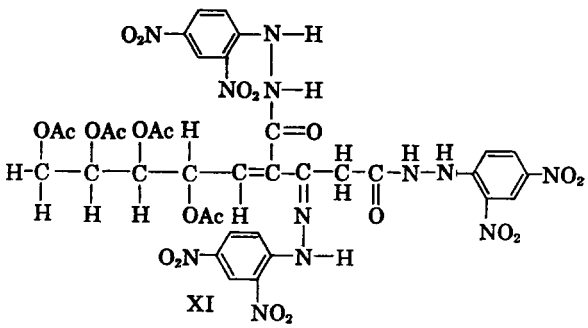
VIII



IX



X

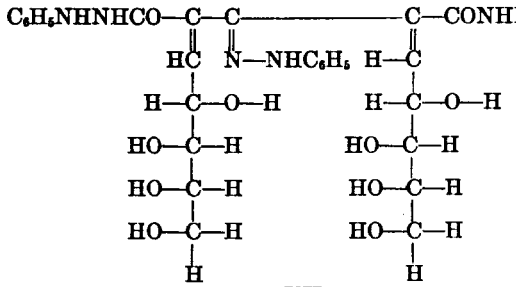


XI

The results indicate that under the conditions of the experiments the reaction of the L-arabinose to diethyl acetonedicarboxylate took place in a 1:1 molar proportion.

In later experiments with L-arabinose the reaction time period was extended to three days. After the addition of the sodium acetate the ether and ethyl acetate did not extract any significant amount of material. The water solution containing the product (inorganic salts and acetic acid) was evaporated and the residue was treated with phenylhydrazine (phenylhydrazine hydrochloride + excess sodium acetate solution), and the derivative was processed and isolated.

In one experiment analysis of the product for nitrogen gave the values 12.21, 12.40, and 12.38; calculated for $C_{33}H_{40}O_{10}N_6$, nitrogen is 12.31% which may be represented by formula XII.



XII

In another experiment where excess phenylhydrazine was used with longer period of heating the product obtained was divided into two parts, A and B, where the A part was the more readily soluble in alcohol. The analysis of the material from A corresponds to formula XIII. The analysis of the material from B may be represented by formula XIV. (See previous discussion concerning formula II.)

The experiment was repeated and the product obtained was recrystallized from boiling water and then dried under 3 mm. pressure and room temperature for four hours. The analysis of the product corresponded to a dihydrate of formula XIV. A similar experiment with D-xylose rendered a phenylhydrazine derivative the analysis of which for carbon, hydrogen, and nitrogen corresponds to $C_{46}H_{52}O_8N_{10}.2H_2O$ and may be represented by formula XV. Further work is in progress.

EXPERIMENTAL

The reaction of diethyl acetonedicarboxylate with D-*glucose in concentrated hydrochloric acid at 0°.* To a solution of 3.6 g. of glucose dissolved in concd. hydrochloric acid at 0°, 2.02 g. of diethyl acetonedicarboxylate was added with stirring. This mixture was neutralized with cold sodium hydroxide solution. The mixture was extracted with ether to remove any unchanged diethyl acetonedicarboxylate. The water solution containing the product was treated with phenylhydrazine, (phenylhydrazine hydrochloride + sodium acetate solution). A yellow precipitate formed which was filtered, then dissolved in alcohol, and reprecipitated with distilled water. The precipitate was filtered and dried *in vacuo* and 100° temperature, m.p. 202°, formula VI.

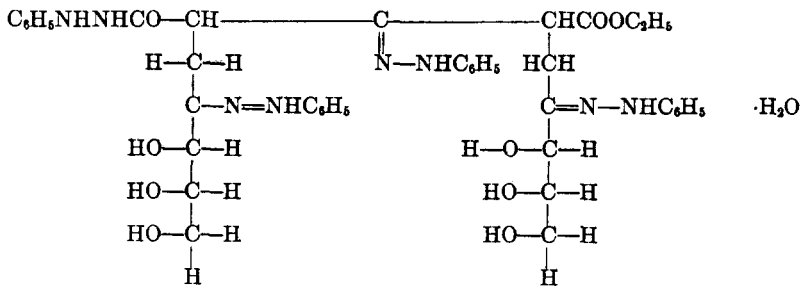
Anal. Calcd. for $C_{29}H_{32}O_6N_6$: C, 62.11; H, 5.71; N, 14.99. Found: C, 61.81; H, 5.80; N, 14.98; 14.83.

The experiment was repeated. Instead of neutralizing the hydrochloric acid with sodium hydroxide, sodium acetate was used, and the material was dried at room temperature and atmospheric pressure in a desiccator. The rest of the procedure was the same as before. The phenylhydrazine derivative thus obtained melted at 186°, formula V.

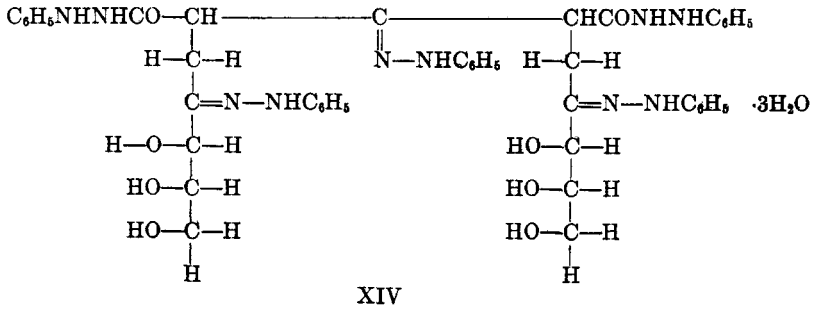
Anal. Calcd. for $C_{29}H_{34}O_7N_6$: C, 60.20; H, 5.88. Found: C, 60.15; H, 6.30.

The reaction of diethyl acetonedicarboxylate with L-*arabinose in concentrated hydrochloric acid at 0°.* To a solution of 21 g.

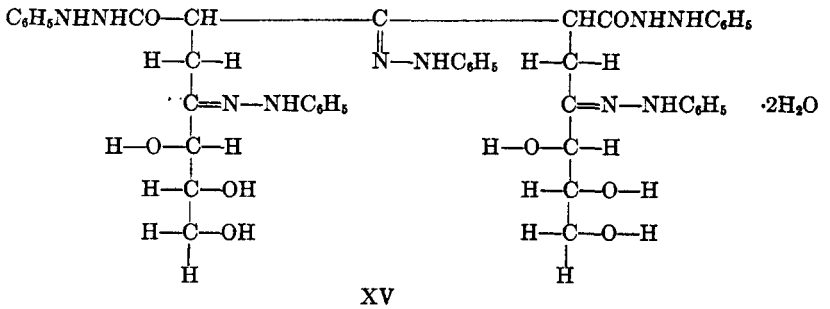
(3) N. D. Cheronis and J. B. Entrikin, *Semimicro Qualitative Organic Analysis*, Thomas Y. Crowell Co., New York, N. Y., 1947, p. 247.



XIII



XIV



XV

of L-arabinose in concd. hydrochloric acid at 0°, 14 g. of diethyl acetonedicarboxylate was added with stirring; the mixture was kept at 0° for 3 hr.; then it was extracted several times with 30-ml. portions of ethyl acetate. The combined ethyl acetate was shaken with silver oxide, filtered, and the filtrate concentrated to a thick sirup. The latter was stirred with ether and petroleum ether (b.p. 39.9–44.5°) to extract any uncharged diethyl acetonedicarboxylate.

The part that did not dissolve in the ether was treated with phenyl hydrazine acetate. A yellow precipitate formed and some gum which rendered a brown powder after drying. The brown material was washed with ether, then it was dissolved in alcohol and reprecipitated with distilled water. A brown orange material resulted, formula VIII.

Anal. Calcd. for $C_{28}H_{30}N_6O_6$: C, 61.52; H, 5.53. Found: C, 61.28; H, 5.40.

To the water solution after the ethyl acetate extraction enough sodium acetate was added to react with the hydrochloric acid. The water of the solution was distilled *in vacuo*. The mixture was subjected to acetylation using acetic anhydride. The acetylated material was stirred with ice water, filtered and dried; m.p. 97°, formula IX.

Anal. Calcd. for $C_{26}H_{38}O_{17}\cdot 2CH_3COOH$: C, 50.15; H, 6.15. Found: C, 49.90; H, 5.87.

Part of the acetylated product was dissolved in methanol and treated with a methanol solution of 2,4-dinitrophenylhydrazine.[3] A light yellow precipitate formed which was recrystallized from methanol, m.p. 127°, formula X.

Anal. Calcd. for $C_{28}H_{34}O_{16}N_4H_2O$: C, 48.00; H, 5.18. Found: C, 47.68; H, 5.08.

With excess 2,4-dinitrophenylhydrazine and longer heating and standing a red brown precipitate was formed which began to sinter at 144° and melted at 166°, phenylhydrazide derivative of formula XI.

Anal. Calcd. for $C_{36}H_{34}O_{22}N_{12}\cdot 3H_2O$: C, 41.54; H, 3.87. Found: C, 41.73; H, 3.60.

In the following experiments the method was varied. The molar proportion of the L-arabinose to the ester was 2:1. The reaction time period was extended from 3 hr. to 3 days. The temperature was 0°. Little more than the calculated amount of sodium acetate was used to neutralize the concd. hydrochloric acid. The water solution was extracted with petroleum ether and with ethyl acetate. The water layer containing the product and inorganic salts was treated with phenylhydrazine solution in the usual way and the precipitate formed was filtered, dissolved in alcohol, and reprecipitated with distilled water. It was dried and analyzed for nitrogen; Formula XII.

Anal. Calcd. for $C_{32}H_{40}N_6O_{10}$: %N, 12.31. Found: %N, 12.21; 12.40; 12.38.

The experiment was repeated using excess of phenylhydrazine and heating a longer period of time. The product was processed as before but in the process of purification, the phenylhydrazine derivative was divided in two portions. The part which was more readily dissolved in alcohol was marked A and the less soluble was marked B. The material processed from A, m.p. 146° gave the following analysis: Formula (XIII).

Anal. Calcd. for $C_{41}H_{50}O_9N_8\cdot H_2O$: C, 60.27; H, 6.01; N, 13.71. Found: C, 60.72; H, 6.42; N, 13.62.

The material from B gave the following analysis: Formula (XIV).

Anal. Calcd. for $C_{45}H_{52}O_8N_{10}\cdot 3H_2O$: C, 59.08; H, 6.34; N, 15.31. Found: C, 58.98; H, 6.37; N, 14.95.

The experiment was repeated as above with the following modification. Instead of separating the phenylhydrazine derivative on the basis of its solubility in alcohol into fractions A and B, the product was recrystallized from boiling distilled water. The material obtained was dried first on porous tile and second under reduced pressure, 3 mm., at room temperature; Formula XIV—H_2O.

Anal. Calcd. for $C_{45}H_{52}O_8N_{10}\cdot 2H_2O$: C, 60.26; H, 6.25; N, 15.60. Found: C, 60.04; H, 5.98; N, 15.77.

The reaction of diethyl acetonedicarboxylate with D-*xylose in concentrated hydrochloric acid at 0°.* To a solution of 3 g. of xylose in concd. hydrochloric acid at 0°, 2 ml. of diethyl acetonedicarboxylate was added with stirring. The mixture was placed in a refrigerator and allowed to stand for 3 days, then the calculated amount of sodium acetate was added to neutralize the hydrochloric acid. The mixture was shaken with ether and petroleum ether to remove any unchanged ester. The product in the water layer was converted to a phenylhydrazine derivative in the usual way. The precipitate was dissolved in alcohol and reprecipitated with distilled water. The precipitate was filtered and dried in a desiccator, m.p. 176°; Formula (XV).

Anal. Calcd. for $C_{45}H_{50}O_8N_{10}\cdot 2H_2O$: C, 60.26; H, 6.29; N, 15.60. Found: C, 60.14; H, 5.95; N, 15.91.

Further work is in progress with other reagents having active *alpha* carbon hydrogen adjacent to a carbonyl or other appropriate group, with the aldoses, ketoses, and dialdehyde monoses.

Acknowledgment. The author wishes to express his appreciation to his student, Marshall Jacks, for his cooperation.

OMAHA, NEB.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Hydrolysis of 5,5-Disubstituted Barbituric Acids

MORRIS FREIFELDER, ADOLPH O. GEISZLER, AND GEORGE R. STONE

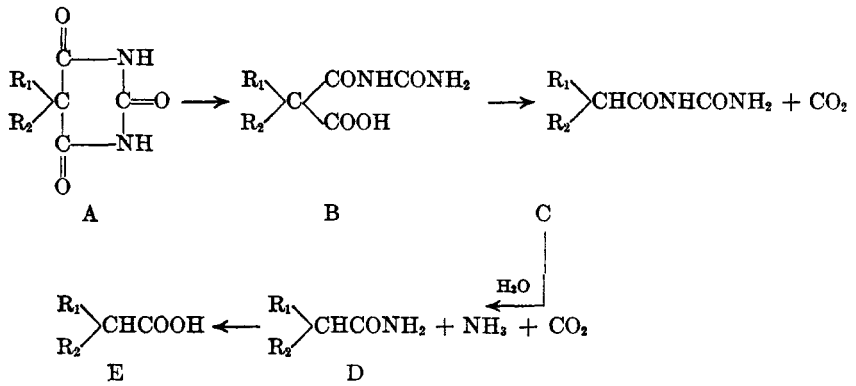
Received May 18, 1960

A rapid and simple method of hydrolysis of 5,5-disubstituted barbituric acids to the corresponding amides is reported. High yields are obtained when the reactions are carried out in dilute aqueous ammonia at 200° for five to ten minutes. In only one case was acylated urea obtained. Twenty-three of the compounds reported are new.

Amides of the type $R_1R_2CHCONH_2$ (where R_1 and R_2 are one or both of alkyl, unsaturated alkyl, and cycloalkyl groups) are widely reported. They normally are prepared from disubstituted acetic acids $-R_1R_2CHCOOH-$ by classical methods. The substituted acetic acids generally are obtained by hydrolysis and decarboxylation of dialkylated malonic or cyanoacetic esters.

The conversion of these esters to the corresponding acetic acids is time consuming and often troublesome.[1a,b] However, it is well known that the condensation of such esters with urea in the presence of sodium ethoxide[2] gives 5,5-disubstituted barbituric acids in good yield. Therefore it appeared advantageous to investigate their hydrolysis as a method of preparing disubstituted acetamides.

The hydrolysis of barbituric acids proceeds first by opening of the pyrimidine ring and decarboxylation to form an acylurea (C), followed by decomposition to the corresponding amide (D), carbon dioxide, and ammonia. More vigorous hydrolysis leads to E.



The alkaline hydrolysis of A at atmospheric conditions and at 100° in a bomb[1b] has been reported to give ureas (C). In a study of the hydrolysis of 5-substituted barbituric acids at 5–10 atmospheres pressure under various *p*H conditions Ruhkopf[3] obtained both ureas and amides. He

(1) (a) F. F. Blicke and P. Centolella, *J. Am. Chem. Soc.*, **60**, 2923 (1938), (b) E. H. Volwiler and D. L. Tabern, *J. Am. Chem. Soc.*, **58**, 1352 (1936) report on the difficulty of hydrolyzing certain higher substituted malonic esters.

(2) W. J. Doran, *Medicinal Chemistry*, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 5.

(3) H. Ruhkopf, *Ber.*, **73**, 938 (1940). The author also cites references describing the path of hydrolysis.