[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

The Synthesis of a Lactone Related to Auxin b[1]

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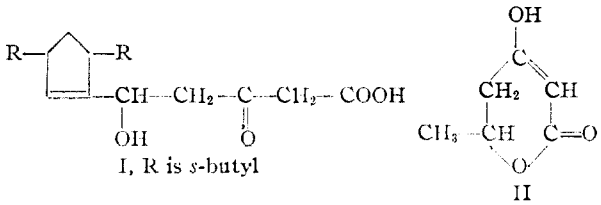
As a possible direct route to the synthesis of compounds related to auxin b, the Reformatsky reaction between ethyl γ-bromo-β-ethoxycrotonate and benzaldehyde was investigated. This reaction is shown to form 4-ethoxy-6-phenyl-5,6-dihydro-2-pyrone. The latter, on loss of its ethoxy group, gives 4-hydroxy-6-phenyl-5,6-dihydro-2-pyrone, which is the phenyl analog of auxin b, in enol-lactone form. The hydroxypyrone appears to exist in dimorphic modifications. Attempts to prepare the open chain β-keto-δ-hydroxy acid from the pyrone were without success. The synthetic steps described in this paper should be of general application for the preparation of 4-ethoxy-6-substituted-5,6-dihydro-2-pyrones and their hydroxy derivatives.

The brilliant researches of Kögl and co-workers[3] on the structures of the phytohormones, auxins a and b, culminated in the proposal of rational structures for these substances. Common to each substance is the 3,5-di-*s*-butylcyclopentene unit, attached through the one-position to the side-chain. Auxin b (Fig. 1, structure I) contains a 5-hydroxy-3-ketovaleric acid side-chain. The closely related auxin a contains a 2,3,5-trihydroxyvaleric acid unit attached to the ring.



I, R is *s*-butyl

II

Fig. 1.

Attempts to synthesize compounds with structures related to these hormones have, up to the present, made use of two very different approaches. The Reformatsky reaction between aldehydes and γ-bromocrotonic ester[4,5] has been utilized by English and Gregory,[6] and by Jones, O'Sullivan and Whiting[7] to prepare 5-substituted-5-hydroxy-2-pentenoic acids, of obvious importance in projected syntheses of compounds structurally related to auxin a. The second approach, due to Jones, *et al.*,[8,9,10] involved the catalyzed addition of amines or alcohol to methyl 5-hydroxy-2-hexynoate, and resulted in the spontaneous formation of 4-substituted-6-methyl-5,6-dihydro-2-pyrones, from which 4-hydroxy-6-methyl-5,6-dihydro-2-pyrone (II) was obtained. The latter compound is the methyl analog of auxin b, in enol-lactone form.

Since auxin b may be considered to be formed by a condensation reaction between 3,5-di-*s*-butyl-1-cyclopentenealdehyde[11] and the γ-carbon atom of acetoacetic acid, it seemed desirable to investigate the Reformatsky reaction between ethyl γ-bromo-β-ethoxycrotonate and various aldehydes. We report here a study of this direct approach, which is a modification of the first method mentioned above, carried out with benzaldehyde. As the sequel will show, this approach leads to the phenyl analog of auxin b, in lactone form. This compound differs, not unexpectedly, from both auxin b, and the methylpyrone of Jones and Whiting.

The Reformatsky reaction between ethyl γ-bromo-β-ethoxycrotonate and benzaldehyde proceeded readily and furnished crystalline material in satisfactory yields. The product was a non-enolic neutral compound which, on degradation with hot acid, formed benzalacetone (Fig. 2, X). This behavior was to be anticipated on the basis of the hydroxy-ester (III), or its dehydration product. Benzalacetone would also be expected from compound IV, which might form as the result of an allylic shift within the ester moiety during the Reformatsky reaction,[6,7] followed by dehydration. However, it rapidly became apparent that none of these possible structures could accommodate the properties of the reaction product. The substance was adamantine to catalytic dehydration,[12] and analysis and Zeisel determinations showed that it possessed the empirical formula $C_{13}H_{14}O_3$, and contained *one* ethoxy group. Attempts to remove this group by basic hydrolysis were unsuccessful; there was formed a *non-enolic isomeric acid*, which retained the ethoxy group. Clearly the Reformatsky product resulted from a *cyclization* process, and this consideration leads to three appropriate structures. The vinylethoxy-lactone (V) could result from lactonization of the allylic[6,7] organozinc adduct.[13] On the other hand this lactone conceivably could undergo a retroallylic shift to form the unsaturated lactone (VI). Normal Reformatsky addition, followed by lactonization, would result in formation of the pyrone (VII).

It has been mentioned that basic hydrolysis of the lactonic product formed a non-enolic ethoxy-acid. This compound furnished a convenient starting point for a series of reactions that enabled us to reach a decision regarding the identity of the Reformatsky product. Structures V and VI must give, on basic hydrolysis, *i.e.*, ring opening with dehydration, 2-benzal-3-ethoxy-3-butenoic acid (XVI). The latter compound, on loss of ethoxyl, should furnish α-benzalacetoacetic acid (XVII). On the other hand, basic hydrolysis applied to the

(1) This is the third paper describing work in this field. For the second, which deals with the synthesis of the ring system present in the auxins, see Reid and Yost, THIS JOURNAL, **72**, 5232 (1950).

(2) From the doctoral dissertation of William R. Ruby, The Johns Hopkins University.

(3) Kögl, Erxleben, Michaelis and Visser, *Z. physiol. Chem.*, **235**, 181 (1935).

(4) Fuson, Arnold and Cooke, THIS JOURNAL, **60**, 2272 (1938).

(5) Ziegler, Schumann and Winkelmann, *Ann.*, **551**, 120 (1942).

(6) English and Gregory, THIS JOURNAL, **69**, 2123 (1947).

(7) Jones, O'Sullivan and Whiting, *J. Chem. Soc.*, 1415 (1949).

(8) Jones and Whiting, *ibid.*, 1419 (1949).

(9) Jones and Whiting, *ibid.*, 1423 (1949).

(10) Jones, Tilden Lecture, *ibid.*, 754 (1950).

(11) Experiments directed toward the synthesis of this compound in its various stereochemical forms are in progress in this Laboratory.

(12) Hibbert, THIS JOURNAL, **37**, 1748 (1915).

(13) Compare Gilman and Speeter, *ibid.*, **65**, 2255 (1943), who observed spontaneous β-lactam formation during a Reformatsky reaction with benzalaniline.

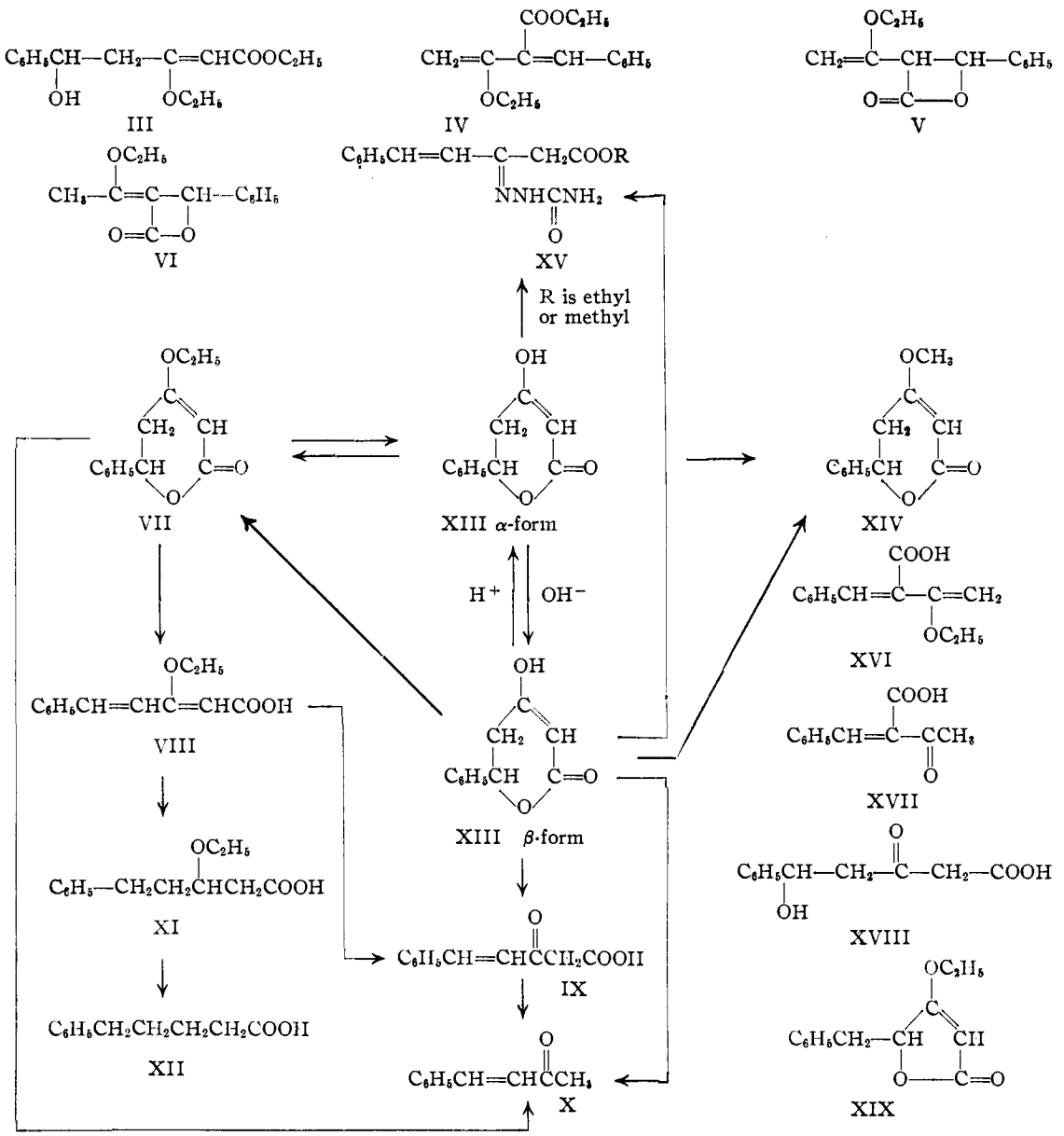


Fig. 2.

pyrone (VII) would lead to 3-ethoxy-5-phenyl-2,4-pentadienoic acid (VIII), and this molecule, on loss of its ethoxyl, would give γ-benzalacetoacetic acid (IX). It was found that removal of the ethoxy unit from our ethoxy-acid resulted in the formation of a strongly *enolic acid* that decarboxylated with extreme ease to form benzalacetone (X). The abnormal lactonic structures are therefore eliminated, since α-benzalacetoacetic acid (XVII) should show no enolic characteristics. This conclusion was supported by our observation that the ethyl ester of α-benzalacetoacetic acid[14] was inert to ferric chloride solution; however, we were thwarted in attempts to prepare the free acid from this ester, apparently due to polymerization. Beyond this, a series of reduction experiments afforded complete substantiation for the above view. Thus, when the sodium salt of the unsaturated ethoxy-acid was carefully reduced with catalytic hydrogen, the main product was a liquid acid whose analysis showed it to be a phenylethoxyvaleric acid. That this acid contained the phenyl group in the terminal position was clearly demonstrated by its final reduction with hydriodic acid to δ-phenylvaleric acid.

The Reformatsky reaction between ethyl γ-bromo-β-ethoxycrotonate and benzaldehyde thus leads to a union between the γ-carbon atom of the ethoxy-ester and the carbonyl group of the aldehyde, with concomitant cyclization. The product must, therefore, be either 4-ethoxy-6-phenyl-5,6-dihydro-2-pyrone (VII), or the ethyl ether of 5-benzyltetronic acid (XIX). Although it is difficult to rationalize the formation of the latter compound *via* the Reformatsky reaction, nevertheless, it is possible to account for the transformations mentioned above in terms of this substance. Accordingly, 5-benzyltetronic acid was synthesized, by a modification of Benary's method.[15] It proved to be differ-

(14) Knoevenagel, *Ber.*, **31**, 730 (1898).

(15) Benary, *ibid.*, **44**, 1757 (1911).

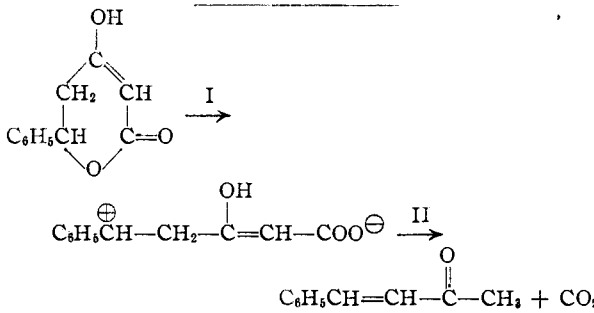
ent from the enolic compound obtained by removal of the ethoxy group from the Reformatsky product. The Reformatsky product is therefore 4-ethoxy-6-phenyl-5,6-dihydro-2-pyrone (VII), and this substance, on warming with base, undergoes ring-opening with facile dehydration to furnish 3-ethoxy-5-phenyl-2,4-pentadienoic acid (VIII). Catalytic reduction of the latter must give 3-ethoxy-5-phenylvaleric acid (XI), while the acid obtained by removal of the ethoxy unit from the dienoic acid must be given by γ-benzalacetoacetic acid (IX), or the enolic form of this molecule.

The direct formation of the dihydropyrone (VII) deserves comment since English and Gregory[6] were unable to lactonize their 5-hydroxy-5-phenyl-2-pentenoic acid. These authors concluded that their acid possessed the *trans*-structure, since lactonization was spontaneous after reduction of the double bond. Jones, O'Sullivan and Whiting[7] were likewise unable to induce cyclization of the same acid and, moreover, they were unable to isomerize it to the *cis*-form. It thus appears certain that the ethyl γ-bromo-β-ethoxycrotonate used in our experiments possessed the apposite *cis*-structure.

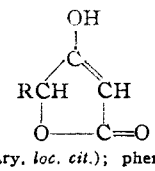
We now turned to a study of the phenylpyrone (VII). Removal of the ethoxy unit was smoothly accomplished by brief treatment with hydriodic acid. The product was acidic and exhibited a strong enol (ferric chloride) test, and the fact that it decomposed at the melting point to form benzalacetone (X), suggested that possibly the ring had opened during the removal of the ethoxy group. However, analysis proved that this acid was *isomeric* with the β-ketoacid (IX), which we described earlier. Further, we were able to show by alkylation experiments that the lactonic structure had been preserved during the hydriodic acid treatment. Thus, in the presence of either ethanol and hydrogen chloride, or ethyl iodide and silver oxide, the new enolic acid regenerated the parent phenylethoxypyrone (VII). The new acid is thus 6-phenyl-4-hydroxy-5,6-dihydro-2-pyrone (XIII, α-form), and all the evidence we have at hand is in accord with this structure.[16]

All attempts to obtain 5-phenyl-5-hydroxy-3-ketovaleric acid (XVIII), which would be the phenyl analog of auxin b (Fig. 1, I), were without success. When the enolic lactone (XIII, α-form) was treated with mild base under gentle conditions, an *isomer* was obtained, whose melting point (with decomposition) was approximately twenty degrees below that of the original substance. That ring opening and dehydration had not occurred was clearly established, again through alkylation experiments. The isomer was converted back to the original Reformatsky product (VII), on treatment with either ethanol and hydrogen chloride, or ethyl iodide and silver oxide. The methoxypyrone (XIV) resulted from interaction with either diazomethane or methanol and hydrogen chloride. At first sight it appeared that the relationship between the two isomeric lactones was that of a relatively stabilized keto-enol system, since the lower-melting form was produced under circumstances known to convert the ketonic form of ethyl acetoacetate into the enolic isomer.[17] Other chemical evidence also pointed to this possibility. Thus, the lower-melting isomer was completely converted into the higher-melting form by acid[18] (hydrogen chloride in cold dioxane). Moreover, mild heating caused the melting point of the higher-melting form to drop toward that of the lower, and the complete transition of the higher to the lower form was accomplished by successive recrystallizations from aqueous solvents. Conversely, the lower form (β-isomer) was transformed into the α-isomer by repeated recrystallizations from non-polar solvents. Isomerization of the β-form into the higher melting α-form was also accomplished by heating with acetyl chloride in ethereal solution. However, attempts to differentiate between the two compounds by bromine titrations[19] were entirely unsatisfactory since erratic results were obtained that indicated enol contents in excess of 100%.[20]

In order to obtain definitive evidence, the infrared absorption spectra of these isomers were determined.[21] The measurements were made on



(16) All tetronic acids of structures comparable to that of our pyrone, *viz.*,



where R is methyl (Benary, *loc. cit.*); phenyl (Lecocq, *Compt. rend.*, **222**, 299 (1946)); or benzyl (prepared in the present work), melt *without* decomposition. Such compounds are strong acids (Kumler, THIS JOURNAL, **60**, 859 (1938), and **62**, 3292 (1940); Edsall and Sagall, *ibid.*, **65**, 1312 (1943)), and in the free state owe their stability and non-lactonic properties to dipolar resonance. Alkylation of such compounds gives exclusively O-alkyl derivatives (Conrad and Gast, *Ber.*, **31**, 2726 (1898)). Our dihydropyrone should partake of these properties and alkylate predominantly on the oxygen atom. It is also clear that the benzyl group, through its electron releasing properties (Johnson, Ch. 25 in Gilman's "Organic Chemistry, An Advanced Treatise," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1865), makes possible the transformation

A case in point is 3,3,5,5-tetramethyl-6-phenyl-δ-valerolactone (Zeltner, *Ber.*, **41**, 592 (1908)) which obviously could not undergo step II. This compound melts without decomposition. Also in accord with this is the 6-methylpyrone of Jones and Whiting, *loc. cit.*, which is reported to be unstable above its melting point, while the 3,6-dimethylpyrone of the same authors gives some decomposition at the melting point. It is difficult to explain the lack of oxygen alkylation in the pyrone of Jones and Whiting.

(17) K. H. Meyer, *Ann.*, **380**, 230 (1911).

(18) Nachod, *Z. physik. Chem.*, **A182**, 193 (1938), has demonstrated the transformation of enolic to ketonic form of acetylacetone by hydrogen chloride.

(19) K. H. Meyer, *Ber.*, **45**, 2846 (1912).

(20) The necessary and sufficient conditions for the applicability of the Kurt Meyer enol titration method to compounds other than acetoacetic esters have been pointed out by Meyer and Kappelmeier, *Ber.*, **44**, 2718 (1911).

(21) We wish to thank Dr. Lester P. Kuhn of The Ballistics Research Laboratory, Aberdeen Proving Grounds, Md., for these determinations. The instrument was a Baird Associates double-beam infrared spectrophotometer.

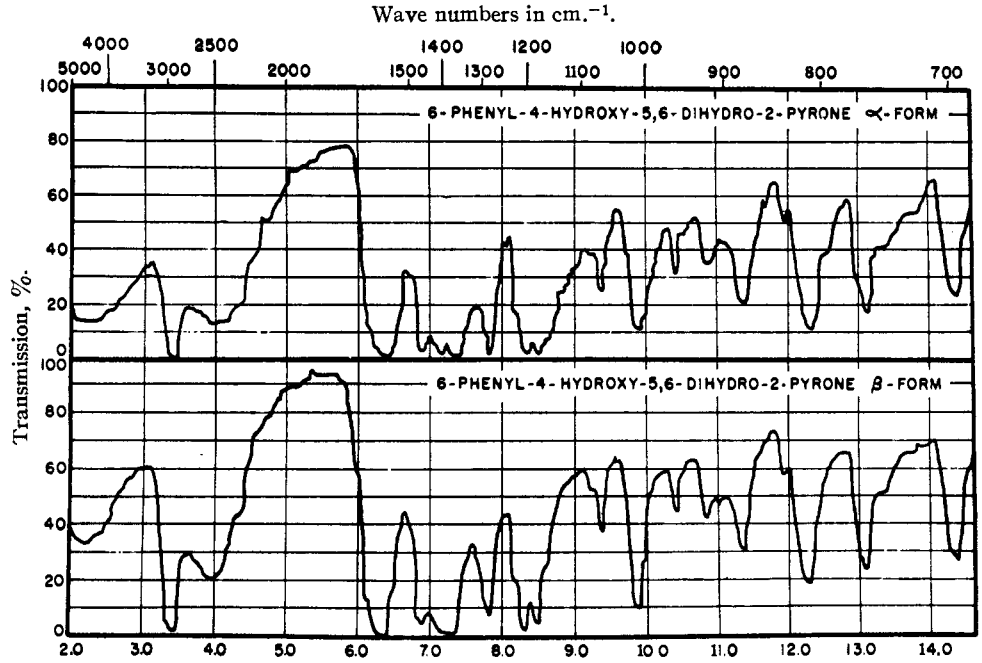


Fig. 3.—α-Form above; β-form below.

solid samples mulled in mineral oil. Figure 3 reproduces the absorption curves. The bands at 3.3–3.4, 6.8–6.9 and 7.2–7.3 μ are due to the mineral oil used. Two facts are clear from these curves. First, from the great similarity of the two curves, the relationship between the two isomers appears to be that of dimorphism rather than keto–enol tautomerism. Second, the characteristic OH vibration is apparently absent. However, from infrared determinations made on 5-substituted-tetronic acids[22] it has been established that the OH band is shifted to longer wave lengths, and forms a wide shallow band at about 4 μ. The presence of this type of band in both curves we assume to be due to the enolic OH group.[23] Corresponding to the strongly enolic natures of these isomers is the absence of unconjugated carbonyl absorption (about 5.9 μ) and the presence of a wide absorption band at about 6.1–6.5 μ. This would appear to indicate almost complete enolization, since the 6.1–6.5 μ range has been ascribed to the carbonyl vibration of a conjugated chelated structure, and it also covers the wave length (6.23 μ) of the OH vibration when external hydrogen bonding is involved.[23]

The spectral evidence, indicating dimorphism, is thus somewhat at variance with the chemical evidence, since we were unable to convert the higher-melting form, which should be the metastable one (despite its lesser solubility) into the lower form by crystallization from an evaporating solution.[24] Also, a clear proof of dimorphism by means of a transformation at the fusion point[24] was impossible because of the vigorous decomposition of both compounds at their melting points, to form benzalacetone. At the present time we rely upon the spectral evidence and consider the two compounds as dimorphic modifications, but in view of the lack of both chemical and spectral data of pyrones of this type, the final solution to this question must be deferred.[25]

The action of strong bases on our pyrone was investigated as a possible means of preparing the open-chain hydroxy-acid (XVIII). Under these conditions, however, polymerization occurred, along with degradation. Finally, the involved polyfunctionalism permitted by the lactonic structures (XIII, α- and β-forms) is clearly exemplified by the behavior of these isomers toward ketonic reagents. Treatment with semicarbazide reagent in alcoholic solutions resulted in the formation of semicarbazones of *open-chain*, γ,δ-unsaturated-β-keto-esters[26] (Fig. 2, XV) wherein the ester group was derived from the alcohol used as *solvent*. The extreme ease with which the lactone ring is opened, with dehydration following automatically, is due to the benzyl group functioning in its well-known electron-releasing capacity. Jones and Whiting[8,9] report normal semicarbazone formation, without ring-opening, for their methyl-lactone, and Kögl, *et al.*,[3] state that auxin b gives a normal open-chain derivative.

Acknowledgment.—One of the authors (W. R. R.) acknowledges with thanks receipt of a grant-in-aid from the Hynson, Westcott and Dunning Fund.

Experimental

Ethyl γ-Bromo-β-ethoxycrotonate.—This substance, b.p. 97–100.5° at 1.5 mm., $n^{29}D$ 1.4912, was prepared in 81% yield

(22) Unpublished results from these laboratories.

(23) Compare Rasmussen, Tunnicliff and Brattain, THIS JOURNAL, **71**, 1068 (1949).

(24) Findlay, "The Phase Rule and its Applications," Longmans, Green and Co., Seventh Edition, 1931, New York, N. Y., p. 36.

(25) A series of pyrones is being prepared for infrared study. The results will be described later.

(26) It is presumed that the unsaturation resides between the γ- and δ-carbons.

by the bromination of ethyl β-ethoxycrotonate[27] with N-bromosuccinimide.[28] The procedure was adapted from that of Wohl and Jaschinowski,[29] who used N-bromoacetamide to brominate the same ester. With thiourea the bromoester formed the known 2-amino-4-thiazoleacetate[30]; m. p. 94–95°.

4-Ethoxy-6-phenyl-5,6-dihydro-2-pyrone.—Commercial benzaldehyde was washed free of all traces of benzoic acid by shaking with 10% sodium carbonate solution. After washing with water it was dried over sodium sulfate and fractionally distilled under nitrogen *in vacuo*. The fraction boiling sharply at 69° at 15 mm., was used. The zinc dust was activated by washing with 2% hydrochloric acid, distilled water, 95% ethanol, acetone and finally anhydrous ether. It was not dried in an oven, as is usually recommended,[31] but was used directly. The apparatus was all-glass, and was dried by washing with acetone, and then with anhydrous ether. The apparatus consisted of a three-necked flask equipped with mechanical stirrer, reflux condenser fitted with a calcium chloride tube, and a dropping funnel. In this apparatus were placed 17.1 g. (0.2605 mole) of the activated zinc dust, and to this was added, from a dropping funnel, a mixture of 50 g., (0.211 mole) of ethyl γ-bromo-β-ethoxycrotonate and 27.4 g., (0.258 mole) of purified benzaldehyde, dissolved in a solution of 35.8 ml. of dry benzene and 9.0 ml. of absolute ether. After the addition of a few ml. of the above mixture, a crystal of iodine was added, and the flask was heated with a micro-flame until an exothermic reaction was initiated. Then, with rapid stirring, the remainder of the reactants was added at such a rate that vigorous reflux was maintained. The mixture quickly developed a muddy-green appearance. After complete addition of the reactants to the zinc dust, stirring and refluxing were maintained during the dropwise addition of a further 6.0 g. of benzaldehyde.

The reaction mixture was then cooled and slowly poured, with stirring, into a paste made of 30 g. of "Super-Cel," 50 ml. of water and 50 g. of cracked ice. The resultant viscous mass was collected on a Büchner and sucked dry. The product was extracted by boiling with 100 ml. of 95% ethanol for 15 minutes, and again filtered. This process was repeated three times, and the alcoholic filtrates were combined and concentrated to small bulk on the steam-bath under reduced pressure (aspirator). Ether (120 ml.) was then added to the yellow-orange residue, and the solution was dried over sodium sulfate and filtered. The filtrate was cooled by the addition of small pieces of Dry Ice, and stirred rapidly. Large amounts of yellow solid separated as the mixture became progressively colder. This was collected on the Büchner, and became chalk-white when washed with 30 ml. of ether that had previously been made very cold by the dissolution of Dry Ice. Evaporation of the filtrate to one-half volume and chilling again with Dry Ice furnished only a small second crop. The combined solids were damp with ether and weighed 45.5 g. Recrystallization from ether–ethanol (3:1), furnished 27.9 g. (60.7% yield) of fluffy, gleaming white needles with m. p. 93–94°. The m. p. was not changed by further recrystallization.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.58; H, 6.46. Found: C, 71.56; H, 6.47.

The substance was insoluble in dilute sodium carbonate, and gave no enol test with ferric chloride solution. Zeisel determinations showed the presence of 21.2% ethoxyl; theory requires 20.6% for one ethoxy group.

Attempts were made to distil the reddish oil obtained by concentration of the mother liquor, but even *in high vacuum*, deep polymerization occurred, and only a few drops of highly colored and high boiling oil were obtained.

3-Ethoxy-5-phenyl-2,4-pentadienoic Acid.—The procedure of Jones, O'Sullivan and Whiting[7] was modified as follows. Five grams of 4-ethoxy-6-phenyl-5,6-dihydro-2-pyrone was dissolved in 250 ml. of methanol. To this was added, with stirring, a solution of 5 g. of potassium hydroxide in 250 ml. of water. After standing at room temperature overnight the mixture was filtered, and water was added to the filtrate until the volume was doubled. The filtrate was chilled by the addition of 200 g. of cracked ice, and the *p*H was adjusted to approximately 1 by the dropwise addition of cold 10% hydrochloric acid to the rapidly stirred mixture. The pale-yellow solid that precipitated was collected on the filter and dried by suction. The yield of crude product was 4 g., or 80%. It had m. p. 151–153° (dec.), and after one recrystallization from absolute methanol it was obtained in the form of small elongated colorless prisms with m. p. 153–154° (dec.).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.58; H, 6.46. Found: C, 71.54; H, 6.36. Neutral equivalent determinations gave 215.5 and 217.1; calculated for the monobasic acid, 218.1. Zeisel determinations showed 20.9% ethoxyl; theory requires 20.6% for one ethoxy group.

The compound decomposed carbonate solution, and gave a negative enol test with ferric chloride solution.

5-Phenyl-3-keto-4-pentenoic Acid.—Many comparative experiments were tried before this compound was obtained pure and in quantity. It was early found that grinding 3-ethoxy-5-phenyl-2,4-pentadienoic acid with concentrated hydriodic acid in a mortar produced a mixture, from which benzalacetone and unchanged dienoic acid were obtained, together with small quantities of a highly enolic acid of m. p. 106–108° (dec.). For the preparation of the substance in quantity, the following procedure was most successful. For *four* minutes dry hydrogen chloride was passed, in the form of a fine stream from a capillary, into a solution of 300 mg. of the ethoxy-dienoic acid in 40 ml. of diethyl ether which had been saturated previously with water. During the addition of the hydrogen chloride the solution became slightly opalescent due to the separation of droplets of hydrochloric acid. The mixture was stoppered and kept at room temperature for about 9 hours. Evaporation in a vacuum desiccator under aspirator pressure left a sticky residue that possessed the typical odor of benzalacetone. The residue was washed onto a Büchner funnel with petroleum ether, and dried by suction. The crude solid weighed 140 mg. (54.5% yield), and had m. p. 105–106° (dec.). With ferric chloride solution a brilliant purple coloration developed immediately. The tan-colored product was recrystallized from a mixture of petroleum ether and ether, and was obtained as tiny gleaming flakes possessing a pale yellow color, m.p. 108–109° (dec. with the odor of benzalacetone). The acid was unstable, and after keeping for a few weeks had decomposed to benzalacetone.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.49; H, 5.30. Found: C, 69.42; H, 5.32.

Reduction of 3-Ethoxy-5-phenyl-2,4-pentadienoic Acid.—Great difficulty was experienced in reducing this compound due to its tendency to overreduce and to give by-products that appeared to arise from hydrogenolysis. The best procedure consisted in using a relatively inactive catalyst and treating the acid in the form of its salt, but even under these conditions, large amounts of by-products formed. Three grams of the dienoic acid was dissolved in 30 ml. of water containing 2.5 g. of potassium carbonate, and the solution, to which was added 200 mg. of 5% palladium black on barium sulfate, was shaken with hydrogen at 46 p.s.i. The reduction was slow; after 10 hours approximately 75% of the theoretical amount of hydrogen had been absorbed. At this time more catalyst (200 mg.) was added. After a further 3 hours, an addition of 200 mg. of catalyst was necessary, and after 5 hours this addition was repeated. The mixture was shaken overnight, resulting in approximately 20% excess hydrogen absorption.

After removal of the catalyst, the basic solution was extracted with ether, which removed about 1 g. of pleasant smelling oil.[32] The chilled aqueous solution was acidified with 10% hydrochloric acid, which caused some precipitation. The gummy solid was collected on the Büchner, washed with cold petroleum ether and dissolved in ether. The ether solution was washed with water, dried and

(27) Blaise and Maire, *Ann. chim. phys.*, [8] **15**, 567 (1908).

(28) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551–552**, 80 (1942).

(29) Wohl and Jaschinowski, *Ber.*, **54B**, 476 (1921).

(30) Steude, *Ann.*, **261**, 30 (1891); Lespieau, *Bull. soc. chim.*, [3] **33**, 464 (1905).

(31) Shriner, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 16.

(32) This ethereal oil was obtained from reductions performed in either absolute ethanol or in glacial acetic acid. The odor was reminiscent of di-*n*-butyl ether. It is possible that it is 2-ethoxy-4-phenylbutane resulting from hydrogenolysis of the dienoic acid. Compare Sprague and Adkins, THIS JOURNAL, **56**, 2069 (1943).

evaporated. The residual oil solidified to colorless grain-like crystals, m. p. 109–112°; weight 195 mg.[33]

The acidic filtrate (above) was extracted with ether. After drying over sodium sulfate, the ether was evaporated leaving a yellowish oil. The oil was taken up in 10% potassium hydroxide solution and boiled with a mixture of "Super-Cel" and decolorizing charcoal. This did not remove the yellow color. Extraction of the basic filtrate with ether removed a trace of the odoriferous ethereal oil referred to above.[32] The residual basic solution was heated to drive off the last traces of ether, and acidified to *p*H 4. This caused precipitation of 120 mg. of the acid, m. p. 109–112°.[33] The filtrate was then acidified to *p*H 1 and exhaustively extracted with ether. The extracts were dried and evaporated, leaving 1.3 g. of an acidic oil possessing a disagreeable odor. This oil could not be induced to crystallize; it was therefore distilled *in vacuo*, under nitrogen. Two fractions were obtained, (1) b. p. 139–141° at 0.09 mm. (200 mg.); (2) b. p. 142° at 0.09 mm. (980 mg.), $n^{25}D$ 1.5029. This material analyzed for 3-ethoxy-5-phenylvaleric acid.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.19; H, 8.12.

For the final reduction, 270 mg. of 3-ethoxy-5-phenylvaleric acid was heated with 2 ml. of 57% hydriodic acid in a sealed tube at 200–210° (bath temperature) for 9 hours. The reaction mixture was dark red in color. It was washed out of the tube with benzene, ether added and the red iodine color discharged with sodium sulfite solution. Evaporation of the dried solution left an oil that was completely soluble in dilute potassium hydroxide. The basic solution was extracted with ether (which left no residue on evaporation), acidified to *p*H 1 and again extracted with ether. The extracts were washed with water, dried over sodium sulfate and evaporated. The residual oil was diluted with petroleum ether and cooled by the addition of small pieces of Dry Ice. White crystals formed and a sticky mass settled out. The crystals were collected and weighed 101 mg., m. p. 47–52°. The sticky residue was again dissolved and cooled, furnishing 30 mg., m. p. 42–50°. The fractions were combined and recrystallized from petroleum ether. Large prisms formed, m. p. 57–58°, either alone or admixed with authentic δ-phenylvaleric acid.[34] The amide, prepared from our product had m. p. 102–104°, that prepared from authentic δ-phenylvaleric acid had m. p. 104.5–105.5°, and the mixed m. p. was 104–105°. The literature[35] gives 104–105° for the m. p. of the amide of δ-phenylvaleric acid.

Acid Hydrolysis of 4-Ethoxy-6-phenyl-5,6-dihydro-2-pyrone.—The pyrone (4 g.) was refluxed for one-half hour in 40 ml. of a solution prepared by adding enough sulfuric acid to 22 ml. of water and 18 ml. of 95% ethanol to make the solution approximately 3% with respect to acid. After cooling, the reaction mixture was neutralized by the addition of powdered potassium carbonate and extracted with ether. The extracts were dried and evaporated, leaving a light yellow oil with a characteristic odor. It solidified on standing; yield 2.2 g. or 82%, m. p. 34–38°. After purification through the sodium bisulfite addition compound and recrystallization from petroleum ether, the m. p. was 41–42°; the reported m. p. for benzalacetone[36] is 42°. With hydroxylamine reagent it formed the oxime, m. p. 114.5–115.5°; the reported m. p.[37] of benzalacetone oxime is 116°. The semicarbazone was prepared and had m. p. 186–187°; the literature[38] gives 186° for the m. p. of the semicarbazone.

4-Hydroxy-6-phenyl-5,6-dihydro-2-pyrone (α-Form).—The following procedure was devised as the result of many comparative studies. To 15 g. (0.0687 mole) of the 4-ethoxypyrone, was added 30 ml. of hydriodic acid (sp. gr. 1.5). The mixture was rapidly stirred and *gently* warmed on the steam-bath until a clear solution resulted. This required from 1 to 2 minutes. The solution was allowed to cool, with stirring, until precipitation began, at which point it was added slowly to a rapidly stirred mixture of 300 ml. of ice and water. If the addition was not made slowly, a gum formed which was difficult to work up; normally the product separated as small granular particles. After complete addition, stirring was maintained for about 30 seconds. The product was collected by rapid suction filtration, quickly stirred to a paste with 100 ml. of iced water and again filtered. It was washed on the Büchner with 15 ml. of methanol which had been made very cold by the dissolution of Dry Ice, and then with 15 ml. of ether, similarly cooled. After air-drying, the product was white to cream in color, and had m. p. 141–143° (dec.). The yields varied from 65–75% (8.2–10 g.). The ferric chloride enol test was strong, but not as intense as with ethyl acetoacetate.

For analysis a sample was recrystallized from absolute methanol. Small shiny pale-yellow grains were obtained, m. p. 140–142° (dec.). A specimen, on drying in a Fischer pistol, *in vacuo*, at 78° for three hours, showed a lowering of m. p. to 134–136.5° (dec.). The analysis was therefore made on material dried at room temperature, *in high vacuum* for 6 hours.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.51; H, 5.46. Neutral equivalent determinations gave 186.4 and 194.5. The theoretical value for the pyrone (as enol) is 190.

Thermal Decomposition of 4-Hydroxy-6-phenyl-5,6-dihydro-2-pyrone.—Thirty-mg. samples of α- and β-forms of the pyrone were each heated to 160–170° for 30 minutes to effect complete decarboxylation. The residual brown oils were treated with 2,4-dinitrophenylhydrazine reagent. Small orange-red needles formed which after recrystallizations from ethanol–ethyl acetate gave no depression in mixed m. p. determinations with authentic benzalacetone-2,4-dinitrophenylhydrazone (221–222°).

Alkylation Studies on 4-Hydroxy-6-phenyl-5,6-dihydro-2-pyrone (α-Form).—I. One gram (0.00526 mole) of the pyrone was shaken mechanically for 7 hours (in a brown bottle) with a mixture of 2.05 g. (0.0132 mole) of ethyl iodide, 1.5 g. (0.00647 mole) of U.S.P. silver oxide and 5 ml. of absolute ethanol. The solid was separated by filtration and 10 ml. of hot ethanol was used to complete the transfer of products and to wash the silver oxide and halide on the filter. The careful addition of 40 ml. of ice-cold water to the stirred filtrate caused the separation of minute white needles. The product was occasionally contaminated with yellow material, but this was removed by washing the crystals with 5 ml. of ether, previously made very cold by the dissolution of Dry Ice. The fluffy product had m. p. 92–93°, raised to 93–94° by one recrystallization from aqueous ethanol. The yield of crude ether-washed material was 62.5%; that of recrystallized product, 52.4%. The mixed m. p. with the Reformatsky product (93–94°) was 93–94°.

II. One hundred and thirty milligrams of the hydroxypyrone, m. p. 139–140° (dec.), was dissolved in 8 ml. of absolute ethanol, and dry hydrogen chloride was passed into the solution at room temperature for 5 minutes. After standing for 2 hours the solution was evaporated under reduced pressure. The slightly yellow residue was taken up in 4 ml. of hot ethanol, boiled with a mixture of decolorizing charcoal and "Super-Cel" and filtered. Careful dilution of the filtrate with ice-cold water furnished a mass of small white needles. These were washed on the Büchner with a little ether which had previously been made very cold with Dry Ice. The m. p. of the material was 93–94°, either alone or admixed with the Reformatsky product; yield 67.1%.

III. Three hundred milligrams (0.00158 mole) was treated with ethereal diazomethane exactly as is described for the lower-melting isomer (*vide infra*). The reaction was very slow, presumably due to the insolubility of the pyrone in ether. At the end of two days the reaction mixture was worked up. The product was a light yellow crystalline solid, m. p. 139–141°, with some decomposition; yield 235 mg., or 73%. After recrystallization from methanol, the compound had m. p. 143–144° with no decomposition up to 160°. This material showed no depression of m. p. on admixture with 4-methoxy-6-phenyl-5,6-dihydro-2-pyrone.

(33) This solid acid was also obtained in reductions carried out in ethanol or in acetic acid. It was difficult to obtain pure, and gave erratic analysis, but the figures obtained approximated to those calculated for 3-hydroxy-5-phenylvaleric acid. The latter is one of the products to be expected from hydrogenolysis of the ethoxy-dienoic acid; compare Sprague and Adkins, *loc. cit.*

(34) Cinnamalmalonic acid was prepared by the method of Liebermann, *Ber.*, **28**, 1438 (1895), and reduced to the saturated acid in acetic acid using Adams catalyst (compare Borsche, *Ber.*, **45**, 622 (1912); Paal, *ibid.*, **45**, 2223 (1912)). Decarboxylation furnished the required acid.

(35) Eijkman, *Chem. Weekblad.*, **5**, 655 (1908).

(36) Kohler, *Am. Chem. J.*, **35**, 403 (1906).

(37) Harries and de Osa, *Ber.*, **36**, 2998 (1903).

(38) Borsche and Merkwitz, *ibid.*, **37**, 3183 (1901).

Interconversion of the α- and β-Forms of 4-Hydroxy-6-phenyl-5,6-dihydro-2-pyrone.—It was early noticed that successive recrystallizations of the hydroxypyrone from hydroxylic solvents progressively lowered the m. p. of the compound. Thus, material that had m. p. 140–142° (dec.) when crude, when recrystallized from aqueous ethanol four times gave material with m. p. 120–123.5° (dec.). The mixed m. p. of this compound with the high melting form was 120–127° (dec.).

The same transformation was more conveniently accomplished as follows. One and one-half grams of the high-melting pyrone was carefully dissolved in a solution of 20 ml. of water and 15 ml. of methanol containing 0.5 g. of potassium hydroxide. After standing at room temperature for 30 hours, water was added until the volume of the solution was doubled. The solution was allowed to stand a further 20 hours. Some decolorizing charcoal and "Super-Cel" were then added, and the mixture was stirred occasionally during an hour. This treatment effectively removed traces of yellowish material (odor of benzalacetone). Cracked ice was added to the filtrate and the mixture was carefully acidified with very cold 10% hydrochloric acid. A white powder precipitated, m. p. 119–120° (dec.). A mixed m. p. with material obtained from successive recrystallizations of the high-melting form showed no depression. The low-melting β-form, obtained from treatment with base, was recrystallized from methanol and analyzed.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.43; H, 5.40.

The substance gave a strong enol test with ferric chloride solution. The solubility of this material was different from that of the higher-melting form, being *more* soluble in hydroxylic solvents and *more* soluble in diethyl ether.

The reverse transformation was accomplished by several methods: (1) successive recrystallizations of the lower-melting form from benzene; (2) allowing the β-form to stand for about 30 minutes in dry dioxane containing hydrogen chloride; (3) refluxing a solution of the lower isomer in acetyl chloride for 4 minutes.

Alkylation Studies on 4-Hydroxy-6-phenyl-5,6-dihydro-2-pyrone (β-Form).—I. Seventy-five milligrams of the pyrone was treated with ethyl iodide and silver oxide in ethanol according to the previously described procedure. This yielded 28 mg. (35% yield) of the 4-ethoxy-derivative; m. p. and mixed m. p. 91–92°.

II. One hundred and seventy-five milligrams was treated with dry hydrogen chloride in absolute ethanol, as earlier described. The product was the ethoxypyrone; yield 68 mg. (33.8%), m. p. and mixed m. p. 91–92.5°.

III. One hundred and seventy-five milligrams were treated with hydrogen chloride in absolute methanol, and worked up by the usual procedure. The 4-methoxy-derivative formed; yield 125 mg. of small colorless prisms (66.5%), m. p. 140–142°. After recrystallization from methanol, the m. p. was 143–144°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93. Found: C, 70.46; H, 6.01.

IV. To 300 mg. of the hydroxypyrone was added excess ethereal diazomethane.[39] Gas was rapidly evolved for a few minutes, and then the reaction subsided. After two days the solvent was removed *in vacuo*. The white crystalline product was washed with very cold ether; yield 220 mg. (68.4%), m. p. 138–140° with some decomposition. After recrystallization from methanol, the m. p. was 143–144.5° with no decomposition as high as 160°. The mixed m. p. with the 4-methoxypyrone was not depressed.

Action of Strong Base on 4-Hydroxy-6-phenyl-5,6-dihydro-2-pyrone.—I. A sample was refluxed for an hour in ethanol–water solution containing 5% potassium hydroxide. This resulted in the formation of a neutral, red, insoluble amorphous powder, which was not further studied.

II. A sample was refluxed for one-half hour in ethanol-water solution containing 2% potassium hydroxide. The mixture was filtered and the filtrate was cooled and carefully acidified. The precipitate had m. p. 111–114° (dec.). It appeared to consist of a mixture of benzalacetone and the β-form of the hydroxypyrone.

III. A sample of the higher-melting α-form (2.5 g.) was allowed to stand for 4 days in 10% potassium hydroxide solution (methanol–water). A small amount of red amorphous precipitate was removed by filtration, and the cooled filtrate was acidified. A light yellow powder (2.01 g.) was obtained, m. p. 106–109° (dec.). The solid was washed with very cold ether and dried. The m. p. was then 104.5–105° (dec.). This material appeared to consist of a mixture of benzalacetone (odor) and the β-form of the hydroxypyrone. Three hundred milligrams of the product were treated with an ethereal solution of diazomethane. As soon as the vigorous effervescence ceased, the solvent was removed. The crystalline residue was washed with very cold ether and dried. The yield was 200 mg. (62%) of yellow crystals, m. p. 135–138°, with some decomposition. After recrystallization from methanol, the pale yellow prisms had m. p. 143–144°, with no decomposition as high as 160°.

Kurt Meyer Titrations.—These determinations were very unsatisfactory when applied to either isomer. Values obtained were in excess of 100%. When checked against ethyl acetoacetate, our determination gave 7.67% enol. The literature[13] gives 7.71%.

Semicarbazide Reagent on the α- and β-Isomers.—One hundred-mg. samples of each compound were treated with semicarbazide hydrochloride and sodium acetate in *aqueous ethanol* in the usual manner. The solid products were dissolved in a boiling mixture of 7 ml. of absolute methanol and 4.5 ml. of glycerol, filtered and crystallized from the filtrate after dilution with water to twice the volume. The white flaky crystals were washed several times with cold methanol and dried. The m. p. of each product was 247–248° (dec.), not depressed on admixture.

Anal.[40] Calcd. for the semicarbazone of ethyl 3-keto-5-phenyl-4-pentenoate, $C_{14}H_{17}O_3N_3$: N, 15.27. Found for α-product: N, 15.53. Found for β-product: N, 15.43.

The mother liquors from the above preparation were diluted with water and chilled. Small amounts of crystalline material were obtained, which, after recrystallization from methanol–water had m. p. 188–190°, not depressed on admixture of authentic benzalacetone semicarbazone.

A second preparation of the semicarbazone, wherein *methanol* was used as solvent, and in which the reactants were warmed merely to the point of solution, formed identical derivatives. Each product, on recrystallization from water, gave gleaming white crystals, m. p. 234.5–236° (dec.).

Anal.[40] Calcd. for the semicarbazone of methyl 3-keto-5-phenyl-4-pentenoate, $C_{13}H_{15}O_3N_3$: N, 16.09. Found for α-product: N, 15.92. Found for β-product: N, 16.34.

5-Benzyltetronic Acid.—The acid chloride of hydrocinnamic acid was carefully brominated,[41] and the bromo-acid bromide (b. p. 136° at 9.0 mm.), was added dropwise to a stirred suspension of ethyl sodiomalonate (2 moles) in ether.[15] The oily reaction product was stirred with aqueous cupric acetate and the copper salt of 5-benzyl-3-carbethoxytetronic acid was collected by filtration. The free ester, obtained by saturating a suspension of the copper salt in water with hydrogen sulfide followed by ether extractions, was recrystallized from absolute ethanol as small colorless prisms, m. p. 126.5–128°. It gave a red color with ferric chloride solution.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.13; H, 5.38. Found: C, 63.73; H, 5.47. Zeisel determination.[42] Calcd: 17.18. Found: 16.97.

For the preparation of 5-benzyltetronic acid, the above carbethoxy derivative (1 mole) was dissolved in an aqueous solution of barium hydroxide (1 mole). After keeping for 5 days, a copious white precipitate had formed. This was suspended in water and strongly acidified with 1:1 hydrochloric acid. Upon warming the reaction mixture to 50°, vigorous evolution of carbon dioxide occurred, with the deposition of the free tetronic acid. After recrystallization from benzene the white fluffy crystals had m. p. 130.5–132°, with no decomposition as high as 165°. The enol test was strong.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.77; H, 5.29.

For comparison, the sodium nitrite test[43] was applied to several tetronic acids, and to the pyrones described in this paper.

(39) Arndt, "Organic Syntheses," Vol. 15, John Wiley and Sons, Inc., New York, N. Y., 1935, p. 4.

(40) We are indebted to Mrs. Joan E. Buck for these microanalyses.

(41) Shriner and Damschroder, THIS JOURNAL, **60**, 895 (1938); Fourneau and Nicolitch, *Bull. soc. chim.*, **43**, 1232 (1928).

(42) We wish to thank Mr. B. E. Harrell, Jr., for this determination.

(43) Wolff, *Ann.*, **291**, 244 (1896).

Compound	Color
5-Methyltetronic acid[15]	Deep purple
5,5-Dimethyltetronic acid[44]	Deep purple
5-Benzyltetronic acid	Deep purple
6-Phenyl-4-hydroxy-5,6-dihydro-2-pyrone (α- and β-forms)	Pale pink on standing

(44) Reid, Fortenbaugh and Patterson, *J. Org. Chem.*, **15**, 572 (1950).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

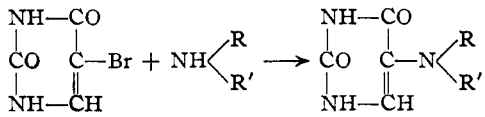
Some 5-Substituted Aminouracils

BY ARTHUR P. PHILLIPS

Investigation of the reaction of 5-bromouracil with a variety of amines showed that short refluxing in two or more molecular proportions of primary and some secondary amines rapidly gave excellent yields of 5-substituted aminouracils.

In connection with attempts to discover new chemotherapeutic agents among possible antimetabolites of nucleic acid derivatives[1,2] it became desirable to obtain a variety of 5-substituted aminouracils.

The route explored was the reaction of 5-bromouracil with the appropriate amines

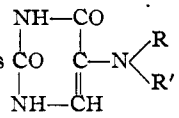


Although the high reactivity for replacement reactions of pyrimidines bearing a 2,4- or 6-chloro group is well known, little has been done with halogen in the 5-position. Previously 5-bromouracil has been treated only with ammonia[3] and dimethylamine,[4a,4b] both reactions having been carried out in a sealed tube at 150–180°. Moreover, Lythgoe[5] and Johnson[6] both state that replacing chlorine or bromine in the 5-position by ammonia is a difficult or impractical procedure.

In the present work it has been found that 5-bromouracil reacts rapidly to give excellent yields of the substituted aminouracils when refluxed for brief intervals with two to five molecular proportions of the amines. The amines used included a variety of aliphatic primary and secondary types, cyclohexylamine, piperidine and morpholine. Yields in general ranged between 70 and 100%. So far numerous attempts to obtain 5-anilinouracils by this method have failed. This apparent failure of aniline to react may possibly be related to its lesser basicity and other ways of overcoming this lack are being considered.

As an alternative route in the preparation of 5-methylamino- or ethylaminouracils, to avoid the necessity of long reaction times at elevated temperatures and in closed systems required for the volatile reactants involved, benzylmethyl- and benzylethyl-amines have been employed. When 5-bromouracil is boiled for about 5 minutes with two equivalents of benzylmethylamine at least 80% of 5-benzylmethylaminouracil (VII) is obtained. The hydrochloride of VII when submitted to catalytic hydrogenation over palladized charcoal according to the

TABLE I

5-SUBSTITUTED AMINOURACILS 

Cmpd. no.	R	R′	Yield, %	M.p., °C.	Crystn.[a] solvent	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I[b]	CH_3	H	100	243–244[c] foams chars >280	M,E	33.8	33.7	4.6	4.4
II	C_2H_5	H	72	243–245[c]	M	37.6	37.5	5.3	5.4
III	n-C_3H_7	H	90	264–265[c] sinters	A	40.9	41.3	5.9	5.6
IV	n-C_4H_9	H	100	250–253[c] sinters	A	43.7	44.0	6.4	6.3
V	Cyclohexyl	H	100	>305	Neutr.	57.4	57.1	7.2	7.4
VI	$HOCH_2CH_2$	H	85	267–268	M	42.1	42.2	5.3	5.3
VII	CH_3	$C_6H_5CH_2$	90	267–269	Aq. HOAc	62.3	62.3	5.7	6.0
				242–243[c]	M	53.8	53.6	5.3	5.3
VIII	C_2H_5	$C_6H_5CH_2$	50	201–202[c]	A.E	Cl, 12.6	12.5		
IX	Piperidino		78	285–290[c]	M.E	46.6	46.7	6.1	6.0
X	Morpholino		75	>310	Aq.	48.7	49.0	5.6	5.6
XI[d]	C_6H_5NH	H	40	250–255	HOAc				

[a] A, ethanol; Aq., water; E, ether; HOAc, acetic acid; M, methanol; Neutr., dissolved in aqueous alkali, then reprecipitated with dilute acid. [b] Compound I was prepared by catalytic debenzylation of compound VII. [c] Melting point and analysis are of the hydrochloride. [d] Known compound; P. A. Levene, *J. Biol. Chem.*, **63**, 653 (1925).

(1) G. H. Hitchings, *et al.*, *J. Biol. Chem.*, **183**, 1 (1950).
(2) G. H. Hitchings, *et al.*, *Ann. N. Y. Acad. Sci.*, **52**, 1318 (1950).
(3) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **31**, 603 (1904).
(4) (a) H. L. Wheeler and H. F. Merriam, *ibid.*, **32**, 355 (1904); (b) T. B. Johnson and I. Matsuo, THIS JOURNAL, **41**, 788 (1919).
(5) B. Lythgoe, *Quart. Reviews*, **3**, 181 (1949).
(6) T. B. Johnson in Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, 1st edition, Vol. II, p. 965.