[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES, UNIVERSITY OF LOUISVILLE]

2-Pyrones. X.[1] The Chemistry of Isodehydroacetic Acid Derivatives. A Hydrazine Degradation, Di- and Dialkylaminoethyl Esters and Anilides

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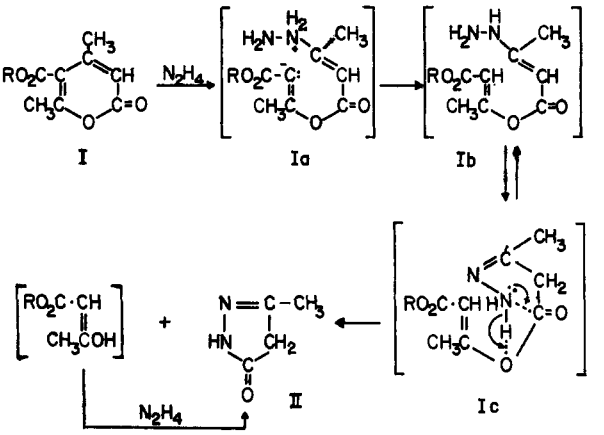
Ethyl isodehydroacetate has been observed to react spontaneously and exothermally with hydrazine to give 3-methyl-5-pyrazolone in a previously unrealized reversal of the aldol-type condensation by which two molecules of ethyl acetoacetate condense to form the isodehydroacetate. Ammonia and primary amines, which react with ethyl isodehydroacetate only at elevated temperatures, react readily with isodehydroacetyl chloride to give amides of a type hitherto unavailable. Several new isodehydroacetates of dialkylaminoethanols and of polyfunctional hydroxy compounds are described. The unusual stability of the isodehydroacetate molecule to pyridone formation is related to hyperconjugation possibilities (IIIb–c).

In continuing our studies of 2-pyrones, which as unsaturated lactones are of considerable interest in biological evaluations, we have prepared and characterized several new types of isodehydroacetic acid derivatives and have encountered a reaction between ethyl isodehydroacetate and hydrazine which has been shown to give degradation products by a previously unencountered reversal of the aldol-type condensation in which the ester is formed.

In an attempt to prepare hydrazides of isodehydroacetic acid, we have observed that hydrazine hydrate, in marked contrast to ammonia or amines toward which the ester is relatively inert,[2] reacts exothermally with ethyl isodehydroacetate (I) to give an 18% yield of 3-methyl-5-pyrazolone (II), the same pyrazolone that is formed from acetoacetic ester and hydrazine. In order for this product to be formed from ethyl isodehydroacetate, it is necessary that the aldol-type condensation by which two molecules of ethyl acetoacetate were combined to give ethyl isodehydroacetate be reversed with rupture at the C–C linkage formed by reaction of the active methylene group of one acetoacetic ester molecule with the keto group of another. This is apparently the first time that reversal of this particular aldol-type condensation has been demonstrated, although the reversibility of aldol condensations has been observed with a variety of reaction types[3] including Knoevenagel reactions involving carbonyl active methylene systems.[4] Because ethyl isodehydroacetate is unreactive at the lactone carbonyl carbon, it appears necessary to postulate attack by hydrazine at the number 4 carbon atom followed by elimination of the carbanion (formula Ia) as the initial step in this degradation. Subsequent tautomerism (Ib, Ic) and a second displacement (Ic) results in formation of the pyrazolone (II). Presumably, resonance stabilization of the enol form of the pyrazolone is an important factor in providing the necessary driving force for this reaction. The postulated changes are shown in the formulas.



Isodehydroacetamide, and the anilides, reported herein are the first such compounds to be described. They were prepared readily in 25–69% yields from the acid chloride and ammonia or the amine. These compounds cannot be the isomeric pyridonecarboxylic acids because they are insoluble in base. They have shown no tendency to isomerize to the pyridones. The only previously known isodehydroacetamides were prepared from secondary amines[5] apparently in the belief that ammonia and primary amines would give pyridones readily from the 2-pyrone. We have shown previously[2] that the 2-pyrone ring in ethyl isodehydroacetate is remarkably resistant toward amines. In fact, only at elevated temperatures does any reaction take place and the reaction at these high temperatures is not pyridone formation but a profound decomposition, in which 1,3-bis-ureas are obtained. This situation is quite different from that with methyl coumalate which is readily converted to pyridones at room temperature by amines. Conversion of ethyl isodehydroacetate to an amide is undoubtedly difficult because of the steric effect of the two methyl groups in the *ortho* positions but it is not obvious why it should be so remarkably resistant toward pyridone formation. Pyridone formation, which requires an electron deficient carbon at the ring carbonyl for attack by the amine, is probably difficult in the isodehydroacetates, as compared to the coumalates, because the necessary electron deficiency is distributed over the molecule through hyperconjugation in which six no-bond resonance structures such as IIIb–c contribute significantly. Such hyperconjugation possibilities are not present in the coumalates.

The new esters described in this report were prepared from the isodehydroacetyl chloride and the alcohol or glycol. The diethylamino-, dibutylamino- and dimethylaminoethyl esters were obtained

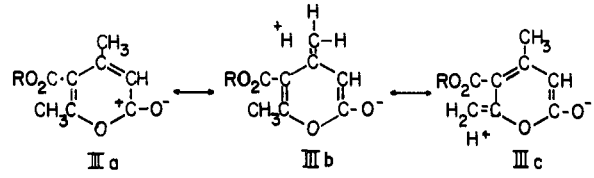
(1) Previous paper in this series, R. H. Wiley and A. J. Hart, THIS JOURNAL, **76**, 1942 (1954).

(2) R. H. Wiley, Patricia Beasley and L. H. Knabeschuh, *ibid.*, **76**, 311 (1954).

(3) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 439, 465.

(4) A. C. Cope, THIS JOURNAL, **59**, 2327 (1937).

(5) H. Martin, W. Baumann, H. Zaeslin and H. Gysin, U. S. Patent 2,364,304 (1944).



IIIa IIIb IIIc

in 55–61% yields and were readily converted to their methiodides. In isolation of the esters, the by-product hydrogen chloride was separated from the ester product by precipitation of the amino alcohol hydrochloride. A large excess of amino alcohol was used to avoid coprecipitation of the ester hydrochloride. The dimethylaminoethyl ester decomposes on heating and attempts to obtain analytically pure samples by fractionation were unsuccessful. The glycol and pentaerythritol esters were obtained in 60–91% yield. These reactions were run at elevated temperatures to obtain solutions of the relatively insoluble glycols in the acyl chloride.

The tumor damaging properties of several of the 2-pyrones reported in this and previous papers in this series are being investigated by several laboratories and will be reported in detail elsewhere. Of eleven compounds evaluated in a multiple injection screening test using S-180 tumor transplants in mice,[6] under the direction of Dr. Louis H. Goodson of the Midwest Research Institute, six have been rated as having questionable activity showing a slight inhibition of tumor growth and are being studied further. At daily dose levels of 400–500 mg. per kg. the tumor weight treated/tumor weight control ratios were: for pentaerythritol tetraisodehydroacetate, 0.70; for thiodiethylene glycol diisodehydroacetate, 0.86; for triethyleneglycol diisodehydroacetate, 0.77; and for diethyleneglycol diisodehydroacetate (at 300 mg./kg.), 0.96. On this scale a compound which shows a ratio of 0.50–0.79 is rated as a mild, doubtful or questionable inhibitor and rescreened. No toxic reactions were observed during these tests except with the diethylene glycol ester which caused the death of one out of ten test animals. The slight inhibition noted with these compounds may be due to biological variation or systemic toxicity rather than a specific action on the tumor.

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Experimental[7]

The isodehydroacetyl chloride used in the following experiments was prepared as previously described.[8] The authors wish to thank the Carbide and Carbon Chemical Corporation for generously providing samples of dimethyl-, diethyl- and dibutylaminoethanol, diethylene glycol, thiodiethylene glycol and triethylene glycol.

Isodehydroacetamide.—A solution of 5.0 g. (0.027 mole) of isodehydroacetyl chloride in 150 ml. of dry ether was cooled and saturated with dry ammonia. The precipitate was collected, washed with 10 ml. of water, and recrystallized from hot water to give 1.1 g. (25%) of isodehydroacetamide, m.p. 220°.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.59; H, 5.40; N, 8.63.

Isodehydroacetanilide.—A solution of 5.0 g. (0.054 mole) of aniline in 50 ml. of dry ether was added to a solution of 5.0 g. (0.027 mole) of isodehydroacetyl chloride in 100 ml. of dry ether. After standing one hour, the precipitated solids were collected, washed with ether, and taken up in 100 ml. of hot ethanol leaving an insoluble residue. Addition of water to the ethanol solution precipitated 3.5 g. (54%) of isodehydroacetanilide, m.p. 204–205°.

Anal. Calcd. for $C_{14}H_{13}O_3N$: N, 5.76. Found: N, 5.66.

Recrystallization of the ethanol-insoluble residue from methyl cellosolve gave an unidentified compound, $C_{15}H_{13}NO_2$, m.p. 179–180°.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.18; H, 5.46; N, 5.90.

4'-Dimethylaminoisodehydroacetanilide.—This compound was prepared from 5.0 g. (0.027 mole) of the chloride and 7.3 g. (0.054 mole) of *p*-dimethylaminoaniline by the above process. There was obtained 5.3 g. (69%) of white crystals, m.p. 255–256°.

Anal. Calcd. for $C_{16}H_{18}O_3N_2$: N, 9.79. Found: N, 9.70.

4'-Diethylaminoisodehydroacetanilide.—This compound was prepared from 5.0 g. (0.027 mole) of the chloride and 8.9 g. (0.054 mole) of *p*-diethylaminoaniline by the process described for the anilide. There was obtained 5.7 g. (68%) of yellow crystals which soften and turn colorless at 148° and melt at 191°.

Anal. Calcd. for $C_{18}H_{22}O_3N_2$: C, 68.79; H, 7.06; N, 8.92. Found: C, 68.56; H, 6.90; N, 9.04.

β-Diethylaminoethyl Isodehydroacetate.—A solution of 22.4 g. (0.192 mole) of β-diethylaminoethanol was added to a cooled solution of 6.0 g. (0.032 mole) of isodehydroacetyl chloride in 70 ml. of anhydrous ether. After stirring for one hour and standing ten hours, the precipitated hydrochloride was separated by filtration and the ethereal filtrate washed with water, dried, and fractionated to give 5.22 g. (61%) of a liquid, b.p. 178.5–180° (2 mm.), $n^{27.7}D$ 1.5061.

Anal. Calcd. for $C_{14}H_{21}O_4N$: C, 62.88; H, 7.86. Found: C, 62.85; H, 7.70.

β-Diethylaminoethyl Isodehydroacetate Methiodide.—Methyl iodide (1.5 g., 0.0024 mole) was added to 0.50 g. (0.0018 mole) of the β-diethylaminoethyl ester in 5 ml. of anhydrous ether. The white solid which had formed after ten hours was collected, washed with ether, and dried to give 0.40 g. (55%) of the methiodide, m.p. 148–150°.

Anal. Calcd. for $C_{15}H_{24}O_4NI$: I, 31.03. Found: I, 31.04.

β-Dibutylaminoethyl Isodehydroacetate.—This compound was prepared from 6.15 g. (0.033 mole) of isodehydroacetyl chloride and 38.2 g. (0.221 mole) of β-dibutylaminoethanol by the above procedure to give 6.81 g. (68%) of a liquid, b.p. 188–191° (1 mm.), $n^{28}D$ 1.4953.

Anal. Calcd. for $C_{18}H_{29}O_4N$: C, 66.87; H, 8.97. Found: C, 66.96; H, 9.18.

β-Dibutylaminoethyl Isodehydroacetate Methiodide.—This compound was prepared from 0.5 g. (0.0015 mole) of the ester and 1.5 ml. (0.0024 mole) of methyl iodide by the procedure described above to give 0.26 g. (42%) of the methiodide, m.p. 155–156°.

Anal. Calcd. for $C_{19}H_{32}O_4NI$: I, 25.14. Found: I, 25.05.

β-Dimethylaminoethyl Isodehydroacetate Methiodide.—Fifteen ml. of β-dimethylaminoethanol was added to 4.5 g. (0.024 mole) of isodehydroacetyl chloride. The residue was triturated with absolute ether and filtered to separate the hydrochloride. The ether was removed from the ether layer and the residue fractionated to give 1.6 g. (24%) of the ester, b.p. 161–8° (8 mm.), $n^{25}D$ 1.5128. Two ml. of methyl iodide was added to 0.5 g. of this product in 5 ml. of ether to precipitate 0.6 g. (75%) of the methiodide, m.p. 207°.

Anal. Calcd. for $C_{13}H_{20}O_4NI$: C, 40.95; H, 5.29; I, 33.28. Found: C, 41.15; H, 5.43; I, 33.55.

Diethylene Glycol Diisodehydroacetate.—A mixture of 3.9 g. (0.021 mole) of isodehydroacetyl chloride and 1.0 g. (0.0094 mole) of diethylene glycol was heated in an oil-bath at 160° for six hours. The solid product was recrystallized

(6) This information is being given here with the permission and approval of Dr. L. H. Goodson to whom the authors wish to acknowledge their appreciation. A detailed description of the test procedure is given in L. H. Goodson, *et al.*, *Cancer Research*, Supplement No. 1, 45 (1953).

(7) Carbon, hydrogen and nitrogen analyses by Micro-Tech Laboratories, Skokie, Illinois. All melting points are corrected.

(8) R. H. Wiley, N. R. Smith and J. A. Bauer, THIS JOURNAL, **75**, 244 (1953).

from methanol to give 3.5 g. (91%) of crystals, m.p. 119–120°.

Anal. Calcd. for $C_{20}H_{22}O_9$: C, 59.10; H, 5.46. Found: C, 59.19; H, 5.51.

Triethylene Glycol Diisodehydroacetate.—A mixture of 4 g. (0.0215 mole) of isodehydroacetyl chloride and 1.5 g. (0.010 mole) of triethylene glycol was heated in an oil-bath at 120–135° for six hours. The residue, recrystallized from methanol, gave 4.0 g. (89%) of crystals, m.p. 108°.

Anal. Calcd. for $C_{22}H_{26}O_{10}$: C, 58.66; H, 5.82. Found: C, 59.10; H, 6.02.

Thiodiethylene Glycol Diisodehydroacetate.—A mixture of 1.3 g. (0.011 mole) of thiodiethylene glycol and 4.1 g. (0.022 mole) of isodehydroacetyl chloride was heated for six hours in an oil-bath. The reaction product was recrystallized from benzene–ligroin to give 2.7 g. (60%) of crystals, m.p. 80–81° (from toluene).

Anal. Calcd. for $C_{20}H_{22}O_8S$: C, 56.88; H, 5.25. Found: C, 56.69; H, 5.26.

Pentaerythritol Tetraisodehydroacetate.—A mixture of 0.54 g. (0.0040 mole) of pentaerythritol and 3.0 g. (0.0166 mole) of isodehydroacetyl chloride was heated to 150° and cooled to deposit a solid residue which was recrystallized from acetic acid to give 2.3 g. (77%) of crystals, m.p. 225–227°.

Anal. Calcd. for $C_{37}H_{36}O_{16}$: C, 60.32; H, 4.93. Found: C, 60.32; H, 5.03.

Reaction of Hydrazine Hydrate with Ethyl Isodehydroacetate.—To 15.0 g. (0.0765 mole) of ethyl isodehydroacetate cooled in an ice-bath was slowly added 7.5 g. (0.15 mole) of hydrazine hydrate. After one hour, 25 ml. of water was added to precipitate a white solid which was collected, dried, and recrystallized from ethanol to give 2.8 g. (18%) of 3-methyl-5-pyrazolone, m.p. 216–218° (cor.); reported m.p. 219°.[9]

Anal. Calcd. for $C_4H_6ON_2$: C, 48.98; H, 6.17; N, 28.56. Found: C, 49.22; H, 6.11; N, 28.62.

The compound gives a positive ferric chloride enol test and no depression of m.p. on admixture with a sample of 3-methyl-5-pyrazolone, m.p. 216–218°, prepared from ethyl acetoacetate and dihydrazine sulfate.[10] The monoacetyl derivative was prepared from each sample,[11] m.p.'s and mixed m.p.'s 153–154° (cor.); reported[10] m.p. 140°.

Anal. Calcd. for $C_6H_8O_2N_2$: N, 19.98. Found: N, 19.92.

(9) F. K. Beilstein, "Handbuch der organischen Chemie," J. Springer, Berlin, 1936, Vol. XXIV, p. 19.

(10) L. Knorr, *Ber.*, **29**, 253 (1896).

(11) T. Curtius, *J. prakt. Chem.*, **50**, 511 (1894).

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Conjugate Addition Reactions of Azoles: 1,2,3-Triazole and Benzotriazole

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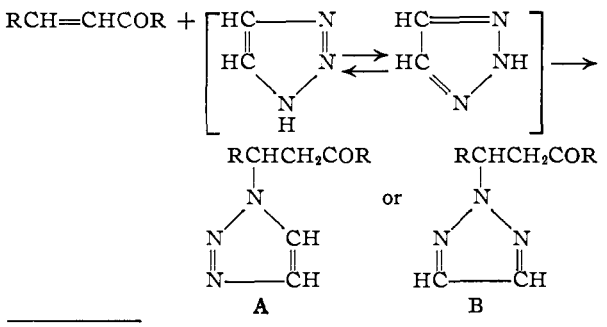
The addition of azoles having an unsubstituted, exocyclic imino group to conjugated, unsaturated systems is presented for additions of 1,2,3-triazole and benzotriazole to acrylic acid, acrylamide, acrylonitrile, crotonic acid, benzalacetophenone, *p*-methoxybenzalacetone, benzalacetone, dibenzalacetone and cinnamaldehyde. Ultraviolet absorption data for the five benzotriazole adducts show clearly the double maxima at 255 mμ and 283 mμ characteristic of 1-substituted benzotriazoles and the data for the benzalacetophenone adducts from both benzotriazole and triazole show the absorption maximum at 245 mμ characteristic of the carbonyl group conjugated with the benzene ring. On this basis, the products are assigned β-(1-benzotriazolyl or 1-triazolyl) carbonyl (or related) structures.

The experimental data presented in this paper establish the 1,4-addition of 1,2,3-triazole to acrylic acid, benzalacetophenone (chalcone), benzalacetone and dibenzalacetone (1,5-diphenylpentadiene-one-3); the 1,4-addition of benzotriazole to acrylic acid, crotonic acid, benzalacetophenone (chalcone), *p*-methoxybenzalacetone and acrylonitrile; and the simultaneous 1,4- and 1,2-addition of benzotriazole to cinnamaldehyde. The addition reaction is carried out by warming the reactants together in the presence of pyridine or Triton B (trimethylbenzylammonium hydroxide) as the basic catalyst.

The structure of the addition product formed on addition of an iminoazole such as 1,2,3-triazole or benzotriazole to an unsaturated system is complicated by the possibility for linkage at either of two different nitrogen atoms. Thus, with 1,2,3-triazole addition can occur to give either a 1- or a 2-substituted triazole.



Of various methods available for establishing the structure of a product obtained when such isomerism is possible, an analysis of ultraviolet absorption spectra is most direct. The ultraviolet absorption data summarized in Table I establish the 1-benzotriazole structure and the presence of the carbonyl group in products obtained in this study. The ultraviolet absorption spectra of 1- and 2-alkyl benzotriazoles have been shown previously[2,3] to differ. The 1-substituted types show double maxima at 255 mμ (log ε 3.81) and 283 mμ (log ε 3.68) and the 2-substituted types show a single maximum at 275 mμ (log ε 3.90). Our data show that the benzotriazole adducts with acrylic acid, acrylonitrile, acrylamide, crotonic acid and cinnamaldehyde, are unmistakably of the 1-substituted type. All have two characteristic maxima with similar extinction coefficients. Perhaps because of a slightly greater resolution than was obtained previously we observed a double maxima at each of the principal maxima for each of these compounds. The benzotriazole and 1,2,3-triazole adducts from benzalacetophenone

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(2) F. Krollpfeiffer, H. Pötz and A. Rosenberg, *Ber.*, **71B**, 596 (1938).

(3) H. Specker and H. Gawrosch, *ibid.*, **75B**, 1338 (1942).