[Contribution from the Chemistry Department of the College of Arts and Sciences of the University of Louisville]

2-Pyrones. V.[1] New Derivatives of Isodehydroacetic Acid

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Several glycol and aryl esters of isodehydroacetic acid, of interest for pharmacological evaluation, and isodehydroacetic anhydride have been prepared by reaction of the acid chloride with glycols, phenols and isodehydroacetic acid. Ultraviolet absorption curves for the esters show absorption in the 248–252 mμ and 290–300 mμ regions characteristic of unsaturated esters but the curves for the anhydride and chloride differ significantly. Molecular refraction data show an exaltation less than is associated with ethyl sorbate, a similar but acyclic structure, which is consistent with resonance stabilization in the 2-pyrone ring structure.

Interest in the preliminary pharmacological evaluation of a variety of 2-pyrones prepared during previous studies[2–5] has led to the suggestion that additional compounds of this structure be characterized and evaluated. Among other types currently under study in our laboratories, derivatives of isodehydroacetic acid were of particular interest for evaluation as tumor damaging agents. This interest developed from a preliminary evaluation which indicated that ethyl isodehydroacetate showed possible slight activity in one test and from continued interest in unsaturated lactones of all types. Bifunctional compounds such as the glycol esters reported herein are of particular interest in further evaluation of current theories based on the possibility that bifunctional compounds may cause abnormal cell division by initiating crosslinking reactions in chromosomes. In the course of these studies we have obtained considerable data on previously unevaluated chemical and physical characteristics of these compounds which we wish to present here as part of a fundamental study of the chemistry of the 2-pyrone ring system.

Although isodehydroacetic acid[6] and its ethyl ester[7] have been known for many years, other derivatives such as the acid chloride,[5,8] simple alkyl esters[5] and amides[8] have been characterized but recently. In the course of our present studies we have prepared and characterized the anhydride, seven aryl esters and five glycol esters. Pharmacological evaluations of some of these compounds will be reported elsewhere.

Isodehydroacetic anhydride, m.p. 144°, was first obtained inadvertently in an attempt to prepare the cetyl ester[5] of the acid from the acid chloride and the alcohol in ether in the presence of pyridine. The anhydride has also been prepared in 66% yield by a conventional procedure described in the experimental section in which the acid and the acid chloride were treated with pyridine in dry ether. The two samples were alike in all respects observed. The anhydride is reasonably stable toward hydrolysis by water, dilute acid and dilute alkali but can be hydrolyzed to the acid by boiling with water. It can be recrystallized from warm alcohol without complete conversion to the ester and its ultraviolet absorption characteristics measured in ethanol are not those of ethyl isodehydroacetate.

The aryl esters described in Table I were prepared by reaction of the acid chloride with the appropriate phenol. Our experience with these and other esterification reactions has indicated that this procedure is the most reliable for esterification of 2-pyrone acids. Apparently other esterification procedures are likely to involve the lactone ring system in numerous possible side reactions. Although alkali is commonly used in the esterification of phenols,[9] it was not used in our esterification because of the possibility that the pyrone ring in the acid chloride would be cleaved by the alkali. Preliminary experiments indicated that low yields were in fact obtained if alkali were used. In addition to the esters described in Table I, attempts were made to obtain aryl esters from salicylic acid, catechol and resorcinol. The last two gave products m.p. 118–138° and 135–155°, respectively, without change even after repeated recrystallization. The salicylic acid derivative was isolated as a solid, m.p. 148°, from nitropropane. The neutral equivalent of 150–180 is not in accord with any obvious possible structure and indicates a lack of homogeneity.

Table I

Aryl Esters of Isodehydroacetic Acid

Aryl group	M.p., °C. (uncor.)	Yield, %	Analyses Carbon Calcd.	Found	Hydrogen Calcd.	Found
Phenyl	109	85	68.84	69.05	4.95	5.07
o-Methoxyphenyl	98–99	72	65.68	65.86	5.14	5.24
m-Methoxyphenyl	79–80	67	65.68	65.74	5.14	5.29
p-Methoxyphenyl	139	78	65.68	66.09	5.14	5.36
2,6-Dimethoxyphenyl	167	80	63.15	62.80	5.30	5.37
p-Phenylene	244–246	85	64.39	64.17	4.42	4.54
β-Naphthyl	140	60	73.46	73.52	4.79	4.58

The glycol esters listed in Table II were prepared using isodehydroacetyl chloride with the indicated

Table II

Glycol Esters of Isodehydroacetic Acid

Glycol	M.p., °C.	Yield, %	Analyses Carbon Calcd.	Found	Hydrogen Calcd.	Found
Ethylene	135–136	86	59.7	59.68	4.98	5.17
Trimethylene	78	76	60.63	60.70	5.36	5.66
Tetramethylene	98	78	61.53	61.51	5.68	5.75
Pentamethylene	66–67	87	62.37	62.37	5.98	6.17
Decamethylene	96–97	75	65.80	65.59	7.22	7.25

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(1) For previous papers in this series see references 2–5.

(2) R. H. Wiley and N. R. Smith, This Journal, **73**, 1383 (1951).

(3) R. H. Wiley and N. R. Smith, *ibid.*, **73**, 3531 (1951).

(4) R. H. Wiley and N. R. Smith, *ibid.*, **74**, 3893 (1952).

(5) R. H. Wiley, N. R. Smith and J. A. Bauer, *ibid.*, **75**, 244 (1953).

(6) A. Hantzsch, *Ann.*, **222**, 9 (1893).

(7) C. Duisberg, *ibid.*, **213**, 178 (1882).

(8) H. M. Basel, U. S. Patent 2.364 304 (December, 1944).

(9) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Company, New York, N. Y., Second Edition, 1948, pp. 96–97.

glycol. The products are all bis-esters with both of the hydroxyl groups esterified. No attempt was made to prepare the mono-esters. The esters are solids with only slight if any water solubility.

Molecular refraction data for five liquid esters[5] are given in Table III. The density values were determined with a self-filling pycnometer similar to that described by Hennion[10] and the refractive index values in an Abbe refractometer with thermostatically controlled temperature. The esters show a uniform exaltation of the molecular refraction of 2.06 ± 0.07. Ethyl sorbate shows a slightly greater exaltation of 2.35.[11] The additional conjugation in the isodehydroacetates might be expected to cause a greater exaltation in the isodehydroacetates than in the sorbate. This decreased exaltation suggests some degree of resonance stabilization since a lower exaltation than is normally found in similar acyclic conjugated systems is often associated with resonance stabilized ring structures.[12] This is in accord with previous indications[3] of resonance stabilization in 2-pyrones of the isodehydroacetic acid type.

TABLE III

MOLECULAR REFRACTION DATA

Ester	Density 30°	n^{30}_D	Molecular refraction Obsd.	Calcd.	Exaltation
Ethyl	1.161	1.5103	50.54	48.55	1.99
n-Propyl	1.130	1.5054	55.17	53.17	2.00
i-Propyl	1.123	1.5020	55.24	53.17	2.07
n-Butyl	1.107	1.5033	59.87	57.79	2.08
i-Amyl	1.088	1.5005	64.53	62.41	2.12

The ultraviolet absorption spectra of the esters (Table IV) can be considered as sums of the spectra of isodehydroacetic acid and the alcohol or phenol used to make each ester. Saturated alcohols having no absorbancy in the ultraviolet form esters with virtually the same spectrum as isodehydroacetic acid. This spectrum has two approximately equal and symmetrical absorption bands, and is referred to as a "type 1" spectrum in the table. The phenyl ester exhibits a slight bathochromic shift of the absorption maximum near 250 mμ due to the absorbancy of the phenol type in this region. Methoxy substituted phenols give esters with an additional shoulder in their spectra ("type 2" spectra in Table IV) at about 275 mμ resulting from the absorption maxima of methoxy phenols between 265 and 290 mμ[13] and with considerably decreased absorption at 290 mμ. The high absorbancy of β-naphthol at short wave lengths results in higher molar absorbancies at short wave lengths for this ester as compared to the other aromatic esters. The spectra of isodehydroacetic anhydride and chloride appear similar to each other although run in different solvents. They show only one maximum at 270–274 mμ with a shoulder at 290–310 mμ. The differences with isodehydroacetic acid may possibly be shifts resulting from the auxochromic properties of the chloride and anhydride as compared to the acid itself and are consistent with a higher degree of resonance stabilization in the anhydride and chloride. Generally, absorption curves for acid chlorides and anhydrides more closely resemble those of the corresponding acids than is observed with these isodehydroacetic derivatives.

TABLE IV

ULTRAVIOLET ABSORPTION CHARACTERISTICS OF ISODEHYDROACETIC ACID AND ITS DERIVATIVES

Compound	log ε (λ_{max}^{248})	log ε (λ_{max}^{295})
Compounds showing type 1 curves		
Isodehydroacetic acid	3.90	3.92
Isodehydroacetates:		
Ethyl	4.00	3.98
n-Propyl	3.91	3.89
Isopropyl	3.80	3.78
n-Butyl	3.88	3.82
Isoamyl	3.87	3.79
Ethylene	4.12	4.11
Trimethylene	4.07	4.01
Tetramethylene	4.12	4.05
Pentamethylene	4.03	3.97
Decamethylene	4.03	4.00
Compound	log ε (λ_{max}^{250-2})	log ε/λ_{max}
Compounds showing type 2 curves		
Isodehydroacetates:		
Phenyl	3.92	3.71/295
o-Methoxyphenyl	3.96	3.79/280–292
m-Methoxyphenyl	3.95	3.73/290–296
p-Methoxyphenyl	4.01	3.80/288–292
2,6-Dimethoxyphenyl	3.91	3.77/270–300
β-Naphthyl	4.22	4.00/280
	log ε/λ_{max}	log ε/λ_{max}
Isodehydroacetyl chloride	3.92/276	3.64/305
Isodehydroacetic anhydride	4.24/270	4.00/300

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Experimental[14]

Isodehydroacetic Anhydride.—A solution of 0.5 g. of isodehydroacetic acid,[3] 100 ml. of dry ether and 3 ml. of pyridine was mixed with a solution of 0.5 g. of isodehydroacetic acid chloride[5] with cooling. This mixture was stored overnight in a low temperature storage cabinet. The precipitate which formed was collected on a filter and washed first with cold, dilute hydrochloric acid, then with cold, dilute sodium carbonate, and finally with cold water. The product was dried in a vacuum to give 0.6 g. (66% of the theoretical amount) of isodehydroacetic anhydride, m.p. 144°. Careful recrystallization from 95% ethanol gave an analytical sample, m.p. 145–146°.

Anal. Calcd. for $C_{10}H_{14}O_7$: C, 60.37; H, 4.43. Found: C, 60.62; H, 4.45.

Pentamethylene Diisodehydroacetate.—One and six-tenths grams of isodehydroacetyl chloride[5] (0.00857 mole) was melted and poured into a tared, 4″ × 1″ test-tube. Forty-five hundredths of a gram (0.00429 mole) of pentamethylene glycol was added and the mixture heated under a reflux condenser in an oil-bath at 90–100° for 15 minutes. The

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(10) G. F. Hennion, *Ind. Eng. Chem., Anal. Ed.*, **9**, 479 (1937).

(11) K. v. Auwers and F. Eisenlohr, *J. prakt. Chem.*, [2] **84**, 92 (1911).

(12) J. A. Leermakers and A. Weissberger in H. Gilman, ed., "Organic Chemistry," 2nd ed., Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1752.

(13) Landolt-Börnstein, "Zahlenwerte und Funktionen," Sixth Edition, Vol. III, part III, Springer-Verlag, Berlin, 1951, p. 89.

(14) Analyses by Micro-Tech Laboratories, Skokie, Illinois.

reaction mixture was cooled to give a red-brown oil which was dissolved in about 20 ml. of 95% boiling ethanol. Norite was added and the solution was filtered hot to give a yellow solution which deposited 1.51 g. (87.5% of the theoretical amount) of gray crystals on cooling. After two successive recrystallizations from ethanol (norite), a white product was obtained which melted at 66–67°.

This same procedure was also used for the trimethylene, tetramethylene, *m*-methoxyphenyl and *o*-methoxyphenyl esters, all of which gave oils as crude reaction products.

***p*-Methoxyphenyl Isodehydroacetate.**—Two and five-tenths grams of isodehydroacetyl chloride (0.0134 mole) was melted and poured into a 4" × 1", tared test-tube. One and sixty-six one hundredths grams (0.0134 mole) of *p*-methoxyphenol was added. The mixture was heated under a reflux condenser in an oil-bath at 90–110° for 15 minutes. On cooling a gray-green solid remained. About 20 ml. of 95% ethanol was added and the mixture heated until solution was complete. Norite was then added and the solution was filtered hot. The clear filtrate deposited 2.88 g. (78.6% of the theoretical amount) of white crystals, m.p. 139°, on cooling.

This same procedure also was used for the phenyl, hydroquinone, decamethylene, 2,6-dimethoxyphenyl and β-naphthol esters, all of which gave solids as crude reaction products.

Ultraviolet Absorption Data.—Ultraviolet absorption measurements were made with a Beckman DU photoelectric spectrophotometer using 1.00-cm. silica cells and hydrogen and tungsten discharge lamps as light sources. The esters and anhydride were all measured as solutions in 95% ethanol. The acyl chloride was measured in ether.

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[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH AND FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

α- and γ-Additions in the Reformatsky Reaction with Methyl γ-Bromocrotonate[1]

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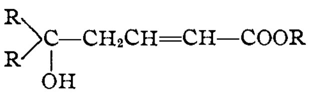
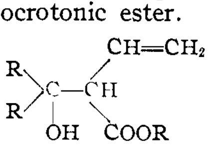
A study of the Reformatsky reaction with methyl γ-bromocrotonate showed that the nature of the product depended on the solvent at the boiling point of which the reaction was performed and on the structure of the carbonyl compound. Thus with cyclohexanone, 4-methylcyclohexanone, β-tetralone and 3,4,5-trimethoxybenzaldehyde, a condensation occurred at the *γ-position* of the bromoester to give γ-substituted crotonic esters ("normal" products, type A) when the reaction was conducted in *boiling benzene*. *In boiling ether*, the same carbonyl compounds added to the *α-position* of the bromoester to afford α-substituted vinylacetic esters ("abnormal" products, type B). The same Reformatsky reaction with 2-methylcyclohexanone and with α-tetralone yielded predominantly the "normal" products (type A) both in ether and in benzene at their boiling points. With alkali, some of the "normal" Reformatsky esters were saponified to the corresponding unsaturated hydroxyacids, while the "abnormal" esters underwent a reversal of the Reformatsky reaction to give the corresponding carbonyl compound. By suitable dehydrations, hydrogenations and saponifications a number of unsaturated acids were prepared from both the "normal" and "abnormal" Reformatsky esters. Unexpected shifts of the double bonds away from the carboxyl group occurred during the dehydration and saponification of the "normal" esters in the cyclohexanone series. The structures of the products were deduced from their reactions and from their ultraviolet and infrared absorption spectra.

Methyl γ-bromocrotonate has been successfully used in the Reformatsky reaction[2] to give structures of type A which were formed from the attack of the γ-position of the zinc complex of γ-bromocrotonic ester on the respective carbonyl compounds. These esters will be called the "normal" Reformatsky products. It has recently been found[3,4] in a few cases that another product, the "abnormal" Reformatsky ester, may appear which resulted from the reaction of the carbonyl compound with the α-position of γ-bromocrotonic ester.



$\mathrm{RR'C(OH)—CH_2CH{=}CH—COOR}$

A, "normal" Reformatsky ester



$\mathrm{RR'C(OH)—CH(CH{=}CH_2)—COOR}$

B, "abnormal" Reformatsky ester

In the present investigation it was found that the temperature at which the reaction is performed or the nature of the solvent and certain structural features of the carbonyl compound influenced the course of the methyl γ-bromocrotonate Reformatsky reaction. With a number of ketones and one aromatic aldehyde, the "normal" Reformatsky esters (A) resulted when the reaction was performed in boiling benzene, while the "abnormal" products (B) predominated in boiling ether. With two ketones, the reaction in both solvents resulted in the "normal" compounds.

When the reaction with methyl γ-bromocrotonate and an excess of cyclohexanone was conducted in refluxing benzene or 1,2-dimethoxyethane the major product was a 30 and 39% yield, respectively, of methyl γ-(1-hydroxycyclohexyl)-crotonate (ester of I)[5] which exhibited an absorption maximum at 211 mμ (ε 16,200), characteristic of α,β-unsaturated acids or esters.[6] In this reaction there was some self-condensation of cyclohexanone to give a 19 and 15% yield (based on methyl γ-bromocrotonate) of a mixture of the known 2-cyclohexenylcyclohexanone and 2-cyclohexylidenecyclohexanone. Evidence for the carbon skeleton of the ester was obtained when hydrogenation, followed by

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(1) A part of this work was supported by institutional grants from the Michigan Cancer Foundation, the American Cancer Society, Inc., and The Kresge Foundation.

(2) For early references see G. Stork, THIS JOURNAL, **69**, 2936 (1947). See also (a) J. W. Cook and R. Philip, *J. Chem. Soc.*, 162 (1948); (b) W. E. Bachmann and A. S. Dreiding, *J. Org. Chem.*, **13**, 317 (1948); (c) J. F. Ahrens and D. A. van Dorp, *Rec. trav. chim.*, **65**, 338 (1946); (d) I. M. Heilbron, E. R. H. Jones and D. G. O'Sullivan, *J. Chem. Soc.*, 866 (1946); (e) J. English, Jr., and J. D. Gregory, THIS JOURNAL, **69**, 2123 (1947); (f) W. E. Bachmann and N. L. Wendler, *ibid.*, **68**, 2582 (1946).

(3) E. R. H. Jones, D. G. O'Sullivan and M. C. Whiting, *J. Chem. Soc.*, 1415 (1949).

(4) J. English, Jr., J. D. Gregory and J. R. Trowbridge, II, THIS JOURNAL, **73**, 615 (1951).

(5) In a similar reaction with cyclohexanone and ethyl γ-iodocrotonate in benzene Fuson, Arnold and Cooke, *ibid.*, **60**, 2272 (1938), isolated ethyl cyclohexylidenecrotonate (ester of VII), as indicated by carbon and hydrogen analysis.

(6) For several references see H. E. Ungnade and I. Ortega, *ibid.*, **73**, 1564 (1951).