Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57. Found: C, 68.32; H, 8.64.

Reaction of β-Pinene with Methylenemalonic Ester.—β-Pinene (8.3 g., 0.06 mole) and methylenemalonic ester[13] (10.3 g., 0.06 mole) were refluxed in xylene (200 ml.) under an atmosphere of nitrogen for 111 hr. The solvent was removed under vacuum (60° (20 mm.)) and the residue distilled in an oil-jacketed flask to give diethyl nopylmalonate, yield 9.5 g. (51%), b.p. 128° (0.2 mm.), $n^{25}D$ 1.4668, $[\alpha]^{26}D$ −20.52°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.13; H, 9.15. Found: C, 69.89; H, 9.35.

Diethyl Nopylmalonate.—Diethylmalonate (24 g.) was added to a solution of sodium (5.6 g.) in absolute ethanol (400 ml.). A solution containing nopyl tosylate (49.8 g.) and absolute ethanol (100 ml.) was added dropwise over 1 hr. to the stirred reaction mixture held at its boiling point. Heating and stirring were continued for 48 hr., and the cooled mixture was poured into water (2 l.) and extracted with ether (500 ml.). The ether solution was dried over magnesium sulfate, filtered and fractionally distilled to give diethyl nopylmalonate, yield 14 g. (28%), b.p. 127° (0.2 mm.), $n^{25}D$ 1.4678, $[\alpha]^{26}D$ −21.5°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.13; H, 9.15. Found: C, 69.97; H, 9.21.

All the physical properties of this substance, including its infrared spectrum, were indistinguishable from those for the material obtained directly from β-pinene and methylenemalonic ester.

Reaction of 10-Pinen-2-ylsuccinic Anhydride (II) with Methanol.—The anhydride (1 g.) was refluxed with anhydrous methanol (30 ml.) for 16 hr. The excess methanol was removed under partial vacuum and the oily residue was held at 70° at a pressure of 0.05 mm. for 3 hr. A value of 275 was obtained as neutral equivalent (calcd. for half acid-ester, 266). This residue showed no anhydride bands in the infrared but exhibited strong absorption at 5.8 (ester) and 5.9 μ (carboxylic acid). Following distillation of the oily residue (b.p. 155° (0.08 mm.)), the product exhibited strong anhydride bands at 5.43 and 5.63 μ in addition to those for the ester (5.8 μ) and carboxylic acid (5.9 μ). The undistilled crude half-ester reacted rapidly with diazomethane in ether to form dimethyl 10-pinen-2-ylsuccinate (IV).

NEW YORK, N. Y.

(13) G. B. Bachman and H. A. Tanner, *J. Org. Chem.*, **4**, 493 (1939).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

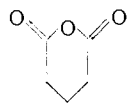
2*H*-Pyran-3,5(4*H*,6*H*)-Diones

BY MARY ANNE MORGAN[1] AND EARLE VAN HEYNINGEN

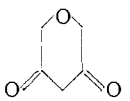
RECEIVED AUGUST 13, 1956

A synthesis is reported for the previously undescribed 2*H*-pyran-3,5(4*H*,6*H*)-diones.

In contrast to the many syntheses of 4,5-dihydro-2*H*-pyran-2,6(3*H*)-diones (I) appearing in the literature, there is no report of the synthesis of the isomeric 2*H*-pyran-3,5-(4*H*,6*H*)-diones (II). Gulland and Farrar[2] do mention their interest in compounds of this type as possible chemotherapeutic agents; they had prepared some substituted cyclotelluropentane-3,5-diones which had exhibited marked activity and the pyran-3,5-diones are their oxygen analogs. There is, however, no subsequent report of their preparation by these authors.



I



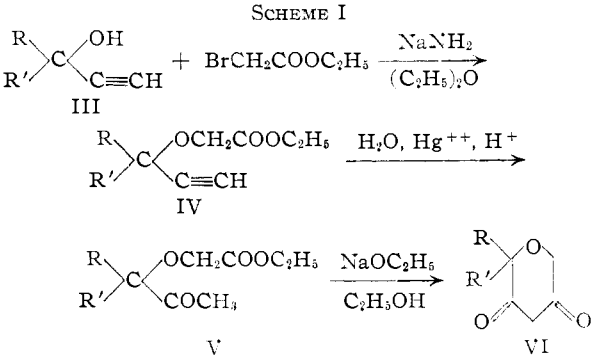
II

Our interest in their synthesis lay both in the compounds' intrinsic novelty as well as in the possibility that the β-hydroxyvinyl ketone grouping, common to their mono-enolic form and to salicylic acid, might impart to them the pharmacological activity of the salicylates.

The route chosen is indicated in Scheme I. Initial attempts to make the ketones V from acyloins and α-bromoesters *via* an ether synthesis were unsuccessful for no single, pure product could be isolated. But when the acetylenic alcohols III were used in the ether formation, acceptable yields of pure acetylenic ether-esters could be obtained.

In general, the hydration of the acetylene moiety to the methyl ketone proceeded as expected. However, in the hydration of 3-carbethoxymethoxy-1-hexyne (IV, R = H, R′ = C_3H_5) the solvent used was methanol, and transesterification occurred during the reaction to give as a product an inseparable mixture of methyl and ethyl esters. Since the alkoxyl group is lost in the ring closure, this mixture was as useful as a pure ester. The hydration of 3-carbethoxymethoxy-3-methyl-1-butyne (IV,

SCHEME I



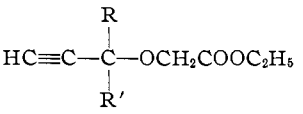
R = CH_3, R′ = CH_3) gave a mixture which was not separated after repeated distillation, and the chemical tests for a terminal acetylene group were positive. One might anticipate that the steric hindrance afforded by the three groups on the carbon atom adjacent to the acetylene group would render the hydration of this compound more difficult than that of the others. The results seem to substantiate this conclusion.

The ketoesters V were cyclized with sodium ethoxide in ethanol to give the pyrandiones VI in relatively poor yields. The diketones on distillation decompose to leave sizable residual distil-

(1) University of Minnesota, Minneapolis, Minn.

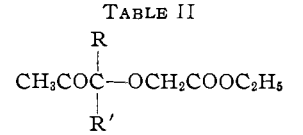
(2) J. M. Gulland and W. V. Farrar, *Nature*, **154**, 88 (1944).

TABLE I



R	R′	Yield, %	B.p. °C.	Mm.	$n^{25}D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	61	48.5–59	2	1.4305–1.4297	$C_9H_{14}O_3$	63.51	63.80	8.29	8.50
C_2H_5	H	50.2	66–71	2	1.4308–1.4300	$C_9H_{14}O_3$	63.51	63.69	8.29	8.39
$CH_3CH_2CH_2$	H	33.7	69–70.5	2	1.4312–1.4314	$C_{10}H_{16}O_3$	65.19	65.05	8.75	8.73
$(CH_3)_2CHCH_2$	H	61	83.5–89	2	1.4330–1.4327	$C_{11}H_{18}O_3$	66.64	66.46	9.15	9.07
$CH_3(CH_2)_4CH_2$	H	56	114–119	2	1.4375	$C_{13}H_{22}O_3$	68.99	68.94	9.80	9.79

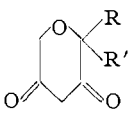
TABLE II



R	R′	Yield, %	B.p. °C.	Mm.	$n^{25}D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	41[a]	77–94	2	1.4288–1.4281	$C_9H_{16}O_4$				
C_2H_5	H	70	90–93	2	1.4263–1.4258	$C_9H_{16}O_4$	57.43	57.24	8.57	8.80
$CH_3CH_2CH_2$	H	70[b]	86–90	2	1.4297–1.4298	$C_{10}H_{18}O_4$	59.38[c] 57.43[d]	57.82	8.97[c] 8.57[d]	9.22
$(CH_3)_2CHCH_2$	H	54	104.5–108	2	1.4317–1.4308	$C_{11}H_{20}O_4$	61.09	61.30	9.32	9.35
$CH_3(CH_2)_4CH_2$	H	66	134.5–139	2	1.4350	$C_{13}H_{24}O_4$	63.90	63.67	9.90	10.08

[a] Based on weight of distilled crude product. [b] Based on methyl ester. Ethyl ester. [d] Methyl ester.

TABLE III



R	R	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	CH_3	23.3	102–105	$C_7H_{10}O_3$	59.14	59.25	7.09	7.30		
C_2H_5	H	18	70–75	$C_7H_{10}O_3$	59.14	58.99	7.09	7.18		
$CH_3CH_2CH_2$	H	21.9	76–79	$C_8H_{12}O_3$	61.52	61.36	7.75	7.83		
$(CH_3)_2CHCH_2$	H	87[a]	122–124[b]							
			220–221 d.	$C_{11}H_{20}N_6O_3$[d]					29.56	29.32
$CH_3(CH_2)_4CH_2$	H	15.2[c]	143–150[b]							
			213 d.	$C_{13}H_{24}N_6O_3$[d]					26.91	26.83

[a] Crude yield before distillation. [b] B.p. (3 mm.). [c] Crude yield after distillation. [d] Bis-semicarbazone derivative of compound above.

lands. This decomposition was at least partially responsible for the poor yields. The pyrandiones substituted with longer alkyl groups, VI (R = H, R′ = *i*-C_4H_9 or *n*-C_6H_{13}), could not be purified by distillation because of their great thermal instability. They were identified as their bis-semicarbazones. To establish further the identity of the isobutyl and hexyl analogs, they were examined spectroscopically and compared with a pure sample of the dimethyl compound VI (R, R′ = CH_3). In the ultraviolet all the compounds show a maximum for the enol at 252 mμ and for the enolate ion at 278 mμ. The infrared spectra of these compounds are also very similar with very intense keto and enol absorption. The titration curves in 66% dimethylformamide indicated that the isobutyl derivative was 90% pure and the *n*-hexyl derivative only 84% pure.

None of these compounds showed pharmacological activity similar to the salicylates either as antipyretics in febrile rats, *i.v.*, or as anti-inflammatory agents, *i.v.*, in rats with inflamed ankles. In a chemotherapy screening test against 38 representative microörganisms, the dimethyl derivative (at 200 mcg. per ml.) showed inhibition of *V. cholera* and *A. solani*, while the ethyl derivative at the same level inhibited *T. interdigitale* and *A. solani*.

Acknowledgment.—We wish to thank the following for their assistance: Messrs. W. L. Brown, H. L. Hunter and G. M. Maciak and Miss G. Beckmann for the microanalyses; Dr. H. E. Boaz for the interpretation of the spectra and Misses M. Hofmann and A. Van Camp, and Mrs. H. Arndt for the spectra and titration data; and Mr. C. L. Rose and Miss D. Fleming for the pharmacological and microbiological tests.

Experimental[3]

The preparations of 2*H*-pyran-3,5(4*H*,6*H*)-diones were all performed in the same manner so only the detailed method is given below for the 3-ethyl derivative. The physical properties, analyses and yields of the products are listed in the Tables. When deviations from the general method were necessary, they have been indicated in the appropriate places.

Preparation of 3-Carbethoxymethoxy-1-pentyne (IV, R = H, R′ = C_2H_5).—In a 3-l. flask sodium amide was prepared from 27.6 g. (1.2 atoms) of sodium in 1.25 l. of anhydrous ammonia with ferric nitrate as catalyst. Then 96.2 g. (1.145 moles) of ethylethynylcarbinol, prepared by the

(3) All melting points and boiling points are uncorrected.

method of McGrew and Adams,[4] was added dropwise with stirring. The ammonia was driven off by heat, and 1.3 l. of anhydrous ether was added. A solution of 191.5 g. (1.145 moles) of ethyl bromoacetate in an equal volume of dry ether was added dropwise with stirring which was continued for 16 hr. Water was then added dropwise until all salts had dissolved. The ether layer was separated, and the water layer was extracted with ether. The combined ether portions were dried and evaporated. The residue was distilled to give 3-carbethoxymethoxy-1-pentyne.

Preparation[5] of 3-Carbethoxymethoxy-2-pentanone (V, R = H, R′ = C_2H_5).—In a 300-ml. flask 0.5 g. of red mercuric oxide and 2 ml. of 50% sulfuric acid were stirred and heated until some white mercuric sulfate was formed. A solution of 7 g. of water in 32 g. of ethanol was added and heated to reflux. Then 47.9 g. (0.282 mole) of 3-carbethoxymethoxy-1-pentyne was added dropwise during 1 hr. Stirring and refluxing were continued for 3 hr. The ethanol was distilled off, and the residue was saturated with sodium chloride. The organic layer was separated, and the water layer was extracted with ether. The combined ether and organic layers were washed with saturated sodium chloride solution, with sodium carbonate solution and again with saturated sodium chloride solution. After drying, the ether was evaporated and the residue was distilled to give 3-carbethoxymethoxy-2-pentanone.

In the preparation of 3-carbethoxymethoxy-3-methyl-2-butanone, the product isolated could not be purified by distillation and was known to contain some starting material. This was shown by the positive test for a terminal acetylene group obtained by adding alcoholic mercuric chloride to an ethanolic sodium ethoxide solution of the compound to give a white precipitate.

In the preparation of 3-carbethoxymethoxy-2-hexanone, an acidic methanol solution was used instead of an ethanol solution. This evidently resulted in some transesterification so that, as indicated by the analysis, the product was a mixture of the methyl and ethyl esters. Purification could not be achieved by distillation. In the hope that the esters could be separated as their 2,4-dinitrophenylhydrazones, this derivative was made of a sample of the mixture.[6] Recrystallization of the derivative gave material with a fairly sharp melting point not improved by repeated recrystallization from ethanol, m.p. 62–63.5°, but the analysis indicated it was still a mixture of the esters. Attempts at purification were abandoned and the mixture was used for the cyclization.

Preparation[7] of 2-Ethyl-2*H*-pyran-3,5(4*H*,6*H*)-dione (VI, R = H, R′ = C_2H_5).—In a 1-l. flask 4.8 g. (0.208 atom) of sodium was dispersed in hot toluene which was cooled and replaced by 400 ml. of dry ether. Then 10.0 g. (0.217 mole) of anhydrous ethanol was added, and the solution was stirred until the sodium ethoxide had formed. A solution of 37.0 g. (0.197 mole) of 3-carbethoxymethoxy-2-pentanone in an equal volume of ether was added dropwise. Stirring was continued for 1 hr. The sodium salt was collected, washed with dry ether and added to 70 ml. of 3 *N* sulfuric acid. The aqueous solution was extracted with ether, and the ether was dried and evaporated. The residue was distilled, giving a thick yellow oil, b.p. 108–110° (2 mm.), which crystallized on standing. The product was recrystallized from benzene–petroleum ether (60–62°) to give 2-ethyl-2*H*-pyran-3,5(4*H*,6*H*)-dione.

In the preparation of the 2-isobutyl and 2-*n*-hexyl derivatives the oily products partially decomposed on distillation so they could not be purified in this manner. They were identified through their bis-semicarbazone derivatives which were prepared by the method of Shriner and Fuson[8] and purified by trituration with boiling ethanol.

To characterize further the 2-isobutyl and 2-*n*-hexyl compounds several physical measurements were made on them and these properties compared with those of a pure sample of the 2,2-dimethylpyrandione. The absorption maxima in the infrared for the dicarbonyl system of all three of these compounds appeared at the same wave lengths, 5.82 and 5.74 μ, the latter slightly more intense than the former, and a broad band at 6.25 μ. The last is assigned to the enol form. In the ultraviolet spectra taken in methanol, again the maxima were at the same wave lengths, 251 mμ (ϵ 14500) and at 278 mμ (ϵ 26000), *p*H 10.5, which are assigned to the enol and enolate ion, respectively. The titrations in 66% dimethylformamide gave the following results: dimethyl, pK'_a 5.8, apparent molecular weight 145 (theory 142); isobutyl, pK'_a 5.8, A.M.W. 186 (theory 170 or 90% pure); *n*-hexyl, pK'_a 5.9, A.M.W. 237 (theory 198 or 84% pure).

(4) F. C. McGrew and R. Adams, THIS JOURNAL, **59**, 1497 (1937).

(5) G. F. Hennion and B. R. Fleck, *ibid.*, **77**, 3253 (1955).

(6) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

(7) R. Robinson and R. C. Shah, *J. Chem. Soc.*, 1491 (1934).

(8) R. L. Shriner and R. C. Fuson, ref. 6, p. 142.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE CHEMICAL DEPARTMENT, TEMPLE UNIVERSITY AND SOCONY MOBIL OIL CO., RESEARCH AND DEVELOPMENT LABORATORY]

Disubstituted Phosphine Oxides. IV. Addition Reactions with Aldehydes and Ketones[1]

BY ROBERT CLAY MILLER,[2,3] CAROLINE D. MILLER,[2,3] WILLIAM ROGERS, JR., AND LYLE A. HAMILTON

RECEIVED AUGUST 22, 1956

Two disubstituted phosphine oxides have been added to a series of aldehydes and ketones in the presence of traces of sodium ethoxide to yield disubstituted phosphinyl alcohols (III). Reduction of α-(dibenzylphosphinyl)-benzyl alcohol (IIIa) with red phosphorus and hydriodic acid gave the known tribenzylphosphine oxide. Heating III with aqueous alcoholic sodium hydroxide resulted in cleavage of the adduct to form the sodium salt of dibenzylphosphinic acid.

Disubstituted phosphine oxides (I) recently have been shown to add in the presence of traces of base to α,β-unsaturated nitriles and carbonyl compounds[1] to form unsymmetrical phosphine oxides. Similar reactions involving dialkyl phosphonates (II) are well known.[4] This paper reports the base-catalyzed addition of I to aldehydes and ketones to form disubstituted phosphinyl alcohols[5] (III). Abramov and co-workers[6] have carried out the

(1) For the third paper in this series, see R. C. Miller, J. S. Bradley and L. A. Hamilton, THIS JOURNAL, **78**, 5299 (1956).

(2) Abstracted in part from dissertations submitted (R.C.M.) and to be submitted (C.D.M.) to the Temple University Graduate Council in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Experimental Station, E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.

(4) A. N. Pudovik and B. A. Arbuzov, *Doklady Akad. Nauk S.S.S.R.*, **73**, 327 (1950); *C. A.*, **45**, 2853 (1951).

(5) These compounds were arbitrarily named as substituted alcohols rather than α-hydroxy tertiary phosphine oxides, since no precedence list exists for naming phosphine oxides bearing a hydroxyl substituted side chain.

(6) A few of the series of papers on this subject by Abramov and co-workers are: (a) V. S. Abramov, *Doklady Akad. Nauk S.S.S.R.*, **73**, 487 (1950); *C. A.*, **45**, 2855 (1951); (b) V. S. Abramov, L. P.