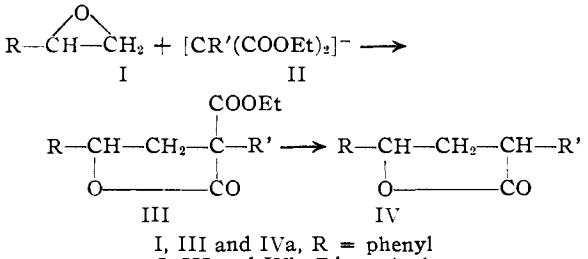
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF HOPE COLLEGE]

The Preparation of 5-Alkyl-5-(β-phenyl- and β-Vinyl-β-hydroxyethyl)-barbituric Acids *Via* the Corresponding α-Carbethoxy-γ-butyrolactones

BY GERRIT VAN ZYL AND EUGENE E. VAN TAMELEN

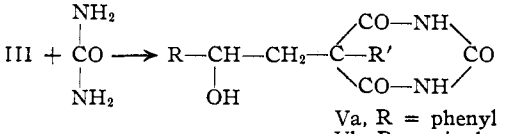
As early as 1899, Traube and Lehmann[1] condensed ethylene oxide and epichlorohydrin with malonic ester to yield α-carbethoxy-γ-butyrolactone and α-carbethoxy-δ-chloro-γ-valerolactone, respectively. Since that time, the epoxide reaction with malonic ester has been extended by various workers.[2,3,4,5] Because of inner transesterification, an α-carbethoxy-γ-butyrolactone was always the only product that could be isolated, except in one instance,[6] where special steric factors allowed the isolation of the intermediate β-hydroxyalkyl malonic ester. The present investigation is concerned with the reaction of styrene oxide (Ia) and butadiene monoxide (Ib) with various malonic esters (II) to yield α-carbethoxy-γ-phenyl-γ-butyrolactones (IIIa) and α-carbethoxy-γ-vinyl-γ-butyrolactones (IIIb). By means of this reaction, the lactones IVa (R′ = H) and IVb (R = H) were prepared without isolation of intermediates by Russell and Vander Werf[7]; they showed that in both cases attack by the malonic ester anion occurred exclusively at the terminal carbon atom of the epoxide ring.



I, III and IVa, R = phenyl
I, III and IVb, R′ = vinyl

The course of the reaction depends to a great extent upon the temperature at which it is carried out. If the oxides are added dropwise to a *boiling* solution of II in alcohol, IVa and IVb are the only products which can be isolated (unless R′ = H). This result is not surprising, since the cleavage of α-disubstituted acetoacetic esters to disubstituted acetic esters by sodium alkoxide is well known; and Cope and McElvain[8] were able to show that disubstituted malonic esters may be decomposed in a similar fashion. If the addition of Ia and Ib, however, is made at 40°, the carbethoxy lactones are isolated in good yields. IIIa and IIIb are of pleasant odor, colorless or light yellow liquids whose properties are listed in Table I. They may be smoothly hydrolyzed to the corresponding lactones IV (Table II). All of these compounds (except IV, R′ = H) possess two asymmetric centers, and therefore two racemic forms are theoretically possible for each; no attempt was made to separate them during fractionation, however.

The 5-alkyl-5-(β-phenyl- and vinyl-β-hydroxyethyl)-barbituric acids Va and Vb were prepared by condensing IIIa and IIIb with urea in the usual manner. Va and Vb possess the distinctive



Va, R = phenyl
Vb, R = vinyl

feature of incorporating both a hydroxyl group and a point of unsaturation in the same molecule. The hydroxyl group should increase the solubility in water, a desirable property, since Sommaire[9] has shown that the hypnotic power of a barbiturate largely depends on this factor. The allyl and the phenyl group are characteristic of the well-known hypnotics Dial and Phenobarbital.

The properties of Va and Vb are summarized in Table III. They are white, microcrystalline solids which were purified by crystallization only with difficulty. If R′ = H (Table I), no trace of barbituric acid was formed under the usual reaction conditions. 5-Alkyl-5-(β-hydroxyethyl)-barbituric acids have previously been made from α-alkyl-α-carbethoxybutyrolactones by Skinner and co-workers.[10]

The pharmacological properties of Va and Vb are being investigated.

Although there is little doubt that the structures of Va and Vb are as formulated, the constitution of one of these, Va (R = ethyl), was proved by its synthesis by an alternative method, *viz.*, the base-catalyzed condensation of 5-ethyl-barbituric acid and styrene oxide. So far as is known to us, this is the first instance of the reaction of a barbituric acid with an epoxide. Five alkyl-barbituric acids have been previously employed successfully as nucleophilic reagents, however, with allyl bromide[11] and benzyl chloride.[12] Although the method is being investigated further, it apparently has little preparative value, since

(1) Traube and Lehmann, (a) *Ber.*, **32**, 720 (1899); (b) **34**, 197 (1901).
(2) Coffey, *Rec. trav. chim.*, **42**, 387 (1923).
(3) Pakendorf, *Compt. rend. acad. sci. U. R. S. S.*, **27**, 956 (1940).
(4) Mousseron, *et al.*, *Bull. soc. chim. France*, 629 (1946).
(5) Cavallito, Fruehauf and Bailey, THIS JOURNAL, **70**, 3724 (1948).
(6) Grigsby, Hind, Chandley and Westheimer, *ibid.*, **64**, 2606 (1942).
(7) Russell and Vander Werf, *ibid.*, **69**, 11 (1947).
(8) Cope and McElvain, *ibid.*, **54**, 4319 (1932).
(9) Sommaire, *Bull. soc. chim.*, **33**, 189 (1923).
(10) (a) Skinner, THIS JOURNAL, **47**, 1124 (1925); (b) **56**, 1339 (1934); (c) **59**, 322 (1937); (d) **63**, 2993 (1941); (e) **69**, 3083 (1947).
(11) Volwiler, *ibid.*, **47**, 2236 (1925).
(12) Dox and Yoder, *ibid.*, **44**, 1141 (1922).

TABLE I

THE PROPERTIES OF α-CARBETHOXY-γ-PHENYL- AND VINYL-γ-BUTYROLACTONES

R	Formula	B. p., °C.	Mm.	$n^{25}D$	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
				IIIa					
H	$C_{13}H_{14}O_4$	188–191	3.0	1.5197	60	66.65	66.54	6.02	6.21
Ethyl	$C_{15}H_{18}O_4$	168–171[a]	2.0	1.5213	65	68.68	68.80	6.92	7.06
Allyl	$C_{16}H_{18}O_4$	150–152	1.5	1.5200	25	70.04	70.20[b]	6.62	6.53[b]
n-Butyl	$C_{17}H_{22}O_4$	167–170	1.0	1.5085	50	70.59	70.49[b]	7.64	7.59[b]
i-Amyl	$C_{18}H_{24}O_4$	180–182	1.3	1.5034	65	71.01	70.93	7.95	7.79
				IIIb					
H	$C_9H_{12}O_4$	149–152[c]	13	1.4585	73	58.68	58.47	6.56	6.65
Ethyl	$C_{11}H_{16}O_4$	147–150[d]	13	1.4597	60	62.25	62.39	7.59	7.50
Allyl	$C_{12}H_{16}O_4$	113–114	1.0	1.4680	54	64.26	63.92[b]	7.20	7.36[b]
n-Butyl	$C_{13}H_{20}O_4$	161–164	11	1.4611	30	64.97	64.82	8.39	8.47
i-Amyl	$C_{14}H_{22}O_4$	122–124	1.0	1.4584	72	66.15	66.30	8.72	8.79

[a] 178–181° (4 mm.). [b] Average of two determinations. [c] 95–97° (1.0 mm.). [d] 165–166° (22 mm.).

TABLE II

THE PROPERTIES OF γ-PHENYL- AND VINYL-γ-BUTYROLACTONES

R'	R	Formula	B. p., °C.	Mm.	$n^{25}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ethyl	Phenyl	$C_{12}H_{14}O_2$	174–175	14	1.5263	75.76	75.65[a]	7.42	7.55
n-Butyl	Phenyl	$C_{14}H_{18}O_2$	190–192	13	1.5166	77.03	77.10	8.32	8.27
Ethyl	Vinyl	$C_8H_{12}O_2$	108–110	14	1.4562	68.53	68.20	8.63	8.66
n-Butyl	Vinyl	$C_{10}H_{16}O_2$	133–135	14	1.4567	71.40	71.70	9.58	9.89

[a] Average of two determinations.

the yield in this one case could not be raised above 10%. The desired acid was contaminated with considerable amounts of polymeric material.

TABLE III

PROPERTIES OF 5-(β-PHENYL- AND VINYL-β-HYDROXYETHYL)-BARBITURIC ACIDS

R'	Formula	M. p.,[a] °C.	Yield, %[b]	Nitrogen, % Calcd.	Nitrogen, % Found
		Va			
Ethyl	$C_{14}H_{16}O_4N_2$	214[c]	80	10.15	9.92[d]
Allyl	$C_{15}H_{16}O_4N_2$	191–192[e]	70	9.75	9.80
n-Butyl	$C_{16}H_{20}O_4N_2$	230–231[f]	66	9.27	8.98[g]
i-Amyl	$C_{17}H_{22}O_4N_2$	238–239[f]	70	8.80	8.78
		Vb			
Ethyl	$C_{10}H_{14}O_4N_2$	193–194[h]	62	12.36	12.40[i]
Allyl	$C_{11}H_{14}O_4N_2$	182.5[h]	52	11.76	11.81
n-Butyl	$C_{12}H_{18}O_4N_2$	174.5–175[f]	38	11.02	11.17
i-Amyl	$C_{13}H_{20}O_4N_2$	187.5–188[e]	50	10.44	10.64

[a] All melting points are corrected. [b] All yields calculated as indicated in experimental section. [c] From dioxane–water. [d] Calcd.: C, 60.85; H, 5.87. Found: C, 61.17; H, 6.17. [e] From methyl alcohol–ether. [f] From ether. [g] Calcd.: C, 63.13; H, 6.63. Found: C, 63.15; H, 6.72. [h] From methyl alcohol–chloroform–pet. ether.

Experimental

α-Ethyl-α-carbethoxy-γ-phenyl-γ-butyrolactone.—The following procedure exemplifies the method used for the preparation of the α-carbethoxylactones. The sodium enolate was prepared from 0.6 mole of diethyl ethylmalonate in 300 cc. of absolute alcohol contained in a one-liter three-neck flask equipped with a stirrer, thermometer, dropping funnel and reflux condenser with a calcium chloride tube attached. Styrene oxide (72.0 g., 0.6 mole) was added dropwise with stirring over a period of two hours. The internal temperature was maintained at 40° during the addition (usually the heat liberated during the addition is sufficient to maintain this temperature automatically). The resulting yellow-orange solution was allowed to stand for several hours. After cooling in an ice-bath to 15°, cooled glacial acetic acid was added slowly until the contents were neutral or slightly acid to litmus; a brei of sodium acetate formed immediately. The excess alcohol was removed under reduced pressure. Water was added and the resulting oily layer separated. The aqueous layer was extracted once with ether. The combined crude ester and extract were dried overnight over sodium sulfate. The material was distilled from a Claisen flask, the fraction boiling at 175–183° (4 mm.) being collected. Refractionation with a column packed with glass helices yielded 102.2 g. of a colorless liquid boiling at 168–171° (2 mm.).

α-Alkyl-γ-phenyl- and Vinyl-γ-butyrolactones.—The following modification of Russell and Vander Werf's method[7] was advantageously used. After the saponification was complete and the excess alcohol distilled, the solution was cooled to room temperature and a slight excess of cold, dilute sulfuric acid added. The resulting mixture was refluxed for one hour, during which time the white solid initially formed changed over completely into the liquid lactone. The lactone layer was separated, two ether extracts of the aqueous layer were added to the lactone and the combined portions dried over anhydrous sodium sulfate and distilled (see Table II).

α-Carboxy-γ-phenyl-γ-butyrolactone.—α-Carbethoxy-γ-phenyl-γ-butyrolactone (11.2 g., 0.05 mole) was shaken manually with a solution of 15 g. of potassium hydroxide in 30 cc. of water until the mixture became homogeneous; the solution was allowed to stand overnight. Acidification was then effected with concentrated hydrochloric acid while the solution of the disodium salt was cooled in a water-bath at room temperature. The white, crystalline carboxy-lactone was filtered off and recrystallized from water to free it from potassium chloride; yield 7.4 g., 75%; m. p. 149.3–150.0°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.06; H, 4.89; neut. equiv., 206.2. Found: C, 64.03; H, 4.74; neut. equiv., 205.7, 206.1.

5-Ethyl-5-(β-phenyl-β-hydroxyethyl)-barbituric Acid. Method A.—Freshly cut sodium metal (13.8 g., 0.6 mole)

was dissolved in 300 cc. of absolute alcohol. The flask was placed in a water-bath at room temperature and dry urea (24.0 g., 0.4 mole) was added with stirring. After the urea was almost all dissolved, α-ethyl-α-carbethoxy-γ-phenyl-γ-butyrolactone (31.4 g., 0.12 mole) was added dropwise over a period of two hours. Stirring was continued for several more hours and the alcohol was distilled under reduced pressure (20–25 mm.) at a temperature not over 40°. Approximately 300 cc. of water was added and the solution extracted with three 50-cc. portions of chloroform. The aqueous solution was then immersed in an ice-bath and made acid to congo red with dilute hydrochloric acid (1:3). The crude barbituric acid was triturated with a small amount of ether to remove oily impurities; yield 26.5 g. The acid purified by recrystallization from dioxane–water or by solution in ether and subsequent concentration under reduced pressure melted at 214°. The procedure was the one essentially used in the preparation of the barbituric acids listed in Table III.

Method B.—5-Ethylbarbituric acid (15.6 g., 0.1 mole) was dissolved in a solution of 5.6 g. of potassium hydroxide in 80 cc. of water. The acidity of the resulting clear solution was adjusted with dilute hydrochloric acid until neutral to litmus, and styrene oxide (12.0 g., 0.1 mole) was added. The mixture was stirred at room temperature for forty-eight hours. The water solution was separated from the remaining styrene oxide and extracted with ether. Upon acidification of the solution of the sodium salt with concentrated hydrochloric acid, a sticky, viscous mass formed; the clear, supernatant solution was decanted immediately and cooled for several hours in the refrigerator. One recrystallization from water yielded 2.6 g. of a compound melting at 212–213° (cor.). No depression was observed in a mixed melting point with the barbituric acid obtained by Method A; the infrared spectra were identical.

Acknowledgment.—We are indebted to the Research Corporation for a grant supporting this work. We also wish to thank Prof. C. A. Vander Werf of the University of Kansas for his interest in this investigation and also the Pittsburgh Plate Glass Corp. for a generous gift of butadiene monoxide.

Summary

A series of α-carbethoxy-γ-phenyl- and vinyl-γ-butyrolactones has been made and used subsequently for the preparation of 5-alkyl-5-(β-phenyl- and vinyl-β-hydroxyethyl)-barbituric acids.

5-Ethyl-5(β-phenyl-β-hydroxyethyl)-barbituric acid has been alternately synthesized by a new reaction, the condensation of styrene oxide with 5-ethylbarbituric acid.

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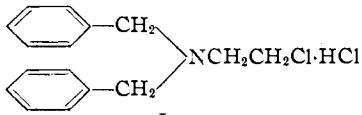
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY AND KALAMAZOO COLLEGE]

N-(β-Chloroethyl)-2,3-dihydro-1-benz[de]isoquinoline Hydrochloride

BY WILLIAM L. GARBRECHT,[1] JAMES H. HUNTER AND JOHN B. WRIGHT

In view of the strong adrenolytic activity reported by numerous investigators[2] for β-chloroethyldibenzylamine hydrochloride (I) and related compounds it appeared of interest to investigate a compound in which the two phenyl rings were



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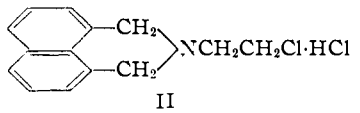
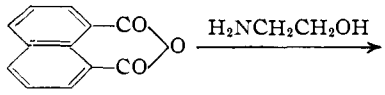
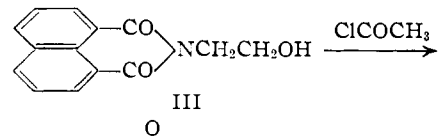


II

fused in a naphthalene ring. Accordingly, N-(β-chloroethyl)-2,3-dihydro-1-benz[de]isoquinoline hydrochloride[3] (II) has been synthesized and screened for adrenolytic activity.

The preparation of II was carried out according to the scheme





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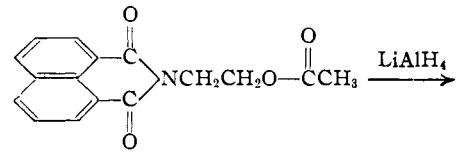

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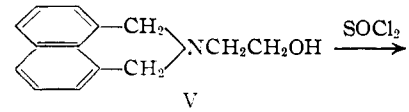

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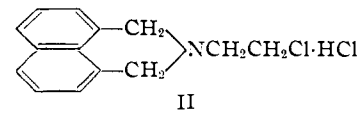

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N-(β-Hydroxyethyl)-naphthalimide (III) was prepared by the reaction between naphthalic anhydride and ethanolamine.[4] The direct reduction of III with lithium aluminum hydride in ether solution was found to be unfeasible due to the extreme insolubility of the compound in ether. After several unsuccessful attempts[5] to reduce III to

(1) Present address: Department of Chemistry, Michigan State College, East Lansing, Michigan.

(2) *Cf.* Nickerson, *J. Pharmacol. Exptl. Therap.*, **95** (Part II), 27 (1949).

(3) This compound has been named according to the nomenclature given for the parent ring system in "The Ring Index," Patterson and Capell, Reinhold Publishing Corp., New York, N. Y., 1940, p. 268.

(4) Fierz-David and Rossi, *Helv. Chim. Acta*, **21**, 1477 (1938).

(5) The use of tetrahydrofuran, in which the compound was somewhat soluble, as a solvent medium in the reaction gave negative results as only a tarry material was isolated from the reaction mixture.