The above fractions were combined and boiled briefly with 50 cc. of dry toluene. The crystals which did not dissolve in the hot toluene were filtered and washed with toluene, m.p. 235–236°. Fractional crystallization of the hot filtrate by cooling to room temperature yielded a product melting at 230–235°. Further cooling to 0° and concentration of the filtrate under diminished pressure gave a product melting at 155–156°. Recrystallization of these fractions from toluene gave 2-diphenylmethylene-3-methyloxazolidine-4,5-dione (IV) (4.6 g., m.p. 238–239°, 35%) and 2-diphenylmethylene-4-methoxy-3-oxazolin-5-one (VI) (11.5 g., m.p. 158°, 65%). Recrystallization of VI from ethyl acetate failed to raise the melting point.

The mixture of XII and IX (39.7 g., 99%) from the action of diazoethane (8.84 g., 0.158 mole) on I could not be separated in the above manner but was partially separated as follows. The crystalline mixture was divided into seven fractions by recrystallization from ethyl acetate. The last fraction obtained from the ethyl acetate was recrystallized from toluene. The next to the last fraction from ethyl acetate was then recrystallized from the toluene mother liquor. This reverse process was continued until all seven fractions had been recrystallized from the preceding toluene mother liquor. Then ethyl acetate was used again starting with the last fractions from toluene. This process was repeated until toluene had been used four times and ethyl acetate five times. This procedure yielded IX (32%) which was less soluble in ethyl acetate, and XII (18%) which was less soluble in toluene. The remainder of the crystalline material was not separated.

The mixture of V and VII (45.5 g. 99%) from the action of 8.15 g. (0.194 mole) of diazomethane on 41.0 g. (0.194 mole) of II was in the form of a viscous yellow oil which contained some crystals. The crystals, VII (6.9 g., 15%), were filtered and recrystallized from benzene, m.p. 122–123°. The viscous mother liquor was treated with a large variety of hydrocarbon and chlorinated hydrocarbon solvents, dioxane and ether. In no case did the mixture show signs of separation and no crystalline material could be obtained. Similarly, vacuum distillation, sublimation and column chromatography using alumina or magnesium trisilicate as absorbents failed to separate the mixture.

A very similar mixture of X and XIII (21.5 g., 97%) was obtained from the action of 5.21 g. (0.093 mole) of diazoethane on 19.5 g. (0.090 mole) of II. No crystalline compounds could be obtained and the viscous oil could not be separated.

The mixture of products (39.8 g., 99%) from the action of 9.54 g. (0.227 mole) of diazomethane on 37.22 g. (0.220 mole) of III was fractionally distilled. There was obtained 19.6 g. (49%) of VIII, b.p. 89.0–89.5° (1.6 mm.), $n^{25}D$ 1.5204, d_{25} 1.0876.

The reaction of 9.31 g. (0.166 mole) of diazoethane with 27.07 g. (0.160 mole) of III gave a yellow oil (27.5 g., 87%) which was distilled. There was obtained 13.0 g. (41%) of XI, b.p. 80.5–81.0° (0.45 mm.), $n^{25}D$ 1.5085, d_{25} 1.0570, and 2.4 g. (7%) of XIV, b.p. 120–122° (0.45 mm.).

Reaction of 3-Oxazolin-5-ones with Methanol and Ethanol.—In a typical reaction (Table II), 1.5 g. (0.0054 mole) of VI was refluxed for 48 hr. with 50 cc. of absolute[7] ethanol. The alcohol was evaporated to dryness under diminished pressure, and the crystalline residue was recrystallized from ethanol to yield 1.7 g. (81%) of pure XVIII, m.p. 142–143°.

These reactions are summarized in Table II. The alcohol used as the reagent was used to recrystallize the product.

Reaction of Mixture of V and VII with Ethanol.—A 5.0-g. sample of the mixture of V and VII obtained from the action of diazomethane on II was refluxed for 48 hr. with absolute ethanol. The ethanol was evaporated under diminished pressure which gave some crystalline material suspended in a viscous oil. The mixture was filtered with suction and the crystalline XIX was recrystallized from ethanol, 0.9 g., m.p. 122.5–123.5°. The filtrate was distilled at 0.65 mm. There was obtained 1.4 g. of 4-ethyl-1-methyl-4-phenylpyrrolidine-2,3,5-trione, b.p. 147–149° (0.65 mm.); 2,4-dinitrophenylhydrazone, m.p. 177–179°. The m.p. showed no depression when mixed with an authentic sample.

Reaction of the Mixture of X and XIII with Ethanol.—A 5.0-g. sample of the mixture of X and XIII from the action of diazoethane with II was refluxed for 48 hr. with absolute ethanol. Evaporation of the ethanol under diminished pressure gave an oil in which was suspended 1.45 g. of XVIII. The mixture was filtered and distillation of the filtrate gave 2.15 g. of 1,4-diethyl-4-phenylpyrrolidine-2,3,5-trione, b.p. 132.0–135.0° (0.35 mm.); 2,4-dinitrophenylhydrazone, m.p. 139–140°. There was no depression when mixed with an authentic sample.

Reaction of 3-Oxazolin-5-ones with Aniline.—The same procedure was used for these reactions as used in the reaction of aniline with oxazolidinediones.[1] In each case, oxanilide and the corresponding amide were obtained.

Reaction of Aminoacetic Acid Esters with Aniline.—In a typical case of 0.5 g. (0.00146 mole) of XV (Table III) was dissolved in 20 cc. of dry benzene, and 0.14 g. (0.00146 mole) of freshly distilled aniline was added. The solution was refluxed for 4 hr. The mixture was evaporated to one-third of its original volume and cooled to 0°. Then the mixture was diluted to three times its volume with petroleum ether (b.p. 30–60°). The white solid (0.50 g.) that precipitated was recrystallized from methanol and gave 0.45 g. of XX, m.p. 159–160°.

(7) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, Mass., 1941, p. 359.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Condensation of Monophenyl- and Diphenylguanidine with Malonates and α-Alkyl-α-carbethoxy-γ-butyrolactones

BY GLENN S. SKINNER, JEANETTA M. RENEBERGER AND HERWART CURT VOGT[1,2]

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Both substituted malonic esters and α-alkyl-α-carbethoxy-γ-butyrolactones condense with monophenylguanidine in alcoholic sodium ethoxide to give 5,5-disubstituted 2-phenyliminobarbituric acids. Substituted malonic esters and diphenylguanidine in alcoholic potassium or sodium ethoxide yield 1-phenyl-2-phenyliminobarbituric acids. Condensation of the lactone esters with diphenylguanidine gives an isomeric intermediate in which the barbituric acid ring has not formed.

It has been reported that α-alkyl-α-carbethoxy-γ-butyrolactones condense with urea[3] to give the 5-alkyl-5-β-hydroxyethylbarbituric acid and with thiourea[4] to form the 2-thiobarbituric acid and an isomeric intermediate which could be converted to the thiobarbituric acid. When the alkyllactone esters were condensed with benzamidine[5] the condensation took place only at the carbethoxy group and the tetrahydropyrimidine ring did not form. Monoalkylureas[6] have been condensed with di-

(1) Research Fellow, Wallace H. Carothers Research Grant.

(2) Based chiefly on the Ph.D. thesis of Herwart Curt Vogt.

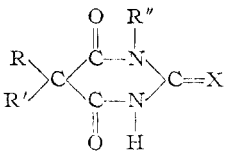
(3) E. F. Rosenberg, R. F. Kneeland and G. S. Skinner, THIS JOURNAL, **56**, 1339 (1934).

(4) G. S. Skinner and J. Mitchell, Jr., *ibid.*, **67**, 1252 (1945).

(5) G. S. Skinner, E. Anderson and R. F. Bogart, *ibid.*, **71**, 1482 (1949).

(6) A. Stein, H. P. Gregor and P. E. Spoerri, *ibid.*, **78**, 6185 (1956).

TABLE I



	R	R′	R″	X	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Found
I	C_2H_5	$HOCH_2CH_2$	H	C_6H_5N	197 d.	89	[a]	[a]
II	C_4H_9	$HOCH_2CH_2$	H	C_6H_5N	141 d.	81	13.85	13.91[b]
III	i-C_5H_{11}	$HOCH_2CH_2$	H	C_6H_5N	148 d.	89	13.24	13.22[c]
IV	C_2H_5	$BrCH_2CH_2$	H	C_6H_5N	190 d.	92	12.42	12.21[d]
V	C_4H_9	$BrCH_2CH_2$	H	C_6H_5N	191 d.	97	11.47	11.24[e]
VI	i-C_5H_{11}	$BrCH_2CH_2$	H	C_6H_5N	180 d.	84	11.05	11.02
VII	C_2H_5	$C_2H_5SC_2H_4$	H	C_6H_5N	174–175 d.	84	13.16	13.30
VIII	C_4H_9	$C_2H_5SC_2H_4$	H	C_6H_5N	141 d.	94	12.09	12.24[f]
IX	i-C_5H_{11}	$C_2H_5SC_2H_4$	H	C_6H_5N	182 d.	94	11.62	11.72[g]
X	C_4H_9	C_2H_5	H	C_6H_5N	193	14	14.62	14.44[h]
XI	i-C_5H_{11}	C_2H_5	H	C_6H_5N	201	20	13.94	14.36[i]
XII	C_2H_5	C_2H_5	C_6H_5	C_6H_5N	176–177	73	12.44	12.27
XIII	C_2H_5	i-C_5H_{11}	C_6H_5	C_6H_5N	143–144	52	11.13	11.10
XIV	i-C_5H_{11}	i-C_5H_{11}	C_6H_5	C_6H_5N	116–117	37	10.01	10.00
XV	C_4H_9	H	C_6H_5	C_6H_5N	128–129	59	12.53	12.66
XVI	C_2H_5	H	C_6H_5	C_6H_5N	163–164	10	13.67	13.62
XVII	H	H	C_6H_5	C_6H_5N	214–215	90	15.04	15.01
XVIII	C_6H_5CH	.....	C_6H_5	C_6H_5N	200	92	11.44	11.44
XIX	C_6H_5CH	.....	C_6H_5	O	240	55	9.62	9.49
XX	C_4H_9	H	C_6H_5	O	141–142	94	10.76	10.65

[a] Calcd.: C, 61.07; H, 6.24. Found: C, 61.03; H, 6.14. [b] Calcd.: C, 63.34; H, 6.99. Found: C, 63.28; H, 6.89. [c] Calcd.: C, 64.32; H, 7.32. Found: C, 64.45; H, 7.61. [d] Calcd.: Br, 23.63. Found: Br, 23.18. [e] Calcd.: Br, 21.81. Found: Br, 21.55. [f] Calcd.: C, 62.20; H, 7.26. Found: C, 62.44; H, 7.06. [g] Calcd.: C, 63.11; H, 7.54. Found: C, 63.27; H, 7.57. [h] Calcd.: C, 66.86; H, 7.38. Found: C, 66.95; H, 7.54. [i] Calcd.: C, 67.73; H, 7.71. Found: C, 68.09; H, 7.76.

alkyl malonates to give barbituric acid derivatives. Symmetrical dialkylthioureas[7] failed to condense under these conditions.

It therefore seemed of interest to compare the products from the lactone esters and malonates and especially to determine the degree of phenylation of guanidine that would prevent ring closure to a β-hydroxyethylbarbituric acid derivative. For this purpose we have used monophenyl- and *sym*-diphenylguanidine. Monophenylguanidine condensed uniformly with the malonates to give 2-phenyliminobarbituric acids (Table I). The structure was shown by acid hydrolysis to the corresponding barbituric acid. Diphenylguanidine condensed to form 1-phenyl-2-phenyliminobarbituric acids which by hydrolysis yielded 1-phenylbarbituric acids. It was found in the case of 1-phenyl-2-phenyliminobarbituric acid that prior condensation with benzaldehyde was necessary to prevent cleavage of the ring during hydrolysis. The barbituric acids thus obtained were identical with those obtained from urea and phenylurea. The identity of the product obtained from monophenylguanidine was further shown by its synthesis from aniline and the 2-thiobarbituric acid derivative.

The lactone esters all condensed smoothly with monophenylguanidine to give 5-alkyl-5-β-hydroxyethyl-2-phenyliminobarbituric acids (Table I). These compounds were converted to the β-bromoethyl and β-ethylmercaptoethyl derivatives. The latter were reduced with the aid of Raney nickel[8] to the 5-alkyl-5-ethyl-2-phenyliminobarbituric acids. These products were identical with those prepared directly from the alkylethylmalonates and monophenylguanidine.

The products obtained from the condensation between the lactone esters and diphenylguanidine (Table II) required much longer periods for their formation. They melted at relatively low temperatures giving aniline and carbon dioxide among their decomposition products. These condensation products all dissolved readily in the fuming hydrobromic acid at room temperature, but unlike the products from monophenylguanidine did not reprecipitate after reaction. Moreover these products, unlike those from monophenylguanidine, were not precipitated from the hydrobromic acid solution by dilution with water. Neutralization of the acid solution at ice temperature caused the reprecipitation of the condensation product. No β-bromoethyl derivative could be obtained from condensation of the lactone esters with diphenylguanidine, indicating that in this case the barbituric acid ring had not formed.

Selected compounds when subjected to pharmacological tests[9] gave no hypnotic action orally (XII, XV) in rats, no anesthesia (XVII) in 1% solution on guinea pig's eyes or skin, no protection against electro or metrazole shock (XIII) by mouth

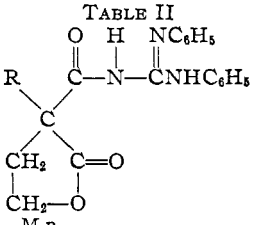
(7) N. V. Koshkin, *J. Gen. Chem. (U. S. S. R.)*, **5**, 1460 (1935); *C. A.*, **30**, 2177 (1936).

(8) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

(9) Tests by Eli Lilly and Co.

in rats, a trace (XVII) or no (XIV, XV) analgesic activity when administered subcutaneously in rats and no inhibition (XV, XVII) to carbonic anhydrase.

TABLE II



	R	M.p., dec., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XXI	C_6H_5	143–143	75	68.35	68.31	6.04	6.19
XXII	C_6H_5	67	42	69.62	69.74	6.65	6.68
XXIII	i-C_6H_{11}	81	46	70.19	69.43	6.93	7.18

Experimental

1-Phenyl-2-phenyliminobarbituric Acids.—In a typical experiment a mixture of 20 cc. of ethanol and 40 cc. of ether was added dropwise to 3.50 g. (0.092 mole) of potassium covered with 50 cc. of ether. To the residual potassium ethoxide solution after distillation of the ether 10.65 g. (0.050 mole) of diphenylguanidine and 8.6 g. (0.045 mole) of diethyl diethylmalonate were added. The mixture was refluxed for 14 hr. The cooled mixture was treated with 175 cc. of ice and water containing 10 cc. of acetic acid and then made slightly alkaline with aqua ammonia. The filtered precipitate was washed with water and petroleum ether and recrystallized from 60% alcohol (XII). When sodium ethoxide was used in place of potassium ethoxide the yield dropped to 52%. To isolate XVI and XVII the alcohol first was removed under diminished pressure.

To prepare XVIII a mixture of 2.0 g. (0.007 mole) of XVII, 20 cc. of ethanol and 0.7 cc. (0.007 mole) of freshly distilled benzaldehyde was refluxed for 30 min. The precipitate which separated on cooling was filtered and washed with hot water, ethanol and ether.

Hydrolysis of 1-Phenyl-2-phenyliminobarbituric Acids.—In a typical case a mixture of 1.00 g. of XIII, 6 cc. of hydrochloric acid (sp. gr. 1.19), 4 cc. of water and 5 cc. of glacial acetic acid was refluxed for 30 min. The cooled mixture was made alkaline with sodium hydroxide, washed with ether and then made acid to congo red. The gummy precipitate was washed with water by decantation and crystallized from 50% alcohol to give a product, m.p. 125–126° (38%). This product was identical with that prepared from phenylurea.[10] Acid hydrolysis of XII and XV yielded the corresponding 1-phenylbarbituric acids which were identical (m.m.p.) with the products from the malonate and phenylurea. Also acid hydrolysis of XVIII gave XIX which was identical with the product obtained by condensation of 1-phenylbarbituric acid with benzaldehyde.

5-Alkyl-5-β-hydroxyethyl-2-phenyliminobarbituric Acids.—In a typical experiment 9.01 g. (0.0275 mole) of monophenylguanidine carbonate was added to a solution of sodium ethoxide prepared from 5.52 g. (0.24 mole) of sodium and 120 cc. of ethanol. The mixture was stirred for 1 hr., cooled to 20° and 9.0 cc. (0.05 mole) of α-ethyl-α-carbethoxy-γ-butyrolactone was added dropwise. The mixture was then warmed to 45° during 1 hr. and maintained at this temperature for 14 hr. The cooled solution was neutralized with standardized alcoholic hydrogen chloride. The solvent was distilled under diminished pressure and the residue was treated with 200 cc. of iced water and 10 cc. of acetic acid. The filtered precipitate was washed with cold water, dried and crystallized from 80% alcohol (I, II, III).

A cold solution of 0.50 g. of I in absolute alcohol was saturated with hydrogen bromide. The residue from removal of the solvent under diminished pressure by treatment with ether and crystallization from alcohol–ether gave the hydrobromide, m.p. 175° dec. It was reconverted to I by treatment with 5% sodium bicarbonate followed by acidification with acetic acid.

Anal. Calcd. for $C_{14}H_{18}BrN_3O_2$: Br, 22.43. Found: Br, 22.50.

(10) J. B. Dickey and A. R. Gray, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p.60.

5-Alkyl-5-β-bromoethyl-2-phenyliminobarbituric acids were prepared as previously described[11] for the 5-alkyl-5-β-bromoethylbarbituric acids and purified by crystallization from benzene (IV, V, VI). The hydrobromide of IV prepared as above melted at 238° dec. and its aqueous solution underwent hydrolysis to IV. The bromide IV was insoluble in both water and ether but could be recrystallized from benzene or toluene. Treatment of IV with cold 20% sodium hydroxide followed by acidification gave the original hydroxyethyl compound I.

Anal. Calcd. for $C_{14}H_{17}Br_2N_3O_2$: Br, 38.15. Found: Br, 38.10.

5-Alkyl-5-β-ethylmercaptoethyl-2-phenyliminobarbituric Acids.—To a solution of sodium ethyl mercaptide prepared from 0.46 g. (0.020 mole) of sodium, 100 cc. of ethanol and 2.5 g. (0.040 mole) ethyl mercaptan was added a solution of IV, V or VI in alcohol. The mixture was refluxed overnight and then evaporated to about 50 cc. The product was precipitated by addition to several volumes of iced water containing an excess of acetic acid. It was purified by crystallization from an alcohol–water mixture (VII, VIII, IX).

Reduction of 5-Alkyl-5-β-ethylmercaptoethyl-2-phenyliminobarbituric Acids.—In a typical experiment a solution of 1.00 g. of VII in 200 cc. of 95% alcohol was refluxed with about 20 g. of Raney nickel for 5 hr. The filtrate after concentration to about 20 cc. slowly deposited crystals, m.p. 253°. Admixture with 5,5-diethyl-2-phenyliminobarbituric acid prepared from monophenylguanidine carbonate and diethyl diethylmalonate showed no depression in m.p.

5,5-Dialkyl-2-phenyliminobarbituric Acids. Method A.—To a solution of sodium ethoxide prepared from 5.52 g. (0.24 mole) of sodium and 80 cc. of ethanol was added 9.0 g. (0.0275 mole) of monophenylguanidine carbonate and 12.2 g. (0.050 mole) of diethyl *n*-butylethylmalonate. After heating 24 hr. at 70° the solvent was removed under diminished pressure and the aqueous ice-cold solution was acidified to congo red. The precipitate was recrystallized from alcohol (X, XI).

Method B.—A mixture of 10.0 g. (0.050 mole) of 5,5-diethyl-2-thiobarbituric acid and 4.66 g. (0.050 mole) of freshly distilled aniline was heated at 80° until a negative test for hydrogen sulfide was obtained (2 days). The solid precipitate was purified with the aid of Darco by crystallization from alcohol, yield 5.1 g. (40%), m.p. 253°, identical with the product by method A, lit.[12] m.p. 251–252° (method B).

The acid hydrolysis of the above 2-phenyliminobarbituric acids gave the corresponding barbituric acids which were identical with those obtained from the malonic esters and urea.

Reaction of Diphenylguanidine with α-Alkyl-α-carbethoxy-γ-butyrolactones.—To a cooled solution of sodium ethoxide prepared from 9.2 g. (0.40 mole) of sodium and 160 cc. of ethanol there was added 31.7 g. (0.150 mole) of diphenylguanidine and 27.9 g. (0.150 mole) of α-ethyl-α-carbethoxy-γ-butyrolactone. The temperature was kept at 45° for 48 hours. The mixture was then treated with the volume of standardized alcoholic hydrogen chloride equivalent to the sodium. The filtrate after concentration deposited the crystalline product which was filtered and washed with cold ethanol (XXI, XXII, XXIII).

These compounds (Table II) were soluble in ethanol, ether, benzene, hot ligroin, 5% hydrochloric acid and 5% sodium hydroxide. They were insoluble in water and 5% sodium bicarbonate. They were recovered by the careful neutralization of either the acid or alkaline solutions.

In an experiment typical of several unsuccessful attempts to convert them to β-bromoethyl derivatives 3.51 g. (0.0100 mole) of α-ethyl-α-(N-phenylaminophenyliminomethyl)-carbamyl-γ-butyrolactone (XXI) was found to dissolve immediately in 30 cc. of cold fuming hydrobromic acid. No crystals separated after 18 hr. at room temperature. Dilution with water caused no precipitation. Distillation of the hydrobromic acid under diminished pressure left a viscous residue which by careful neutralization of its cold aqueous solution gave a quantitative precipitate of the starting material (XXI, XXII, XXIII).

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(11) G. S. Skinner, THIS JOURNAL, **59**, 322 (1937).

(12) R. Barre and A. Jacques, *C. A.*, **36**, 3853 (1942); *Rev. can. biol.*, **1**, 454 (1942).