[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

The Action of Diazoalkanes on Oxazolidine-4,5-diones

BY GLENN S. SKINNER AND EVERETT J. WRIGHT

RECEIVED JUNE 3, 1957

Diazomethane and diazoethane have been shown to react with 2-dialkylmethyleneoxazolidine-4,5-diones to give a mixture of 2-dialkylmethylene-3-alkyloxazolidine-4,5-diones and the isomeric 2-dialkylmethylene-4-alkoxy-3-oxazolin-5-ones. The 3-oxazolin-5-ones react with methanol and ethanol to give alkyl N-dialkylacetyl-α,α-dialkoxyaminoacetates which in turn react with aniline to form a characteristic derivative. A study of the preparation, properties and structure of these compounds has been made.

It has been shown[1] that 2-dialkylmethylene-3-alkyloxazolidine-4,5-diones rearrange to the corresponding 1,4,4-trialkylpyrrolidine-2,3,5-triones in refluxing ethanol. However, when the nitrogen atom is linked to hydrogen, treatment with ethanol results in cleavage of the ring at positions 3 and 5. It also has been noted[2] that isatin, which contains adjacent carbonyl functions, undergoes ring expansion and epoxide formation when treated with diazomethane. It was therefore of interest to study the action of diazomethane and diazoethane on 2-dialkylmethyleneoxazolidine-4,5-diones. For this purpose we have selected three oxazolidinediones: 1, where both radicals on the methylene carbon are phenyl; 2, where one radical is phenyl and the other is ethyl; 3, where both radicals are ethyl.

In the first case, we have succeeded in isolating all of the products from the reaction mixture in the pure crystalline state (Fig. 1). Diazomethane reacts with I to give 2-diphenylmethylene-3-methyloxazolidine-4,5-dione (IV) (35%) and the isomeric 2-diphenylmethylene-4-methoxy-3-oxazolin-5-one (VI) (65%) (Table I). IV was identified by comparison with an authentic sample. The structure of VI was ascertained by hydrolysis with hot aqueous 10% potassium hydroxide solution to yield diphenylacetic acid, ammonia, methanol and oxalic acid. When alcoholic potassium hydroxide was used, diphenylacetamide was obtained. Similarly, diazoethane yielded 2-diphenylmethylene-3-ethyloxazolidine-4,5-dione (XII) and 2-diphenylmethylene-4-ethoxy-3-oxazolin-5-one (IX) in the same ratio. XII was identical with an authentic sample and similar hydrolysis of IX gave diphenylacetic acid, ammonia, ethanol and oxalic acid. Treatment of both VI and IX with refluxing aniline gave diphenylacetamide and oxanilide.

The above 3-oxazolin-5-ones (VI and IX) on treatment with refluxing anhydrous methanol gave methyl N-diphenylacetyl-α,α-dimethoxyaminoacetate (XV). The reaction with IX was slower. XV was hydrolyzed by potassium hydroxide solution to give diphenylacetic acid, ammonia, methanol and oxalic acid. Infrared analysis showed strong absorption at 3.0 and 6.0 μ which indicates the presence of a secondary amide. Treatment of XV with one equivalent of aniline in refluxing benzene resulted in the displacement of one of the methoxy groups and also the elimination of one molecule of methanol. XV gives the hydroxamic acid test for esters whereas the aniline derivative (XX) does not. Moreover the aniline derivative shows strong absorption bands at 3.1 and 6.1 μ (Table IV), which probably are due to the anilide group, as well as a band at 5.9 μ which is attributed to the C=N group. The remaining methyl group was shown to be linked to oxygen rather than nitrogen since the compound on hydrolysis gave diphenylacetamide.

Similarly, VI and IX reacted with refluxing anhydrous ethanol to give ethyl N-diphenylacetyl-α,α-diethoxyaminoacetate (XVIII). XVIII was characterized in the same manner as XV. Treatment of XVIII with one equivalent of aniline in refluxing benzene gave the aniline derivative (XXII).

In the second case, the reaction of diazomethane with II yielded a mixture of V and VII which was not separable. A small amount (14%) of VII could be isolated as pure pale yellow crystals, but the remainder of the reaction mixture was a viscous yellow oil. Both vacuum distillation and sublimation failed to separate the mixture. In contact with magnesium trisilicate or alumina, the mixture gave only ethylphenylacetamide. However, the viscous oil was shown to be a mixture of V and VII. The molecular weight by the freezing point depression of benzene was 232 (calcd. 231). Treatment of the mixture with refluxing ethanol yielded XIX, also prepared from pure VII, and an oil, 4-ethyl-1-methyl-4-phenylpyrrolidine-2,3,5-tri-

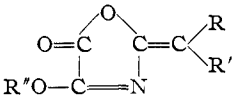


TABLE I

Compound	R	R'	R''	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
VI	C_6H_5	C_6H_5	CH_3	158	73.10	73.26	4.69	4.82	5.02	4.95
VII	C_6H_5	C_2H_5	CH_3	122–123	67.52	67.31	5.67	5.64	6.06	6.04
VIII	C_6H_5	C_6H_5	CH_3	89.0–89.5[a]					7.65	7.71
IX	C_6H_5	C_6H_5	C_2H_5	131.0–131.5	73.70	73.95	5.15	5.07	4.78	4.78
X	C_2H_5	C_2H_5	C_2H_5	80–81[b]					7.10	6.91

[a] B.p. (1.6 mm.). [b] B.p. (0.45 mm.).

(1) G. S. Skinner and R. E. Ludwig, THIS JOURNAL, **78**, 4656 (1956).

(2) G. Heller, *Ber.*, **52**, 741 (1919); **59**, 701 (1926).

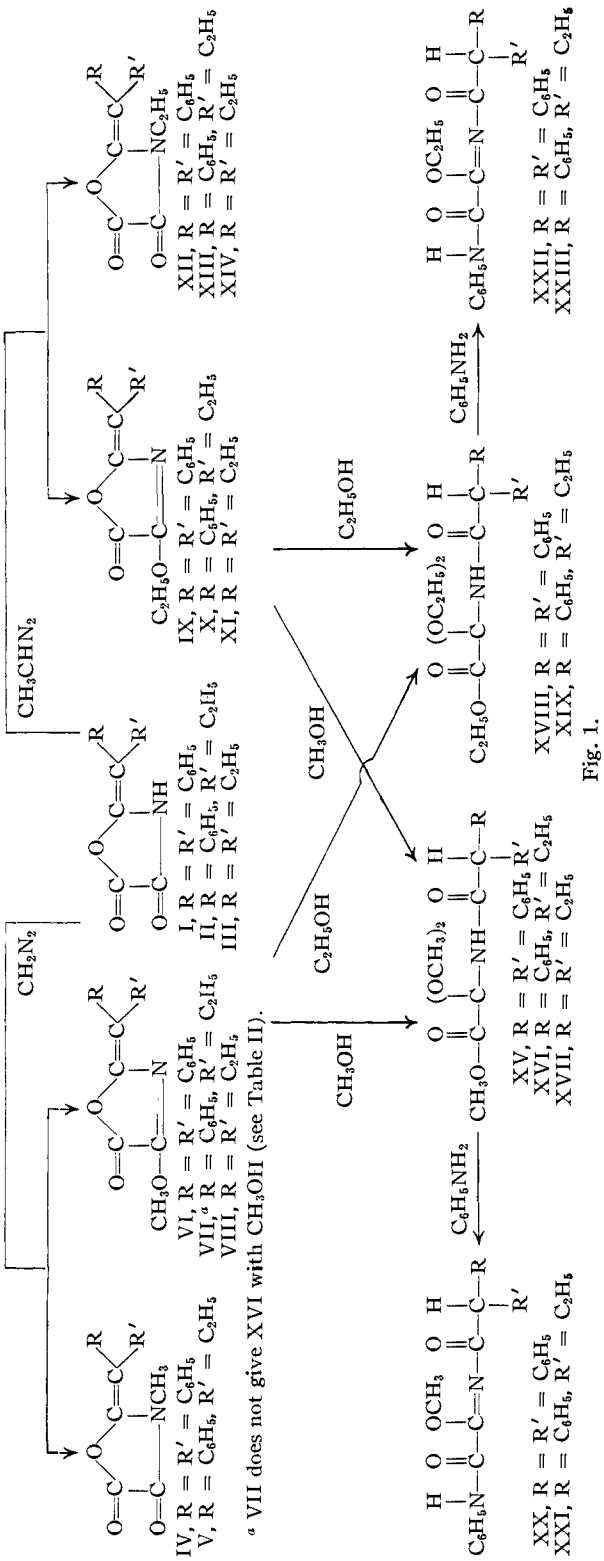


Fig. 1.

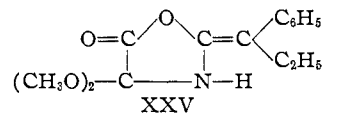
[a] VII does not give XVI with CH_3OH (see Table II).

one, which yielded a 2,4-dinitrophenylhydrazone identical with a sample prepared by an independent method.[3] XIX was identified by basic hydrolysis which gave ethylphenylacetamide, ethanol and oxalic acid. Reaction with aniline in refluxing benzene gave the aniline derivative XXIII.

(3) H. G. Brouns, unpublished results, University of Delaware, 1956.

Diazoethane reacted with II to give a mixture of isomers X and XIII. Again the mixture was a viscous oil which could not be separated. It was shown to be a mixture of X and XIII by the action of refluxing ethanol. X was converted to XIX while XIII was converted to 1,4-diethyl-4-phenylpyrrolidine-2,3,5-trione and the latter to its 2,4-dinitrophenylhydrazone.

Treatment of the mixture of X and XIII with refluxing methanol gave XVI. One equivalent of aniline in refluxing benzene converted XVI to its aniline derivative XXI. However, similar treatment of VII with refluxing methanol failed to give XVI. Instead, only 2-ethylphenylmethylene-4,4-dimethoxyoxazolidine-5-one (XXV) could be obtained which did not give XVI on further refluxing



XXV

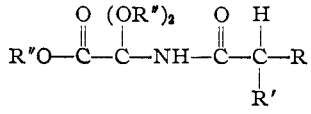
with methanol. The same result was obtained three times. On basic hydrolysis XXV yielded ethylphenylacetamide and oxalic acid. The infrared absorption spectra showed absorption at 5.6 and 5.9 μ which indicated that the lactone ring had not been opened and a band at 3.1–3.2 μ which indicated that an N–H group was present. In all other similar cases (VI, VIII, IX, X, XI) the reaction resulted in cleavage of the ring.

In the third case, diazomethane reacted with III to give an oil which on distillation gave VIII (49%). The large amount of decomposition which accompanied the distillation probably is due, at least in part, to the decomposition of the N-methyl isomer. VIII was hydrolyzed by 15% potassium hydroxide at room temperature and gave diethylacetamide, methanol and oxalic acid. Similarly, diazoethane reacted with III to give an oil. Fractional distillation gave XI (41%) and XIV (7%). These distillations were also accompanied by a large amount of decomposition, particularly when fractions containing XIV were being distilled. XI was hydrolyzed by 15% potassium hydroxide solution at room temperature and gave diethylacetamide, ethanol and oxalic acid. XIV was identified by conversion to the known 1,4,4-triethylpyrrolidine-2,3,5-trione and its 2,4-dinitrophenylhydrazone. Both VIII and XI are converted to diethylacetamide and oxanilide by treatment with refluxing aniline.

Both VIII and XI were converted by refluxing methanol to methyl N-diethylacetyl-α,α-dimethoxyaminoacetate (XVII). However, both VIII and XI were recovered unchanged after refluxing in ethanol for several days. This difference in the behavior of methanol and ethanol, even though unexpected, agrees with observations of Skinner and Ludwig.[1] They found that ethanol is superior to methanol for the rearrangement of oxazolidinediones to pyrrolidinetriones because ethanol did not cause cleavage of the oxazolidinedione, whereas methanol did.

All attempts to convert XVII to the anilide using one equivalent of aniline in refluxing benzene were unsuccessful. However, under these conditions a small sample of a crystalline compound

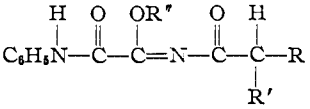
TABLE II



3-Oxazolin-5-one	Alcohol	Reflux time, hr.	Product	R	R′	R″	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
VI	CH_3OH	24	XV	C_6H_5	C_6H_5	CH_3	169–170	66.46	67.01	6.16	6.10	4.08	4.00
IX	CH_3OH	240											
VI	C_2H_5OH	48	XVIII	C_6H_5	C_6H_5	C_2H_5	142–143	68.55	68.91	7.06	7.11	3.63	3.59
IX	C_2H_5OH	27											
VII	CH_3OH	24	XXV[a]				120–121	63.86	63.83	6.51	6.57	5.32	5.24
X	CH_3OH	228	XVI	C_6H_5	C_2H_5	CH_3	133–134	61.00	61.01	7.17	7.33	4.74	4.86
VII	C_2H_5OH	96	XIX	C_6H_5	C_2H_5	C_2H_5	122.5–123.5	64.07	64.26	8.07	8.56	4.15	4.13
X	C_2H_5OH	48											
VIII	CH_3OH	72	XVII	C_2H_5	C_2H_5	CH_3	99–100	53.42	53.91	8.56	8.58	5.66	5.73
XI	CH_3OH	288											
VIII	C_2H_5OH	67	No reaction										
XI	C_2H_5OH	104											

[a] Product is 2-ethylphenylmethylene-4,4-dimethoxyoxazolidin-5-one.

TABLE III

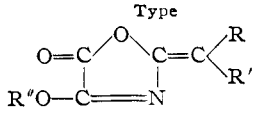
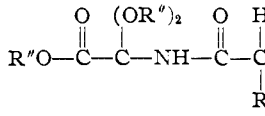
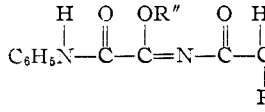
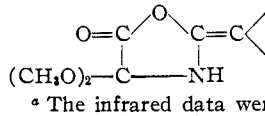


Aminoacetic acid ester	Reflux time, hr.	Product	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XV	4	XX	159–160[a]	74.17	74.16	5.41	5.28	7.52	7.49
XVIII	4	XXII	157–158[b]	74.59	74.77	5.74	5.96	7.25	7.09
XVI	43	XXI	73–74[a]	70.35	70.23	6.21	6.20	8.64	8.62
XIX	74	XXIII	108–109[b]	70.98	70.89	6.55	6.55	8.28	8.33

[a] Recrystallized from methanol. [b] Recrystallized from ethanol.

TABLE IV

INFRARED ABSORPTION SPECTRA[a]

Type	Compound	Wave length in microns			
	VI	5.6	6.1	6.3	
	VII	5.65	6.1	6.3	
	IX	5.65	6.05	6.3	
	XV	3.0	5.7	6.0	
	XVI	3.0	5.65	6.0	
	XVII	3.1	5.7	6.1	
	XVIII	3.0	5.75	5.95	
	XIX	3.05	5.7	6.05	
	XX	3.1	5.7	5.85	6.1
	XXI	3.1	5.7	5.85	6.1
	XXII	3.1	5.75	5.9	6.1
	XXIII	3.1	5.7	5.85	6.05
	XXIV	3.0	5.7	5.9	6.05
	XXV	3.1	3.2	5.6	5.9

[a] The infrared data were obtained under the supervision of Dr. H. C. Beachell.

(XXIV, Table IV), m.p. 86–87°, was obtained which gave infrared absorption bands corresponding to those obtained for the typical compounds XX, XXI, XXII and XXIII.

Compounds IV, VI and VII dissolved in benzene at 0.01 mg./cc. show in the ultraviolet strong absorption bands with maxima at 343, 360 and 334 mμ, respectively. This would be as expected for the conjugated oxazoline structure as assigned. Compound XXV shows a very weak maximum at 323 mμ and weak fine structure at 257 mμ for the dialkylmethylene lactone moiety. Compound XV shows only fine structure from 240–257 mμ indicating no strong absorbers or highly conjugated structure. This would be consistent with the assigned structure.

Experimental

Diazoalkanes.—Diazomethane was prepared by two methods. One from N-methyl-N-nitroso-*p*-toluenesulfonamide[4] in 60–70% yields and the other from nitrosomethylurea[5] in 65–70% yields. Diazoethane was prepared from nitrosoethylurea[5] in 40–50% yields. The ether solutions of the diazoalkanes were dried over potassium hydroxide pellets and aliquot portions were analyzed.

Oxazolidine-4,5-diones.—The three starting oxazolidine-4,5-diones were prepared by the condensation of the appropriate amide with oxalyl chloride.[6]

Reaction of Diazoalkanes with Oxazolidine-4,5-diones.—In each case, the same method was used for the reaction of diazoalkanes with oxazolidinediones as described below for the reaction of diazomethane with 2-diphenylmethyleneoxazolidine-4,5-dione. The method of separation of the reaction products, however, was different in each case and these differences will be described. The 3-oxazolin-5-ones which could be isolated in a pure crystalline form are listed in Table I.

To a stirred solution of 2-diphenylmethyleneoxazolidine-4,5-dione (I) (17.8 g., 0.067 mole) in 750 cc. of anhydrous ether at −5 to 0°, was added, below the surface, a solution of diazomethane (2.83 g., 0.067 mole) in 175 cc. of ether during 20 minutes. The mixture was stirred for an additional 10 minutes after which time the flask was stoppered and kept at 0° for 20 hr. The cold mixture was filtered and the yellow crystals (12.9 g.) were washed with ether, m.p. 165–184°. Concentration of the mother liquor under diminished pressure yielded a second crop of crystals (5.6 g., m.p. 150–160°) (total yield 99%).

(4) T. J. De Boer and R. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

(5) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 165–167.

(6) G. S. Skinner and J. F. Perkins, THIS JOURNAL, **72**, 5569 (1950).

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]

RECEIVED JULY 19, 1957

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).