acetal reacted smoothly with two equivalents of neopentyl glycol in the presence of a little boron fluoride etherate. The theoretical quantity of ethanol (or methanol-ethanol mixture) was collected by slow distillation through a short column, and the residue was distilled directly in an apparatus for distilling solids.

Acetal #43. A mixture of 2,5-diethoxytetrahydrofuran (Union Carbide Chemicals), two equivalents of neopentyl glycol, and a little concentrated hydrochloric acid was warmed until homogeneous and allowed to stand overnight. The solid product was recrystallized from cyclohexane.

Acetal #44. A mixture of 1 mole of 2-ethoxy-3,4-dihydro-2-H-pyran (Union Carbide Chemicals), 2 moles of neopentyl glycol, and 5 ml. of concd. hydrochloric acid warmed spontaneously to about 60°; the clear solution rapidly became cloudy. On cooling, the product solidified. It was dissolved in about 1.2 l. of cyclohexane, 31 ml. of aqueous layer was separated, and the cyclohexane was dried with solid potassium carbonate. The solution was concentrated and crystal crops were taken.

Acetal #46. Reaction of one mole of trimethylolethane (2-hydroxymethyl-2-methyl-1,3-propanediol) (Heyden-Newport) and 1.5 moles of acetaldehyde in the presence of *p*-toluenesulfonic acid led only to the monoacetal #24. The monoacetal with *p*-toluenesulfonic acid and two additional moles of acetaldehyde liberated no more water. Finally, one-fourth mole of calcium chloride was added and the mixture allowed to stand for 3 days. Distillation then yielded the sesquiacetal which still had a weak hydroxyl absorption.

Acetals #52, 53, 54. The acid catalyst was removed before distillation, so that considerable pot residue (linear polyacetals) remained. The yields could have been improved by distillation in the presence of acid.[15]

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A.]

Reactions with α-Substituted β-Propiolactones. I. 4,4-Disubstituted 2-Oxazolidinones

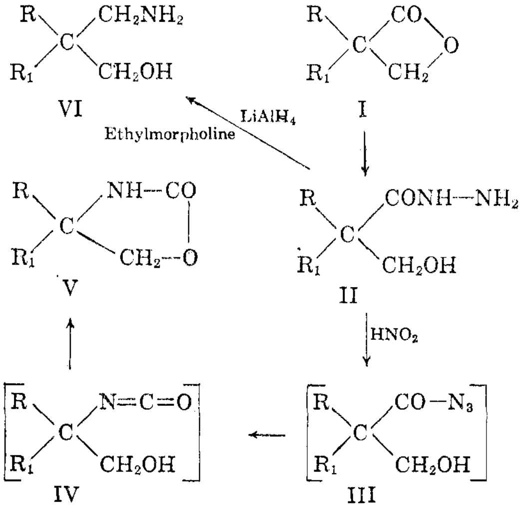
Research on Compounds Active on the Central Nervous System. XXIII[1a]

BRUNO I. R. NICOLAUS, LUIGI MARIANI, GIANGUALBERTO GALLO,[1b] AND EMILIO TESTA

Received October 31, 1960

Several 4-mono- and 4,4-disubstituted 2-oxazolidinones have been prepared by the action of nitrous acid on the substituted β-hydroxypropionic acid hydrazides, which were obtained by the action of hydrazine on β-propiolactones. This reaction also proves the constitution of these hydrazides. The infrared spectra of the 2-oxazolidinones are discussed. The reduction of the foregoing hydrazides by lithium aluminum hydride in ethylmorpholine leads to amino alcohols under cleavage of the N—N bond. Some preliminary pharmacological results are also reported.

During our investigation on compounds active on the central nervous system we carried out a new and general synthesis of α-substituted β-propiolactones.[2-4] In fact, if the easily obtained α-substituted β-aminopropionic acids are diazotized, β-propiolactones are obtained in good yield as colorless (alkyl derivatives) or greenish-yellow (aryl derivatives) fluids (only in a few cases solid compounds were obtained), having an itching action on skin and mucosae.[5] β-Lactones easily react with hydrazine hydrate[4,6] and substituted hydrazines, thus almost generally producing the hydrazides of α-substituted β-hydroxypropionic acids.[7] The latter compounds, the structure of which were previously suggested by chemical analysis (titration of the radical —CO—NH—NH_2, acetylation, etc.) and by infrared spectra (typical bands of the group —CO—NH— at 1650 cm.$^{-1}$),



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(1) (a) Previous paper (note XXII): E. Testa, L. Fontanella, and V. Aresi, *Ann.*, in press. (b) Physical Chemical Department of Lepetit S.p.A.

(2) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **619**, 47 (1958).

(3) E. Testa, L. Fontanella, and L. Mariani, *J. Org. Chem.*, **25**, 1812 (1960).

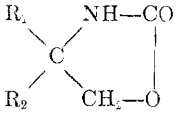
(4) E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Ann.*, **639**, 166 (1961).

(5) A good review on β-lactones has been given by Zaugg in *Org. Reactions*, VIII, 305 (1954).

(6) B. F. Goodrich, Brit. Patent **648,886**; *Chem. Abstr.*, **45**, 8031 (1951).

(7) The research in this field is under investigation. We have seen that under special conditions the corresponding α-substituted β-hydrazinepropionic acids may be isolated.

TABLE I



R_1	R_2	Formula	M.P. or B.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield, %	Lit.
C_2H_5	C_2H_5	$C_7H_{13}O_2N$	160–170°/0.6 mm.	58.71	9.15	9.78	58.41	9.31	9.65	30	—
C_6H_5	C_6H_5	$C_{15}H_{13}O_2N$	178–179°	75.29	5.48	5.85	75.36	5.80	6.12	62.5	21
C_6H_5	CH_3	$C_{10}H_{11}O_2N$	78–79°	67.78	6.26	7.91	67.78	6.52	7.92	91	21
C_6H_5	C_2H_5	$C_{11}H_{13}O_2N$	80–81°	69.08	6.85	7.32	69.32	7.01	7.29	88.8	—
C_6H_5	$(CH_3)_2CH$	$C_{12}H_{15}O_2N$	139–140°	70.22	7.37	6.82	70.4	7.6	7.03	73.9	—
C_6H_5	$C_6H_5CH_2$	$C_{16}H_{15}O_2N$	106–107°	75.85	5.97	5.53	76.0	5.99	5.35	62	—
C_6H_5	H	$C_9H_9O_2N$	137–139°	66.24	5.56	8.58	66.13	5.71	8.20	40	21
iso-C_4H_9	H	$C_7H_{13}O_2N$	130–140°/0.2 mm.	58.72	9.15	9.78	58.9	9.31	10.04	28	—

show very irregular melting points. Consequently, it seemed desirable to gain further evidence for the proposed chemical structure.

In fact, by diazotization of II, azide III was obtained. III was not isolated, but extracted with benzene and by subsequent heating it lost nitrogen and isomerized to the isocyanate IV. This latter compound, by intramolecular reaction, gave in good yield 4-substituted oxazolidine-2-ones. Thus structure II, proposed for the compounds obtained by reaction of β-lactones with hydrazine, is definitively demonstrated.

The class of 2-oxazolidinones has already been investigated and can be obtained by two general methods of synthesis: a) the action of ethyl carbonate or phosgene on β-aminoethanol derivatives [8–10,21] and b) diazotization of hydrazides of β-hydroxypropionic acid derivatives.[13–15,20]

Some procedures are suitable for preparation of peculiar derivatives.[11–13,19,22,23] However only a few 4,4-disubstituted compounds are known.[10,13,21] Perhaps this is because β,β-disubstituted β-aminoethanol derivatives and α,α-disubstituted β-hydroxypropionic acid derivatives are obtained with difficulty. Particularly, the esters of the latter compounds, as we have already observed,[24] do not react with hydrazine.

As the synthesis of α-substituted β-propiolactones is a general one, the method for preparing 4-mono- and 4,4-disubstituted 2-oxazolidinones, which is the object of our present publication, can also become of general use. We have prepared eight 2-oxazolidinones by our method. They are listed in Table I. Five of them appear to be new, and except for two of them, they are crystalline, easily recrystallizable white solids.

The infrared spectra of the synthesized oxazolidine-2-ones were measured using a Perkin-Elmer Model 12 C single beam spectrophotometer fitted with a sodium chloride prism. The compounds were examined as such when liquid and in a Nujol mull when solid. The most typical bands shown by all the oxazolidine-2-ones were selected and assigned as arising from the vibrations of the chemical bonds of the structure. The limits in which fall the frequencies of the bands and the vibrations from which the bands take origin have been suggested in the following way according to Bellamy[25]: 3250–3200 cm.$^{-1}$ (NH stretching), 1750–1730 cm.$^{-1}$ (C=O stretching), 1280–1240 cm.$^{-1}$ (5-1 C—O stretching), 1060–1035 cm.$^{-1}$ (2-1 C—O stretching).

In connection with this work we submitted some hydrazides (α,α-diphenyl-, α,α-diethyl-, α-phenyl-α-ethyl-β-hydroxypropionic acid hydrazides), to the action of lithium aluminum hydride. In ether and tetrahydrofuran, even after prolonged refluxing, no reaction occurred and hydrazides were recovered unaltered; in ethylmorpholine at a temperature

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(21) M. S. Newman and W. M. Edwards, *J. Am. Chem. Soc.*, **76**, 1840 (1954).

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(24) R. Fusco and E. Testa, *Il Farmaco (Pavia), Ed. Sc.*, **12**, 828 (1957).

(25) L. K. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., London, 1958.

between 80° and 100° reduction of the carboxylic function took place, accompanied by the breaking of the N—N bond and the formation of β,β-disubstituted γ-amino alcohols. In the same solvent no reaction occurred when the temperature did not reach 70°. This behavior of primary hydrazides is different from that of secondary and tertiary ones, which leads to the corresponding hydrazines, and as far as we know, has not yet been described.

The prepared compounds, when subjected to broad pharmacological screening, showed some activity on the central nervous system. All compounds revealed convulsant properties, while some of them, at lower dosages, protected mice from electroshock seizures. The convulsant activity was particularly evident for 4,4-diethyl- 2-oxazolidinones, thus paralleling the observation made on the previously described 5,5-diethyl-tetrahydro-1,3-oxazine-2,4-dione.

EXPERIMENTAL

2-*Oxazolidinones.* To a stirred suspension of 0.01 mole of hydrazide (II) in 30 ml. of water at 0° a solution of 0.03 mole of hydrochloric acid in 30 ml. of water was added. Some of the resulting hydrochlorides were soluble, others were sparingly soluble or insoluble. The solution or suspension of the hydrazide hydrochlorides was diazotized with a solution of 0.011 mole of sodium nitrite in 10 ml. of water at 0–5°. The oil which precipitated during the reaction was extracted with benzene and dried over sodium sulfate. The clear solution was gently refluxed for 0.5 hr. While heating a gas evolution was observed. After concentration *in vacuo* the residue was recrystallized from ligroin, ether–petroleum ether, or ethyl acetate–petroleum ether. The two oily compounds (Table I. No. 1 and 8) were distilled by Ronco's technique.[26]

Reductions with lithium aluminum hydride. 1) γ-Amino-β,β-diphenylpropanol. A mixture of 8.5 g. of α,α-diphenyl-β-hydroxypropionic acid hydrazide, 7 g. of lithium aluminum hydride, and 70 ml. of ethylmorpholine was heated for 4 hr. at 100°. The mixture was cautiously treated with water and extracted with ether. After evaporation of the ether the residue was recrystallized from isopropyl ether; yield, 5.1 g.; m.p. 103–105°. After a further recrystallization from diluted ethyl alcohol the m.p. reached 105–106°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.52; H, 7.64; N, 5.87.

N,O-Diacetyl derivative m.p. 134–136°.

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.28; H, 6.80; N, 4.50. Found: C, 73.10; H, 7.04; N, 4.83.

Picrate, m.p. 213–216°.

Anal. Calcd. for $C_{21}H_{20}N_4O_8$: N, 12.28. Found: N, 11.93.

2) γ-Amino-β-phenyl-β-methylpropanol. A mixture of 9.7 g. of α-phenyl-α-methyl-β-hydroxypropionic acid hydrazide, 9.5 g. of lithium aluminum hydride, 150 ml. of ethylmorpholine, and 150 ml. of tetrahydrofuran was refluxed for 24 hr. and worked up further as described in 1). The oily residue was distilled according to Ronco's technique[26]; yield, 4.4 g., b.p. 120–128° at 0.6 mm.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.80; H, 9.30; N, 8.63. Acetylation equivalent: 98.8%.

3) γ-Amino-β,β-diethylpropanol. A mixture of 8.0 g. of α,α-diethyl-β-hydroxypropionic acid hydrazide, 9.5 g. of lithium aluminum hydride and 150 ml. of ethylmorpholine was heated at 100–110° for 24 hr. and worked up further as described in 1). The oily residue was distilled according to Ronco's technique[26]; yield 2.3 g. b.p. 85–87° at 0.6 mm.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.08; H, 13.30; N, 10.52. Acetylation equivalent: 99.1%.

Acknowledgment. We are indebted to Prof. R. Fusco for the very useful discussion on this subject during the experimental work; and to Miss. Dr. G. Pelizza and Mr. A. Restelli for organic and microanalysis.

We thank Prof. Dr. G. Maffii and co-workers of the Pharmacological Department of Lepetit S.p.A. for the preliminary pharmacological results, which will be published elsewhere.

MILAN, ITALY

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[26] K. Ronco, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, 39, 2094 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Synthesis and Properties of Bicyclic Oxetanes[1]

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Received September 13, 1960

The bicyclic oxetanes 7-oxabicyclo[4.2.0]octane and 1-oxaspiro[3.5]nonane were prepared by internal nucleophilic displacement reactions of the appropriate glycol derivatives. The structure assigned to these compounds is supported by their physical properties, as well as by chemical reactions typical of simpler oxetanes, such as acid-catalyzed methanolysis and lithium aluminum hydride reduction, which occur predictably by attack on the least substituted carbon.

Among models once considered in connection with the antibiotic fumagillin[3] were structures containing an oxetane unit attached to a cyclohexane ring. The present paper will be concerned with two of these models, 7-oxabicyclo[4.2.0]-octane[4,5] (I) and 1-oxaspiro[3.5]nonane (II), the latter of which has not been reported previously.

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[1] This research was supported in part by Grant E-1138 of the U. S. Public Health Service.

[2] Abbott Laboratories Fellow, 1959–1960.

[3] D. S. Tarbell *et al.*, *J. Am. Chem. Soc.*, 82, 1005 (1960).

[4] (a) The synthesis of this compound was reported in a preliminary account to the 136th A. C. S. Meeting, Atlantic City, N. J., Sept. 1959, page 67P of the abstract; see also Ref. 5. (b) For the results of a similar study, published after the submission of this manuscript, see H. B. Henbest and B. B. Millward, *J. Chem. Soc.*, 3575 (1960).