3. **Properties of GeH_2.**—Germanium dihydride is readily soluble in liquid ammonia, yielding a colorless solution. It appears to be stable in solution, since it does not become colored on standing for 24 hours. On removal of the ammonia at −33°, it is obtained as a white solid which can be pumped until it appears dry without immediate decomposition. On continued pumping at −33°, or on warming to room temperature, it decomposes to germane and the monohydride, GeH.

Royan and Schwarz[8] have described the preparation of a yellow, amorphous solid hydride of germanium to which they assign the formula, GeH_2. However, this hydride, which was prepared by the hydrolysis of CaGe in aqueous sulfuric acid solution, appears quite different from the dihydride herein described. It was stable when dry; when heated it decomposed producing only germanium and hydrogen.

4. **Action of Sodium on GeH_2.**—One gram atom of sodium reacts with one mole of germanium dihydride without evolution of gas to form a deep red solution. On adding ammonium bromide, monogermane is obtained.

Germanium dihydride was prepared by treating 2.84 mmoles each of sodium germanyl and phenyl bromide. A slight excess over one equivalent of sodium, 2.96 m.atoms, was cut into small pieces and added piecewise to the solution. Just before the last piece was added, the solution assumed a very dark, reddish-brown color. Addition of the last piece gave a blue solution characteristic of free metal. The blue color was discharged with ammonium bromide, the hydrogen was removed and an excess of ammonium bromide was added. This dispelled the red color and gas was evolved. The gas was purified and its molecular weight was determined: vol. of gas (S. T. P.), 25.08; wt. g., 0.0875; mol. wt. found, 78.19; calcd. for GeH_4, 76.63. The reaction was not investigated further.

Summary

1. Ethyl-, methyl- and isoamylgermane react with sodium in liquid ammonia to yield germanyl salts. The reactions are not quantitative; more than one equivalent of germane is required to complete reaction with a given quantity of metal and more than an equivalent amount of hydrogen is evolved.

2. With lithium in ethylamine, the reactions of monoalkylgermanes are more nearly quantitative but even here considerable side reaction occurs. With lithium and ethylgermane in ethylamine, a considerable amount of ethane is evolved; some, if not all, of this appears to come from the amine. Ethylisoamylgermane reacts substantially quantitatively with lithium in ethylamine.

3. Potassium amide reacts with germane in liquid ammonia to form potassium germanyl in considerable amount. The reaction is not quantitative and approximately one atom of hydrogen is evolved per mole of amide.

4. Ethylisoamyl- and diethylisoamylgermane were prepared by reaction of appropriate alkyl halides with lithium germanyls in ethylamine.

5. Phenyl bromide reacts with sodium germanyl according to the equation $C_6H_5Br + NaGeH_3 = C_6H_6 + GeH_2 + NaBr$. The digermane, GeH_2, is soluble in liquid ammonia from which it may be crystallized as a white solid. It decomposes slowly at −33° and rapidly at higher temperatures to form GeH_4 and GeH.

6. One mole of GeH_2 reacts with one atom of sodium to form a soluble salt. On addition of ammonium bromide, GeH_4 is evolved.

PROVIDENCE, R. I. RECEIVED SEPTEMBER 3, 1949

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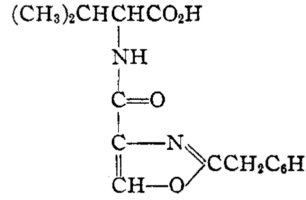
[8] Royan and Schwarz, *Z. anorg. allgem. Chem.*, **211**, 412 (1933).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of N-(2-Benzoyl-4-oxazoloyl)-valine[1,4a]

BY HOMER ADKINS,[2] ROBERT M. ROSS[3] AND DOROTHY C. SCHROEDER[4]

Several investigations that have been carried out recently in this Laboratory were motivated by a desire to study the properties and methods for the preparation of certain substituted oxazoles and oxazolines. Reported in the present communication is the synthesis of a valine-substituted oxazole (I).[4a]


I

The crucial intermediate in the preparation of the oxazole I was found to be 2-benzyl-4-carbethoxyoxazole (VI). The English workers, Cornforth and Cornforth,[5] described an elegant synthesis of 2-methyl-4-carbethoxyoxazole, which method we found conveniently adaptable to the preparation of 2-benzyl-4-carbethoxyoxazole (VI). Since the completion of this investigation in 1948, Cornforth, Fawaz, Goldsworthy and Robinson[6]

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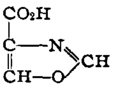
[1] Abstracted in part from the theses of Robert M. Ross and Dorothy C. Schroeder, presented to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the Ph.D. degree.

[2] Deceased August 10, 1949.

[3] Allied Chemical and Dye Corporation Fellow, 1947–1948. Department of Chemistry, University of Illinois.

[4] Wisconsin Alumni Research Foundation Research Assistant, 1947–1948. Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

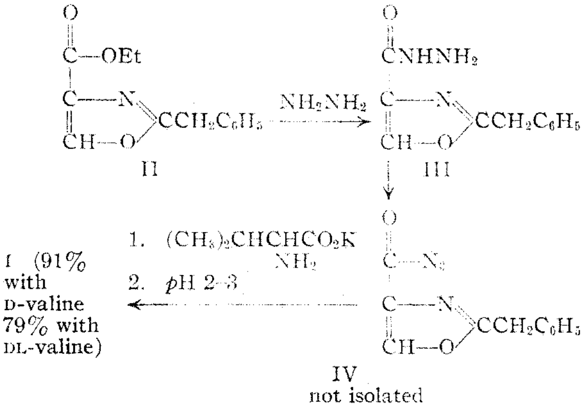
[4a] It was found convenient to name I as a derivative of 4-oxazoloic acid to which we assigned the structure  Thus, I will be referred to in this communication as N-(2-benzyl-4-oxazoloyl)-valine.

[5] Cornforth and Cornforth, *J. Chem. Soc.*, 96 (1947).

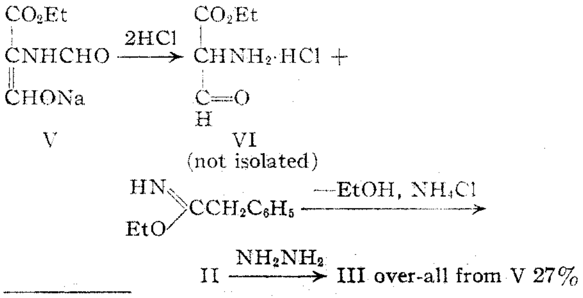
[6] Cornforth, Fawaz, Goldsworthy and Robinson, *ibid.*, 1549 (1949).

reported the synthesis of 2-benzyl-4-carbethoxyoxazole by the same route. Our work was carried out independently of the English workers, and the results confirm their findings.

The preparation of N-(2-benzyl-4-oxazololyl)-valine was completed by a series of reactions which are reminiscent of peptide formation.[7,8,9a] Facile conversion of the ester to the hydrazide III was realized by the action of 85% hydrazine hydrate.[9e] The hydrazide was treated with nitrous acid and the azide (IV) thus formed was condensed with D-valine or DL-valine. In this way N-(2-benzyl-4-oxazoloyl)-valine was produced. Isolation of the intermediate azide was not considered practical because of the instability associated with compounds of this nature. The over-all yield of the oxazole I by the series of three reactions amounted to about 82%, and these results were found to be easily reproducible.



The structure which has been assigned to the hydrazide (III) was substantiated by its preparation through an alternate route. The sodium enolate of ethyl norpenaldate[9b] (ethyl N-formyl-α-formylglycinate) was synthesized in a similar manner to that which was described by the group associated with the Northern Regional Research Laboratories.[9c] When the sodium enolate (V) was caused to react with mineral acid and ethyl phenyliminoacetate, 2-benzyl-4-carbethoxyoxazole was obtained in low yields as a crude, oily residue. No attempts were made to isolate the intermediate products. Cyclization to the oxazole was presumed to involve the intermediate formation of ethyl norpenaldate (VI); the conversion of the sodium enolate to ethyl norpenaldate is a well established reaction.[9d]



The crude ester II was isolated as the hydrazide which, unlike the ester, was readily crystallized and purified. This compound was found to possess identical properties with the hydrazide previously described. Admixture of the two hydrazides produced no depression in melting point.

Characterization of the valine substituted oxazole was aided by analysis of its infrared absorption spectrum,[10] *p*H titration and elemental analysis.

The infrared spectrum of the oxazole I showed the expected carbonyl of a carboxyl at 1722 cm.$^{-1}$. Monosubstituted amide bands were evident at 1633.5 and 1529 cm.$^{-1}$. The functional stretch of $>$N–H was located at 3345 cm.$^{-1}$. A strong band was found present at 1595 cm.$^{-1}$ which might be attributed to the conjugated $>C=C<$ and $>C=N-$ linkages present in the oxazole nucleus; apparently the phenyl band at 1600 cm.$^{-1}$ was masked by the absorption at 1595 cm.$^{-1}$. However, bands were discernible at 763 and 693 cm.$^{-1}$ which provide evidence for the existence of a monosubstituted phenyl.

Experimental[11]

Synthesis of 2-Benzyl-4-carbethoxyoxazole.—Since the method employed for the preparation of 2-benzyl-4-carbethoxyoxazole was analogous to that which was described by Cornforth, Fawaz, Goldsworthy and Robinson,[6] no description of the synthesis will be presented. The physical properties, yields and analyses of the intermediates and end-product corresponded to those reported by the English workers.

It should be pointed out that cyclization of the potassium enolate to 2-benzyl-4-carbethoxyoxazole was carried out in the presence of dry hydrogen chloride by the English investigators whereas we effected cyclization in boiling glacial acetic acid.

Synthesis of N-(2-Benzyl-4-oxazoloyl)-valine 2-Benzyl-4-carboxhydrazideoxazole (from 2-Benzyl-4-carbethoxyoxazole) (III).—To 7 ml. of 85% hydrazine hydrate was added 3 g. of 2-benzyl-4-carbethoxyoxazole. After stirring the mixture for 24 hours, 35 ml. of water was added and the hydrazide was extracted with 30 ml. of chloroform (in three 10-ml. portions). The chloroform extract was concentrated to 15 ml. *in vacuo*. Upon adding an equal volume of petroleum ether to the chloroform solution, the hydrazide precipitated in the form of white, shiny crystals. The product was collected on a filter after thorough chilling of the crystallization mixture. In this way 2.6 g. (87%) of III was isolated, m. p. 95°. An additional 0.1 g. of product, m. p. 92–94°, was recovered from the mother liquor (total 90.5%). Earlier investigators[9e] have prepared this hydrazide in a similar manner, but reported the melting point to be both 80–82° and 81–83°.

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: N, 19.36. Found: N, 19.60.

N-(2-Benzyl-4-oxazoloyl)-D-valine (I).—To 17.15 ml. of *N* hydrochloric acid was added 2.6 g. of 2-benzyl-4-

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[7] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

[8] Fruton, *J. Biol. Chem.*, **146**, 463 (1942).

[9] "The Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, (a) p. 261; (b) p. 486; (c) pp. 490, 492, 512; (d) p. 517; (e) p. 707.

[10] The authors are indebted to Mrs. James L. Johnson and Miss Elizabeth M. Petersen of the University of Illinois Infrared Laboratory for the analysis and interpretation of the spectrum.

[11] All melting points and boiling points are uncorrected.

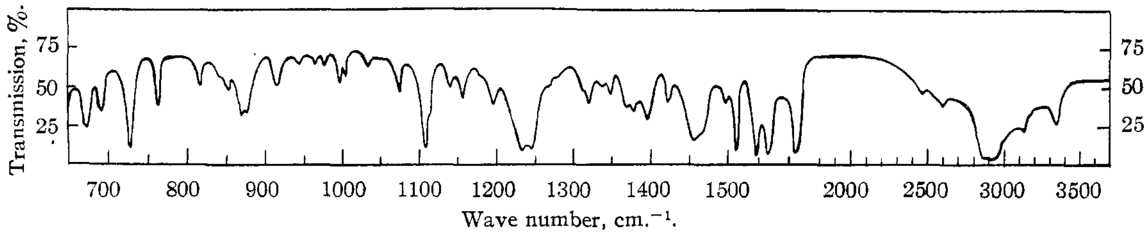

Fig. 1.—Infrared absorption curve of N-(2-benzyl-4-oxazoloyl)-valine (determined in a Nujol mull).

carboxhydrazideoxazole and the resulting solution was cooled to 0°. After addition with swirling of 0.91 g. of sodium nitrite dissolved in 10.5 ml. of water, a white precipitate of azide formed. At the end of 30 seconds, the mixture was added with stirring and with the aid of 3 ml. of water to a vessel containing 1.4 g. of D-valine,[12] 2.95 g. of potassium carbonate and 15 ml. of water. Sufficient dioxane was added to effect homogeneity and the reaction mixture was allowed to stand at room temperature for seven to eight hours.

The solution was cooled to 5° and *N* hydrochloric acid was added to *p*H 2–3. Almost instantly, lustrous white crystals of I appeared.[13] The acid was collected on a filter and dried; this product weighed 2.7 g., m. p. 137–137.5°. Chloroform extraction of the aqueous solution and concentration of the extract yielded an additional 0.6 g. of I, m. p. 130–133°. A total of 3.3 g. (91%) of oxazole was thus obtained.

Anal. Calcd. for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.01; neut. equiv., 302.2. Found: C, 63.85, 63.92; H, 5.95, 5.92; neut. equiv. 302.4 (aqueous ethanol).

The free acid was converted to the benzylamine salt in methanolic solution according to a standard procedure.[14] The salt was precipitated from solution by the addition of dry ether. Recrystallizations from methyl alcohol-ether produced a white, fleece-like solid, m. p. 127.5–129.7°.

Anal. Calcd. for $C_{23}H_{27}O_4N_3$: C, 67.45; H, 6.65. Found: C, 67.37; H, 6.75.

A second product was isolated from the chloroform filtrate which had yielded the acid I. Eighty-five mg. of this material was obtained as a solid, m. p. 148–153°. Although the compound remains incompletely characterized at this time, the evidence in hand suggests that it is 2-benzyl-4-oxazoloic acid.

Sodium Enolate of Ethyl Norpenaldate (V).—Ethyl glycinate hydrochloride was converted to ethyl N-formyl glycinate which in turn was C-formylated according to the method described by the Northern Regional Research Laboratory investigators.[9c] Starting with ethyl glycinate hydrochloride, the crude sodium enolate was isolated in *ca.* 81% over-all yield. In our hands the salt could not be easily purified.

2-Benzyl-4-carboxhydrazideoxazole (from the Sodium Enolate).—To 4.6 g. (0.025 mole) of V was added 300 ml. of dry ether. Stirring was begun and to the slurry was added 5 ml. (0.05 mole) of concd. hydrochloric acid and sufficient ethanol to effect homogeneity (*ca.* 50 ml.). The mixture was stirred for five hours at room temperature. During the first hour a white precipitate appeared. Three ml. of benzene was added and all volatile materials were removed by distillation under reduced pressure, b. p., 30–35° (15–30 mm.). The light tan, sirupy residue was dried further *in vacuo* at pressures of 0.7 mm. or less. Presumably this crude material was ethyl α-formylglycinate hydrochloride and sodium chloride.

To the sirupy residue was added 30 ml. of ethylene chloride and 4.1 g. of freshly distilled ethyl phenyliminoacetate. The mixture was stirred vigorously for 24 hours at room temperature. A white precipitate of ammonium chloride and sodium chloride was removed by filtration; the combined weight of these salts was 2.75 g. After the ethylene chloride was removed from the filtrate under reduced pressure, the residue was heated to 95° (0.7 mm.) for one hour. The residue was extracted with three 30-ml. portions of boiling petroleum ether (100–140°). To this extract was added a pinch of Norit and the boiling mixture was filtered hot. The filtrate was concentrated to dryness *in vacuo*. Two ml. of 85% hydrazine hydrate was added to the residue and the mixture was allowed to stand for 24 hours at room temperature. The hydrazide was isolated according to the procedure described earlier under 2-benzyl-4-carboxhydrazideoxazole (from 2-benzyl-4-carbethoxyoxazole). The product weighed 1.5 g. (27.6%), m. p. 87–93°. Recrystallization from chloroform–petroleum ether yielded a purer hydrazide, m. p. 92–94°. Admixture of the two hydrazides prepared by the different methods produced no melting point depression.

Summary

A total synthesis of N-(2-benzyl-4-oxazoloyl)-valine is described. The method required intermediate formation of 2-benzyl-4-carbethoxyoxazole and subsequent conversion of the latter to the corresponding azide. Coupling of the azide with valine produced the desired oxazole in good over-all yields.

URBANA, ILLINOIS RECEIVED MAY 20, 1950

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[12] We are indebted to Merck and Co. for a generous supply of D-valine.

[13] When DL-valine was employed in the condensation, the free acid separated as an oil. After chloroform extraction and concentration, the DL acid was finally induced to crystallize by the addition of petroleum ether. The product was isolated in 79% yield, m. p. 100–101°. Recrystallization of the oxazole from chloroform–petroleum ether raised its melting point to 101–102°. *Anal.* Calcd. for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.01. Found: C, 63.85; H, 5.59.

[14] See ref. 9 for procedure.