[Contribution from the Department of Chemistry and Chemical Engineering, Stanford University]

# The Beckmann Rearrangement of β-Dihydroumbellulone Oxime[1]

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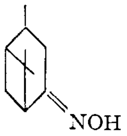
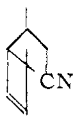
The course of the Beckmann rearrangement of the oxime of a bicyclic ketone having an α-carbon atom which is quaternary, a bridge-head and part of a cyclopropane ring system has been ascertained. The rearrangement proceeds in the usual fashion to produce a lactam, with the cyclopropyl group migrating.

## Introduction

As a rule, bicyclic ketoximes having a bridgehead α-carbon atom yield, under the conditions of the Beckmann rearrangement, an unsaturated nitrile rather than the usual lactam.[3,4] One case of many[5] which is specially pertinent here is that of verbanone oxime (I)[6] which gives a poor yield of an unsaturated nitrile, presumably II.



I



II

On a purely analogical basis, β-dihydroumbellulone oxime (III) might be expected to yield the cyclopropenyl nitrile IV. It gives, in fact, only the lactam V or products derived therefrom in excellent yield under a variety of rearrangement conditions.

**The Structure of the Lactam.**—That the product of the rearrangement was a bicyclic lactam and not an unsaturated nitrile was evident immediately from its saturated character and its infrared absorption spectrum (3.12 μ (NH), 6.04 μ (CO)), characteristic of a six-membered lactam.[7] However, the data permitted no unequivocal choice between the alternatives V and VI.[8] Accordingly the degradation of the lactam was undertaken. The attachment of the nitrogen atom to the cyclopropane ring was revealed when hydrolysis of the lactam in 50% sulfuric acid gave a nitrogen-free, saturated, *keto* acid of ten carbon atoms (V → VIII). When the keto acid was found to be 5-oxo-3,4,6-trimethylheptanoic acid (VIII) by study of its properties and further degradation, the structure assignment V to the lactam became unequivocal.

The keto acid VIII was obtained as a crystalline, dextrorotatory solid of m.p. 49.5–50°, $[\alpha]^{27}\mathrm{D}$ $+50°$. In accord with the assigned structure which contains one labile (a) and one stable (b) asymmetric carbon atom, it underwent rapid mutarotation ($+50° \rightarrow -23°$) on being dissolved in 10% potassium hydroxide solution. Furthermore, when oximation of the crystalline keto acid was carried out in pyridine a single oximino acid of m.p. 156° was obtained,[9] but when carried out in aqueous potassium hydroxide a mixture of stereoisomeric oximino acids was obtained that was separated into forms melting at 134° and 156°, the latter being identical with that from the reaction in pyridine. Oximation of the oily residue from the crystallization of the acid of m.p. 49.5–50° gave the oximino acid of m.p. 134°.

The relationship of the ketone and carboxyl groups in the keto acid VIII was demonstrated by preparation of the enol lactone IX which showed bands at 5.72 and 5.93 μ characteristic of a six-membered enol lactone,[10] yet no bands corresponding to =C—H out-of-plane deformation.[7] Permanganate oxidation of the enol lactone IX produced a keto γ-lactone assigned structure X on the basis of analysis, infrared spectrum and solubility properties. As a by-product of the oxidation, isobutyric acid was evident, and the integrity and position of the isopropyl group in the keto acid VIII was established by isolation of isobutyric acid and isopropylamine from the hydrolysis of the Beckmann rearrangement product of the aforementioned oximino acid derived from VIII.

One property of the keto acid VIII which is not at first glance in accord with its structure is its ability to produce bromoform in significant amounts in the haloform reaction. It is proposed that under the strongly alkaline conditions of the reaction, acetic acid is eliminated in a reverse Michael reaction, producing a double bond between carbon atoms a and b in formula VIII, and that the resulting α,β-unsaturated ketone, $(CH_3)_2CHCOC(CH_3)=CHCH_3$, provides acetaldehyde for the haloform reaction through retrograde aldol condensation.[11]

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[1] Reported in part at the Meeting of the American Chemical Society, Dallas, Texas, April 10, 1956, Abstracts, 37N.

[2] Taken from the Doctoral Dissertation of W. D. Burrows in the Department of Chemistry, Stanford University.

[3] A. H. Blatt, *Chem. Revs.*, **12**, 218 (1933).

[4] It is to be noted that the α-carbon atom involved need not be at a bridge-head since menthone oxime gives both unsaturated nitrile and normal lactam depending on conditions [O. Wallach, *Ann.*, **277**, 157 (1893); **312**, 197 (1900)].

[5] For some other examples see A. Weiner and A. Piquet, *Ber.*, **37**, 4308 (1904); O. Wallach, *Ann.*, **315**, 289 (1901); W. H. Glover, *J. Chem. Soc.*, **93**, 1299 (1908).

[6] H. Wienhaus and P. Schumm, *Ann.*, **439**, 38 (1924.)

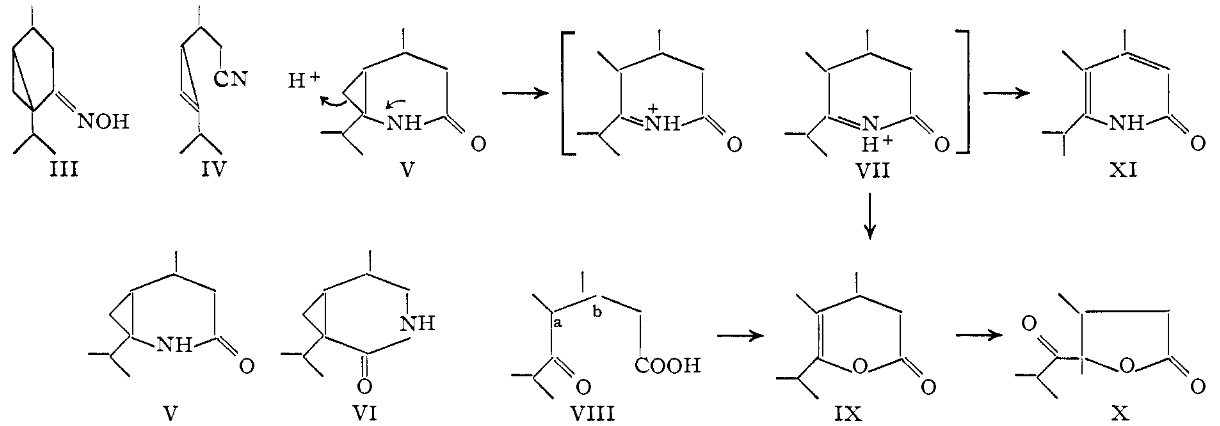
[7] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 176.

[8] The preparation of the *p*-toluenesulfonate and *p*-bromobenzenesulfonate derivatives of the oxime III and their conversion to the lactam indicated structure V if it was assumed that bulk considerations required a *trans* orientation of the sulfonate group and the bridge-head connection, and that the rearrangement proceeded by the usual migration of *trans*-oriented groups.

[9] The oximino acid of m.p. 156° was found to be identical in rotatory power and infrared absorption with an oximino acid (m.p. 154°) reported earlier (R. H. Eastman and J. C. Selover, This Journal, **76**, 4118 (1954)) as an anomalous product of the nitrosation of β-dihydroumbellulone.

[10] G. I. Fujimoto and J. Prager, *ibid.*, **75**, 3259 (1953).

[11] Reversal of the aldol condensation under the conditions of the haloform test has been observed for pulegone which gives a similar anomalous positive result in the test [O. Wallach, *Ann.*, **289**, 337 (1896)]. As precedent for the retrograde Michael condensation may be cited the formation of tanacetophorone from α-tanacetonedicarboxylic ester ["The Terpenes," R. H. Eastman and C. R. Noller in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, Vol. IV, p. 632].



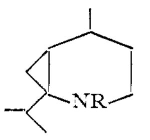
III IV V VII XI

V VI VIII IX X

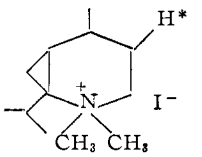
**Products Derived from the Lactam.**—The smooth hydrolytic degradation of the lactam V to the keto acid VIII came only at the end of a series of unsuccessful degradations whose course became clear with the structure of the lactam established. Some observations on the properties of the compounds prepared are of interest.

When the lactam V, dihydroumbellulone oxime (III) or its *p*-toluenesulfonate were heated at the steam-bath in concentrated sulfuric acid, sulfur dioxide was evolved and the pyridone XI was produced in good yield, presumably through oxidation by the sulfuric acid of the intermediate VII. In accord with the structure assigned, the pyridone (m.p. 220°) was optically inactive, weakly basic, inert to neutral permanganate and had ultraviolet maxima at 232 mμ (ε 6020), and 308 mμ (ε 6620) similar to those reported for 2-pyridone.[12] It showed one active hydrogen by the Zerevitinov method, was not reduced by lithium aluminum hydride and could be distilled through zinc dust intact.

Lithium aluminum hydride reduction of the lactam V proceeded smoothly to the bicyclic amine XII (R = H) which was cleanly methylated by the formic acid–formaldehyde method, then quaternized to XIII with methyl iodide. The ultraviolet absorption spectrum of the tertiary amine XII (R = $CH_3$) showed $\lambda^{alc}_{max}$ 213 mμ (ε 1450) comparable to that reported[13] for 1-methylpiperidine, $\lambda^{alc}_{max}$ 213 mμ (ε 1600), to be contrasted with that for 1-ethyl-2-methyl-$\Delta^2$-tetrahydropyridine,[13] $\lambda^{alc}_{max}$ 231 mμ (ε 5100), and further indicative[9] of the inability of the cyclopropane ring to act as an electron acceptor as does a vinyl group[14] in establishing a chain of conjugation.



XII



XIII

Surprisingly, and in contradistinction to the behavior of cyclopropyltrimethylammonium hydroxide which yields cyclopropene under the conditions of the Hofmann elimination,[14a] the methiodide XIII reverted to the tertiary amine XII (R = $CH_3$) with loss of methanol. Failure of β-elimination to occur is not rationalized readily on steric grounds, for a nearly coplanar four-center transition state involving the starred hydrogen atom in XIII can be obtained with an approximate model of the system. The situation parallels that found for the quaternary salt of tetrahydroquinoline which also eliminates methanol under the conditions of the Hofmann degradation.[15] The two systems have in common an electron-rich, highly polarizable group attached to the quaternary nitrogen which may so diffuse the positive pole on the nitrogen as to reduce the acidity of the starred proton on the β-carbon below the level required for elimination.[16]

As a base, the secondary amine XII (R = H) ($pK_B'$ 4.9) was 1.6 $pK_B'$ units weaker than piperidine ($pK_B'$ 3.3)[17] and comparable in strength with cyclopropylamine ($pK_B'$ 5.34).[18] The low basic strength of the amine XII (R = H) relative to piperidine can as well be attributed to the base-weakening effect of the cyclopropane ring attachment[18] and a decrease in solvation of the ammonium ion on account of blocking by the isopropyl group as to any specific interaction of the bicyclic system.[19]

The lactam V, absorbing maximally at 211 mμ (ε 5190), showed only a moderate exaltation over ε-caprolactam, absorbing maximally at 208 mμ (ε 3700), definitely not of the magnitude found for the unsaturated lactam, 7-oxo-3,5,5-trimethyl-$\Delta^2$-tetrahydroazepine which contains the system

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[12] H. Specker and H. Gawrosch, *Ber.*, **75B**, 1342 (1942).

[13] N. I. Leonard and D. M. Locke, THIS JOURNAL, **77**, 438 (1955).

[14] See, however, R. J. Mohrbacher and N. Cromwell, *ibid.*, **79**, 401 (1957), for arguments to the contrary.

[14a] M. J. Schlatter, *ibid.*, **63**, 1733 (1941).

[15] H. Embde, *Ann.*, **391**, 92 (1912).

[16] E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

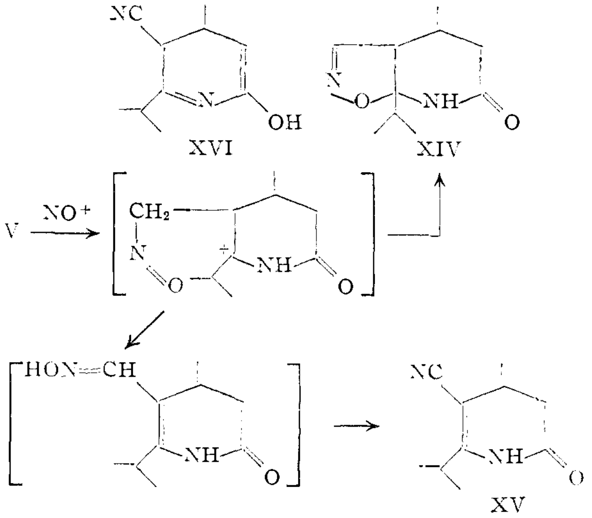
[17] The $pK_B'$ values are apparent values obtained by titration of the amines in 50% by volume ethanol using a Beckman *p*H meter standardized against aqueous buffers in the manner of Roberts and Chambers (ref. 18).

[18] J. D. Roberts and Vaughan C. Chambers, THIS JOURNAL, **73**, 5031 (1951).

[19] A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949). The difference of 1.6 in $pK_B'$ values between the amine XII (R = H) and piperidine is only slightly greater than that of 1.0 $pK_B'$ unit between dimethylcyclopropylamine ($pK_B'$ 6.3) and cyclopropylamine ($pK_B'$ 5.3) (ref. 18). The small increment may be attributed to less hindrance to solvation in the dimethyl compound than that encountered in XII (R = H).

C=C—NH—COR and is reported[20] to absorb maximally at 218.5 mμ (ε 10,700). The absorption of the vinylamide is what might be expected of the dienoid system, $C{=}C{-}\overset{+}{N}H{=}C{-}O^-$, an important contributor to both ground and photoexcited states. The bathochromic shift in absorption from that observed for a saturated lactam may be attributed to stabilization of the photo-excited state by contribution of $\overset{-}{C}{-}C{=}\overset{+}{N}H{-}C{=}O$ in which the vinyl group acts as an electron acceptor but not by contributions wherein the double bond is an electron donor, since $\overset{+}{C}{-}C{=}\overset{+}{N}H{-}\overset{-}{C}{-}O^-$ would be of disproportionately high energy as a consequence of adjacent like-charges. Since the cyclopropane system apparently operates efficiently only as a donor of electrons[21] to adjacent unsaturated centers, the small shift observed is not unexpected.

Nitrosation of the lactam V either by the use of nitrogen tetroxide or nitrosyl chloride failed to produce an N-nitrosoamide for rearrangement with nitrogen elimination to the corresponding lactone according to the method of White,[22] but gave instead products resulting from attack of the nitrosating agent on the cyclopropane ring in the same sense as that envisioned for the attack of a proton in the sulfuric acid hydrolysis of the lactam (V→VII). Structures XIV and XV are proposed for two of the products on the basis of properties and spectroscopic data. The substance assigned structure XIV was a colorless solid, m.p. 164°, which was optically active, insoluble in dilute acid or base, not readily oxidized by permanganate in acetone, and of ultraviolet absorption essentially identical with that of the lactam V. The infrared absorption spectrum showed bands characteristic[7] of the NH (3.12, 3.22), amide carbonyl (5.94) and C=N (6.21) groups.



The compound assigned structure XV was a white solid, m.p. 156°, which was optically active and insoluble in dilute acid or base. It reduced permanganate in acetone instantly but did not readily react with bromine in carbon tetrachloride. The infrared absorption spectrum revealed bands at 3.12–3.22, 4.53, 5.92 and 6.12 μ attributed[7] to NH, C≡N, C=O and C=C groups, respectively. The ultraviolet absorption spectrum showed maxima at 261 mμ (ε 9200) and 280 mμ (ε 8150). Surprisingly, hydrogen cyanide, detected by the formation of prussian blue, was one of the products of hydrolysis of the nitrile XV. This bizarre property is not unreasonable in terms of the tautomeric structure XVI which reveals the nitrile as the product of the addition of hydrogen cyanide across one of the double bonds of the enol form of a pyridone. Difficulty in obtaining the nitrile precluded further investigation of this unusual property.

**Acknowledgment.**—We wish to express our sincere appreciation to the Eli Lilly Co. and the Nichols Fellowship donor for their generous aid to W. D. B. during this investigation.

## Experimental

**The Beckmann Rearrangement of Dihydroumbellulone Oxime: Preparation of 5-Methyl-1-isopropyl-2-azabicyclo-[4.1.0]heptanon-3 (V).**—Dihydroumbellulone oxime[23] (III) (14.4 g.) was dissolved in 30 ml. of dry pyridine, cooled to 0°, and added to a chilled solution of 25 g. of *p*-toluenesulfonyl chloride (or *p*-bromobenzenesulfonyl chloride), in 30 ml. of dry pyridine. The mixture was allowed to stand one hour, then heated on a steam-bath. After 20 min. of heating the mixture turned dark red and began boiling. Heating was continued another 10 min., and the reaction mixture was allowed to stand at room temperature about two hours, after which it was poured on a mixture of 25 ml. of sulfuric acid and 120 g. of ice. The product solidified in two hours and was separated and washed with cold water, leaving 10.3 g. of white, crystalline material with a soapy odor. Ether extraction of the filtrate and washings yielded another 2.7 g. The product melted at 102.2–102.7°[24] after recrystallization from cyclohexane and had $[\alpha]^{27}\text{D}$ +60 ± 1° (*l* 0.5, *c* 4, 95% ethanol); spectra[25]: $\lambda_{max}^{alc}$ 211 mμ, ε 5190; $\lambda_{max}^{mull}$ 3.12, 6.04 μ.

*Anal.*[26] Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.92; H, 10.14; N, 8.48.

**Dihydroumbellulone Oxime *p*-Toluenesulfonate.**—Two grams of oxime III was dissolved in 5 ml. of dry pyridine. The solution was cooled to 0° and added to a chilled solution of 4.0 g. of toluenesulfonyl chloride in 5 ml. of pyridine. After standing at room temperature for four hours the mixture was poured into 50 ml. of 3 *N* sulfuric acid, chilled and extracted with ether. Recrystallization of the product from medium boiling petroleum ether yielded 1.0 g. of white solid melting at 84.6–85.3°.

*Anal.* Calcd. for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36; S, 9.97. Found: C, 63.31; H, 7.41; N, 4.52; S, 10.18.

When the oxime toluenesulfonate was heated with dry pyridine a slow decomposition to tarry products was the result. The addition of concentrated hydrochloric acid to the heated pyridine solution produced a fair yield of the lactam V. Heating the toluenesulfonate with aqueous or

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(20) R. S. Montgomery and G. Dougherty, *J. Org. Chem.*, **17**, 823 (1952).

(21) See refs. 9, 14 and R. H. Eastman and S. K. Freeman, THIS JOURNAL, **77**, 6642 (1955).

(22) E. H. White, *ibid.*, **77**, 6008, 6014 (1955).

(23) The oxime was prepared by the method of H. Wienhaus and K. T. Todenhöfer, *Schimmel's Report*, 285 (1929), and had m.p. 72–73° (reported 72°).

(24) All melting points were observed on a calibrated Kofler hot-stage.

(25) Ultraviolet absorption spectra were observed on alcohol solutions unless otherwise noted, using a Beckman DU instrument. The instrument was balanced by varying the slit width, readings were taken at no greater than 5-mμ intervals and the photomultiplier attachment was used below 220 mμ. Infrared absorption spectra were obtained using the Perkin–Elmer model 21 instrument equipped with the rock-salt prism.

(26) Analyses by Microchemical Specialties, Berkeley, Calif.

ethanolic potassium hydroxide produced dihydroumbellulone as the major product.

**5-Oxo-3,4,6-trimethylheptanoic Acid (VIII).**—The lactam V (10.0 g.) dissolved in 60 g. of 50% sulfuric acid was heated on a steam-bath for six hours. The reaction mixture was poured on ice, made basic with sodium hydroxide, extracted with ether, reacidified, and extracted with chloroform. The chloroform was removed under vacuum leaving 9.0 g. of pale-yellow, odorless oil, about 25% of which crystallized when diluted with one volume of hexane and chilled to −10°. The material melted at 49.5–50° after recrystallization from hexane; $[\alpha]^{27}\text{D}$ +50 ± 0.5° (*l* 0.5, *c* 4, 95% ethanol); spectrum: $\lambda^{\text{mull}}_{\text{max}}$ 5.82 (sh.), 5.85, 6.04 (sh.) $\mu$.

*Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.47; H, 9.75. Found: C, 64.71; H, 9.89.

MUTAROTATION OF THE KETO ACID VIII

| Time, hr. | Base | Concn. of XIII, g./100 ml. | $[\alpha]\text{D}$ (28–30°) |
|---|---|---|---|
| 0 | 5% $NaHCO_3$ | 4 | 58° |
| 0.5 | 11% KOH | 4.5 | − 7.5 |
| 2 | 11% KOH | 4.5 | −20 |
| 24 | 11% KOH | 4.5 | −23 |

The **oxime** was prepared by refluxing 0.25 g. of the crystalline keto acid, 0.25 g. of hydroxylamine hydrochloride, 2 ml. of dry pyridine and 2 ml. of absolute alcohol two hours on a steam-bath. The solvents were evaporated in a current of air, and the residue was stirred with 5 ml. of cold water until the oxime crystallized. After recrystallization from 50% ethanol–water, the oxime melted at 154–156° and had $[\alpha]^{26}\text{D}$ +6.9 ± 0.1° (*l* 0.5, *c* 4, 95% ethanol). The liquid portion of the lactam hydrolysate similarly treated yielded an oxime melting at 132–134° after repeated recrystallizations. The latter was submitted for combustion analysis.

*Anal.* Calcd. for $C_{10}H_{19}NO_3$: C, 59.66; H, 9.52. Found: C, 59.88; H, 9.60.

To 5.0 g. of a mixture of both oximes of VIII dissolved in 15 ml. of dry pyridine was added a chilled solution of 6.0 g. of toluenesulfonyl chloride in 15 ml. of pyridine. The resulting solution was allowed to stand 45 min., then heated 30 min. on a steam-bath, after which it was poured on a mixture of 25 g. of concentrated sulfuric acid and ice. Extraction with ether and evaporation of the solvent left 4.5 g. of very thick, red sirup, which was hydrolyzed, without purification, by boiling it with 50% sulfuric acid for 4 hours. The hydrolysis mixture was extracted with ether, the aqueous portion was set aside and the ether extract was distilled at atmospheric pressure, then redistilled at 20 mm. into two fractions. The low-boiling fraction was shown to be isobutyric acid by its odor, infrared spectrum and index of refraction. The high-boiling fraction was not characterized.

The aqueous portion from the hydrolysis was made strongly basic with 50% sodium hydroxide and was immediately steam distilled into 10% hydrochloric acid, about 50 ml. of distillate being collected. The distillate was evaporated to dryness, leaving 0.5 g. of red, hygroscopic solid. This material was decolorized with Norit in absolute ethanol and left in a drying pistol two hours at 100° and 20 mm. The dry, colorless solid melted at 136–139° dec. in a sealed capillary and was thereby identified as isopropylamine hydrochloride.

**2-Oxo-4,5-dimethyl-6-isopropyl-3,4-dihydropyran (IX).**—Two grams of the keto acid VIII was refluxed for five hours with 6 ml. of acetic anhydride. The acetic acid and most of the acetic anhydride were then distilled off, and the residue was dissolved in ether and extracted with sodium carbonate solution. The ether solution was evaporated and the residual oil was distilled at 15–20 mm. with bath temperature near 125°, yielding 1.2 g. of colorless, fragrant oil. The oil, purified by liquid–vapor partition chromatography, had $n^{24}\text{D}$ 1.4583; spectrum, $\lambda^{\text{film}}_{\text{max}}$ 5.72, 5.93 $\mu$.

*Anal.* Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.49; H, 9.42.

One gram of enol lactone IX was suspended in 25 ml. of water with 2 g. of sodium bicarbonate in a 100-ml. r.b. flask equipped with a mechanical stirrer, and 1.25 g. of potassium permanganate was added in small portions. The color produced by 0.1 g. of additional permanganate was not dispelled after one hour of stirring. The reaction mixture was filtered through Celite and the manganese dioxide cake was washed with water. Filtrate and washings were acidified to *p*H 1 with sulfuric acid, resulting after 20 min. in the separation of an oil. The oil was extracted with chloroform and the extract was distilled at 20 mm. with bath temperature near 125° to yield 0.5 g. of colorless oil with a camphor-like odor. The product, purified by liquid–vapor partition chromatography, had $n^{20.2}\text{D}$ 1.4519, and is assigned the structure of **$\beta,\gamma$-dimethyl-$\gamma$-isobutyryl-$\gamma$-butyrolactone (X)**; spectrum, $\lambda^{\text{film}}_{\text{max}}$ 5.65, 5.86 $\mu$.

*Anal.* Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.84; H, 8.67.

**4,5-Dimethyl-6-isopropyl-2-pyridone (XI).**—Five grams of lactam V was dissolved in 25 ml. of concentrated sulfuric acid and heated on a steam-bath one hour. The reaction mixture was poured on 100 g. of ice and extracted with ether to remove acidic and neutral material. The aqueous portion was diluted with water to 250 ml., made basic with sodium carbonate, and continuously extracted four days with ether. Most of the product crystallized out on the sides of the ether reservoir, and by evaporation of the solvent there was obtained 1.63 g. of white, crystalline solid melting at 219–220° with rapid sublimation and having $[\alpha]\text{D}$ 0.0 ± 0.2° (*l* 0.5, *c* 4, chloroform); spectra, $\lambda^{\text{alc}}_{\text{max}}$ 232 m$\mu$ ($\epsilon$ 5190), 308 m$\mu$ ($\epsilon$ 6620); $\lambda^{\text{mull}}_{\text{max}}$ 3.20 (sh.), 6.03, 6.50 $\mu$.

*Anal.* Calcd. for $C_{10}H_{15}NO$: C, 72.70; H, 9.15. Found: C, 72.98; H, 9.08.

Dihydroumbellulone oxime (III), treated with sulfuric acid as described above for the lactam V, gave a 12% yield of the pyridone.

**5-Methyl-10-isopropyl-2-azabicyclo[4.1.0]heptane** (XII, R = H).—To 20 g. of lactam V in 750 ml. of absolute ether was added in small portions 12 g. of lithium aluminum hydride. The mixture was refluxed gently for five hours, then allowed to stand at room temperature 12 hours, and finally decomposed with 100 ml. of ethanol followed by 100 ml. of water. The ether was decanted and the residual hydroxides were washed with several hundred milliliters of absolute ether. The ethereal portions were combined, evaporated on a steam-bath, and the residual product was distilled, yielding 11.1 g. of colorless oil with an odor like crushed geraniums, boiling at 35–35.5° at 2–3 mm., $[\alpha]^{24}\text{D}$ +108.5 ± 0.5° (*l* 0.5, neat), $d^{20}{}_4$ 0.864, $n^{20}\text{D}$ 1.4561.

*Anal.* Calcd. for $C_{10}H_{19}N$: C, 78.35; H, 12.50; N, 9.15. Found: C, 78.44; H, 12.31; N, 9.18.

The picrate, m.p. 164.5–166.5° (Found: C, 50.42; H, 5.91), and the benzenesulfonamide, m.p. 98.8–99.8° (Found: C, 65.58; H, 7.86), were prepared in the usual ways.

**2,5-Dimethyl-1-isopropyl-2-azabicyclo[4.1.0]heptane** (XII, R = $CH_3$).—To 4.8 g. of reduced lactam (XII, R = H) were added, with cooling, 4.5 g. of 85% formic acid and 3.0 g. of 36–38% formaldehyde. The solution was allowed to stand overnight, then heated two hours on a steam-bath, after which 3 ml. of concentrated hydrochloric acid was added. The mixture was evaporated on a steam-bath to remove excess formaldehyde and formic acid. The residue was diluted with several volumes of water, made strongly basic with 20% sodium hydroxide, and steam distilled. The distillate was made strongly basic with solid potassium hydroxide, extracted with ether, and the extract was distilled without ebullator to give in about 50% yield a colorless oil boiling at 57–59° at 7 mm., $[\alpha]^{24}\text{D}$ +34.4 ± 0.1° (*l* 0.5, neat), $d^{27}{}_4$ 0.867, $n^{20}\text{D}$ 1.4578.

*Anal.* Calcd. for $C_{11}H_{21}N$: C, 78.96; H, 12.65; N, 8.38. Found: C, 78.86; H, 12.40; N, 8.44.

The picrate, m.p. 160–165° dec., was prepared by adding the amine to a hot, saturated solution of picric acid in ethanol.

The methiodide XIII was prepared by refluxing 0.51 g. of XII, R = $CH_3$, with a fivefold excess of methyl iodide. The product (0.58 g.), recrystallized from methanol, decomposed above 280° and had $[\alpha]^{25}\text{D}$ −29.2 ± 0.4° (*l* 0.5, *c* 5, methanol).

*Anal.* Calcd. for $C_{12}H_{24}NI$: C, 46.60; H, 7.82. Found: C, 46.49; H, 7.96.

The Hofmann elimination was attempted by boiling this methiodide (0.10 g.) under reflux with 10 ml. of 50% sodium hydroxide solution for 10 minutes followed by steam distillation of the oil which had separated. The oily layer from the steam distillate was identical in infrared absorption characteristics with the tertiary amine XII, R = $CH_3$.

**Nitrosation of the Lactam V with Nitrogen Tetroxide.**—Five grams of lactam dissolved in 25 ml. of glacial acetic acid was chilled to 0° and saturated with dry nitrogen tetroxide. After standing one hour at room temperature the solution was poured on 100 g. of ice. A yellow solution resulted which turned red-brown when made basic with 50% sodium hydroxide. The basic solution was extracted with ether and the aqueous portion was set aside. In the best run, evaporation of the ether extract left about 0.25 g. of white, crystalline solid melting at 162–164° after recrystallization from ethyl acetate. The solid had $[\alpha]^{26}D$ +288 ± 5° (*l* 0.5, *c* 4, 95% ethanol), and is assigned structure XIV; spectrum, $\lambda_{max}^{mull}$ 3.12, 3.22, 5.94, 6.21 $\mu$.

*Anal.* Calcd. for $C_{16}H_{16}N_2O_2$: C, 61.20; H, 8.22. Found: C, 61.33; H, 8.33.

The aqueous portion from the extraction was acidified with concentrated sulfuric and extracted with ether. The extract was evaporated on a steam-bath to remove ether, then under reduced pressure to remove acetic acid. A black tar remained that slowly crystallized to yield 0.75 g. of white needles melting at 155–156° after recrystallization from ethanol–water; $[\alpha]^{26}D$ −104 ± 5° (*l* 0.5, *c* 4, 95% ethanol). This compound is assigned structure XV; spectra: $\lambda_{max}^{alc}$ 261 m$\mu$ ($\epsilon$ 9200), 280 m$\mu$ ($\epsilon$ 8150); $\lambda_{max}^{mull}$ 3.12, 4.52, 5.92, 6.12 $\mu$.

*Anal.* Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.71; H, 7.88; N, 15.55.

When the nitrile XV (0.20 g.) was warmed for 15 minutes with 10 ml. at 10% sodium hydroxide a colorless solution was obtained. Acidification of the hydrolysis mixture caused an oil to separate and when this oil was dissolved in dilute sodium bicarbonate solution, carbon dioxide and hydrogen cyanide, detected by the formation of prussian blue, were evolved.

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[CONTRIBUTION FROM THE RESEARCH CENTER, HERCULES POWDER CO.]

# Synthesis of Poly-$\beta$-alanine from Acrylamide. A Novel Synthesis of $\beta$-Alanine[1]

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Poly-$\beta$-alanine has been prepared by the base-catalyzed polymerization of acrylamide. By fractionation samples with weight-average molecular weights as high as about 80,000 have been prepared. Acid hydrolysis of the polymer constitutes a simple preparation of $\beta$-alanine in yields of 90% starting with acrylamide. Substituted acrylamides and analogous sulfonamides yield polymers of much lower molecular weight. An unusual mechanism for the polymerization is proposed.

Poly-$\beta$-alanine has been prepared previously by the elimination of HX from a $\beta$-alanine derivative, $H_2NCH_2CH_2COX$, where X is $NH_2$,[2] $OC_2H_5$,[3] Cl[4] or OH,[5] or by the elimination of thiophenol and carbon dioxide from N-carbothiophenyl-$\beta$-alanine.[6] It is questionable whether any of these methods give high molecular weight polymers.[7] Poly-$\beta$-alanine has now been prepared by the base-catalyzed polymerization of acrylamide, a readily available compound.

**Preparation of Polymers.**[9]—Poly-$\beta$-alanine formed a mixture of water-soluble and water-insoluble polymers when acrylamide, usually in an inert diluent, was contacted with a strong base in the presence of an inhibitor for radical-induced polymerization. The technique of polymerization was similar in most cases, typical examples being given in the Experimental section.

The effects of certain variables on the polymerization are shown in Table I.

The highest molecular weight water-insoluble polymer was obtained in pyridine. The largest amount of water-insoluble polymer was formed in the absence of solvent. Phenyl-$\beta$-naphthylamine was superior to hydroquinone as a radical inhibitor, presumably because hydroquinone acted as a chain terminator for basic polymerization. It was possible to carry out small-scale preparations without an inhibitor, but in larger runs the presence of an inhibitor was advantageous. Sodium *t*-butoxide in *t*-butyl alcohol appeared to be the best catalyst; apparently the alcohol did not terminate polymer chains. Dilution lowered the yield and molecular weight of water-insoluble polymer somewhat.

**Properties of Poly-$\beta$-alanine.**—Each polymerization yielded a spectrum of products with fractions soluble in pyridine, fractions soluble in water and fractions soluble only in solvents such as formic acid being obtained. The pyridine-soluble material consisted largely of monomer and dimer, the latter analyzing reasonably well for $CH_2{=}CH{-}CONHCH_2CH_2CONH_2$. This polymerized much like acrylamide itself on addition of base.

Both the water-soluble and the water-insoluble polymers were highly crystalline, melting at about 325° and about 340°, respectively, with considerable decomposition. Both gave the same well-defined X-ray diffraction pattern, the water-insoluble polymer being somewhat more crystalline than the water-soluble. The lattice spacings of 4.6, 3.9 and 3.55 Å. had relative intensities of 60, 10 and 100, respectively, for the water-insoluble polymer.

The water-insoluble polymer showed typical polyamide solubility. Thus, it was soluble in for-

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[1] Presented at the 131st Meeting of the American Chemical Society, Miami, Florida, April, 1957.

[2] A. P. N. Franchimont and H. Friedman, *Rec. trav. chim.*, **25**, 80 (1906).

[3] E. Abderhalden and F. Reich, *Z. physiol. Chem.*, **178**, 169 (1928).

[4] M. Frankel, Y. Liwschitz and A. Zilkha, *Experientia*, **9**, 179 (1953); THIS JOURNAL, **76**, 2814 (1954).

[5] J. S. Chirtel and A. M. Mark, U. S. Patent 2,691,643 (1954).

[6] J. Noguchi and T. Hayakawa, THIS JOURNAL, **76**, 2846 (1954).

[7] Noguchi and Hayakawa reported a molecular weight of 43,500 for their sample of poly-$\beta$-alanine. However, their intrinsic viscosity of 0.063 in formic acid is remarkably low for this molecular weight. Recently Weymouth[8] has shown that several polypeptides made by this procedure have relatively low molecular weights, of the order of 1000–5000.

[8] F. J. Weymouth, *Chem. & Ind.*, Brit. Inds. Fair Rev., April, 1956, R34.

[9] D. S. Breslow, British Patent 736,461 (1955); U. S. Patent 2,749,331 (1956).