*endo*-**2-Hydroxy**-*exo*-**3-iodo**-*endo*-**6-norbornaneacetic Acid Lactone (5).**—A mixture of 5-norbornene-2-acetic acids[7] was prepared from the Grignard reagent of 5-norbornene-2-methyl chloride.[3,7]

The crude acids (40 g, 0.26 mole) were dissolved in 300 ml of water which contained 18.4 g (0.278 mole) of potassium hydroxide and 15.4 g (0.183 mole) of sodium bicarbonate. A solution of 67.0 g (0.264 mole) of iodine and 82.0 g (0.493 mole) of potassium iodide in 300 ml of water was added with stirring over a period of 1 hr. The resulting mixture was stirred for an additional 0.5 hr at 25°. An additional 20 g of potassium hydroxide in 50 ml of water was added followed by solid sodium bisulfite until the iodine color was discharged. The mixture was cooled with ice and extracted with cold chloroform. The dried ($MgSO_4$) extracts were evaporated to give 55.7 g (76%) of the lactone **5**. Crystallization from absolute ethanol gave an analytical sample, mp 101.5–103°.

*Anal.* Calcd for $C_9H_{11}O_2I$: C, 38.87; H, 3.99; I, 45.64. Found: C, 39.09; H, 4.01; I, 45.93.

The infrared spectrum (mull) showed carbonyl absorption at 5.70 μ.

*endo*-**5-Norbornene-2-acetic Acid (4a).**—The crude iodolactone **5** (55.0 g, 0.2 mole) was dissolved in 1.5 l. of glacial acetic acid and treated with three 10-g portions of zinc dust over a 1.5-hr period. The resulting mixture was stirred for 1 hr at 25°. The solids were removed by filtration and the filter cake was washed with additional acetic acid. The washings were combined with the filtrate and the acetic acid was evaporated *in vacuo*. The residue was dissolved in 250 ml of ether. After several washings with saturated ammonium chloride solution, the ether was dried ($MgSO_4$) and evaporated to give 29 g (96%) of crude **4a**. The infrared spectrum (film) of this material displayed carbonyl absorption at 5.80 and a *cis* double bond band at 13.80 μ.

A small sample was distilled for an analytical sample, bp 104–106° (2.05 mm) (lit.[7] *exo*, *endo* mixture: bp 143° (12–13 mm)); $n^{25}D$ 1.4890.

*Anal.* Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.97; H, 7.91.

*Note:* Great difficulty was encountered in repetition of this latter experiment without any obvious explanation. It was decided to work with the *exo*, *endo* mixture in the later stages for this reason. The procedure used is basically that of B. E. Tate and A. Bavely, *J. Am. Chem. Soc.*, **79**, 6519 (1957).

*endo*-**5-(β-Hydroxyethyl)norbornene (4b).**—The acid **4a** (27.5 g, 0.18 mole) in 200 ml of dry ether was added slowly with stirring to a slurry of 7.5 g (0.2 mole) of lithium aluminum hydride in 1.5 l. of dry ether. After addition was complete, stirring was continued for 1 hr at which time the excess reagent was destroyed by careful addition of water. The resulting slurry was filtered and the ether was removed by evaporation. Distillation of the residue gave 19.4 g (78%) of alcohol **4b**; bp 86.0–86.5° (1.7 mm), $n^{25}D$ 1.4919 (lit.[3] bp 93–94° (6 mm), $n^{25.3}D$ 1.4930).

The infrared spectrum showed *cis*-double bond absorption at 13.88 and a C–O stretching band at 9.47 μ.

Several attempts to obtain a carbon–hydrogen analysis gave results ~1.3% low in carbon perhaps due to moisture even after careful collection by gas chromatography.

*endo*-**5-(β-Chloroethyl)norbornene (4c).**[8]—A solution of 4.0 g (0.029 mole) of alcohol **4b** in 15 ml of dry benzene and 2.0 ml of pyridine was cooled in an ice bath. A solution of 7.00 g (0.059 mole) of thionyl chloride in 10 ml of benzene was added with stirring over a period of 1 hr. Stirring at ~0° was continued for 0.5 hr. The excess thionyl chloride was destroyed by shaking the reaction mixture with ice. The aqueous phase was extracted with ether and the combined organic phases were evaporated to give 4.15 g (91%) of crude chloride **4c**. Distillation gave 2.53 g (53%) of pure product with bp 87–90° (14 mm); $n^{25}D$ 1.4984.

*Anal.* Calcd for $C_9H_{13}Cl$: C, 69.00; H, 8.36; Cl, 22.64. Found: C, 68.60; H, 8.18; Cl, 23.58.

**6-(β-Chloroethyl)-3-oxatricyclo[3.2.1.0$^{2,4}$]octane (6).**—A solution of 4.0 g (0.0256 mole) of chloride **4c**[9] in 70 ml of chloroform was cooled in an ice–salt bath. A solution of 3.0 g of sodium acetate in 16.0 ml of 40% peracetic acid was added over 15 min.[10] After stirring for an additional 2.5 hr at 15°, the mixture was neutralized with 20% sodium hydroxide solution. The layers were separated and the aqueous phase was extracted three times with chloroform. The combined extracts were dried ($MgSO_4$) and distilled. A residue was obtained which was purified by evaporative distillation at 0.4 mm. There was obtained 3.42 g (79%) of **6**.[9]

*Anal.* Calcd for $C_9H_{13}OCl$: C, 62.61; H, 7.59; Cl, 20.53. Found: C, 62.38; H, 7.46; Cl, 20.54.

The infrared spectrum (film) showed strong absorption at 11.75 μ, characteristic of epoxides.[11]

*exo*-**2-Hydroxytricyclo[4.2.1.0$^{3,7}$]nonane (1).**—A three-necked flask was fitted with a gas inlet tube, a condenser, and a pressure-equalized dropping funnel. The entire apparatus was flame dried under a nitrogen stream. The nitrogen was flushed by a helium stream. A slurry of 4.0 g (~0.36 g-atom) of lithium dispersion[5] in 50 ml of dry tetrahydrofuran was added to the flask. A solution of 2.8 g (0.0162 mole) of **6** in 30 ml of tetrahydrofuran was added over 10 min with continuous agitation by a magnetic stirrer. The resulting mixture was heated at reflux for 42 hr after which it was poured onto crushed Dry Ice. Dilute hydrochloric acid was added until the resulting solution was acidic to litmus. The water layer was extracted with ether and the combined extracts were washed with sodium bicarbonate solution. The dried extracts were evaporated carefully to yield a light yellow residue. Sublimation of this material at 100° using an oil pump gave 1.0 g (53%, based on 85% epimeric purity) of a semisolid. Purification by gas chromatography (>90% homogeneity) gave a white solid, mp 129–130° (lit.[6] 133.5–134.5°). The infrared and nmr spectra of this material were identical with those of authentic samples.[6]

**Registry No.**—**1**, 14805-44-8; **4a**, 14734-13-5; **4b**, 14734-14-6; **4c**, 14734-15-7; **5**, 14734-16-8; **6** (*exo*), 14754-85-9; **6** (*endo*), 14754-86-0.

**Acknowledgments.**—Financial support from the Colgate-Palmolive Co. and the National Institutes of Health (RG-08701) is gratefully acknowledged.

(7) K. Alder and E. Windemuth, *Ber.*, **71**, 1939 (1938).

(8) C. R. Noller and R. A. Bannerot, *J. Am. Chem. Soc.*, **56**, 1563 (1934).

(9) An *exo*, *endo* mixture (15:85) was used in this experiment and the product was carried through the cyclization steps without separation into the pure *endo* isomer.

(10) H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, **76**, 5396 (1954).

(11) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960).

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## L-Proline-N-oxalic Anhydride[1]

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*Received May 22, 1967*

As part of an investigation of oxalyl derivatives of α-amino acids,[2] we have prepared the cyclic N-oxalic anhydride (I) of L-proline by treatment of the amino acid in an inert solvent with excess oxalyl chloride. To our knowledge, the only N-oxalic anhydride of an α-amino acid previously reported is that of 4-carbomethoxy-5,5-dimethylthiazolidine-2-carboxylic acid, obtained in the same manner.[3]

In both of these cases the N atom acylated was in the form of a secondary amine in a five-membered ring.

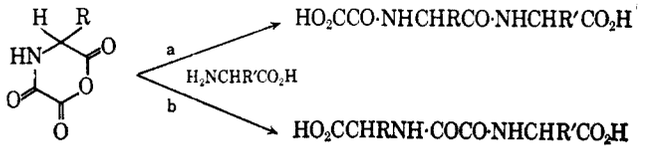
(1) Journal Paper No. J-5677 of the Iowa Agricultural and Home Economics Experiment Station, Ames, Iowa, Project No. 1384. Abstracted from the Ph.D. Thesis of R. E. Worthington, Iowa State University, Ames, Iowa, 1961.

(2) W. R. Hearn and R. A. Hendry, *J. Am. Chem. Soc.*, **79**, 5213 (1957).

(3) R. Bentley, A. H. Cook, J. A. Elvidge, and G. Shaw, *J. Chem. Soc.*, 2351 (1949).

When amino acids with primary $\alpha$-amino groups were treated with oxalyl chloride under conditions successful for proline, no anhydride could be isolated. Many variations of concentration, temperature, and solvent were tried without success, the products in most cases being intractable tars. These tarry products generally gave a positive hydroxamic acid test even after treatment with boiling water; the positive test may indicate the presence of acid anhydrides or possibly of azlactones formed by an alternative cyclodehydration reaction of the N-acylamino acid. Azlactones would be expected to polymerize under relatively mild conditions.[4] The impossibility of forming azlactones from cyclic imino acids would account for the ease of isolation of the cyclic anhydride in the two successful cases.

The N-oxalic anhydrides are six-membered analogs of N-carbonic anhydrides, reagents particularly useful in the synthesis of poly-$\alpha$-amino acids.[5] Under favvorable conditions the N-carbonic anhydride reacts with a trace of free amino acid, forming a dipeptide with an N-carboxyl group; loss of $CO_2$ frees the dipeptide amino group to react with another molecule of anhydride, and so on. We had originally thought that N-oxalic anhydrides might yield N-oxalyl dipeptides on reaction with amino acids (a); such derivatives might be useful in stepwise syntheses of polypeptides if the N-oxalyl group could be removed under mild conditions. It was recognized that attack by the amino group on the carboxyl belonging to the oxalic acid moiety (b) would also probably occur, opening the ring to yield an N,N′-oxalylbis(amino acid) instead of the desired N-oxalyl dipeptide.

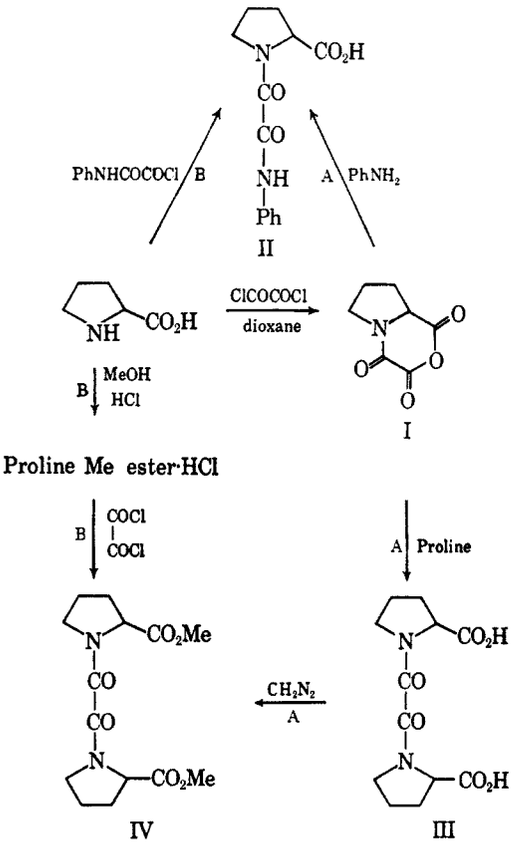



The analogous ring opening to yield N,N′-carbonylbis(amino acids) is an undesirable side reaction in peptide synthesis with N-carbonic anhydrides.[5]

When L-proline-N-oxalic anhydride was treated with aniline the ring-opening attack took place on the oxalic side of the anhydride, giving N-oxanilyl-L-proline (II). With L-proline the ring opened in the same manner to give N,N′-oxalybis(L-proline) (III). The carbon actually attacked by the amino group was thus the ring carbon expected to be most electrophilic on simple theoretical grounds. Since ring opening was unfavorable in the proline case and since other N-oxalic anhydrides were not easily obtained, consideration of N-oxalic anhydrides as possible reagents for peptide synthesis was abandoned.

### Experimental Section[6]

**L-Proline-N-oxalic Anhydride (I).**—L-Proline (7.0 g, 0.06 mole) was suspended in 150 ml of dioxane. The suspension was




added in small portions and with constant stirring to a large excess of oxalyl chloride (30 g) in 500 ml of dioxane contained in a flask protected from moisture by a calcium chloride tube. The reaction mixture was warmed to about 80° with constant stirring and after 30 min was filtered to remove a small amount of undissolved solid material. Concentration of the filtrate to about 20 ml gave 7.6 g (74%) of the hygroscopic anhydride. Similar yields of I were obtained with THF as solvent. Recrystallization from acetone gave an analytical sample, mp 146–149° dec with evolution of gas.

*Anal.* Calcd for $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.18; H, 4.28; N (micro Kjeldahl), 8.26.

The anhydride was moderately soluble in hot dioxane and THF, insoluble in diethyl ether and ligroin. A 50.0-mg sample dissolved in 50 ml of water with warming was assumed to be completely hydrolyzed to N-oxalyl-L-proline; the free acid was not isolated but the acid solution was titrated with 0.0496 *N* sodium hydroxide to a phenolphthalein end point.

*Anal.* Calcd for $C_7H_7NO_4$: sapon equiv, 84.5. Found: sapon equiv, 84.6.

Glycine, DL-valine, and L-leucine, respectively, were submitted to identical reaction conditions but yielded tarry residues from which no identifiable products could be isolated. With DL-valine, halving or doubling the amino acid concentration or switching from dioxane to THF did not improve the results, although keeping the temperature below 50° gave less darkening of the resinous product. A small sample of this product was rubbed with a stirring rod in boiling water and then dissolved in ethanol; the alcoholic solution gave a negative chloride test but a positive hydroxamic acid test.[7]

**N-Oxanilyl-L-proline (II). A. From L-Proline-N-oxalic Anhydride and Aniline.**—Aniline (1.07 g, 0.011 mole) was added to 0.97 g (0.0057 mole) of I suspended in 50 ml of benzene. The anhydride dissolved in about 1 min and the solution was concentrated to 10 ml. Addition of ligroin produced a turbidity

(4) H. E. Carter, *Org. Reactions*, **3**, 198 (1946).

(5) E. Katchalski and M. Sela, *Advan. Protein Chem.*, **13**, 243 (1958).

(6) Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., except for nitrogen by micro Kjeldahl, performed in our own laboratory. Infrared spectra were obtained on KBr-pelletized samples with a Model 21 Perkin-Elmer spectrophotometer. Optical rotations were obtained in a 2-dm tube with a Model 123 Rudolph polarimeter. Oxalyl chloride and aniline were redistilled just before use. Tetrahydrofuran (THF) and other solvents were redistilled and kept over appropriate drying agents; dioxane was purified by distillation from metallic sodium. The ligroin used was Skellysolve B (Skelly Oil Co.), bp 60–70°. Aniline hydrochloride was recrystallized before use; reagent grade amino acids were used without further purification.

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 122.

which cleared in a few minutes with deposition of crystals; this process was repeated until no further turbidity was produced by addition of ligroin. The yield of anilide was 1.2 g (87%). Recrystallization from ethanol gave an analytical sample, mp 158–160°, $[\alpha]^{23}D$ −83° (*c* 1.0, absolute EtOH).

*Anal.* Calcd for $C_{13}H_{14}N_2O_4$: neut equiv, 262. Found: neut equiv, 259.5.

The anilide was soluble in dioxane and THF, sparingly soluble in water and diethyl ether, and insoluble in ligroin. For positive identification it was also prepared by the alternate route described below.

**B. From Oxanilyl Chloride and L-Proline.**—Oxanilyl chloride[8] was prepared by addition of aniline hydrochloride in small portions to three parts of oxalyl chloride in ten parts of THF, with stirring and protection from moisture. After 30 min of continued stirring, a small amount of undissolved solid material was removed by filtration, and the solvent and excess oxalyl chloride were removed in a rotary evaporator. Without further purification, the oxanilyl chloride was redissolved in a little THF and added to an equivalent quantity of L-proline suspended in THF. An excess of trimethylamine was added slowly, the solid material removed by filtration, and the filtrate concentrated to dryness in a rotary evaporator. The residue was recrystallized from ethanol to yield crystalline II, mp 158–160°, identical with that obtained *via* route A by mixture melting point and comparison of infrared spectra.

**N,N'-Oxalylbis(L-proline methyl ester) (IV). A. By Methylation of the Product (III) from L-Proline-N-oxalic Anhydride and L-Proline.**—To 1.2 g (0.0071 mole) of I suspended in dioxane was added 0.82 g (0.0071 mole) of proline under anhydrous conditions. After the reaction mixture had been stirred for 2 hr at 60°, the solution was decanted from a small amount of undissolved material and the solvent was evaporated to give 1.0 g (53%) of N,N'-oxalylbis(L-proline) (III) melting at 135–145° after one recrystallization from dioxane. Without further purification, 0.7 g of III was suspended in ether and treated with an excess of ethereal diazomethane. As soon as the rapid evolution of gas had ceased, the ether was decanted from a small amount of undissolved material and evaporated to give 0.42 g (53%) of slightly yellow crystals. Decolorization with charcoal and two recrystallizations from water gave an analytical sample, mp, 147.5–148.5°.

*Anal.* Calcd for $C_{14}H_{21}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 54.10; H, 6.40; N, 8.91.

**B. From Oxalyl Chloride and L-Proline Methyl Ester.** For comparison IV was also synthesized by a general method[9] for N,N'-oxalylbis(amino acid esters). L-Proline (10.0 g, 0.087 mole) was dissolved in 100 ml of methanol. Anhydrous HCl was passed into the solution until evolution of heat had ceased and the mixture was then refluxed gently for 8 hr with exclusion of moisture. After removal of excess methanol and HCl in a rotary evaporator, L-proline methyl ester hydrochloride was obtained as a thick syrup which did not crystallize readily. To the syrup was added with constant stirring 70 ml of sodium-dried benzene, followed over a period of 1 hr by small portions of 5.5 g (0.043 mole) of oxalyl chloride dissolved in 30 ml of benzene. The reaction mixture was refluxed for 4 hr and the benzene solution then decanted from a considerable amount of undissolved material. Evaporation of the solvent gave a thick syrup which crystallized upon standing for 24 hr. The yield of crystalline IV was 1.5 g (12.5%). Decolorization with charcoal and two recrystallizations from water gave an analytical sample, mp 147.5–148.5°.

*Anal.* Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 54.36; H, 6.55; N, 9.02.

This product was found to be identical with IV obtained *via* A by mixture melting point and comparison of infrared spectra.

**Registry No.**—I, 13673-68-2; II, 13673-69-3; IV, 13673-70-6.

**Acknowledgment.**—Support of this work in part by Research Grant RG-5781(A) of the Division of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., is gratefully acknowledged.

(8) I. G. Farbenindustrie A.-G., German Patent 463,140 (July 1928); *Chem. Abstr.*, **22**, 4130 (1928).

(9) J. Bornwater, *Rec. Trav. Chim.*, **31**, 105 (1912).

## Reaction of Nitro Anions with N,N-Dimethyl-*p*-hydroxybenzylamine. A New Synthesis of α-Methyltyrosine

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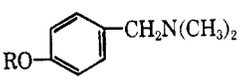
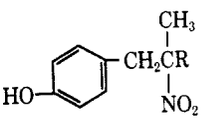
The reactions of nitroparaffin anions with benzyl halides may proceed to give products resulting from either carbon or oxygen alkylation.[1] The O-alkylation product, a nitronic ester, is not usually stable under the conditions of the reaction and it is assumed that it decomposes to give the observed products, an oxime and a carbonyl compound.[1a,2] In a study of the reaction of a series of *para*-substituted benzyl halides with the sodium salt of 2-nitropropane, only the *para*-nitro derivative was observed to give carbon alkylation.[1a,3] All other *para*-substituted benzyl halides investigated led to products resulting from reaction at oxygen.

The hydroxy derivative, N,N-dimethyl-*p*-hydroxybenzylamine (**1**), has now been found to give predominately carbon alkylation in reactions with the sodium salts of 2-nitropropane and ethyl α-nitropropionate. One of these products, ethyl 2-(*p*-hydroxybenzyl)-2-nitropropionate (**3**), has been converted to α-methyltyrosine, a potent inhibitor of tyrosine hydroxylase, an enzyme involved in the biosynthesis of norepinephrine.[4]

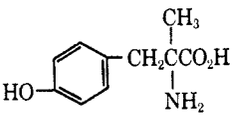
Reaction of **1** (prepared by the reductive alkylation of dimethylamine with *p*-hydroxybenzaldehyde) with ethyl α-nitropropionate and a catalytic amount of sodium hydride in refluxing toluene gave **3** in 57% yield, based on isolated material.[5] Thin layer chromatography of the crude reaction product indicated that only a small amount of the O-alkylation product, *p*-hydroxybenzaldehyde, was formed in the reaction.



**1**, R = H
**2**, R = $CH_3$



**3**, R = $CO_2C_2H_5$
**4**, R = $CH_3$



**5**

The infrared spectrum ($CHCl_3$) of **3** contains absorption bands at 1745, 1550, and 1345 $cm^{-1}$ indicating the presence of aliphatic ester[6a] and nitro[6b] functions.

(1) (a) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949); (b) H. B. Hass, E. J. Berry, and M. L. Bender, *ibid.*, **71**, 2290 (1949); (c) R. C. Kerber, G. W. Urry, and N. Kornblum, *ibid.*, **87**, 4520 (1965); (d) N. Kornblum and P. Pink, *Tetrahedron, Suppl. 1*, **19**, 17 (1963).

(2) N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.*, **86**, 2681 (1964).

(3) The nature of the leaving group is also important since some *p*-nitrobenzyl derivatives give predominately oxygen alkylation.[1c,d]

(4) S. Udenfriend, *Pharmacol. Rev.*, **18**, 43 (1966).

(5) Formation of carbon–carbon bonds by displacement of tertiary amines has been reviewed: J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953).

(6) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 179; (b) pp 298–301.