[JOINT CONTRIBUTION FROM ABBOTT LABORATORIES AND ROHM AND HAAS COMPANY]

The Preparation and Analgesic Activity of Certain Cyanolactams. I

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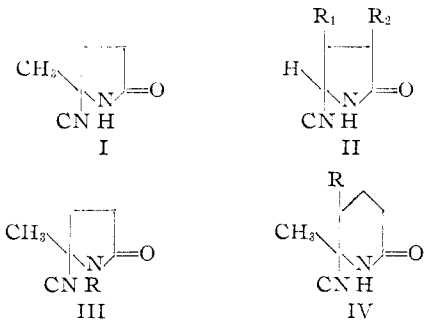
The unexpected, mild pain-threshold elevating activity of γ-cyano-γ-valerolactam (I) has led to the synthesis of a number of related lactams, some of which bear a substituent on the nitrogen atom. An improved method of synthesis for I is reported. Of all the compounds prepared none surpassed I in pain-threshold elevating activity.

The discovery by Kueter and Richards[3] of the mild pain-threshold elevating activity and low acute and chronic toxicities of γ-cyano-γ-valerolactam (I) has led to the study of the synthesis of a number of analogs, homologs and N-substituted derivatives.

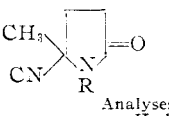


The reported synthesis[4] of γ-cyano-γ-valerolactam (I) from ethyl levulinate, hydrogen cyanide and ammonia is not particularly attractive. A study of this synthesis led to much improved yields, particularly when butyl levulinate was used as the starting ester. The improved preparation is reported in this paper.

The analogs and homologs (II) of γ-cyano-γ-valerolactam were prepared from appropriate γ-oxo esters by reaction with hydrogen cyanide and ammonia. In some cases the intermediate cyanohydrins, some of which were prepared with the aid of basic ion exchange resins, were isolated. The aldehydo-esters were prepared conveniently by the Oxo reaction on α,β-unsaturated esters[5] and were isolated as acetals. The specificity of this reaction in producing only the γ-oxo esters (or their acetals) provided several starting materials otherwise obtainable only with difficulty. Of the three γ-oxo esters thus available from acrylic, crotonic and methacrylic esters, only ethyl β-methyl-γ-oxobutyrate (from ethyl crotonate) gave the lactam product in reasonable purity, though in low yield, by reaction with ammonia and hydrogen cyanide. Lactams from ethyl γ-oxobutyrate and methyl α-methyl-γ-oxobutyrate were obtained, but in low yield and rather low purity as indicated by nitrogen analysis. This is undoubtedly a result of the poor stability of α-aminonitriles derived from the aldehydes. More favorable results were obtained from the ketonic homologs of levulinic esters.

All of the N-substituted derivatives of γ-cyano-γ-valerolactam (III) with the exceptions of N,N-ethylene-bis-(γ-cyano-γ-valerolactam) and N-(β-cyanoethyl)-γ-cyano-γ-valerolactam were prepared by treating ethyl γ-hydroxy-γ-cyanovalerate with the appropriate amine in alcohol. The physical properties of these compounds are given in Table I. Methyl levulinate gave a fair yield of N,N-ethylene-bis-(γ-cyano-γ-valerolactam) by reaction with ethylenediamine and hydrogen cyanide. N-(β-Cyanoethyl)-γ-cyano-γ-valerolactam was prepared by the cyanoethylation of I.

TABLE I

N-SUBSTITUTED-γ-CYANO-γ-VALEROLACTAMS 

R	B.p. or m.p. °C.	Mm.	$n^{25}D$	Yield, %	Analyses, %[f] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3[a]	107–109	2.8	1.4785	85					20.28	20.28
C_2H_5[a]	90–91	2.8	1.4689	55.6[c]	63.13	63.12	7.95	7.72		
CH_2=$CHCH_2$[d,a]	78–79	2.25	1.4852	37	65.82	65.94	7.37	7.14		
n-C_4H_9[b]	97–98.5	2.5	1.4642	31.6	66.63	66.78	8.95	8.70	15.55	15.13
$C_6H_5CH_2$[a]	M. 74–77[e]			34.6						

[a] Prepared by procedure A. [b] Prepared by procedure B. [c] A solution of 8.60 g. (0.05 mole) of ethyl γ-cyano-γ-hydroxyvalerate and 5 cc. (0.086 mole) of ethylamine in 50 cc. of 12A alcohol was heated only four hours at 125°. [d] Prepared by Dr. K. M. Beck of Abbott Laboratories. [e] O. Kuhling and L. Frank, *Ber.*, **42**, 3952 (1909), report a melting point of 76–77° for this compound. [f] See footnote 17.

The δ-caprolactams IV, δ-cyano-δ-caprolactam and γ-methyl-δ-cyano-δ-caprolactam, were prepared in fair to good yields and purity from γ-acetobutyric acid and methyl γ-acetovalerate, respectively.

For the sake of additional structure-activity studies, γ-valerolactam,[6] γ-cyano-γ-valerolactone[7] and γ-methyl-γ-valerolactam[8] were prepared and tested. Also investigated were the following acy-

(1) Abbott Laboratories, North Chicago, Illinois.

(2) Rohm and Haas Company, Philadelphia, Pennsylvania.

(3) K. E. Kueter and R. K. Richards, *J. Pharmacol. Exptl. Therap.*, **106**, 402 (1952).

(4) O. Kuhling, *Ber.*, **22**, 2364 (1889).

(5) (a) C. H. McKeever and G. H. Agnew, U. S. Patent 2,533,276; (b) H. Adkins and G. Krsek, THIS JOURNAL, **70**, 383 (1948).

(6) J. Tafel, *Ber.*, **19**, 2414 (1886); **22**, 1860 (1889).

(7) J. Block, K. Kreckler and B. Tollens, *Ann.*, **238**, 287 (1887).

(8) G. D. Buckly, T. J. Elliott, F. G. Hunt and A. Lowe, *J. Chem. Soc.*, 1505 (1947).

clic analogs: γ-aminovaleric acid,[6] 2-acetylaminoisobutyronitrile[9] and ethyl γ-cyano-γ-dimethylaminovalerate.

Pharmacological studies were performed on all of the compounds reported here by Dr. R. K. Richards, Kenneth Kueter and their associates of Abbott Laboratories. In general, all of the lactams showed low acute toxicity in mice. Pain-threshold elevating activity was determined using a modified Wolff, Hardy and Goodell procedure in dogs. The only compounds showing measurable pain-threshold elevating activity were γ-cyano-γ-valerolactam (I), N-methyl-γ-cyano-γ-valerolactam (III, R = methyl), N-(β-cyanoethyl)-γ-cyano-γ-valerolactam (III, R = β-cyanoethyl) and γ-valerolactam. Compound I proved repeatedly to be very active in dogs, but in human clinical trial, when compared under identical conditions with aspirin and placebos, it was shown to be slightly less active than aspirin.[3]

Experimental[10]

n-Butyl levulinate was prepared by a modification of the method of Schuette and Cowley[11] using Amberlite XE-77AG[12] (ground to no. 60 mesh) as a catalyst. At the end of the reaction the resin was removed by filtration and the mixture was distilled to recover the product in 96.7% yield.

γ-Cyano-γ-valerolactam.—To a mixture of 172 g. (1 mole) of *n*-butyl levulinate, 175 g. (2.36 moles) of *n*-butyl alcohol and 1.0 g. of triethanolamine was added 28.2 g. (1.04 moles) of liquid hydrogen cyanide at 2–30°. After stirring for 2 hours, 28.2 g. (1.66 moles) of anhydrous ammonia was passed into the closed system. The temperature immediately rose to 50° where it remained for the total addition time of 2.5 hours. The mixture was stored in a refrigerator overnight, then heated at 80° for 4.5 hours and finally cooled in an ice-bath for one hour. The solid formed was filtered off and dried to yield 75.6 g. An additional 33.2 g. of product was recovered from the filtrate giving a total yield of 108.9 g. (87.8%), m.p. 141–142°.[13]

γ-Cyano-γ-butyrolactam.—To a chilled mixture of 163 g. (0.94 mole) of ethyl γ,γ-dimethoxybutyrate,[5a] 50 cc. of Amberlite XE-77AG,[12] 50 cc. of Amberlite IRA 400[14] and 25 cc. of water was added 30 g. (1.1 moles) of liquid hydrogen cyanide. This mixture was stirred at room temperature for 4 hours, then filtered to remove resins. The filtrate was stabilized with 5 drops of phosphoric acid before concentrating. The residue was dissolved in ether, the aqueous layer was removed and the ethereal layer was dried over anhydrous magnesium sulfate. The ether was distilled off and the residue now was used without further purification. To 22.5 g. (0.14 mole) of crude cyanohydrin was added 6.8 g. (0.4 mole) of ammonia dissolved in 200 g. of anhydrous ethanol and the mixture was stirred in an ice-bath for 0.25 hour. The mixture was allowed to warm to room temperature, then refluxed for 24.5 hours. After cooling it was filtered to remove a small amount of insolubie material. The filtrate was freed of the solvent and the gummy residue was crystallized from benzene to yield 3.4 g. (22%) of product. Recrystallization from *n*-butyl alcohol gave a solid, m.p. 92–93°.

Anal.[15] Calcd. for $C_5H_6N_2O$: N, 25.4. Found: N, 24.8.

β-Methyl-γ-cyano-γ-butyrolactam.—To a mixture of 14.4 g. (0.1 mole) of ethyl β-methyl-γ-oxobutyrate[5b] and 1.0 g. of Amberlite XE-77AG,[12] cooled in an ice-bath, were added first 8.3 g. of a 24.6% methanolic ammonia solution (0.12 mole) and then a solution of 3.0 g. of hydrogen cyanide (0.11 mole) in 25 g. of methanol. The flask was stoppered tightly and allowed to stand at room temperature for 46 hours. The solvent was distilled off and the residual oil was crystallized from *n*-butyl alcohol with the aid of a seed from a previous preparation. The solid was filtered off, washed with chilled *n*-butyl alcohol and dried to give 2.4 g. of product, m.p. 110–112°. It was recrystallized from *n*-butyl alcohol to yield 2.3 g. (18.5%) of product, m.p. 110–111.5°.

Anal.[15] Calcd. for $C_6H_8N_2O$: N, 22.6. Found: N, 22.0.

Attempts to prepare **α-methyl-γ-cyano-γ-butyrolactam** by a similar procedure from appropriate starting materials resulted in a product which was low in nitrogen and resisted purification.

δ-Cyano-δ-caprolactam.—A mixture of 9.2 g. (0.07 mole) of γ-acetobutyric acid,[16] 25 g. of Amberlite XE-77AG[12] and 128 g. (4 moles) of methanol was refluxed 72 hours and then allowed to cool. The resin was removed by filtration and the filtrate was charged into a stainless steel autoclave, together with 2.0 g. (0.074 mole) of hydrogen cyanide and 1.3 g. (0.076 mole) of liquid ammonia. The autoclave was heated on a steam-bath for 23 hours, then cooled. The solid that was formed was removed, washed with ether and dried to give 4.0 g. of product. It was recrystallized from anhydrous ethanol to yield 3.1 g. (32%) of product, m.p. 170–173°. A repeat preparation gave a yield of 49.7% product, m.p. 170–171°.

Anal.[15] Calcd. for $C_7H_{10}N_2O$: N, 20.3. Found: N, 19.9.

γ-Methyl-δ-cyano-δ-caprolactam.—A mixture of 360 g. (5 moles) of methyl ethyl ketone and 86 g. (1 mole) of methyl acrylate was heated to reflux. To this 20 g. of a 51.2% solution of choline in methanol was added dropwise over a period of 30 minutes. After refluxing the mixture for 2.25 hours it was cooled and neutralized with a solution of 1:1 hydrochloric acid and water and distilled to yield 26.9 g. (17%) of product, b.p. 72–76° at 2 mm. Since the saponification number for this ester corresponded to methyl γ-acetylvalerate (calcd. for $C_8H_{14}O_3$ 355, found 368) it was converted directly to the lactam without further purification. To a cooled solution of 16.4 g. (0.1 mole) of this ester and one drop of piperidine in 75 g. of ethanol was added 5.4 g. (0.2 mole) of liquid hydrogen cyanide. The solution was stirred at 5° for 0.75 hour and then at room temperature for an additional hour. To this was added 3.4 g. (0.2 mole) of ammonia in 25 g. of ethanol with cooling. The mixture was stirred at 5–15° for one hour, at room temperature for another hour and finally at reflux for 26.5 hours. It was allowed to cool, dried over anhydrous magnesium sulfate and treated with Nuchar C-190. The solvent was removed and the residual solid was slurried in ether, filtered and dried to yield 10.8 g. (71.2%) of product, m.p. 139–140.5°.

Anal.[15] Calcd. for $C_8H_{12}N_2O$: N, 18.4. Found: N, 18.1.

N-Ethylene-bis-(γ-cyano-γ-valerolactam).—To a cooled mixture of 72.5 g. (0.5 mole) of methyl levulinate, 5 g. of Amberlite XE-77AG[12] and 75 cc. of methanol was added first 16.2 g. (0.6 mole) of hydrogen cyanide in 50 cc. of methanol and then 16.9 g. (0.25 mole) of 89% aqueous ethylenediamine in 50 cc. of methanol. The stopper was closed tightly and the flask allowed to stand at room temperature for 6 days. The resin was removed by filtration and the filtrate freed of part of the solvent. *n*-Butyl alcohol was added and the mixture heated until only *n*-butyl alcohol distilled off. It was then cooled and the solid which had precipitated was filtered off and dried to give 41.2 g. (60.2%) of gummy product. This was recrystallized from 75 cc. of butanol to yield 32.5 g. (47.4%) of product, m.p. 133–143°.

Anal.[15] Calcd. for $C_{14}H_{18}N_4O_2$: N, 20.4. Found: N, 20.0.

Ethyl γ-Cyano-γ-hydroxyvalerate.—To a solution of 220 g. (2.1 moles) of sodium bisulfite in 800 cc. of water was added in a thin stream 250 g. (1.73 moles) of ethyl levulinate with stirring. After cooling the solution to an internal temperature of 5°, to it was added a solution of 103 g. (2.1 moles) of sodium cyanide in 500 cc. of water at such a rate that the internal temperature did not rise above 15°. An

(9) G. Hellsing, *Ber.*, **37**, 1921 (1904).

(10) Melting points reported in this paper are corrected.

(11) H. A. Schuette and M. A. Cowley, THIS JOURNAL, **53**, 3485 (1931).

(12) Amberlite XE-77AG is a sulfonic acid ion-exchange resin manufactured by Rohm and Haas Co.

(13) O. Kuhling, ref. 4, reports a melting point of 141°.

(14) Amberlite IRA 400 is a strong base ion-exchange resin manufactured by Rohm and Haas Co.

(15) Analysis under the direction of C. W. Nash and T. P. Callan, Rohm and Haas Co.

(16) N. F. Albertson, THIS JOURNAL, **70**, 669 (1948).

oil separated. The mixture was stirred cold (ice-bath) for one hour and then for 2 hours at room temperature. After adding just enough water to dissolve the solid salts that had formed, the two liquid layers were separated. The aqueous layer was extracted well with ether and the ether washings were added to the original oil. This ether solution was washed well with saturated sodium bisulfite solution, water, saturated brine and then dried over anhydrous magnesium sulfate. After filtering, the ether solvent was removed under reduced pressure with very gentle external heating and the residual oil dried to constant weight. The yield of crude colorless product was 270 g. This could not be distilled and thus was used directly in the following preparations without further purification.

N-Methyl-γ-cyano-γ-valerolactam.—(Procedure A) A solution of 34.2 g. (0.2 mole) of ethyl γ-cyano-γ-hydroxyvalerate and 20 cc. (0.5 mole) of methylamine in 50 cc. of 12A alcohol was heated in a bomb for 8 hours at 125°. The solvent was removed on a steam-bath under reduced pressure and the residual red oil was distilled to give 23.3 g. (85%) of a faint yellow oil, b.p. 102–103° at 1.7 mm., $n^{25}D$ 1.4793. This was redistilled to give 19.8 g. of product, b.p. 107–109° at 2.8 mm., $n^{25}D$ 1.4785.

Anal.[17] Calcd. for $C_7H_{10}N_2O$: N, 20.28. Found: N, 20.28.

N-Butyl-γ-cyano-γ-valerolactam.—(Procedure B) A solution of 6.00 g. (0.035 mole) of ethyl γ-cyano-γ-hydroxyvalerate and 2.90 g. (0.04 mole) of *n*-butylamine was allowed to stand about 16 hours at room temperature. The two layers which had formed were separated and the organic layer was dissolved in 50 cc. of 12A alcohol and the solution was refluxed 15 hours. After standing overnight at room temperature the solvent was removed under reduced pressure. The residual oil was dissolved in ether and the ether solution washed with 5% hydrochloric acid, water, saturated brine, clarified with Darco and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed to give 4.20 g. of a crude oil. This was distilled to give 2.28 g. (31.6%) of a colorless oil, b.p. 97–98.5° at 0.5 mm., $n^{26}D$ 1.4642.

Anal.[17] Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 66.78; H, 8.70; N, 15.13.

N-(β-Cyanoethyl)-γ-cyano-γ-valerolactam.—A mixture of 5.60 g. (0.045 mole) of γ-cyano-γ-valerolactam, 2.50 g. (0.047 mole) of acrylonitrile and one pellet of sodium hydroxide was warmed gently on a steam-bath with occasional shaking until liquefaction had taken place. Heating was then continued for an additional 30 minutes. The resulting sirup was cooled and scratched until it solidified. Recrystallization from 3A alcohol gave 2.97 g. of colorless needles, m.p. 78–80°. From the mother liquor was isolated an additional 0.53 g. of product, m.p. 72–80°, making a total yield of 43.9%. A further recrystallization from 3A alcohol gave colorless prisms, m.p. 75–77°.

Anal.[17] Calcd. for $C_9H_{11}N_3O$: N, 23.71. Found: N, 23.87.

Ethyl γ-Cyano-γ-dimethylaminovalerate.—A solution of 60.0 g. (0.575 mole) of sodium bisulfite and 72.0 g. (0.5 mole) of ethyl levulinate in 150 cc. of water was stirred 2 hours at room temperature. To this was added 135 g. (0.75 mole) of a 25% solution of dimethylamine and the resulting solution stirred 2 hours at room temperature. After the addition of 28.2 g. (0.575 mole) of sodium cyanide the resulting mixture was stirred two hours at room temperature. Sufficient water was added to dissolve the solids that had formed and the layers were separated. After extracting the aqueous phase three times with ether the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. After filtering, the ether was removed under reduced pressure and the residual oil was distilled to give 10.1 g. (14%) of recovered ethyl levulinate, 3.8 g. of an intermediate fraction and 37.2 g. (37.8%) of the desired product, b.p. 130–132° at 15 mm., $n^{26}D$ 1.4462.

Anal.[17] Calcd. for $C_{10}H_{18}N_2O_2$: N, 14.13. Found: N, 14.02.

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(17) Analysis by E. F. Shelberg and staff, Abbott Laboratories.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Compounds Related to Chloromycetin.[1] 1-Biaryl-2-dichloroacetamido-1,3-propanediols

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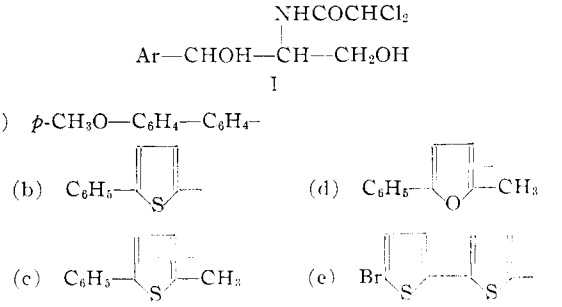
Several compounds related to DL-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol have been synthesized. These include analogs having thiophene, 2-methylthiophene and 2-methylfuran groups substituted for the phenyl attached to the side chain. The preparations of 1-(4'-methoxybiphenylyl)- and 1-(2-bromobithienyl)-2-dichloroacetamido-1,3-propanediol are also given.

The demonstration of the marked antibacterial activity of D-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol and of the corresponding racemic *p*-methylbiphenylyl and *p*-bromobiphenylyl derivatives[2] has motivated the preparation of a number of related compounds Ia, Ib, Ic, Id and Ie. These include the *p*-methoxybiphenylyl analog, as well as compounds having either or both of the phenyl rings replaced with heterocyclic aromatic rings. The syntheses of 2-dichloroacetamido-1-(2-naphthyl)-1,3-propanediol and its 4-nitro-1-naphthyl analog have previously been described by Long and Troutman[3] while Feitelson, *et al.*,[4] have prepared the 2-quinolyl compounds. In a recent publication Morris and Smith[5] outlined the synthesis of 1-(*p*-thiazoylphenyl)-2-dichloroacetamido-1,3-propanediol.



Starting materials for the synthesis of these compounds were the corresponding biaryls: 2-phenyl-

(1) Parke, Davis & Company registered trademark for chloramphenicol.

(2) M. C. Rebstock, C. D. Stratton and L. L. Bambas, THIS JOURNAL, **77**, 24 (1955).

(3) L. M. Long and H. D. Troutman, *ibid.*, **73**, 542 (1951).

(4) B. N. Feitelson, J. T. Gunner, R. J. Moualim, V. Petrow, O. Stephenson and S. W. F. Underhill, *J. Pharm. Pharmacol.*, **3**, 149 (1951).

(5) D. S. Morris and S. D. Smith, *J. Chem. Soc.*, 1680 (1954).