solution was diluted with aqueous sodium bicarbonate solution and extracted with chloroform. The crude product was isolated from the chloroform layer after washing with water, drying and concentrating. Two crystallizations from methanol afforded 88 mg. of 5α-methyl-androstane-17β-ol-3-one (VII), m.p. 196–201°, $\alpha^{25}D$ + 40° (*c* 0.7, $CHCl_3$); infrared: λ_{max}^{Nujol} 2.92, 5.83 μ; nuclear magnetic resonance spectrum: the presence of three quaternary C-methyl groups is indicated. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.73; H, 10.79.

A sample of VII, m.p. 201–202°, was obtained by recrystallization from methanol; $[\alpha]D$ + 43°, $[\alpha]_{400}$ +141°, $[\alpha]_{350}$ +302°, $[\alpha]_{325}$ +832°, $[\alpha]_{315}$ +1110°, $[\alpha]_{300}$ +369°, $[\alpha]_{286}$ −351° [*c* 0.18, dioxane]. Chromatography of the mother liquors on 20 g. of basic alumina and elution with ether–petroleum ether (2:8) followed by crystallization from methanol afforded 50 mg. of a fraction, m.p. 203–204°, presumably 5α-methyl-androstane-17β-ol. A sample for analysis was recrystallized from methanol, m.p. 204–207°; infrared: λ_{max}^{Nujol} 2.95–3.05 μ. *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.54; H, 11.53. Further elution with ether–petroleum ether (8:2 and 9:1) and crystallization from methanol yielded an additional 95 mg. of VII, m.p. 196–200°, a total of 183 mg. (60% yield).

5α-Methyl-androstane-17β-ol-3-one Propionate (IX).—Acylation of VIII with propionic anhydride in pyridine at room temperature overnight afforded 5α-methylandrostane-17β-ol-3-one propionate (IX). A sample for analysis was crystallized from methanol, m.p. 157–160°, $\alpha^{26}D$ +32° (*c* 0.8, $CHCl_3$); infrared: λ_{max}^{KBr} 5.77, 5.84 μ. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.25; H, 10.11.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TRINITY COLLEGE, HARTFORD 6, CONN.]

Parallel Amide Groups[1]

BY W. SCOTT WORRALL

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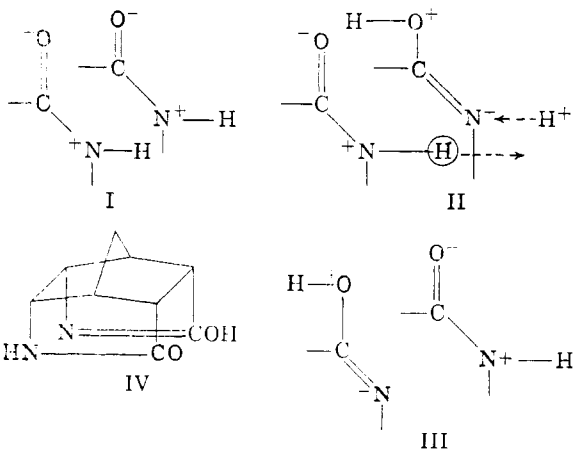
The synthesis of the dilactam of *endo-cis*-2,3-dicarboxy-*endo-cis*-5,6-diaminonorbornane, which contains two amide groups held rigidly side by side in space, is described. This work is the beginning of a search for possible changes in the normal properties of functional groups due to intramolecular action of neighboring amide groups.

Functional groups, which participate in reactions catalyzed by proteolytic enzymes, during the reaction are probably in the more or less immediate neighborhood of amide groups, *i.e.*, peptide linkages. The phrase, functional groups, is intended to include both groups in the substrate molecules and groups in the protein enzyme. Therefore it is of interest to attempt to synthesize molecules in which various functional groups are held in well defined orientations with respect to one or more amide groups. A search can then be made for possible changes in the normal properties, *e.g.*, nucleophilicity, of the functional groups. As the beginning of such a project a novel arrangement of two amide groups is speculatively presented in this paper and the synthesis is reported of a molecule containing this arrangement of amide groups.

It is possible to imagine two planar[2] amide groups held rigidly side by side in space, *i.e.*, parallel amide groups, with the oxygen opposite the oxygen, and the nitrogen opposite the nitrogen, etc. (I). However, in this configuration the large dipoles associated with each amide group[3] would oppose each other and, therefore, it is reasonable to assume that one of the amide groups would exist in the enolic form (II). In this way the two dipoles would complement each other and conceivably would interact to form four regions of intense localized charge. Speculation in this area leads to the concept of a chemical reaction in which parallel amide groups participate by simultaneously giving and accepting a proton and, at the same time, the parallel amide groups are converted to their mirror image, *i.e.*, II→III. In this process the original quadrupole disappears in the transition state and then reappears in the reverse orientation. This intense reciprocating quadrupole hypothetically present in parallel amide groups is novel, and, therefore, the properties of parallel amide groups are of interest both with respect to the isolated structure and also with respect to any possible relationship with neighboring functional groups. It is conceivable that such an arrangement, *i.e.*, parallel, of amide groups occurs in protein molecules. The dilactam of *endo-cis*-2,3-dicarboxy-*endo-cis*-5,6-diaminonorbornane (IV) contains parallel amide groups and the synthesis of this molecule is described in this paper.



I II IV III

The carbon framework of norbornane was used as a rigid framework to which the paired amide groups were fastened. Treatment of *endo-cis*-2,3-dicarboxy-*exo-cis*-5,6-dibromonorbornane anhydride[4] (V) with concentrated aqueous ammonia

(1) This work was presented at the 136th Meeting of the American Chemical Society, September, 1959, and was supported by a research grant, G-1951, from the National Science Foundation.

(2) L. Pauling, R. B. Corey and H. R. Branson, *Proc. Natl. Acad. Sci. (U. S.)*, **37**, 205 (1951); L. Pauling and R. B. Corey, *ibid.*, **37**, 272 (1951).

(3) W. W. Bates and M. E. Hobbs, THIS JOURNAL, **73**, 2151 (1951).

(4) J. A. Berson and R. Swidler, *ibid.*, **76**, 4060 (1954).

followed by passage of the product mixture through a strongly basic anion exchange resin gave a solid (VI). When the solid VI was heated to about 185° a gas (basic to *p*H paper) was smoothly evolved to give a nicely crystalline compound (XI), m.p. 192–192.5°, which is considered to be the lactone-lactam of *endo-cis*-2,3-dicarboxy-*endo*-5-amino-*endo*-6-hydroxynorbornane (XI) for the following reasons. This structure is the only one which corresponds to the requirements of the elemental analysis, the infrared spectrum, the neutrality of an aqueous solution, inertness to catalytic hydrogenation and a plausible mechanistic route. An essential consideration is the fact that the reaction is not of a type in which rearrangements of the norbornane carbon framework have been found.[5] It is not known whether the lactam group is in the enol form as shown in the structural formula XI or is in the keto form although there are infrared bands at 6.04 and 6.19 μ corresponding to the amide group. The band at 6.04 μ is expected for the amide group in the usual keto form, but the second band at 6.19 μ is ordinarily absent in cyclic secondary amides.[6] The band at 5.68 μ is reasonable for the lactone group.[7]

Some information about the reaction path of the ammonolysis is provided by the fact that, when the reaction time was shortened, a relatively large yield of *endo*-2-carboxy-*endo*-3-amido-*exo*-5-bromo-*endo*-6-hydroxynorbornane lactone (VII) could be isolated. Evidence for the structure is the elemental analysis, and the infrared spectrum, 5.6 μ (lactone) and 5.9 and 6.1 μ (primary amide). The amido-lactone VII rearranged very easily to *endo-cis*-2,3-dicarboxy-*exo*-5-bromo-*endo*-6-hydroxynorbornane imide (VIII) either when heated very briefly in water or when dissolved in dilute base and reprecipitated with acid. Evidence for the structure of the dicarboximide VIII is the elemental analysis and the fact that the infrared spectrum in the carbonyl region, *i.e.*, bands at 5.6 and 5.8 μ, are identical in wave length and distinctive shape to the spectra of two norbornane compounds (of fairly certain structure) with *endo*-2,3-dicarboximide groups. These compounds are *endo-cis*-2,3-dicarboxy-5-norbornene imide[8] (IX) and *endo-cis*-2,3-dicarboxy-*exo*-5,6-epoxynorbornane imide (X) which was prepared by oxidation of the unsaturated imide IX with hydrogen peroxide. The assignment of the *exo* configuration to the epoxy group is by analogy[9] and from the general view of *exo* addition.[10]

Permanganate oxidation of the solid VI gave a new solid (XII) with a carbonyl peak at 5.7 μ which dissolved in water to give a neutral solution. Hydrogenation of a variation of XII (*vide infra*) at room temperature with platinum after the uptake of one mole of hydrogen gave a solid (XIII) which on heating gave the lactone-lactam XI as evidenced by mixed melting points and identical infrared spectra. This hydrogenation is another example of *exo* addition. With respect to the solid VI: because of the elemental analysis, conversion to the lactone-lactam XI, neutrality of an aqueous solution, and successful passage through the strongly basic ion exchange column, the solid is considered to be essentially *endo*-2-carboxy-*endo*-3-amido-*endo*-5-hydroxy-*endo*-6-aminonorborane lactam. However, the infrared spectrum of VI was similar but not identical to the spectrum of XIII. Furthermore, treatment of the lactone-lactam XI with concentrated aqueous ammonia gave a solid with an infrared spectrum identical to XIII.

Low temperature recrystallization from water of the carbonyl containing solid XII gave a solid with a satisfactory elemental analysis, m.p. 232–234°, and no change in the infrared spectrum, but repeated recrystallization of XII from hot water gave a solid (XIV), m.p. 234–235.5°, with apparently the same properties as XII in every way including an essentially unchanged elemental analysis except that there are two infrared bands in the carbonyl region at 5.7 and 5.8 μ. The material used in the above hydrogenation was XIV. The solid XII was soluble in 5% sodium hydroxide and acidification of the basic solution gave a precipitate with a spectrum identical to that of XIV. With respect to the solids XII and XIV: because of the elemental analyses, the conversion *via* hydrogenation to the lactone-lactam XI, the infrared spectrum, conversion to an oxime (*vide infra*), and the neutrality of the aqueous solutions, a reasonable structure is *endo*-2-carboxy-*endo*-3-amido-5-keto-*endo*-6-aminonorbornane lactam.

Compound VI appears to be very similar to XIII and compound XII very similar to XIV. In brief, the nature of the compounds VI, XII, XIII and XIV is clear in certain fundamental respects, but the more intimate details remain unsettled. Because of the number of functional groups concentrated in a small volume, complications are not surprising. The two carbonyl bands in XIV and the base solubility of XII and XIV are of particular interest; further experimental work is required to choose from among various possible explanations.

The solid XIV was converted to the corresponding oxime XV with the loss of the carbonyl infrared bands. Hydrogenation of the oxime (*exo* addition) with platinum gave (after drying *in vacuo* at 100° for 3 hours) a nicely crystalline compound (IV), m.p. 210.5–211°. The fact that compound IV is the dilactam of *endo-cis*-2,3-dicarboxy-*endo-cis*-5,6-diaminonorbornane is evidenced by the elemental analysis, the absence of increased solubility in dilute base or dilute acid, the neutrality of an aqueous solution, and the nature of the synthetic route. Like the lactone-lactam XI it is not known whether or not one of the lactam groups exists in the enolic form as shown in the structural formula.

A possible complication was the fact that when the dilactam IV was isolated from an aqueous solution a compound was obtained which lost a gas on rapid heating and was converted to the dilactam

(5) For example, see H. Kwart and L. Kaplan, THIS JOURNAL, **76**, 4078 (1954).

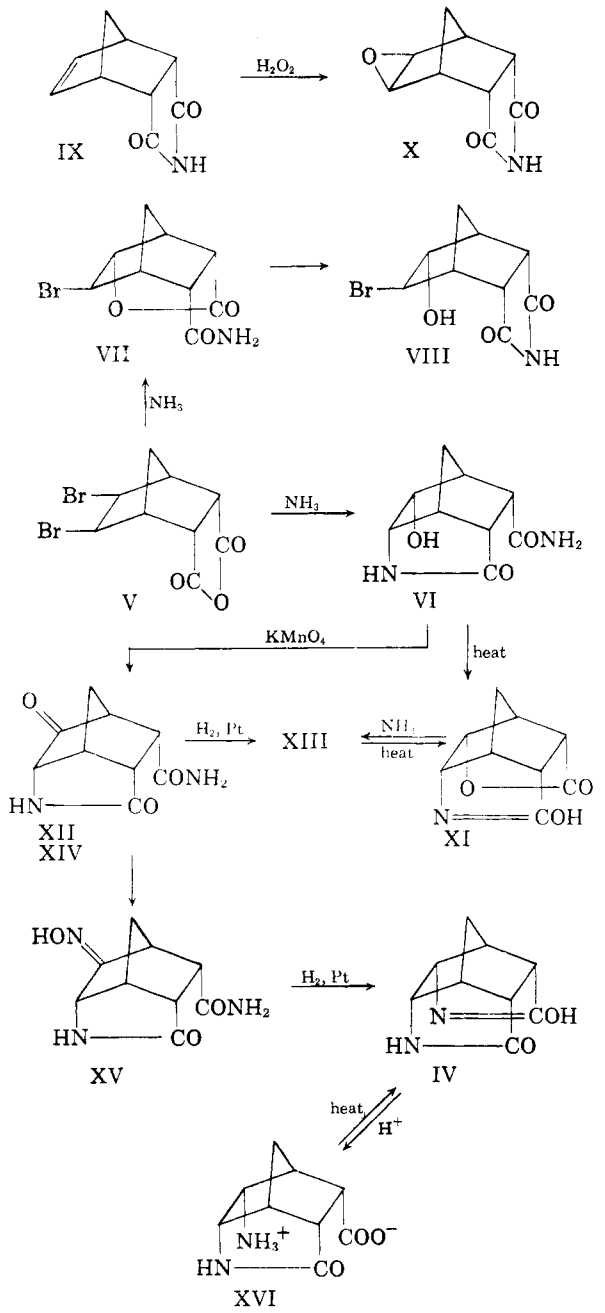
(6) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 217.

(7) J. A. Berson, THIS JOURNAL, **76**, 4975 (1954).

(8) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

(9) J. A. Berson and S. Suzuki, THIS JOURNAL, **80**, 4341 (1958).

(10) For other recent examples and references see S. J. Cristol and R. T. LaLonde, *ibid.*, **81**, 1655 (1959), footnote 14.



IV. The question was whether this compound was simply the hydrate of the dilactam or whether the dilactam opened very readily in water to form an amino acid, the monolactam of *endo-cis*-2,3-dicarboxy-*endo-cis*-5,6-diaminonorbornane (XVI). The compound was shown to be the hydrate because it was possible to synthesize the amino acid XVI by acid hydrolysis of the dilactam. The amino acid could be converted to the dilactam by loss of water on heating, but the conditions required were considerably more vigorous than in the case of the hydrate. Evidence for the structure of the amino acid XVI is its method of synthesis, the elemental analysis, solubility in dilute acid and dilute base, and the conversion to the dilactam. The carbon and hydrogen analyses of the amino acid were satisfactory, but the nitrogen was somewhat low. This seems to be an example of the fact that many of the above compounds are quite reactive in water and an examination of the effects of the functional groups on each other remains of interest.

Experimental[11]

Ammonolysis of *endo-cis*-2,3-Dicarboxy-*exo-cis*-5,6-dibromonorbornane Anhydride (V).—A mixture of the dibromoanhydride[4] V (153 g.) and concentrated aqueous ammonia (1530 ml.) was stirred at room temperature under a positive pressure of 2 mm. The clear solution which formed within about 12 hours was maintained at room temperature for a total of 10 days and then was evaporated *in vacuo* (the temperature of the solution was kept less than 40°) to about 1000 ml.[12,13] The solution, after dilution with water to 1600 ml., was passed through the following column. Amberlite IRA-400[14] (400 g.) was stirred in 4% sodium hydroxide (1.0 l.) for 0.5 hour, deposited on a thin layer of glass wool covered by a little coarse sand at the bottom of a glass tube 121 cm. long and 2.7 cm. inside diameter, and washed with 4% sodium hydroxide (4.0 l.) followed by water (2.0 l.). The reaction solution was introduced into the column through a glass tube (8 mm.) in such a way as to furnish a head of liquid of about 80 cm. which ensured a throughput rate of about 35 ml. per minute. The reaction mixture was passed through the column portionwise in four cycles. A cycle was the passage through the column of: (1) 400 ml. of reaction solution, (2) 1.0 l. of water, (3) 4.0 l. of 4% sodium hydroxide, (4) 2.0 l. of water. In each cycle the first two effluents were collected and the last two discarded. In each cycle at the end of step 3, *i.e.*, the base regeneration, a little of the water rinse, *i.e.*, step 4, was passed through the column in the reverse direction in order to extend the resin to the top of the column and then the resin was allowed to settle before completion of the rinse. In this way the same batch of resin was used indefinitely and the collected effluents never gave a positive test for bromide ion with silver nitrate. The collected effluents were evaporated at less than 30°[15] as rapidly as possible[16] by a stream of air from an electric fan over the solution in a large evaporating dish with appropriate heating. The resulting crystalline residue[17] was recrystallized from water (75 ml.) by heating and cooling as rapidly as possible to minimize any reaction with water. After drying, the resulting solid was recrystallized in a similar way from twice its weight of water to give the solid labeled VI in the discussion. When the solid was heated in a melting point tube at about 185° there was a copious evolution of a gas (presumably ammonia) which turned wet *p*H paper blue. The solid was fairly soluble in water and insoluble in organic solvents. The *p*H of an aqueous solution of the solid was 7 (measured with *p*H paper). The yield (based on the amido-lactam structure VI) varied in typical runs from 18.7 g. (20%) to 24.5 g. (27%). The material used for analysis was recrystallized a third time.

(11) The elemental analyses were determined by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. The infrared spectra of the lactone-lactam XI and the dilactam IV were determined with a Perkin–Elmer model 13 spectrophotometer using Nujol mulls. The remainder of the infrared spectra were determined with a Perkin–Elmer model 137 spectrophotometer using Nujol mulls.

(12) The purpose of the evaporation was to remove the bulk of the excess ammonia which otherwise was an inconvenience in the next operation.

(13) The optimum reaction time for the ammonolysis is not known. However, in one run in which the evaporation was begun, after 20 hours the yield of the bromo-amido-lactone VII was 40% and the yield of the desired product VI was approximately half of that obtained with a reaction time of 10 days; *vide infra*.

(14) A strongly basic anion exchange resin, Rohm & Haas Co., Philadelphia, Pa.

(15) In one run when the evaporation was speeded by boiling, the residue was much more water-soluble than VI. This residue has not been investigated, but its formation indicated that the solid VI was labile in hot water.

(16) The aspect of speed is stressed because of the possibility that the solid VI can react at an appreciable rate with water at room temperature.[16,17]

(17) The total time to this point should be about 13 days. Longer periods appeared to result in the lower yields.

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.10; H, 6.17; N, 14.28. Found: C, 54.81; H, 6.18; N, 13.81.[18]

endo-2-Carboxy-*endo*-3-amido-*exo*-5-bromo-*endo*-6-hydroxynorbornane Lactone (VII).—The above reaction was repeated exactly except that evaporation of the reaction mixture was begun 20 hours after the original mixing. The reaction mixture was evaporated as above to about 800 ml. A heavy precipitate was present at this stage in contrast to the above experiment. Filtration gave 49 g. (40% yield) of the bromo-amido-lactone VII, m.p. 189–191°. Treatment of the filtrate as above gave 9.3 g. (10% yield) of the amidolactam VI. The analytical sample of VII, m.p. 194–195.5°, was obtained by two recrystallizations from acetone which caused no change in the infrared spectrum. Compound VII was insoluble in water, 5% sodium bicarbonate, 5% hydrochloric acid and dissolved readily in 5% sodium hydroxide; infrared spectrum: 2.8, 3.0, 5.6, 5.9 and 6.1 μ.

Anal. Calcd. for $C_9H_{10}NO_3Br$: C, 41.56; H, 3.88; N, 5.39; Br, 30.73. Found: C, 41.72; H, 3.96; N, 5.46; Br, 30.72.

endo-cis-2,3-Dicarboxy-*exo*-5-bromo-*endo*-6-hydroxynorbornane Imide (VIII).—A portion of the bromo-amido-lactone VII was dissolved in 5% sodium hydroxide and reprecipitated with 5% hydrochloric acid to give the imide VIII. Two recrystallizations from methanol gave the analytical sample, m.p. 189–190.5°. The infrared spectrum was not changed by the methanolic recrystallization or by redissolving in base and reprecipitating with acid. Brief heating of the bromoamido-lactone VII in water and cooling results in the precipitation of VIII as evidenced by the infrared spectrum; infrared spectrum: 2.9, shoulder at 3.0, 5.6 (sharp and medium), 5.8 μ (strong).

Anal. Calcd. for $C_9H_{10}NO_3Br$: C, 41.56; H, 3.88; N, 5.39; Br, 30.73. Found: C, 41.60; H, 3.88; N, 5.33; Br, 30.76.

endo-cis-2,3-Dicarboxy-5-norbornene Imide (IX).—A convenient preparation is: A mixture of *endo-cis*-2,3-dicarboxy-5-norbornene anhydride[19] (379 g.) and concentrated aqueous ammonia (2.0 l.) in a 5-liter flask equipped with a condenser was refluxed for 9 hours. The solid dissolved within 1 hour and the temperature gradually rose to 100°. Cooling and filtration gave the imide IX (327 g., 87% yield), m.p. 185.5–187°; infrared spectrum: 5.6 (sharp and medium), 5.8 μ (strong).

endo-cis-2,3-Dicarboxy-*exo-cis*-5,6-epoxynorbornane Imide (X).—The unsaturated imide IX (100 g.), formic acid (87–88%) (1.0 l.) and 30% hydrogen peroxide (73 g.) were mixed and stirred at 23–28° for 2 hours. A little cooling was required. Then, after standing at room temperature for 48 hours, the solution was evaporated *in vacuo* (the temperature of the evaporating mixture was about 55°) to almost dryness. The residue was crystallized from water (1100 ml.) to give 91.8 g. of the epoxyimide X, (84% yield), m.p. 267.5–272°. The analytical sample was obtained in an earlier run by repeated recrystallization from absolute methanol, m.p. 271–273.5°. Later work indicated that water is probably a better recrystallizing solvent. The compound X was insoluble in 5% sodium bicarbonate and soluble in 5% sodium hydroxide; infrared spectrum: 5.6 (sharp and medium), 5.8 μ (strong).

Anal. Calcd. for $C_9H_9NO_4$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.01; N, 8.21.

Pyrolysis of the Amido-lactone VI to the Lactone-lactam of *endo-cis*-2,3-Dicarboxy-*endo*-5-amino-*endo*-6-hydroxynorbornane (XI).—The amido-lactone VI (2.00 g.) in a 50-ml. erlenmeyer flask was heated in an oil-bath at 204–209° for 15 minutes. At the end of this period the gas evolution had about stopped. The resulting melt was cooled to room temperature, stirred with chloroform (20 ml.) for 30 minutes, and the solid present filtered to give 0.099 g. of a material which became a hard, brown glass on drying. Evaporation of the filtrate gave a nice, crystalline residue, m.p. 175–187° (1.66 g.). Two recrystallizations from a methanol-water mixture (5-to-1 by volume) raised the m.p. to 192–192.5°. The compound was fairly soluble in water and less soluble in acetone and chloroform. The *p*H of an aqueous solution was 7 (measured with *p*H paper). Treatment of a methanolic solution wih hydrogen and platinum oxide at room temperature and 1 atmosphere caused no uptake of hydrogen; infrared spectrum: 2.93, 3.00, 3.04, 3.11, 5.68, 6.04 and 6.19 μ.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.32; H, 5.06; N, 7.82 Found: C, 60.55; H, 5.39; N, 7.99.

Oxidation of the Hydroxy-amido-lactam VI to the Keto-amido-lactams XII and XIV.—The solid VI (18.1 g.) was powdered and stirred with water (300 ml.) at room temperature to give a clear solution within 15 minutes. To this solution was added a solution of potassium permanganate (9.80 g.) in water (300 ml.) followed by rinse water (50 ml.) and 5% sodium hydroxide (22 ml.). The stirring was continued with no external heating or cooling for 22 hours and filtered to give a clear, colorless filtrate. Glacial acetic acid (13.9 ml.) was added (to give a *p*H of 3–4) and the solution was evaporated at room temperature. The residue, slightly moist crystals, was recrystallized from water (32 ml.) to give a white solid (XII), 12.6 g., m.p. 213–217°; neutral aqueous solution (*p*H paper). The material at this stage was called the initial product; infrared spectrum 5.7 μ. A portion of this material (2.00 g.) was stirred with water (10 ml.) at room temperature for 18 hours. The undissolved material was filtered, 1.40 g., m.p. 231–235°. The filtrate was refrigerated for 12 days, filtered and the precipitate (not weighed but estimated at least 0.2 g.) dried *in vacuo* at room temperature for 16 hours; m.p. 232–234°; infrared spectrum: band at 5.7 μ.

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.50; H, 5.41; N, 14.15.

The initial product XII, m.p. 213–217°, was recrystallized five times from water (each time using twice the weight of water) to give the material XIV. The melting point appeared to level off at 234–235.5°. The melting points were somewhat unreliable because apparently gas evolution began, at first slowly and within seconds more rapidly, practically simultaneously with the formation of the melt. An aqueous solution was neutral (*p*H paper); infrared spectrum: bands at 5.7 and 5.8 μ.

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 55.67; H, 5.19; N, 14.43. Found: C, 56.25, 56.14; H, 5.54, 5.58; N, 14.55.

A portion of the initial product XII, m.p. 213–217°, was dissolved in a minimum of 5% sodium hydroxide. The addition of glacial acetic acid to *p*H 3–4 caused an immediate precipitate which was filtered at once and washed with a few drops of water; m.p. 232–234°. The infrared spectrum was identical to that of the recrystallized material XIV, m.p. 234–235.5°.

In some runs with at least very similar conditions and starting material from parallel preparations of VI the initial product was the solid XIV with the doublet in the infrared carbonyl region. For example, a run starting with 43.7 g. of solid VI gave 32.1 g. of XIV as the initial product, m.p. 217–221°. The reason that the infrared doublet appeared in the initial product in some runs but appeared only after repeated recrystallization in others is not known.

Conversion of the Keto-amido-lactam XIV to the Lactone-lactam XI.—The solid XIV (0.92 g., 4.7 mmoles based on the keto-amido-lactam structure; (the initial product from a run in which the infrared spectrum of the initial product contained a doublet in the carbonyl region, m.p. 215–218°) in water (20 ml.) was stirred with hydrogen at 25° and 756 mm. in the presence of prereduced platinum oxide (0.21 g.). Within 4 hours 110 ml. (4.3 mmoles, 92%) of hydrogen was taken up and the absorption stopped completely. The residue obtained by filtration and evaporation *in vacuo* at less than 40° was a white solid (XIII), m.p. 187° with gas evolution. The infrared spectrum was similar to but not identical to that of the solid VI. Pyrolysis of the solid XIII (0.50 g.), in a way identical to the pyrolysis of the solid VI described above, gave a white, crystalline solid, 0.38 g., m.p. 184–190°. The melting point was raised to 191–193° by recrystallization from methanol and water. The mixed melting point with the lactone-lactam XI was not depressed. The infrared spectrum was identical to that of the lactone-lactam XI.

(18) The fact that the analyses of the alcohol VI, the corresponding ketone XIV, and the corresponding oxime XV (all recrystallized from hot water) were not completely satisfactory while the one case, in which low temperature water recrystallization for the ketone XII was used, did give a satisfactory analysis, indicated that compounds of this type were sensitive to hot water and that in further investigation of these compounds attention should be directed toward the use of mild conditions.

(19) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

Ammonolysis of the Lactone-lactam XI.—The lactone-lactam XI (0.20 g.) was stirred with concentrated aqueous ammonia (35 ml.) at room temperature for 13 hours. The residue, a fluffy glass, obtained by evaporation *in vacuo* at 60°, was stirred with absolute methanol (4.0 ml.) for 10 minutes. Filtration gave a white solid, m.p. 193° with gas evolution. The infrared spectrum of this solid was identical to that of the solid XIII.

Preparation of the Oxime XV.—To a mixture of the solid XIV (29.1 g.) and water (300 ml.) was added hydroxylamine hydrochloride (13.9 g.) followed by sodium hydroxide (8.0 g.). The resulting solution was boiled over a free flame for 2.0 minutes and immediately cooled in an ice-bath to room temperature. Glacial acetic acid (50 ml.) was added to a *p*H of 3–4 and the solution was evaporated to dryness *in vacuo* with a heating bath temperature of 60°. Water (60 ml.) was added to the solid residue, the suspension shaken for 5 minutes and refrigerated overnight. Filtration gave the oxime XV, 22.2 g., m.p. 219° dec. This material was recrystallized 3 times from water to prepare a sample for analysis, m.p. 226° dec.; infrared spectrum: no bands around 5.7 μ.

Anal. Calcd. for $C_9H_{11}O_3N_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.25; H, 5.79; N, 19.97.

Dilactam of *endo-cis*-2,3-Dicarboxy-*endo-cis*-5,6-diaminonorbornane (IV).—The oxime XV (5.0 g. material which had not been recrystallized) in water (300 ml.) was shaken at room temperature in the presence of platinum oxide (0.5 g.) with hydrogen at 45 pounds per square inch for 64 hours. After removal of the catalyst the solution was refluxed for 0.5 hour[20] and evaporated *in vacuo* at 70° to give a crystalline residue (pink coloration). Recrystallization from water (about 20 ml., Norite) gave a crystalline product, the hydrate of the dilactam IV, which was dried *in vacuo* at 100° for 3 hours to give the dilactam (2.1 g., 49% yield), m.p. 202–207°. The analytical sample, m.p. 210.5–211°, was obtained by two recrystallizations from a methanol–water mixture. After each recrystallization the above drying procedure was necessary to remove the water of hydration. The dilactam IV was somewhat soluble in water to give a neutral solution (*p*H paper) and insoluble in organic solvents. The aqueous solubility was not appreciably increased in 5% sodium hydroxide or in 5% hydrochloric acid at room temperature within 1 hour (for longer periods *vide infra*); infrared spectrum: 2.89, 3.17, 5.92, 6.05, 6.24 μ.

(20) In an early run a compound, which gave a basic aqueous solution, was isolated. Pyrolysis of this compound (or more slowly by standing at room temperature in aqueous solution) gave the dilactam IV. The direct formation of the dilactam IV was assured by refluxing.

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.78; H, 5.64; N, 15.71.

Hydrate of the Dilactam IV.—The hydrate (prepared as above) when heated rapidly in a melting point tube typically bubbled at about 190° to form a new solid which melted at 205–210°; when heated more slowly from room temperature there was no evidence of change until the solid melted at about 205–210°. The hydrate was soluble in absolute methanol in contrast to the anhydrous dilactam, but otherwise the solubility characteristics were the same as the anhydrous dilactam. The hydrate (air-dried) typically lost from 0.56 to 1.1 moles of water when dried *in vacuo* at 100° for 3 hours (calculated from weight loss).

A portion of the anhydrous dilactam IV was dissolved in water at room temperature and evaporated at room temperature to dryness to give the hydrate as evidenced by the infrared spectrum; infrared spectrum: 2.9, 3.0, 3.1, 5.9, 6.2 μ. The over-all spectrum was quite similar to that of the anhydrous dilactam.

Monolactam of *endo-cis*-2,3-Dicarboxy-*endo-cis*-5,6-diaminonorbornane (XVI).—The dilactam IV (1.00 g.) and 5% hydrochloric acid (10 ml.) were stirred together at room temperature for 67 hours (after 44 hours and before 67 hours all of the solid dissolved). The solution was filtered to remove a trace of insoluble colored material and the filtrate was evaporated at room temperature. The crystalline residue was dissolved in water (100 ml.) and the chloride ions were removed by passage of the solution through Amberlite IR-4B (45 g.) in a manner analogous to that described by Meyers and Miller.[21] The residue from evaporation of the effluent at room temperature was a yellow, gummy solid (0.7 g.). Two recrystallizations (Norite) from water (3 parts by weight) gave the analytical sample. The compound XVI bubbled at about 235°, and was much more soluble in 5% sodium hydroxide and in 5% hydrochloric acid than in water. After drying the amino acid *in vacuo* at 100° for 3 hours the behavior on heating to about 235°, *i.e.*, bubbling, was unchanged; infrared spectrum: 2.9, 3.1, 6.0, 6.2, 6.6, 7.1 μ.

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.23; H, 6.37; N, 13.61.

Conversion of the Monolactam XVI to the Dilactam IV.—A portion of the monolactam XVI (0.10 g.) was heated in a small test-tube with an oil-bath at 250–255° for 3 minutes. At the end of this period gas evolution had about stopped. The melt was dissolved in hot water (0.5 ml.) and the precipitate obtained on cooling was dried *in vacuo* for 3 hours at 100° to give 0.060 g. of a solid, m.p. 208–209°. The mixed melting point with the dilactam IV was not depressed. The infrared spectrum was identical to that of the dilactam IV.

(21) C. Y. Meyers and L. E. Miller, *Org. Syntheses*, **32**, 13 (1952).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J., AND THE RESEARCH DIVISION OF PARKE, DAVIS AND CO., DETROIT, MICH.]

Pyrimido[4,5-d]pyrimidines. Part I

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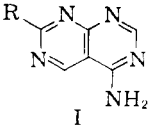
A number of pyrimido[4,5-d]pyrimidines have been prepared as potential diuretic agents. The synthesis of the requisite starting materials, 4-amino-5-cyanopyrimidines and 4-aminopyrimidine-5-carboxamides, and their conversion to pyrimido-[4,5-d]pyrimidines, are described. Many of the amino and substituted amino derivatives, unavailable by direct synthesis, were prepared by displacement of mercapto and alkylthio groups with amines.

In the search for new types of diuretic agents a variety of heterocyclic compounds were prepared and studied. One of the compounds prepared was 2,5-diaminopyrimido[4,5-d]pyrimidine (I, R = NH_2), which was found to be very active orally. Therefore, a series of aminopyrimido[4,5-d]pyrimidines was prepared and examined for diuretic activity and possible antagonistic activity in other biological systems.



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