[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. IV. A Synthetic Approach to Azasteroids[1]

BY NORMAN A. NELSON, JOAN E. LADBURY AND RICHARD S. P. HSI

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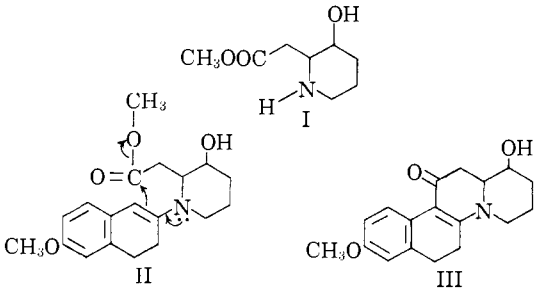
The condensation of 2-tetralone and methyl β-methylaminopropionate gave an enamine which was converted by an intramolecular acylation reaction to 1-methyl-4-ketohexahydrobenzo[f]quinoline, a substance representing the A, B and C rings of an azasteroid. Reduction of this substance with lithium aluminum hydride yielded 1-methylhexahydrobenzo[f]-quinoline. Reduction of 1-methylhexahydrobenzo[f]quinoline with Adams catalyst or reduction of the perchlorate of this material with sodium borohydride gave the same isomer of 1-methyloctahydrobenzo[f]quinone. The structure of the latter substance was established by its conversion to 1-propyltetralin by Hofmann's exhaustive methylation procedure.

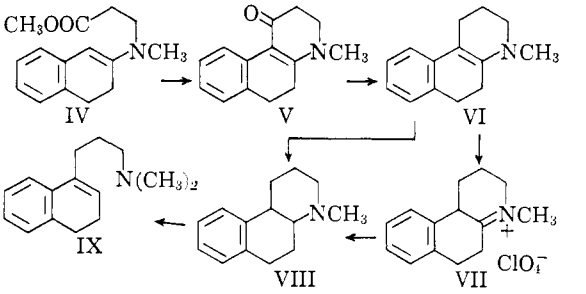
In view of the vast amount of work which has been done on the preparation and testing of steroidal hormone analogs,[2] it is surprising that so little is known regarding azasteroids.[3] The incorporation of nitrogen into the ring system of an active hormone should not alter the size or shape of the molecule appreciably. Therefore, one might expect that the resulting azasteroid would be capable of reacting with the enzyme systems associated with the parent hormone,[4] albeit the presence of nitrogen in the molecule might cause striking changes in biological action.

This paper describes an investigation of a method which is being considered for the elaboration of 14-aza-D-homo steroids. Condensation of the amino ester I[5] with 6-methoxy-2-tetralone would be expected[6,7] to yield the enamine II. An intramolecular acylation reaction[6] should result in the formation of the tetracyclic substance III which could be used in the preparation of a number of 14-aza-D-homo steroids. As a test of this synthetic approach, readily available model compounds were employed in analogous reactions.



2-Tetralone was condensed with methyl β-methylaminopropionate, the water formed in the reaction being removed by azeotropic distillation with benzene or toluene. The enamine product IV was too unstable to isolate; however, its infrared and ultraviolet spectra are fully consistent with the structural assignment. Under more drastic conditions (refluxing ethylene glycol) the enamine IV underwent cyclization to yield 53% of the crystalline 1-methyl-4-keto-1,2,3,4,7,8-hexahydrobenzo-[f]quinoline (V). The infrared and ultraviolet spectra as well as further chemical transformations support the structural assignment for this substance. Direct heating (210–215° at 0.4 mm.) of the enamine failed to give any V, but did give 5% of a different crystalline substance which has not been identified.

Reduction of the vinylogous amide V with lithium aluminum hydride[8] gave 1-methyl-1,2,3,4,7,8-hexahydrobenzo[f]quinoline (VI) in 85% yield which was characterized by its conversion to a methiodide (68%). The ultraviolet spectrum of the methiodide indicates that alkylation had occurred on nitrogen rather than on carbon.[6] Other reductions of V were carried out in an attempt to reduce the double bond, but retain the oxygen as a carbonyl or hydroxyl group. Reductions with either sodium and alcohol or lithium in liquid ammonia gave inseparable mixtures.



Further reduction of the enamine VI using platinum in absolute ethanol gave 89% of 1-methyloctahydrobenzo[f]quinoline (VIII). The stereochemistry of the ring fusion is tentatively assigned as *cis*.[9] Treatment of the enamine with sodium and alcohol (in an attempt to reduce the double bond and obtain the *trans* fused product) gave only unchanged starting material. In another attempt to obtain a different isomer of VIII, a method of reduction analogous to that of Leonard and co-workers[10] was investigated. The enamine VI was treated with perchloric acid to give the perchlorate

(1) This investigation was supported in part by a research grant, CY-2999, from the National Cancer Institute, Public Health Service.

(2) For a recent review see J. Grundy, *Chem. Revs.*, **57**, 281 (1957).

(3) (a) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938); (b) W. E. Bachmann and F. Ramirez, THIS JOURNAL, **72**, 2527 (1950); (c) St. Kaufmann, *ibid.*, **73**, 1779 (1951); (d) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, *ibid.*, **76**, 552 (1954); (e) G. R. Clemo and L. K. Mishra, *J. Chem. Soc.*, 192 (1953); (f) D. G. Bew and G. R. Clemo, *ibid.*, 1775 (1955); (g) Y. Nomuro, *J. Chem. Soc. Japan*, **75**, 77 (1954); (h) Y. Nomuro, *Bull. Chem. Soc. Japan*, **27**, 167 (1954).

(4) The preparation[3h] of an active nitrogen analog of hexesterol supports this hypothesis.

(5) For the preparation of the corresponding amino acid, see B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph and J. H. Williams, *J. Org. Chem.*, **18**, 153 (1953).

(6) G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).

(7) F. W. Heyl and M. E. Herr, *ibid.*, **75**, 1918 (1953).

(8) N. G. Gaylord, *Experientia*, **10**, 166 (1954).

(9) The catalytic reduction of 1-methyloctahydroquinoline has been reported to give *cis*-1-methyldecahydroquinoline; see N. J. Leonard, L. A. Miller and P. D. Thomas, THIS JOURNAL, **78**, 3463 (1956).

(10) N. J. Leonard, P. D. Thomas and V. W. Gash, *ibid.*, **77**, 1552 (1955).

VII.[11] Reduction of the perchlorate with sodium borohydride gave 79% of the same stereoisomer of 1-methyloctahydrobenzo[f]quinoline described above, as determined by a comparison of infrared and ultraviolet spectra and melting points of the methiodides.

To establish beyond doubt that the ring closure in the conversion of IV to V had occurred at the position shown, the amine VIII was degraded by Hofmann's exhaustive methylation procedure to 1-propyl-1,2,3,4-tetrahydronaphthalene. The Hofmann degradation of the methiodide of 1-methyloctahydrobenzo[f]quinoline gave 73% of 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene (IX). In one experiment this amine was converted to the methiodide and subjected to a Hofmann degradation. The product was not an olefinic substance, but rather 1-propylnaphthalene, which was formed presumably by a series of double bond shifts during the pyrolysis of the quaternary ammonium hydroxide.[13] When the unsaturated amine IX was reduced and then subjected to a Hofmann degradation, the expected product, 1-allyl-1,2,3,4-tetrahydronaphthalene, was formed, which on reduction gave 1-propyl-1,2,3,4-tetrahydronaphthalene. The infrared spectrum of the latter compound was identical with the spectrum of an authentic sample; however, its ultraviolet spectrum revealed the presence of about 7% 1-propylnaphthalene.

Experimental[14]

1-Methyl-4-keto-1,2,3,4,7,8-hexahydrobenzo[f]quinoline (V).—A solution of 29.2 g. (0.2 mole) of β-tetralone[15] and 23.4 g. (0.2 mole) of methyl β-methylaminopropionate[16] in 300 ml. of toluene was heated under reflux for 6 hours in a nitrogen atmosphere. The water produced during the condensation reaction was removed from the mixture by means of a Dean–Stark apparatus. The solvent was removed under reduced pressure yielding the pale yellow enamine IV which was used without further purification, λ_{max}^{EtOH} 211 (ε 17,100) and 305 mμ (ε 11,600) with a shoulder at 228 mμ (ε 11,300), $\nu_{max}^{CCl_4}$ 1740 cm.$^{-1}$ (s, ester carbonyl).

The intermediate enamine was dissolved in 250 ml. of ethylene glycol and heated under reflux for 8 hours. The reaction mixture was cooled, dissolved in ether and the resulting solution was washed repeatedly with water and dried. Concentration of the ether solution and cooling gave 21.6 g. (51%) of the crude product, m.p. 104–106.2°. Chromatographic purification of the residue from the crystallization, using Alcoa F-20 alumina and benzene–ether (9:1) as the eluent, gave an additional 1.94 g. (4%) of product, m.p. 104.5–106.3°. The analytical sample of 1-methyl-4-keto-1,2,3,4,7,8-hexahydrobenzo[f]quinoline (V) was crystallized from aqueous alcohol, m.p. 106–107°, λ_{max}^{EtOH} 229.5 (ε 10,700) and 308 mμ (ε 16,400), $\nu_{max}^{CCl_4}$ 1665 (s, conj. carbonyl) and 1640 cm.$^{-1}$ (s, double bond).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.56. Found: C, 79.01; H, 7.01; N, 6.40.

Attempted ring closure of the enamine IV by simply distilling it between 210–215° (0.38 mm.) did not yield the desired product. Treatment of the distillate with ether gave a different substance in about 5% yield, m.p. 120.5–121.4°, which has not been characterized.

1-Methyl-1,2,3,4,7,8-hexahydrobenzo[f]quinoline (VI).—Fifteen grams of 1-methyl-4-keto-1,2,3,4,7,8-hexahydrobenzo[f]quinoline was introduced by Soxhlet extraction into a mixture of 5.36 g. of lithium aluminum hydride and 600 ml. of anhydrous ether. When the addition was complete, the reaction mixture was heated under reflux for 2 hours before decomposing the excess reducing agent by the addition of 12 ml. of ethyl acetate followed by a solution of 14.1 g. of potassium hydroxide in 15 ml. of water. The ether solution was filtered through anhydrous potassium carbonate and concentrated to give a residue which on distillation yielded 11.9 g. (85%) of product, b.p. 119–125° (0.2 mm.), $n^{28}D$ 1.6420. The analytical sample of 1-methyl-1,2,3,4,-7,8-hexahydrobenzo[f]quinoline (VI) had b.p. 132° (0.5 mm.), $n^{28}D$ 1.6429, λ_{max}^{EtOH} 234.5 (ε 8,060) and 314.5 mμ (ε 11,700).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.42; H, 8.60; N, 6.98. Found: C, 84.38; H, 8.43; N, 6.93.

1-Methyl-1,2,3,4,7,8-hexahydrobenzo[f]quinoline perchlorate (VII) was prepared by adding an excess of a solution (1:1) of absolute ethanol and 70% perchloric acid to a chilled solution of 5.5 g. of the enamine VI in 50 ml. of anhydrous ether with swirling. The crude product (8.1 g., 98%) was recrystallized from ethanol to give 7.9 g. of colorless needles, m.p. 137.5–138°; λ_{max}^{EtOH} 248.5 mμ (ε 3,560), ν_{max}^{KBr} 1675 cm.$^{-1}$ (s, carbon–nitrogen double bond).

Anal. Calcd. for $C_{14}H_{18}ClNO_4$: C, 56.09; H, 6.01; Cl, 11.85; N, 4.67. Found: C, 56.14; H, 6.00; Cl, 11.89; N, 4.75.

1-Methyl-1,2,3,4,7,8-hexahydrobenzo[f]quinoline methiodide was crystallized from ethanol–ether in 68% yield, m.p. 186.5° dec.; λ_{max}^{EtOH} 215 (ε 35,600), 221 (ε 30,600) and 257 mμ (ε 11,330).

Anal. Calcd. for $C_{15}H_{20}IN$: C, 52.79; H, 5.90; I, 37.19; N, 4.11. Found: C, 52.86; H, 5.68; I, 37.48; N, 4.27.

1-Methyloctahydrobenzo[f]quinoline (VIII). (A) From 1-Methyl-1,2,3,4,7,8-hexahydrobenzo[f]quinoline (VI).—A solution of 10.0 g. of 1-methyl-1,2,3,4,7,8-hexahydrobenzo-[f]quinoline in 100 ml. of absolute ethanol was hydrogenated at atmospheric pressure using 0.5 g. of Adams catalyst. The hydrogenation was completed in about 10 hours with the uptake of one molecular equivalent of hydrogen. Removal of the catalyst and distillation of the product gave 8.93 g. (89%) of VIII, b.p. 90–92° (0.15 mm.), $n^{25.5}D$ 1.5570, λ_{max}^{EtOH} 265.5 (ε 540) and 272.5 mμ (ε 570). The analytical sample had b.p. 92° (0.13 mm.), $n^{24}D$ 1.5582.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.57; H, 9.51; N, 6.96. Found: C, 83.36; H, 9.54; N, 7.06.

1-Methyloctahydrobenzo[f]quinoline methiodide was prepared by the addition of 25 g. of methyl iodide to a solution of 17 g. of VIII in 100 ml. of anhydrous ether. Recrystallization of the product from ethanol gave 23.7 g. of colorless needles, m.p. 282–284° dec., which was used in the Hofmann elimination experiment described below. The analytical sample of the methiodide was crystallized from an alcohol–acetone mixture, m.p. 295° dec.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46; I, 36.97; N, 4.09. Found: C, 52.43; H, 6.52; I, 37.06; N, 4.14.

(B) From 1-Methyl-1,2,3,4,7,8-hexahydrobenzo[f]quinoline Perchlorate (VII).—Sodium borohydride (11.4 g.) was added cautiously in small portions to a stirred solution of 4.5 g. of the perchlorate VII (see above) in 150 ml. of methanol. The mixture was then refluxed for 2 hours before concentrating it to about 50 ml. The mixture was diluted with 250 ml. of 5% sodium hydroxide solution, extracted with ether, and the ether extract was dried over potassium carbonate. Distillation of the product through a semi-micro column gave 2.4 g. (79%) of VIII, b.p. 94° (0.35 mm.), $n^{25.5}D$ 1.5565, λ_{max}^{EtOH} 266 (ε 500) and 273 mμ (ε 526). The infrared spectrum of this material is essentially the same (36 identical absorption bands) as the spectrum of VIII described in part A.

(11) The infrared spectrum of the perchlorate shows a band (1675 cm.$^{-1}$) characteristic of a typical[12] imine salt structure; however, the ultraviolet spectrum suggests that this substance exists in ethanol solution partly as VII and partly as N-protonated VI.

(12) (a) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, THIS JOURNAL, **77**, 439 (1955); (b) N. J. Leonard, R. W. Fulmer and A. S. Hay, *ibid.*, **78**, 3457 (1956).

(13) The classical example of this type of rearrangement is found in the Hofmann degradation of piperidine to piperylene.

(14) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird (model B) spectrophotometer fitted with a sodium chloride prism. In reporting infrared spectra, (s) denotes strong, (m), medium and (w), weak absorption. Ultraviolet spectra were determined with a Cary recording spectrophotometer (model 11 MS). The microanalyses were performed by Dr. S. M. Nagy and his associates.

(15) A. J. Birch, *J. Chem. Soc.*, 431 (1944).

(16) R. W. Holley and A. D. Holley, THIS JOURNAL, **71**, 2124 (1949).

The melting point (284–285° dec.) of the methiodide derivative was not depressed on admixture with a sample of the methiodide described in part A, and the infrared spectra of the two samples are identical.

1-Propyl-1,2,3,4-tetrahydronaphthalene. (A) **From 1-Methyloctahydrobenzo[f]quinoline Methiodide by Hofmann's Exhaustive Methylation Procedure.**—A solution of 10 g. of the methiodide in 100 ml. of water and 100 ml. of tetrahydrofuran was stirred overnight with neutral silver oxide freshly prepared from 10 g. of silver nitrate. The inorganic salts were filtered and the filtrate was concentrated under reduced pressure at a bath temperature below 70° to give a residue which was heated at 100° (0.5 mm.) for about 30 minutes before distilling the product through a semi-micro column. The yield of 1-(**3-dimethylaminopropyl**)-**3,4-dihydronaphthalene (IX)** was 4.59 g. (73%), b.p. 108–110° (0.5 mm.); λ_{max}^{EtOH} 212.5 and 218.5 (ε 18,040), 225 (ε 13,350) and 261 mμ (ε 8,750). There are no shoulders or inflections in the ultraviolet spectrum at 272.5, 282.5 or 289.5 mμ, indicating the absence of naphthalenic material at this stage.

A solution of 4.5 g. of the unsaturated amine IX and 40 ml. of absolute ethanol was shaken in the presence of 0.25 g. of Adams catalyst in a hydrogen atmosphere until one molecular equivalent of hydrogen was absorbed and the rate of hydrogenation slowed. Filtration of the mixture and concentration of the filtrate gave a residue which was diluted with ether and treated with excess methyl iodide to give 6.8 g. of material which on recrystallization from ethanol–ether afforded 6.22 g. (84%) of 1-(**3-dimethylamino**)-**1,2,3,4-tetrahydronaphthalene methiodide**, m.p. 170–172°; λ_{max}^{EtOH} 218 (ε 23,000), 265.5 (ε 1,280) and 273 mμ (ε 1,100). The molar extinction coefficients of the product are not characteristic of a 1,2,3,4-tetrahydronaphthalene chromophore and indicate the presence of a small amount of a 1-substituted 3,4-dihydronaphthalene or 1-substituted naphthalene impurity.

The above methiodide (6.2 g.) was dissolved in 200 ml. of a 1:1 ethanol–water mixture and stirred overnight with silver oxide prepared from 6 g. of silver nitrate. The mixture was filtered and the filtrate concentrated and finally heated at 120° (15 mm.) for 30 minutes before distilling the product, b.p. 120–130° (15 mm.), mostly at 126–127°. To remove traces of amine, the distillate was diluted with ether and washed with dilute hydrochloric acid and water. The ether solution was dried and concentrated under reduced pressure to give 1.86 g. (63%) of crude 1-allyl-1,2,3,4-tetrahydronaphthalene which was used directly in the next step; λ_{max}^{EtOH} 214.5 (ε 11,900), 218 (ε 12,300), 266 (ε 937), 273 (ε 1,180), 282.5 (ε 684) and 289 mμ (ε 493) with an inflection at 223.5 mμ (ε 9,370) and a shoulder at 292 mμ (ε 480); $\nu_{max}^{CCl_4}$ 1640(m), 993(m) and 913(s) cm.$^{-1}$ (vinyl grouping). The ultraviolet absorption bands at 223.5, 282.5, 289 and 292 mμ in the crude product undoubtedly are due to the presence of about 7–10% 1-propylnaphthalene (see below).

A solution of 1.72 g. of 1-allyl-1,2,3,4-tetrahydronaphthalene and 30 ml. of absolute ethanol was hydrogenated in the presence of 0.1 g. of Adams catalyst until one molecular equivalent of hydrogen was absorbed and the rate of hydrogenation slowed. After removal of the catalyst and solvent, the residue (1.68 g., 96%) was distilled through a semi-micro column to give 1.44 g. of 1-propyl-1,2,3,4-tetrahydronaphthalene, b.p. 105–126° (14 mm.), $n^{25}D$ 1.5254–1.5278. The bulk of the product had b.p. 126° (14 mm.), $n^{25}D$ 1.5278; λ_{max}^{EtOH} 214.5 (ε 11,200), 218 (ε 11,650), 223.5 (ε 8,800), 266 (ε 835), 273 (ε 1,000), 282.5 (ε 623), 289 (ε 427) and 292 mμ (ε 412). From a comparison of molar extinction coefficients of pure 1-propyl-1,2,3,4-tetrahydronaphthalene (part B) and β-(1-naphthyl)-propionic acid,[17] it was estimated that the product was contaminated with about 7% 1-propylnaphthalene. The infrared spectrum of the product did not show the presence of this impurity.

In a different experiment, 16.2 g. of 1-methyloctahydrobenzo[f]quinoline methiodide was carried through two successive Hofmann exhaustive methylation reactions without hydrogenation of the intermediate 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene (IX). Distillation of the product from the second Hofmann reaction gave 2.74 g. (34%) of crude 1-propylnaphthalene, b.p. 123–126° (12 mm.); λ_{max}^{EtOH} 223.5 (ε 82,500), 272.5 (ε 5,970), 282.5 (ε 6,970), 289.5 (ε 4,790), 292.5 (ε 4,640). Attempted hydrogenation of this material using Adams catalyst in ethanol resulted in a negligible uptake of hydrogen.

(B) **From 1-Tetralone.**—A solution of 23.0 g. of 1-tetralone[18] and 100 ml. of anhydrous ether was added slowly with stirring and under a nitrogen atmosphere to the Grignard reagent prepared from 4.0 g. of magnesium and 21.3 g. of *n*-propyl bromide in 150 ml. of ether. When the addition was completed, the ether solution was refluxed for 2 hours before being washed with cold dilute hydrochloric acid and water. The dried ether solution was concentrated and the residue of crude 1-hydroxy-1-propyl-1,2,3,4-tetrahydronaphthalene was distilled slowly in the presence of a few crystals of potassium bisulfate to give 15.6 g. (58%) of a mixture of olefins, b.p. 124–126° (10 mm.). A portion (4.0 g.) of the olefinic mixture in 50 ml. of glacial acetic acid was hydrogenated in the presence of 1.0 g. of a 10% palladium-on-charcoal catalyst. The crude product was chromatographed on alumina to remove traces of oxygen-containing impurities and then distilled through a semi-micro column to give 1.9 g. of 1-propyl-1,2,3,4-tetrahydronaphthalene, b.p. 125° (13 mm.), $n^{25}D$ 1.5225 (lit.[19] $n^{20}D$ 1.5229); λ_{max}^{EtOH} 213 (ε 9,000), 266 (ε 521) and 273 mμ (ε 545). The infrared spectra of this product and the same product from part A are identical.

(17) M.p. 156.5–157.5°; λ_{max}^{EtOH} 224.5 (ε 89500), 271.5 (ε 6860), 282 (ε 8140), 289 (ε 5620) and 292.5 mμ (ε 5560) with an inflection at 264 mμ (ε 4540).

(18) C. E. Olson and A. R. Bader, *Org. Syntheses*, **35**, 95 (1955).

(19) Z. J. Vejdelek and B. Kakac, *Chem. Listy*, **48**, 1215 (1954).

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Synthesis of Peptides with Strepogenin Activity[1]

BY R. B. MERRIFIELD AND D. W. WOOLLEY

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Four new pentapeptides and one new tetrapeptide have been synthesized. The peptides were L-seryl-L-histidyl-L-leucyl-L-valyl-L-phenylalanine, L-cysteinyl-L-histidyl-L-leucyl-L-valyl-L-glutamic acid (disulfide), L-leucyl-L-cysteinyl-L-leucyl-L-valyl-L-glutamic acid (disulfide), L-seryltriglycyl-L-glutamic acid and L-seryl-L-leucyl-L-valyl-L-glutamic acid. These were all closely related to the strepogenin-active peptide L-seryl-L-histidyl-L-leucyl-L-valyl-L-glutamic acid. Comparison of their activities in the growth of *Lactobacillus casei* was made, and some general conclusions about the structural features needed for this kind of biological action were discussed.

The recent isolation, determination of structure and synthesis of a peptide with high strepogenin activity in the stimulation of growth of *Lactobacillus casei*[2,3] has allowed the problem of how it functions to be approached. The active peptide was L-

(1) Supported in part by grant A 1260 from the U. S. Public Health Service.

(2) R. B. Merrifield and D. W. Woolley, THIS JOURNAL, **78**, 358 (1956).

(3) R. B. Merrifield and D. W. Woolley, *ibid.*, **78**, 4646 (1956).