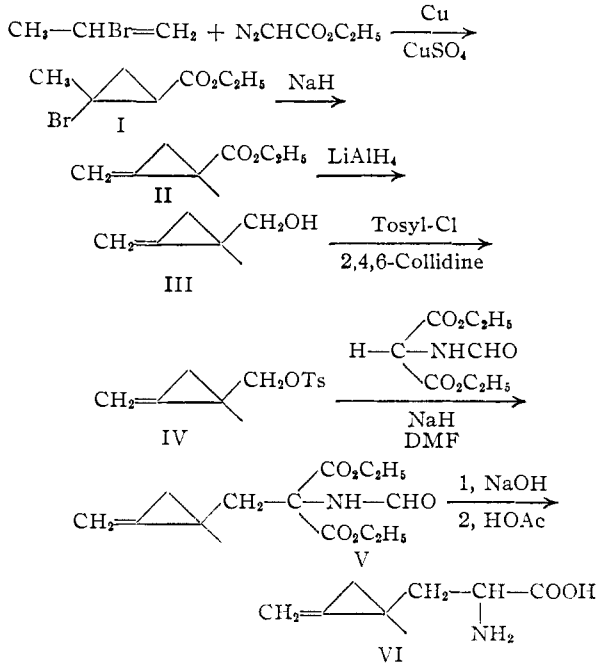
SYNTHESIS OF α-AMINOMETHYLENECYCLOPROPANEPROPIONIC ACID (HYPOGLYCIN A)

Sir:

We wish to report on the synthesis of Hypoglycin A, a natural product obtained from the unripe fruit of *Blighia sapida*.[1] This interesting material, which exhibits marked hypoglycemic properties, was first assumed to possess a polypeptide structure.[1,2] However, recent work has shown the compound to be a new amino acid, α-aminomethylenecyclopropanepropionic acid (VI).[3] We have now succeeded in synthesizing racemic VI and have shown it to be identical with the natural material.

The synthetic route which was finally successful is shown below



Treatment of 2-bromopropene with ethyl diazoacetate in the presence of a copper–bronze catalyst resulted in a 17–20% yield of ethyl 2-bromo-2-methylcyclopropanecarboxylate (I), obtained as a mixture of the *cis* and *trans* forms, b.p. 71–86° (11 mm.); $n^{25}D$ 1.4653–1.4666. *Anal.* Calcd. for $C_7H_{11}BrO_2$: C, 40.59; H, 5.36; Br, 38.59. Found: C, 40.88; H, 5.14; Br, 38.42. Although the bromoester I was inert to boiling 2,4,6-collidine, it reacted with sodium hydride in refluxing ether containing a few drops of ethanol[4] to form a 60% yield of ethyl methylenecyclopropanecarboxylate (II), b.p. 152–154°; $n^{25}D$ 1.4447. *Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99; O, 25.37. Found: C, 66.68; H, 8.11; O, 25.45. Compound II was also obtained by treatment of allene with ethyl diazoacetate.

(1) C. H. Hassall, K. Reyle and P. Feng, *Nature*, **173**, 356 (1954); C. H. Hassall and K. Reyle, *Biochem. J.*, **60**, 334 (1955).

(2) C. v. Holt and W. Leppla, *Bull. soc. chim. Belges*, **65**, 113 (1956); W. Leppla and C. v. Holt, *Arch. exp. Pathol. Pharmakol.*, **228**, 166 (1956).

(3) C. v. Holt, W. Leppla, B. Kroner and L. v. Holt, *Naturwissenschaften*, **43**, 279 (1956); C. v. Holt and W. Leppla, *Angew. Chem.*, in press.

(4) M. S. Newman and S. Merrill, THIS JOURNAL, **77**, 5549 (1955).

This unsaturated ester II could not be prepared by the treatment of I with sodium ethoxide in ethanol, due to the predominant formation of the ether, ethyl 2-ethoxy-2-methylcyclopropanecarboxylate.[5] The ester II was reduced readily in 75% yield to methylenecyclopropanemethanol (III), b.p. 138–139°; $n^{25}D$ 1.4644. *Anal.* Calcd. for C_5H_8O: C, 71.41; H, 9.59; O, 19.00. Found: C, 71.40; H, 9.86; O, 18.95. The infrared spectrum of this alcohol exhibited bands at 5.73 and 11.26 μ, which are considered typical of methylenecyclopropane.[6] Conversion of compound III in 2,4,6-collidine[7] to the tosylate IV proceeded in 63% yield (crude). This tosylate IV was used to alkylate sodio diethyl formamidomalonate in N,N-dimethylformamide and the crude reaction product was hydrolyzed and decarboxylated. The crude amino acid was purified by chromatography over powdered cellulose, using *n*-butanol saturated with water as the eluent. α-Amino-methylenecyclopropanepropionic acid (VI) was thus obtained as colorless leaflets from water–acetone; darkens above 200° and does not melt to 300°. *Anal.* Calcd. for $C_7H_{11}NO_2$: C, 59.54; H, 7.85; N, 9.92. Found: C, 59.73; H, 7.78; N, 9.92. Although VI is capable of existing as two diastereoisomers, only one form could be isolated from the reaction. This material was shown to be identical with natural Hypoglycin A by paper chromatography, electrophoresis and infrared spectra.

(5) A similar result has been reported recently by K. B. Wiberg, R. K. Barnes and J. Albin, *ibid.*, **79**, 4994 (1957), who obtained only ethyl 2-*t*-butoxycyclopropanecarboxylate from the treatment of ethyl 2-bromocyclopropanecarboxylate with potassium *t*-butoxide.

(6) J. T. Gragson, K. W. Greenlee, J. M. Derfer and C. E. Boord, *ibid.*, **75**, 3344 (1953).

(7) C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145 (1952).

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THE SIZE AND SHAPE OF BOVINE SERUM ALBUMIN AS A FUNCTION OF *p*H, DETERMINED BY SMALL-ANGLE SCATTERING OF X-RAYS

Sir:

The size and shape of bovine serum albumin molecule at different *p*H has been studied recently in several laboratories by viscosity, diffusion, sedimentation and light scattering experiments.[1] Since the interpretation of the observed data is still incomplete,[2] we have tried to collect some new information by small-angle X-ray scattering techniques.

The protein was supplied by Armour Laboratories. Its molecular weight is 66,400[1]; the sample we used contains a small amount (8% by weight) of a heavier impurity.[1]

The X-ray diffraction experiments were carried out with strictly monochromatic radiation (Cu $K\alpha_1$, as obtained with a bent quartz monochromator), *in vacuo*. The protein solution was kept in a small, vacuum tight, Plexiglas cell, provided with

(1) M. Champagne, *J. chim. phys.*, **378**, 410 (1957).

(2) Yang and Foster, THIS JOURNAL, **76**, 1588 (1954); Tanford, *et al.*, *ibid.*, **77**, 6421 (1955); Harrington, *et al.*, *Biochem. J.*, **62**, 569 (1956); Aoki and Foster, THIS JOURNAL, **79**, 3385 (1957); J. F. Foster, *J. Phys. Chem.*, **61**, 704 (1957).