Tetrahedron Letttrs No. 16, pp. 1065-1067, 1963. Pergamon Press Ltd.
Printed in Great Britain.

A NEW SYNTHESIS OF HYPOGLYCIN A

D.K. Black and S.R. Landor
Woolwich Polytechnic, London, S.E.18

(Received 16 April 1963)

Hypoglycin A, (III), a new aminoacid with marked hypoglycaemic properties was isolated by Hassal[1] from unripe ackee fruit (Blighia sapida) and subsequently synthesised in six stages from 2-bromo-propene by Carbon, Martin and Swett[2]. In our three stage synthesis 1-bromo-buta-2,3-diene[3] was condensed with ethyl formylaminomalonate in the presence of sodium hydride to give diethyl buta-2,3-dienylformylamino-malonate (I), m.p. 80°, ν max 1950 cm^{-1} in 80% yield. Treatment of (I) with diiodomethane and zinc-copper couple[4] resulted in the addition of methylene to the non terminal double bond (we had already shown[5] that carbenes add to allenes at the more substituted double bond) to give II (71%) which was hydrolysed (Sodium hydroxide) and

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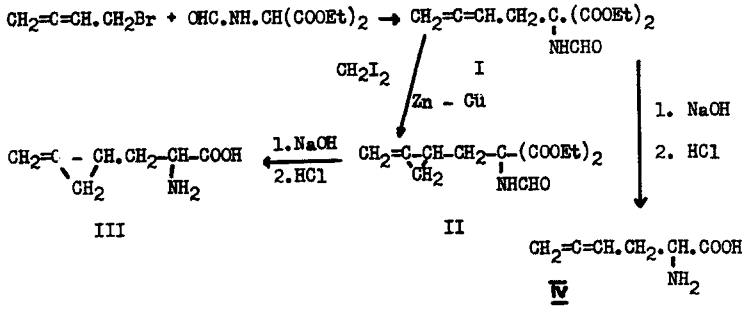
1. Hassall, Reyle and Feng. Nature 1954, **173**, 356
   Hassall and Reyle. Biochem. J. 1955, **60**, 334
2. Carbon, Martin and Swett. J.Amer.Chem.Soc., 1958, **80**, 1002.
3. Carothers and Berchet. J.Amer.Chem.Soc., 1933, **55**, 2807; better prepared from buta-2,3-dien-1-ol (Bailey & Pfeifer, J.Org.Chem. 1955, **20**, 1337) by the triphenyl phosphite dibromide method, Black, Landor, Patel and Whiter, Tetrahedron Letters No. 8, 483 (1963).
4. Simmons and Smith, J.Amer.Chem.Soc., 1958, **80**, 5323
5. Ball and Landor, Proc.Chem.Soc., 1961, 246.

decarboxylated (hydrochloric acid) and evaporated to dryness. Paper chromatographic separation [butan-1-ol-acetic acid-water (4:1:5)] and elution gave as the main product, 2-amino-4,5-methylene-hex-5-enoic acid (III), (28%), R_F 0.58 with correct analysis, and identical infra-red spectrum and R_F value to that of a sample of hypoglycin A[6]. (I) was hydrolysed and decarboxylated yielding 2-amino-hexa-4,5-dienoic acid (IV), ν_{max} 1955 cm^{-1}, R_F 0.51 which gave norleucine on hydrogenation. We have also prepared a series of analogous allenic amino-acids from different allenic halides and these will be described elsewhere.



Isolation of only one of the two possible diastereoisomerides as the major component indicates considerable stereo-specificity in the decarboxylation (also found by Carbon, Martin and Swett[2]). This can be rationalised by postulating reversible δ-lactone formation under strong acid conditions[7], decarboxylation to a planar transition

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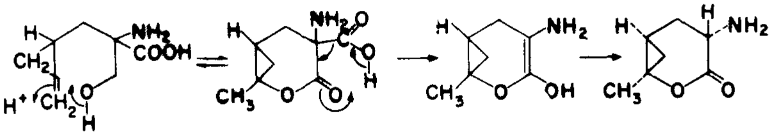
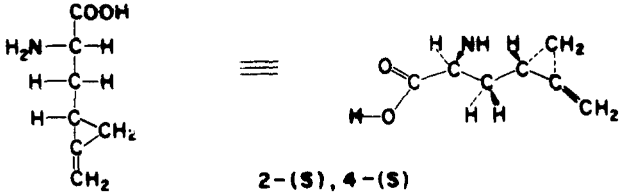
[6] Very kindly made available by Dr. S.Wilkinson.

[7] Goering, Cristol and Dittmar. J.Amer.Chem.Soc., 1948, **70**, 3310.

state, protonation to give the more stable α-amino-δ-lactone A,[8] followed by fission to the acid. If these mechanistic considerations are correct, the relative configuration of the two asymmetric centres can be deduced as 2-(R), 4-(R) and 2-(S), 4-(S) for the two enantiomorphs.[9] Accepting the L-configuration at carbon 2[10] we suggest hypoglycin A is (+) -2-(S), 4-(S)-2-amino-4,5-methylene-hex--5-enoic acid (V).



V



2-(S),4-(S)

We thank Dr. P.W.G.Smith for helpful discussion and the D.S.I.R. for a maintainance grant to D.K.B.

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8. Mathieson, Tetrahedron Letters 1963, 81, discusses the consequences of the planar lactone group in six-membered rings. Combined with the planar cyclopropane, the whole of the cyclohexane ring becomes planar but considerable angular strain is introduced. Some deviation from planarity is likely but does not affect the stereochemical argument.

9. The reaction sequence as shown starts with one enantiomorph; similar considerations apply to the other enantiomorph.

10. de Ropp, van Meter, De Renzo, McKerns, Pidacks, Bell, Ullman, Safir, Fanshawe and Davis, J.A.C.S., 1958, 80, 1004.