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A New Synthesis of Racemic Coronamic Acid and Other Cyclopropyl Amino Acids

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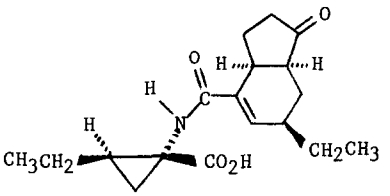
Summary A new method, in which various diazocompounds are added to a dehydro alanine derivative, allows the synthesis of coronamic acid and several other cyclopropyl amino acids

The structure[1] and synthesis[2] of coronatine (1), a bacterial toxin, have recently been reported In connection with our recent work[3] on cyclopropyl amino acids (VAA)[4], we had occasion to prepare racemic coronamic acid[5] (2) by a procedure somewhat simpler than that previously reported and one which is useful in the synthesis of other cyclopropyl amino acids



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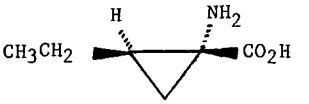

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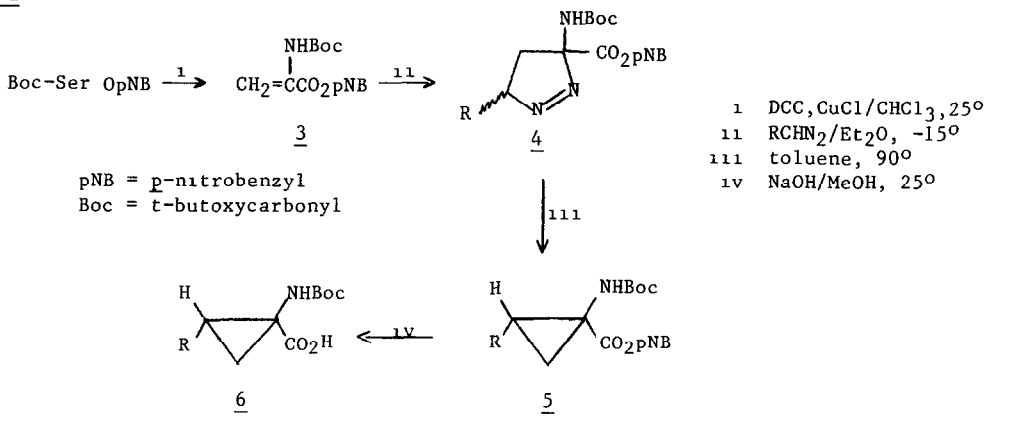
The ready availability of dehydroalanine derivatives by dehydration[6] of the corresponding serine derivatives makes these compounds attractive as intermediates in the synthesis of cyclopropyl amino acids Scheme I outlines the reaction sequence used The dehydro compound (3) was

Scheme I



prepared in 80% yield,[7] mp 94-95°, vinyl H at δ6 2 and 5 75 ppm Treatment of 3 with various diazo compounds (Table I) in cold ether solution gave pyrazolines[7] (4) which showed a characteristic ^{1}H NMR multiplet in the δ4 4-5 2 range Pyrolysis of the pyrazolines at ~90° in

Table I Yields (%) and Melting Points of Products

$RCHN_2$	4	5	6
H	89(80°)	100(118°)	96(177°)
CH_3	96(111°)	94(98°)	37(158°)
CH_3CH_2	59(oil)	77(100°)	50(124°)
$(CH_3)_2CH$	98(79°)	95(143°)	73(197°)
Ph	92(116°)	---	67(160°)

toluene gave excellent yields of the cyclopropanes[7] (5) Hydrolysis of 5 under very mild conditions gave the N-Boc cyclopropyl amino acids[7] in good yields as expected The ∇Phe derivative (6,R=Ph) was compared directly with previously prepared[3] Boc-∇^EPhe OH and found to be identical In the case of 6, R=CH_2CH_3, the coronamic acid derivative, deblocking with CF_3CO_2H/CH_2Cl_2 (50%) was carried out in the usual manner to give the TFA salt of racemic coronamic acid[7] in 81% yield, mp 168-169° Comparison of this sample with the IR and ^{1}H NMR spectra of the TFA salts prepared from samples of racemic coronamic and allo-coronamic acids[8] showed it to be identical to racemic coronamic acid

Since both the coronamic acid and the ∇Phe derivatives obtained by this method are shown to have the E-configuration, it appears that this procedure provides a single pure isomer We assume, therefore, that the other ∇AA derivatives (5,6,R=CH_3,$(CH_3)_2CH$) also have the E-configuration Based on the known[9] configurational crossover during pyrolysis of 3,5-disubstituted pyrazolines, we expect that the pyrazolines (4) have the Z-configuration

References

1 A Ichihara, K Shiraishi, H Sato, S Sakamura, K Nishiyama, R Sakai, A Furusaki and T Matsumoto, J Am Chem Soc 1977, **99**, 636

2 a) A Ichihara, K Shiraishi, S Sakamura, K Nishiyama and R Sakai, Tetrahedron Lett , 1977, 269, b) M E Jung and K M Halweg, ibid, 1981, **22**, 2735

3 a) S W King, J M Riordan, E M Holt and C H Stammer, J Org Chem , 1982, **47**, 3270, b) H Kimura and C H Stammer, J Org Chem , 1983, in press

4 The inverted triangle, ∇, is used to indicate amino acids in which the C_α,C_β-bond is one side of a cyclopropane ring Superscripts, ∇^E and ∇^Z, are used to designate the configuration about the ring

5 In the nomenclature of amino acid chemistry, coronamic acid is 2R,3S-∇^ENle It is surprising that L-acylase hydrolyzed the 2R,3S-isomer of racemic N-acetylcoronamic acid and rejected the 2S,3R-isomer [2a] We might have expected the latter to be recognized by the enzyme as corresponding to the natural L-amino acid having the 2S-configuration

6 L Somekh and A Shanzer, J Org Chem , 1983, **48**, 907 and references therein

7 All new compounds showed elemental analytical values for C,H and N in agreement with the calculated

8 We are extremely grateful to Dr Akitami Ichihara, Hokkaido University, Sapporo, Japan for his generous gifts of these compounds

9 (a) R J Crawford and A Mishra, J Am Chem Soc , 1965, **87**, 3768, b) T C Clarke, L A Wendling and R G Bergman, 1975, **97**, 5638

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