Synthesis of 2-Carboxy-4-imidazolidinones

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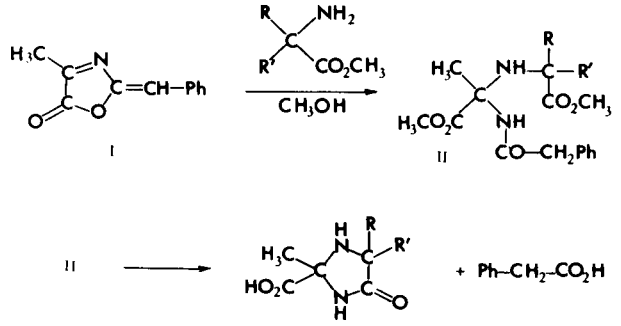
Different methods have been used to synthesize a large number of substituted 4-imidazolidinones. However, no compounds with a carboxy group at C-2 have previously been prepared, although Birch *et al.*, (1) have reported the isolation of 2-carboxy-2-(*p*-hydroxybenzyl)-5-methyl-4-imidazolidinone from the degradation of mycelianamide.

In previous papers (2a-b) we reported the preparation of 2,2-diaminopropionic acid derivatives; these were formed by addition of esters of α-amino acids to 2-benzylidene-4-methyl-5(2*H*)oxazolone in methanol, and were assigned structure II; only one of the two possible diastereomers produced in the reaction was isolated when racemic or optically active α-amino esters were used as starting material.

While studying the reactivity of these compounds we found that the interaction between the amide and ester groups leads to the formation of cyclic compounds, to which we have assigned structure III of 2-carboxy-2-methyl-4-imidazolidinones, as shown by the following scheme:

Reaction Scheme



The cyclization reactions were performed at room temperature, in aqueous ethanol and sodium hydroxide; the resulting 2-carboxy-2-methyl-4-imidazolidinones (III), whose elemental analysis and melting points are given in Table I, melt with decomposition and when hydrolyzed with hydrochloric acid give pyruvic acid and the amino acid used to obtain compounds II. Nmr values for some of compounds III are reported in Table II.

Diazomethane reacts easily with imidazolidinones (III), giving the corresponding methyl esters (see Table III).

Taking advantage of the decarboxylation reaction promoted by melting of 2-carboxy-2-methyl-4-imidazolidinones, the following confirmatory experiment was performed: diphenylglycine methyl ester was used to obtain α-(phenylacetamido)-*N*-(α'-carbomethoxy-α'-phenylbenzyl)alamine methyl ester (II: R = R' = Ph) according to the already mentioned reaction scheme. Cyclization of II (R = R' = Ph) gave the expected 2-carboxy-2-methyl-5,5-diphenyl-4-imidazolidinone (IIIg). Decarboxylation of IIIg gave a compound which was found to be identical with 2-methyl-5,5-diphenyl-4-imidazolidinone, prepared according to the method of H. Biltz (3). This result provides further confirmation of the proposed scheme.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a copper block and are not corrected. Anhydrous sodium sulphate was used throughout as drying agent. Nmr spectra were recorded on a Varian A-60 spectrometer at 30° with dimethylsulfoxide-d_6 as solvent and tetramethylsilane as internal standard.

2-Carboxy-2-methyl-4-imidazolidinones (III: Table I).

The general procedure was as follows: 1 *N* sodium hydroxide (3.0 ml.) was added to 1.0 mmole of compound II in ethanol (42 ml.). The solution was allowed to stand at room temperature for three days. Alcohol was then removed under reduced pressure, water was added to the residue and the alkaline solution was washed with methylene chloride. The aqueous phase was acidified (*p*H = 3.5) and extracted with ether to separate phenylacetic acid; imidazolidinones (III) were isolated by crystallization after concentration of the acidic solution to small volume, under reduced pressure and at room temperature.

The ether soluble 2-carboxy-2-methyl-5,5-diphenyl-4-imidazolidinone (IIIg) was separated from phenylacetic acid by fractional crystallization from ether-hexane.

2-Carbomethoxy-2-methyl-4-imidazolindinones (IV: Table III).

The general procedure was as follows: the solution of imidazolidinone (III) in methanol was treated at 0° with an ethereal solution of diazomethane. After evaporation of the solvents under reduced pressure, the residue was crystallized. The oily compounds IVd and IVe were characterized as hydrochlorides obtained by passing dry hydrogen chloride through the ethereal solution of the esters prepared as described above.

α-(Phenylacetamido)-*N*-(α'-carbomethoxy-α'-phenylbenzyl)alanine Methyl Ester (II: R = R' = Ph).

2-Benzylidene-4-methyl-5-(2*H*)-oxazolone (1.67 g.) was added at 0° to a stirred solution of diphenylglycine methyl ester (2.33 g.)

TABLE I

Compound	R	R′	M.p. °C (a)	(Found (%) C	H	N	Molecular Formula	Calcd. (%) C	H	N
IIIa	H	*m*-Pr	172-173 (b)	51.48	7.82	14.82	$C_8H_{14}N_2O_3$	51.60	7.58	15.04
IIIb	H	*sec*-Bu	193-195 (b)	53.80	8.19	14.02	$C_9H_{16}N_2O_3$	53.98	8.06	13.99
IIIc	H	*iso*-Pr	186-188 (c)	51.36	7.13	14.86	$C_8H_{14}N_2O_3$	51.60	7.58	15.04
IIId	Me	Et	212-213 (b)	51.65	7.52	14.99	$C_8H_{14}N_2O_3$	51.60	7.58	15.04
IIIe	H	*iso*-Bu	189-191 (b)	53.94	8.10	13.91	$C_9H_{16}N_2O_3$	53.98	8.06	13.99
IIIf	Me	Me	226-228 (b)	48.79	7.13	16.16	$C_7H_{12}N_2O_3$	48.83	7.03	16.27
IIIg	Ph	Ph	199-200 (d)	68.88	5.51	9.36	$C_{17}H_{16}N_2O_3$	68.90	5.44	9.45

(a) With decomposition - Crystallization from: (b), MeOH; (c), MeOH–Et_2O; (d), Et_2O-hexane.

TABLE II

Nmr values (a-b) for Imidazolidinones (III); δ (multiplicity) (J, Hz).

Protons (s)	Compounds (IIIc)	(IIId)	(IIIe)	(IIIf)
$-CH_3$				
C-2	1.42 (s)	1.39 (s)	1.41 (s)	1.42 (s)
C-5	0.76 (d) (7.2)	1.10 (s)	0.84 (d) (6.5)	1.17 (s)
	0.88 (d) (7.2)	0.74 (t) (7.1)	0.86 (d) (6.5)	1.12 (s)
$-CH_2-$		1.38 (q) (7.1)	1.2-1.4 (m)	
>CH–				
Cycle	3.37 (d) (5.0)		3.37 (double d)	
Side Chain	1.7-1.9 (m)		1.7-1.9 (m)	

(a) Chemical shifts are reported as δ values in parts per million. (b) Multiplicities are expressed as follows: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.

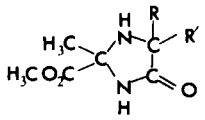
in methanol (50 ml.); the addition was made in small portions over the course of three hours. After complete solution the mixture was allowed to stand at room temperature for 36 hours. Excess methanol was then evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 0.5 *N* hydrochloric acid, 2 *N* sodium carbonate solution and water; evaporation of ethyl acetate *in vacuo* left a white solid (2.5 g.); pure addition compound was obtained by crystallization from ether, m.p. 94-95°.

Anal. Calcd. for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.41; H, 6.13; N, 6.15.

Decarboxylation of 2-Carboxy-2-methyl-5,5-diphenyl-4-imidazolidinone (IIIg).

Imidazolidinone (IIIg) (320 mg.) was heated at 220° under a stream of dry nitrogen for 15 minutes during which time melting and carbon dioxide evolution were observed. The resulting brown oil was dissolved in chloroform and the solution was washed with

TABLE III



Compound	R	R′	M.p. °C	Found (%) C	H	N	Molecular Formula	Calcd. (%) C	H	N
IVc	H	*iso*-Pr	106-107 (b)	53.96	7.83	14.06	$C_9H_{16}N_2O_3$	53.98	8.06	13.99
IVd (a)	Me	Et	153-155 (c)	45.80	7.34	11.72	$C_9H_{17}N_2O_3Cl$	45.67	7.24	11.84
IVe (a)	H	*iso*-Bu	160-162 (c)	47.99	7.84	11.19	$C_{10}H_{19}N_2O_3Cl$	47.90	7.64	11.17
IVf	Me	Me	113-115 (b)	51.76	7.58	15.12	$C_8H_{14}N_2O_3$	51.60	7.58	15.04

(a) The data are for hydrochloride; (IVd) requires Cl, 14.98%; found: 15.00%. (IVe) requires Cl, 14.14%; found: 14.09%. Crystallization from : (b), Et_2O; (c), EtOH–Et_2O.

saturated aqueous sodium hydrogen carbonate and evaporated to give crude decarboxylation product (220 mg.)

Chromatography on neutral Woelm alumina deactivated with 15% water, using benzene-ethyl acetate as eluent, yielded pure 2-methyl-5,5-diphenyl-4-imidazolidinone (180 mg.), m.p. 174-175° (from ethanol).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.13; H, 6.33; N, 11.08.

This compound was found to be identical with an authentic specimen of 2-methyl-5,5-diphenyl-4-imidazolidinone--prepared according to H. Biltz and co-workers (3)--as judged by comparison of spectroscopic and tlc behaviour and by mixed melting point.

REFERENCES

(1) A. J. Birch, R. I. English, R. A. Massy-Westropp and H. Smith, *J. Chem. Soc.*, 369 (1958).

(2a) A. Romeo and A. M. Schimberni, *Atti Accad. Naz. Lincei, Rend. Classe Sci. Fis. Mat. Nat.*, 22, 620 (1957); (b) G. Lucente, G. M. Lucente and A. Romeo, *Ann. Chim.* (Rome), 56, 572 (1966).

(3) H. Biltz, K. Seydel and E. Hamburger-Glaser, *Ann. Chem.*, 428, 198 (1922).

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