NOTES

The Synthesis of α-Amino Acids from Ethyl Alkylidenecyanoacetates

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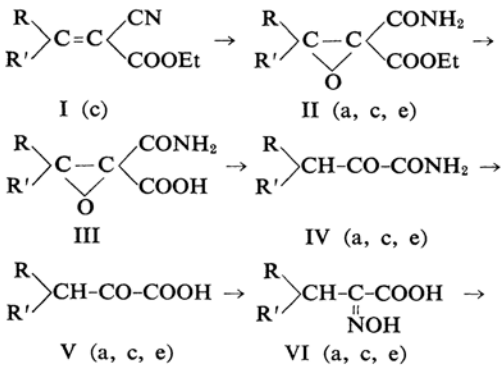
(Received June 24, 1964)

The present paper will describe the synthesis of new α-amino acids (2-amino-3, 6-dimethylheptanoic acid (VIIc) and 2-amino-3-isobutyl-5-methylhexanoic acid (VIIe)) through α-keto acids. The α-keto acids were prepared by a method virtually identical with that previously reported by two of the present authors.[1,2]



I (c) II (a, c, e) III IV (a, c, e) V (a, c, e) VI (a, c, e) VII (a, b, c, d, e)

a $\begin{cases} R=CH_3 \\ R'=iso\text{-}C_3H_7 \end{cases}$ b $\begin{cases} R=CH_3 \\ R'=iso\text{-}C_4H_9 \end{cases}$

c $\begin{cases} R=CH_3 \\ R'=iso\text{-}C_5H_{11} \end{cases}$ d $\begin{cases} R=n\text{-}C_3H_7 \\ R'=n\text{-}C_3H_7 \end{cases}$

e $\begin{cases} R=iso\text{-}C_4H_9 \\ R'=iso\text{-}C_4H_9 \end{cases}$

The reaction sequence is shown in the Chart.

Ethyl alkylidenecyanoacetates (I) were obtained by the condensation of ketones with ethyl cyanoacetate according to the method of Cope and his co-workers.[3] The epoxidation of ethyl alkylidenecyanoacetates with hydrogen peroxide was carried out in the presence of sodium tungstate or trisodium phosphate. In the case of ethyl (1-isobutyl-3-methylbutylidene)cyanoacetate (Ie), the epoxidation could be affected only in the presence of trisodium phosphate. The resulting α-keto acids were converted into the corresponding oximes by the usual method.

The catalytic hydrogenation of the oximes was performed in warm ethanol in the presence of a Raney-nickel as a catalyst. The α-amino acids thus obtained showed a reddish-purple color with ninhydrin and formed the corresponding *N*-benzoyl derivatives.

3, 4-Dimethylnorvaline (VIIa),[4] 3, 5-dimethylnorleucine (VIIb)[4] and 3-*n*-propylnorleucine (VIId)[5] were also prepared by this method (see Tables I—IV).

Experimental

Ethyl Alkylidenecyanoacetates were prepared, according to the method described in the literature[3], from ethyl cyanoacetate and ketones. The cyanoacetate described below is a new compound.

Ethyl(1,4-dimethylpentylidene)cyanoacetate (Ic); b. p. 136—138°C/4 mmHg; yield, 76%.

TABLE I. PREPARATION OF EPOXY AMIDE (II) FROM ETHYL ALKYLIDENECYANOACETATE (I)

Product	M.p., °C (B.p., °C/mmHg)	Yield %	Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	105	71	$C_{10}H_{17}O_4N$	55.81	7.91	6.51	55.89	7.81	6.49
IIc	(186—188/5)	78	$C_{12}H_{21}O_4N$	59.26	8.64	5.76	58.91	8.68	5.81
IIe	97	79	$C_{14}H_{25}O_4N$	61.99	9.22	5.16	62.11	9.06	5.23

1) M. Igarashi and H. Midorikawa, This Bulletin, **34**, 1543 (1961).
2) M. Igarashi and H. Midorikawa, *J. Org. Chem.*, **28**, 3088 (1963).
3) A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
4) P. E. Gagnon, P. A. Boivin and H. M. Craig, *Can. J. Chem.*, **29**, 70 (1951).
5) B. J. Meakin, F. R. Mumford and E. R. Ward, *J. Pharm. Pharmacol.*, **12**, 400 (1960).

Table II. Preparation of α-keto amide (IV) from II

Product	M.p., °C	Yield %	Formula	Anal., % Calcd. C	H	N	Found C	H	N
IVa	78	68	$C_7H_{13}O_2N$	58.74	9.09	9.79	59.21	8.92	9.73
IVc	72	64	$C_9H_{17}O_2N$	63.15	9.94	8.19	62.97	9.71	8.07
IVe	52	74	$C_{11}H_{21}O_2N$	66.29	10.62	7.02	65.98	10.50	6.96

Table III. Preparation of α-keto acid (V) and oxime (VI)

Product	M.p., °C (B.p., °C/mmHg)	Yield %	Formula	Anal., % Calcd. C	H	N	Found C	H	N
Va	43 (75/5)	73	$C_7H_{12}O_3$	58.33	8.33		58.51	8.61	
VIa	141 (decomp.)	75	$C_7H_{13}O_3N$	52.83	8.18	8.80	53.08	8.16	8.73
Vc	(102—104/4)	85	$C_9H_{16}O_3$	62.79	9.30		61.84	9.51	
VIc	103 (decomp.)	73	$C_9H_{17}O_3N$	57.75	9.09	7.49	57.90	8.95	7.45
Ve[a]	(108—111/5)	80	$C_{11}H_{20}O_3$	65.96	10.06		65.49	10.04	
VIe[b]	112 (decomp.)	78	$C_{11}H_{21}O_3N$	61.40	9.77	6.51	61.45	9.64	6.67

a) Lit., b. p. 124—126°C/14 mmHg; G. Freylon, *Ann. Chim. Phys.*, **20**, 101 (1910).
b) Freylon[a] has reported m. p. 159—160°C for this compound.

Table IV. Preparation of α-amino acid (VII) from VI

α-Amino acid	M.p., °C	Yield %	Formula	Anal., % Calcd. C	H	N	Found C	H	N
VIIa	268 (decomp.)	73	$C_7H_{15}O_2N$	57.93	10.34	9.65	57.33	10.51	9.56
Benzoyl deriv.	124		$C_{14}H_{19}O_3N$			5.64			5.64
VIIb[a]	253 (decomp.)	72	$C_8H_{17}O_2N$	60.37	10.69	8.80	59.98	10.79	8.59
Benzoyl deriv.	177		$C_{15}H_{21}O_3N$			5.32			5.18
VIIc	242 (decomp.)	63	$C_9H_{19}O_2N$	62.43	10.98	8.09	61.94	11.01	7.96
Benzoyl deriv.	155		$C_{16}H_{23}O_3N$			5.05			5.42
VIId[b]	283[c] (decomp.)	65	$C_9H_{19}O_2N$	62.43	10.98	8.09	62.17	10.91	7.95
Benzoyl deriv.	137		$C_{16}H_{23}O_3N$			5.05			5.14
VIIe	257 (decomp.)	70	$C_{11}H_{23}O_2N$	65.67	11.44	6.96	64.96	11.42	6.62
Benzoyl deriv.	151		$C_{18}H_{27}O_3N$			4.59			4.59

a) From 2,4-dimethyl-1-oxohexanoic acid oxime[1,2]
b) From dipropylpyruvic acid oxime[1,2]
c) Lit., m. p. 248—252; Ref. 5

Found: C, 68.66; H, 9.12; N, 6.84. Calcd. for $C_{12}H_{19}O_2N$: C, 68.90; H, 9.09; N, 6.70%.

The Epoxidation of Ethyl Alkylidenecyanoacetates. — To a mixed solution of I (0.1 mol.), ethanol (200 g.) and 30% hydrogen peroxide (200 g.), sodium tungstate dihydrate (0.02 mol.) was added. The mixture was then heated on a steam bath for 1—4 hr. to afford II as colorless crystals or as a pale yellow oil.

The Preparation of α-Keto Amides.—To a solution of 10% alcoholic potash (50 g.), II (0.05 mol.) was added at room temperature. The resulting potassium salt of III was dissolved in water and then acidified with dilute hydrochloric acid to give III as colorless crystals. III (0.05 mol.) was dissolved in water (40 cc.) and heated for 20—40 min. After it had been cooled, α-keto amide was obtained as colorless crystals.

The Preparation of α-Keto Acids.—A mixture of IV (0.03 mol.) and 10% hydrochloric acid (50 cc.) was heated on a water bath for about 3—4 hr. The product was obtained by fractionation.

The Preparation of Oximes.—To a mixture of sodium hydroxide (0.03 mol.) in 4 ml. of water and V (0.02 mol.), a solution of hydroxylamine hydrochloride (0.025 mol.) in a mixture of 4 ml. of water and 5 ml. of ethanol was added. The above mixture was then refluxed on a water bath for 1 hr. After cooling, the reaction mixture was acidified with dilute hydrochloric acid to give the product as colorless crystals.

The Catalytic Hydrogenation of Oximes. — A solution of VI (0.01 mol.) in ethanol (15 ml.) was shaken with hydrogen in the presence of a Raney nickel as a catalyst (prepared from 1 g. of nickel-aluminum alloy (50 : 50)) at 50°C under an ordinary pressure. The theoretical amount of hydrogen was absorbed within 5—7 hr. After the catalyst had been removed by filtration, the filtrate was concentrated to a small volume and dry ether was added. The reulting precipitate of α-amino acid was collected by filtration. Recrystallization from dilute ethanol gave colorless crystals.

The authors wish to express their hearty thanks to Dr. Taro Hayashi and Dr. Tatsuo Takeshima for their kindly advice. Thanks are also to Dr. Haruo Homma and his staff for microanalyses.

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