PREPARATION OF SUBSTITUTED AMINO ACIDS BY CYANOALKYLATION OF ESTERS

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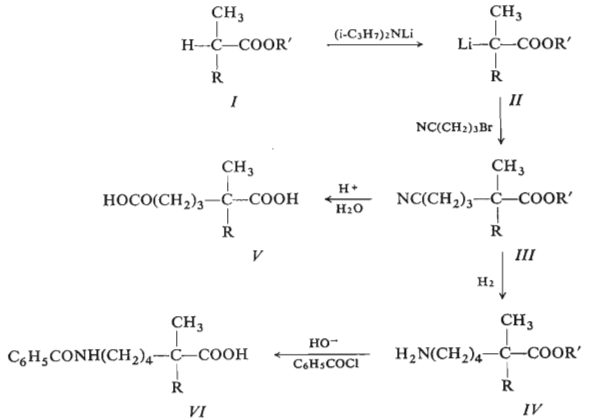
Cyanopropylation of isobutyrates and ethyl malonate was investigated with lithium isopropylamide as the metalation agent. The possibilities of using this reaction for the synthesis of ω-aminoalkane and alkanedioic acids were indicated.

Methods based on the metalation of the starting compound with lithium salts of amines followed by a reaction of the lithio derivative with alkyl halide[1,2] have been suggested for alkylation of carboxylic acids and their esters; in some cases, the esters



Ia—IVa: R = CH_3, R' = CH_3 *Va*, *VIa*: R = CH_3
Ib—IVb: R = CH_3, R' = C_2H_5 *Vc*: R = H
Ic—IVc: R = $CO_2C_2H_5$, R' = C_2H_5 *VIc*: R = CO_2H

The compounds prepared are characterized in Table I.

TABLE I
Characteristics of Compounds Prepared

	Compound	B.p., °C/Torr or m.p., °C (n_D^{20})	Yield
IIIa	methyl 5-cyano-2,2-dimethylvalerate	104—105/3·5 (1·4353)	69·0
IIIb	ethyl 5-cyano-2,2-dimethylvalerate	103—105/1·2 (1·4327)	46·1
IIIc	ethyl 5-cyano-2-ethoxycarbonyl-2-methylvalerate	139·5—140·5/0·95 (1·4404)	50·3
IVa	methyl 6-amino-2,2-dimethylcaproate	69·0—69·5/1·3 (1·4430)	37·3
IVb	ethyl 6-amino-2,2-dimethylcaproate	83—86/1·0 (1·4427)	42·6
IVc	ethyl 6-amino-2-ethoxy-carbonyl--2-methylcaproate	122·5—123·5/0·95 (1·4458)	63·4
Va	2,2-dimethyladipic acid	87—88·5 (water)	90·2
Vc	2-methyladipic acid	50·0—51·5[c] (benzene)	72·5
VIa	6-benzamido-2,2-dimethylcaproic acid	125—127 (chloroform)	50·9
VIc	6-benzamido-2-carboxy-2-methylcaproic acid	162 (decomposition) (acetone–$CHCl_3$)	65·5
VII	6-benzamido-2-methylcaproic acid	146·0—147·5 (chloroform)	99·6[f]

[a] In a thin film with liquids, in a KBr disc with solids. [b] M^+ from mass spectra. [c] *E.g.* in ref.[9] [d] By con- from the determination of released CO_2 as $BaCO_3$.

formed as intermediates have been isolated in a good yield and characterized[3]. The question remained open if also the reaction of cyanoalkyl halides with the lithium esters would proceed in a similar manner, and if a competitive reaction of the lithio ester with the nitrile group would not play a major role here[4,5]. It has been proved now that 4-bromobutyronitrile cyanoalkylates the lithio esters in an acceptable yield, and the reaction can be used for the preparation of the amino acids or their derivatives. The lower yields obtained in this case, compared with the preparation reactions described elsewhere, are compensated for by other advantages. Thus, the synthesis of 6-amino-2-methylcaproic acid from ethyl malonate *via* ethyl 5-bromo-2-

TABLE I
(*Continued*)

Formula (mol. weight: calc.; found)	Calc./Found % C	% H	% N	IR spectra/cm^{-1} [a] C–O–C	–C–CH_3	C=O	N–H (C=N)
$C_9H_{15}NO_2$ (169·2; —)	63·88 63·68	8·94 9·04	8·28 7·88	1 193	1 388	1 727	(2 243)
$C_{10}H_{17}NO_2$ (183·2 —)	65·56 65·07	9·35 9·35	7·65 7·61	1 182	1 385	1 725	(2 245)
$C_{12}H_{19}NO_4$ (241·3; —)	59·73 59·79	7·49 8·11	5·81 5·89	1 183	1 378	1 727	(2 245)
$C_9H_{19}NO_2$ (173·2; 173[b])	62·41 62·40	11·06 10·98	8·08 8·11	1 190	1 385	1 725	1 585 3 370
$C_{10}H_{21}NO_2$ (187·3; 187[b])	64·12 64·80	11·30 11·72	7·48 7·15	1 172	1 390	1 725	1 580 3 380
$C_{12}H_{23}NO_4$ (245·3; —)	58·75 58·68	9·45 9·48	5·71 5·59	—	1 380	1 730	1 596 3 380
$C_8H_{14}O_4$ (174·2; —)	55·15 55·15	8·10 8·11	— —	—	—	—	—
—	—	—	—	—	—	—	—
$C_{15}H_{21}NO_3$ (263·3; 262·8[d])	68·42	8·04	5·32 5·30	—	1 380	1 705[e] 1 615, 1 685	3 350
$C_{15}H_{19}NO_5$ (293·3; 294·1[d])	61·42	6·53	4·78 4·81	—	1 377	1 733 1 615, 1 679	3 377
$C_{14}H_{19}NO_3$ (249·3; 248·6[d])	67·44 66·87	7·68 7·68	5·62 5·32	—	—	—	—

ductometric titration in aqueous propanol. [e] Shoulder. [f] Yield of decarboxylation of compound *VIc*.

ethoxycarbonyl-2-methylvalerate requires a large excess of 1,3-dibromopropane and takes a longer time to proceed[6] than *via* ethyl 5-cyano-2-ethoxycarbonyl-2-methylvalerate. The latter compound can serve as an example of the second intermediate product of the three-step synthesis of 2-alkylalkanedioic acids from malonates. In both cases mentioned above, the easy decarboxylation of free monotopic diacids (*cf.* methylbutylmalonic acid[7]) is made use of; 2-(ω-cyanoalkyl)isobutyrates are the only intermediates during the synthesis of 2,2-dimethylalkanedioic acids and the first intermediate product of the two-step synthesis of ω-amino-2,2-dimethylalkane acids.

EXPERIMENTAL

Cyanoalkylation of esters: To a solution of butyllithium (0·1 mol) in benzene cooled to 0°C in an inert atmosphere, 0·105 mol of diisopropylamine (dried with BaO) is added; after 30 min, 0·09 mol of ester (dried with CaH_2) diluted with benzene (1 : 1 by vol.) is also added to the mixture at room temperature. The mixture is then allowed to stand for two hours; after that, either the precipitated lithio ester is isolated or the mixture is concentrated *in vacuo* almost to dryness. 4-Bromobutyronitrile (0·09 mol) diluted with tetrahydrofuran (1 : 1 by vol.) is added to the solution of lithio ester in 50 ml of tetrahydrofuran at −70°C during 3 min; the mixture is maintained at −70°C for one hour and the temperature is then left to attain room temperature. After addition of 5 ml of acetic acid, concentrating *in vacuo* and dilution with 100 ml of water the oil layer is extracted with ether (3 × 50 ml); ether is removed by distillation from the extract after washing with 10% $NaHCO_3$ (3 × 50 ml) and water (2 × 30 ml), drying with $MgSO_4$ and filtration, and the residue is distilled *in vacuo*.

Hydrolysis of cyanoesters: A solution of 0·01 mol of ester in a mixture of 30 ml of acetic acid and 4·5 ml of diluted sulphuric acid (4 : 5 by vol.) was refluxed for 36 h; after that, 15 ml of acetic acid was removed by distillation, and dicarboxylic acids were extracted from the diluted solution by the mixture ether–benzene (1 : 1).

Hydrogenation of 5-cyanovalerates: A mixture of cyanoester (0·05 mol), 30 ml ethanol, 2·5 ml of 25% ammonia and 3 g catalysts (Raney nickel T 1 paste) was subjected to hydrogenation[8] at 100°C and 90 atm for 1 h. The mixture was then filtered, volatile fractions were removed by distillation, and 6-aminocaproates were obtained by distillation *in vacuo*.

Saponification and benzoylation of amino esters. A solution of 0·002—0·005 mol of ester in aqueous ethanolic potassium hydroxide was refluxed for 6—10 h, ethanol was removed by distillation, the residue was benzoylated after Schotten-Baumann, and the solution was extracted with ether. From the acidified solution, 6-benzamido-2,2-dimethylcaproic acid (*VIa*) was extracted into chloroform and freed from benzoic acid by sublimation *in vacuo*, while 6-benzamido-2-carboxy-2-methylcaproic acid (*VIc*) precipitated directly as a crystalline compound insoluble in chloroform, ether, benzene, but readily soluble in methanol.

Thermolysis of the acid VIc: The acid (0·30093 g, 0·001 mol) was heated in a stream of argon to 165—170°C for 1 h. The carbon dioxide released in the process was absorbed in a 3% solution of barium hydroxide; 0·29970 g $BaCO_3$ was obtained (99·6% of the amount calculated for monodecarboxylation).

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