identified from its spectral data[10] and was confirmed by comparison with an authentic sample prepared by a known procedure:[1] ir 1790 (lactone C=O), 1750 (ester C=O), 1380 and 1370 cm^{-1} [$C(CH_3)_2$]; nmr δ 3.71 (s, 3, OCH_3), 2.71 (m, 3, CH_2 and CH), 1.55 (s, 3, γ-CH_3), and 1.25 (s, 3, γ-CH_3); mass spectrum *m/e* (rel intensity) 172 (1.7), 157 (48.0), 141 (9.0), 129 (32), 116 (13), 115 (39), 69 (20.5), and 55 (100.0).

4-Hydroxy-3,4-dimethylpentanoic Acid γ-Lactone (6).—Irradiation of 5.0 g of *trans*-methyl crotonate in 2-propanol provided 2.9 g of a mixture of methyl 3-butenoate and cis and trans crotonates, 1.1 g of the lactone **6**, bp 74–75° (0.8 mm), and 0.8 g of residue. Lactone **6** was identified from its spectral data and was confirmed by comparison with an authentic sample:[2] ir 1783 (C=O) and 1380 and 1370 cm^{-1} [$C(CH_3)_2$]; nmr δ 2.35 (m, 2, α-CH_2), 1.39 (s, 3, γ-CH_3), 1.21 (s, 3, γ-CH_3), and 1.05 (d, 3, β-CH_3, J = 7 Hz). The methine proton resonance was presumed to be submerged under the methyl resonances as a multiplet; mass spectrum *m/e* (rel intensity) 128 (51), 113 (60), 95 (13), 84 (17), 70 (17), 69 (37), and 59 (100). Crystallization of the residue from ether–petroleum ether (bp 30–60°) gave rise to 0.6 g of dilactone **8**, mp 161–162°, identified on the basis of its spectral data and mechanistic reasoning:[2] ir 1776 (C=O) and 1380 and 1370 cm^{-1} [$C(CH_3)_2$]; nmr δ 2.0–3.0 (m, 2, α and β-CH) 1.5 (s, 3, γ-CH_3), 1.28 (s, 3, γ-CH_3), and 1.02 (d, 3, β-CH_3, J = 6.5 Hz); mass spectrum *m/e* (rel intensity) 254 (12), 239 (55), 221 (7), 193 (5), 128 (32), 127 (12), 113 (55), 109 (17), 95 (20), 74 (17), 70 (32), 69 (30), and 59 (100).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.89; H, 8.62.

Methyl 2-(1-Hydroxyethyl)succinate γ-Lactone (γ-Methylparaconic Acid Methyl Ester) (5).—Dimethyl maleate (5.0 g) when irradiated in ethanol gave rise to 2.0 g of the starting material, 2.1 g of a mixture of cis and trans lactones (**5**) in 34:66 ratio, bp 94–98° (0.2 mm), and 1.0 g of residue. Similar irradiation of dimethyl fumarate yielded 2.3 g of the starting ester, 2.0 g of a mixture of cis and trans lactones **5** in 46:54 ratio, and 0.8 g of residue. The isomeric lactones were separated by glpc analysis and characterized *via* their spectral properties. Stereochemical assignment is only tentative as it is based on glpc retention times and nmr data: ir 1792 (lactone C=O) and 1754 cm^{-1} (ester C=O); nmr δ (cis) 4.6 (m, 1, OCH), 3.8 (s, 3, OCH_3), 2.3–3.0 (m, 3, CH and CH_2), and 1.5 (d, 3, γ-CH_3, J = 7 Hz), (trans) 4.8 (m, 1, OCH), 3.8 (s, 3, OCH_3), 2.3–3.0 (m, 3, CH and CH_2), 1.25 (d, 3, γ-CH_3, J = 7 Hz); mass spectrum *m/e* (rel intensity) 158 (3.8), 143 (10), 130 (19), 127 (22), 116 (32), 115 (26), 114 (49), 111 (6.0), 99 (27), 87 (27), 83 (25), 59 (23), and 55 (100); high-resolution mass data, parent ion, calcd, 158.0579; obsd, 158.0572; (M − 15) ion, calcd, 143.0344; obsd, 143.0343.

4-Hydroxy-3-methylpentanoic Acid γ-Lactone (7).—Irradiation of methyl crotonate (5.0 g) in ethanol gave 2.6 g of a mixture of methyl 3-butenoate and cis and trans crotonates, 0.8 g of a mixture of cis and trans γ-lactones in 50:50 ratio, bp 80–86° (5 mm), and 0.6 g of residue. The lactones were identified from their spectral data and from a comparison of nmr data with reported values:[11] ir 1783 cm^{-1} (C=O); nmr δ (cis) 4.15 (m, 1, OCH), 2–2.9 (m, 3, CH and CH_2), 1.4 (d, 3, γ-CH_3, J = 7 Hz), and 1.15 (d, 3, β-CH_3, J = 7 Hz); (trans) 4.6 (m, 1, OCH), 3.0–2.0 (m, 3, CH and CH_2), 1.25 (d, 3, γ-CH_3 J = 7 Hz), and 1.03 (d, 3, β-CH_3, J = 7 Hz); mass spectrum *m/e* (rel intensity) 114 (69), 99 (88), 86 (18), 71 (92), 70 (100), 56 (35), and 55 (95).

Registry No.—**4**, 6934-77-6; **5**, 35096-31-2; **6**, 2981-96-6; **7**, 6971-63-7; **8**, 35096-34-5.

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(10) Infrared spectra were obtained in chloroform solution with a Perkin-Elmer infracord spectrophotometer. Nmr spectra were determined in $CDCl_3$ solution with a Varian HA-100 or T-60 spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph 200 instrument using a 10 × 0.25 in. column packed with 20% SE-30 on 60/80 mesh Chromosorb W. Mass spectra were obtained on an Atlas CH-4 instrument.

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Catalytic Reduction of Azlactones in Alkaline Media. Synthesis of Amino Acids

A. BADSHAH, NASEEM H. KHAN,* AND A. R. KIDWAI

Department of Chemistry, Aligarh Muslim University, Aligarh, India

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There are three general methods, employing reduction and hydrolysis, for the conversion of azlactones to the corresponding acylamino acids or amino acids. Reduction can be effected with sodium or sodium amalgam in water or ethanol, with hydriodic acid and red phosphorus in acetic acid or acetic anhydride, or catalytically over Pt or Pd in the presence of hydrogen. Though most amino acids, excepting tryptophane, have been synthesized by treatment with hydriodic acid and red phosphorus, the method using sodium or amalgam is not of wide applicability.[1-3] Catalytic reduction has been less favored[4-7] owing, perhaps, to the high cost of Pt and Pd, which becomes a factor in large-scale laboratory preparations, and resistance of azlactones to hydrogenation, which required their initial hydrolysis to the unsaturated acylamino acids.

The present investigations in this direction were undertaken in order to devise a method which combines high yields with few experimental operations. Since catalytic hydrogenation has not received sufficient attention, an attempt has been made to improve this method and make it more economical for large-scale preparations by substituting nickel for the noble metal catalysts which, apart from being expensive, are sensitive to impurities. The sequence of reactions leading to the amino acids generally involves hydrolysis of azlactone to acylaminoacrylic acids, followed by catalytic reduction and finally hydrolysis to the amino acids. It was found that the first two steps could be combined by reductive hydrolysis of a suspension of azlactone (I) in alcoholic ammonia over Raney nickel at elevated hydrogen pressure and room temperature.

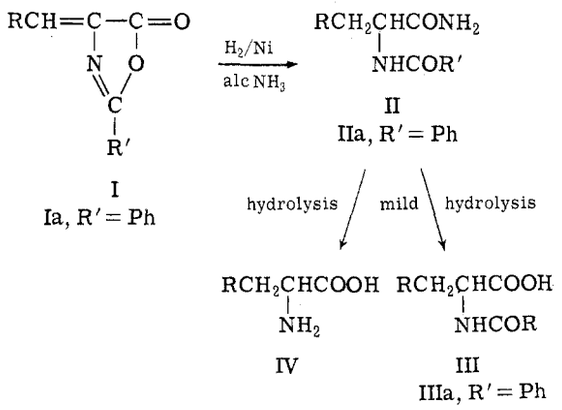

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TABLE I

DL-*N*-BENZOYLAMINO ACID AMIDES

Registry no.	Compd	Hydrogen pressure, psi	Hydrogenation time, hr	Mp, °C	Yield, %
24250-72-4	DL-*N*-Benzoylphenylalanine amide	50	9	197–198	95
34996-77-5	DL-*N*-Benzoyl-*O*-methyltyrosine amide[a,b]	37.5	15	215–216	77.5
34996-78-6	DL-*N*-Benzoyl-3,4-dimethoxyphenylalanine amide[a]	42	3	195–196	78
34996-79-7	DL-*N*-Benzoyltyrosine amide	40	16	238–239	100
34996-80-0	DL-*N*-Benzoyl-3-methoxy-4-hydroxyphenylalanine amide[a]	55	8	209–210	83.5
34996-81-1	DL-*N*-Benzoyl-δ-phenylnorvaline amide[a,c]	52	5	160–161	75
34996-82-2	DL-*N*-Benzoyl-β-furylalanine amide[a,c]	45	5	198–199	74
34996-83-3	DL-*N*-Benzoylvaline amide	39	9	220–221	84
34996-84-4	DL-*N*-Benzoylisoleucine amide	53	4.5	215–216	72.6
34996-85-5	DL-*N*-Benzoylnorleucine amide	37	2	143–144	76
24250-71-3	DL-*N*-Benzoylleucine amide	32	1	171–172	74
34996-87-7	DL-*N*-Benzoylnorvaline amide[a]	41.5	3	180–181	75

[a] Compounds reported for the first time. [b] This was sparingly soluble in hot ethanol and was dissolved in glacial acetic acid for separation from the catalyst and for crystallization. [c] These were soluble in ethanol and no prior heating was required for separation from the catalyst.

TABLE II

DL-*N*-BENZOYLAMINO ACIDS

Registry no.	Compd	Hydrolyzing agent[a]	Time, hr	Mp, °C	Yield, %
2901-76-0	DL-*N*-Benzoylphenylalanine	A	18	184–185	98.8
34996-89-9	DL-*N*-Benzoyl-*O*-methyltyrosine	A	16	175–176	75
34996-90-2	DL-*N*-Benzoyl-3,4-dimethoxyphenylalanine[b]	A	16	180–181	95
34996-91-3	DL-*N*-Benzoyltyrosine	A	16	194–195	89
2901-78-2	DL-*N*-Benzoyl-3-methoxy-4-hydroxyphenylalanine	A	14	162–163	70
34996-93-5	DL-*N*-Benzoyl-δ-phenylnorvaline	A	12	191–192	90
34996-94-6	DL-*N*-Benzoyl-β-furylalanine	B		162–163	80
2901-80-6	DL-*N*-Benzoylvaline	A	15	147–148	89
2901-99-7	DL-*N*-Benzoylisoleucine	A	16	135–136	95
34337-14-9	DL-*N*-Benzoylnorleucine	A	12	135–136	80
17966-67-5	DL-*N*-Benzoylleucine	A	16	138	83
34337-10-5	DL-*N*-Benzoylnorvaline	A	12	151–152	85

[a] A = Hydrochloric acid (36%); B = sodium hydroxide (30%). [b] Compound reported for the first time.

TABLE III

DL-AMINO ACIDS

Registry no.	Compd	Hydrolyzing agent[a]	Reflux time, hr	Mp, °C	Yield, %
150-30-1	DL-Phenylalanine	A	5	274–275 dec	90
7635-29-2	DL-*O*-Methyltyrosine	A	4	264–265 dec	76
33522-62-2	DL-3,4-Dimethoxyphenylalanine	A	6	241–242 dec	84
556-03-6	DL-Tyrosine	A	5	306–307 dec	88
4214-13-5	DL-3-Methoxy-4-hydroxyphenylalanine	A	6	245–246 dec	80
34993-02-7	DL-δ-Phenylnorvaline[b]	B	24	239–240 dec	96
4066-39-1	DL-β-Furylalanine[c]	C	24	256–257 dec	73
516-06-3	DL-Valine	A	1.5	291–292 dec	100
443-79-8	DL-Isoleucine	A	2	270–271	90
616-06-8	DL-Norleucine	A	4	284–285 dec	85
328-39-2	DL-Leucine	A	3	286–287 dec	88
760-78-1	DL-Norvaline	A	2	284–285	82

[a] A = Hydrochloric acid (36%); B = sodium hydroxide (30%); C = barium hydroxide (16%). [b] Obtained from the corresponding *N*-benzoylamino acid amides by refluxing with sodium hydroxide (30%) for 24 hr. [c] Obtained from the corresponding amide by refluxing with barium hydroxide (16%) for 24 hr.

The resulting acylamino acid amide (II) could then be hydrolyzed either to acylamino acid (III) or to the desired amino acid (IV) by mild or stringent treatment with acid or alkali.

In all, 12 amino acids were synthesized and, as evident from the tables given in the Experimental Section, the yields were either comparable to or substantially better than those obtained by existing methods.

Experimental Section

Satisfactory analyses were obtained for all the reported compounds. Melting points (of the analytically pure compounds whose yields are given in the tables) were taken on a Gallen-Kamp melting point apparatus in open capillaries and are uncorrected. The general procedure reported below was adopted in each case with slight modifications which are indicated as footnotes in the appropriate table. Yields are reported for analytically pure samples. All other similar compounds were prepared more or less by the same general procedure.

Raney Nickel Catalyst.—The catalyst was prepared in 5- to 15-g lots using the procedure given in "Organic Syntheses"[8] with the following modifications. Addition of nickel–aluminum alloy (50:50) (BHD) to the sodium hydroxide solution was conducted at room temperature (25–30°) and was completed within 20 min, during which time the temperature rose to 90°. Stirring was continued for another 10 min, and the reaction continued directly at steam bath temperature for another 1–2 hr, when evolution of hydrogen stopped. Catalyst thus obtained could be used for three successive runs without appreciable loss in activity.

Acylamino Acid Amides.—Azlactone[9] either in solution or in the form of a suspension (0.025 mol) in ethanol (95%) and ammonia (0.5 mol) catalyst (3 g) was hydrogenated in a Parr hydrogenation apparatus at 32–55 psi for 1–16 hr. Completion of hydrogenation could be read off the gauge provided with the hydrogenation flask and was further marked in most cases either by change in color (*e.g.*, colored to colorless) or by the formation of a flocculent white precipitate. In case of precipitation, which occurred with benzoylphenylalanine amide, benzoyl-3,4-dimethoxyphenylalanine amide, benzoyl-*O*-methyltyrosine amide, benzoyltyrosine amide, and benzoyl-3-methoxy-4-hydroxyphenylalanine amide, the contents were heated to dissolve the amide before filtration of the catalyst. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue thus obtained was crystallized from ethanol (95%).

Reduction of the azlactones of aliphatic aldehydes and ketones generally required less time (1–9 hr) than that of the aromatic ones. Most amides were purified by recrystallization from ethanol (95%), and some aliphatic amides were crystallized from aqueous ethanol (30–80%) (Table I).

***N*-Benzoylamino Acid.**—The above benzoylamino acid amides were converted into the corresponding *N*-benzoylamino acids by heating on a boiling water bath or a sand bath with hydrochloric acid (36%) till complete dissolution occurred. The required benzoylamino acid crystallized out on keeping the reaction mixture overnight. A single recrystallization from ethanol gave an analytically pure sample (Table II).

Amino Acid.—Amino acids were obtained directly from *N*-benzoylamino acid amides by heating them at reflux temperature with hydrochloric acid (36%) for different lengths of time (1.5–6 hr). The amino acid hydrochlorides so obtained were treated with silver oxide, which made isolation of the free amino acids smooth and quantitative (Table III).

Acknowledgment.—We are indebted to Dr. S. M. F. Rahman, Head of the Department, for providing research facilities. One of us (A. B.) is thankful to the University Grants Commission, New Delhi, India, for financial aid.

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C-3 Nucleophilic Substitution of 3-Azetidinyl Tosylates. Alkylation

ROBERT H. HIGGINS AND NORMAN H. CROMWELL*[1]

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

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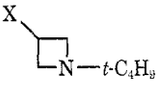
Recently several new 1-*tert*-butylazetidines have been prepared from 1-*tert*-butylazetidines possessing a replaceable functional group at the 3 position. Ohta, *et al.*, reported that 1-*tert*-butyl-3-azetidinyl tosylate reacts with amines and mercaptides to yield 3-aminoazetidines and 3-azetidinyl thioethers, respectively.[2] Gaertner[3] reported that chloroazetidine **2** gives the same results on reaction with these reagents and reacts with alcoholic solutions of alkali metal alkoxides to yield 1-*tert*-butyl-3-alkoxyazetidines. To date, however, the only reported C–C bond forming reaction at C-3 involves the reaction of **1**[2,4] or **2**[3] with cyanide yielding cyanoazetidine **3**. The rate of the reaction



1, X = OTs
2, X = Cl
3, X = CN

of **1** with potassium cyanide in methanol has been shown to be independent of cyanide concentration,[4] which, along with the solvolysis rate data for **1**[4] and the observation that *cis*- and *trans*-1-*tert*-butyl-2-methyl-3-azetidinyl tosylates undergo hydrolysis with stereospecific retention of configuration,[5] seems indicative of an intermediate 1-azabicyclo[1.1.0]butonium ion in the reaction with cyanide and in the solvolysis reactions[4–6] of azetidinyl tosylates.

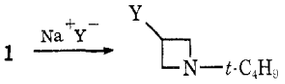
As a continuation of our investigations into the chemistry of functionally substituted azetidines, we have allowed **1** to react with the sodio derivatives of several active methylene compounds. It can be seen from the data in Table I that when the reaction proceeds

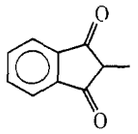
TABLE I
PER CENT YIELDS OF ALKYLATED AZETIDINES OBTAINED FROM THE REACTION OF 1 WITH SODIO DERIVATIVES OF ACTIVE METHYLENE COMPOUNDS

Compd	Solvent	% Alkylation[a]	Solvent	% Alkylation
4	MeOH	0.0	Et_2O	0.0
5	EtOH	11		
6	EtOH	39	Et_2O[b]	~0[c]
7	EtOH	67	Et_2O[b]	8–9[c]

[a] Isolated yield. [b] Contains 1 equiv of ethanol. [c] Per cent of crude azetidinyl product by pmr.

in alcoholic solvent, the yield of alkylated product is significantly better than when the reaction is conducted in ether solvent. Since the reactions in the different solvents were conducted for essentially the same period of time, it may be surmised that the reactions in ether





4, Y =

5, Y = $CN(CO_2Et)CH$
6, Y = $(CO_2Et)_2CH$
7, Y = $Ac(CO_2Et)CH$

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