TABLE I
ESTIMATION OF THE MAGNITUDE OF ANCHIMERIC ASSISTANCE BY THE METHOD OF REFERENCE 5a

No.	Tosylate	Ketone[a] ν_{CO}, cm.$^{-1}$	ϕ, deg.	GS − TS, kcal. nonbonded	log rel. rate Calcd.	log rel. rate Obsd.[a]	log anch. assistance
	(a) Anchimeric assistance > 10^2						
1	*anti*-8-Dicyclopentadienyl	1780	60,60	0.3	−8.8[b]	4.33	13.1
2	*anti*-7-Norbornenyl	1780	60,60	0.3	−8.8[b]	4.11	12.9
3	7-Dibenznorbornadienyl	1792	60,60	0.1	−11.3[b]	−0.79	10.5
4	*anti*-7-Benznorbornenyl	1792	60,60	0.3	−10.3[b]	−1.22	9.1
5	7-Quadricyclyl	1746[c]	60,60	0.0	−4.9	3.31[d]	8.2
6	3-Nortricyclyl	1762	60,60	0.3	−6.2[b]	1.82	8.0
7	*anti*-8-Bicyclo[3.2.1]oct-2-enyl	1758[e]	60,60	0.2	−6.1[b]	−0.13[e]	6.0
8	7-*syn*-Norbornenyl	1780	60,60	0.1	−8.9[b]	−3.28	5.6
9	Cyclobutyl	1791	0,0	0.0	−4.2	0.99	5.2
10	*exo*-2-Benznorbornenyl	1756	0,45	0.3	−2.8[b]	1.63	4.4
11	*exo*-8-Bicyclo[3.2.1]octyl	1752	60,60	0.3	−4.4	−0.21	4.2
12	*exo*-2-Norbornenyl	1745	0,45	0.3	−1.4[b]	2.42	3.8
13	Cholesteryl	1721	60,60	0.0	−1.7[b]	2.01	3.7
14	*exo*-2-Bicyclo[2.2.2]oct-5-enyl	1735	0,60	0.4	0.5[b]	4.10	3.6
15	*exo*-2-Norbornyl	1751	0,40	0.3	−0.6	2.71	3.3
16	*endo*-2-Bicyclo[2.2.2]oct-5-enyl	1735	0,60	0.1	−0.7[b]	2.49	3.2
17	2-Bicyclo[2.1.1]hexyl	1764[f]	0,60	0.2	−3.3	−0.37[g]	2.9
18	Epicholesteryl	1721	60,60	0.4	−1.4[b]	1.40	2.8
	(b) Anchimeric assistance < 10^2						
19	Cyclopropyl	1815	0,0	0.0	−7.2	−5.32	1.9
20	9-Bicyclo[3.3.1]nonyl	1726	60,60	0.6	−1.0	0.48	1.5
21	*exo*-Trimethylenenorborn-*exo*-2-yl	1751	0,40	0.3	−0.6	0.84[h]	1.4
22	*cis*-3-Bicyclo[3.1.0]hexyl	1739[i]	0,40[j]	0.0	−0.2[b]	1.14[i]	1.3
23	*axial*-2-Bicyclo[3.2.1]octyl	1717	50,60	0.6	0.4	1.62	1.2
24	2-Bicyclo[2.2.2]octyl	1731	0,60	0.4	0.9	1.85	0.9
25	*equat.*-2-Bicyclo[3.2.1]octyl	1717	50,60	0.2	0.1	0.47	0.4
26	*trans*-3-Bicyclo[3.1.0]hexyl	1739[i]	0,40[j]	0.6[i]	0.2[b]	0.17	0.0
27	*syn*-8-Bicyclo[3.2.1]oct-2-enyl	1758[e]	60,60	1.1	−5.5	−5.54[g]	0.0
28	Cyclooctyl	1703	40,40?[k]	0.0?	2.8	2.76	0.0
29	Cyclononyl	1703	40,40?[k]	0.0?	2.8	2.70	−0.1
30	Cyclodecyl	1704	40,40?[k]	0.0?	2.7	2.98	+0.3
31	Cycloundecyl	1709	40,40?[k]	0.0?	2.1	2.05	0.0

[a] Data, unless otherwise indicated, taken from Foote.[5b] [b] Corrections for inductive effects: −0.9 in log k for each double bond or phenyl ring and −0.5 in log k for each cyclopropane ring β to the reaction site.[5a] [c] P. R. Story and S. R. Fahrenholtz, *J. Am. Chem. Soc.*, **86**, 1270 (1964). [d] H. G. Richey, Jr., and N. C. Buckley, *ibid.*, **85**, 3057 (1963); P. R. Story and S. R. Fahrenholtz, *ibid.*, **86**, 527 (1964). [e] N. W. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964). [f] Value for 5,5-dimethylbicyclo[2.1.1]hexan-2-one (J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **85**, 57 (1963)). [g] At 75° (J. Meinwald, Abstracts, 18th National Organic Chemistry Symposium, American Chemical Society, Columbus, Ohio, June, 1963, p. 39). [h] See ref. 2b. [i] S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961). [j] Our experience [M. M. Donaldson, Ph.D. Thesis, Princeton University, 1958; *Dissertation Abstr.*, **22**, 738 (1961)] with locked cyclopentane rings suggests this estimate. [k] J. Sicher in P. B. D. De la Mare and W. Klyne, Ed., "Progress in Stereochemistry," Vol. 3, Butterworths, London, 1962, Chapter 6; V. Prelog and J. G. Traynham in P. de Mayo, "Molecular Rearrangements," Vol. 1, Interscience Publishers, Inc., 1963, Chapter 9.

more nearly comparable with classical ions.[6] Compounds **25–31** have no significant anchimeric assistance and the data do not require the formulation of bridged intermediates. Further implications of this treatment will be discussed in the full report.

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(6) See Table I*i*, and ref. 4b, f, and g with regard to compounds **22**, **23**, and **24**.

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Reactions in Strong Acids. II.[1] New Concept in Amino Acid Chemistry: C-Derivatization of Amino Acids[2]

Sir:

In an extension of the results discussed in the first paper of this series,[1] a new type of amino acid chemistry has been established. The chemistry of amino acids (I), as presently known, consists of transformations of functional groups already present in these molecules[3];

their (intact) hydrocarbon moities (R) have not been subjected to chemical reactions.[4] The reason for this is obviously the high reactivity of the functional groups, relative to the inertness of the hydrocarbon chain. In principle, free-radical-type reagents would be expected to overcome this inertness, provided that

(1) Part I: J. Kollonitsch, V. Verdi, M. Boskin [Reactions in Strong Acids. I. Side-Chain Chlorination of Alkylpyridines and Alkylthiazoles in Concentrated Sulfuric Acid], submitted to *Tetrahedron Letters*.

(2) Presented in part at the XIXth International Congress of Pure and Applied Chemistry, London, July 10–17, 1963.

(3) See Greenstein and Winitz, "Chemistry of Amino Acids," Vol. 1–3, John Wiley and Sons, Inc., New York, N. Y., 1961; also Th. Wieland, *et al.*, in E. Muller, Ed., "Methoden der Organischen Chemie," (Houben-Weyl), 4th Ed., Vol. XI/2, Thieme Verlag, Stuttgart, 1958, p. 321.

(4) Irradiation of amino acid solutions by high-energy radiation (X-ray, ultraviolet light, etc.), long known only to degrade amino acids,[3] recently was used to induce complex cleavages leading to rearrangement of the C-skeletons [G. Ferrari and R. Cultrera, *Nature*, **190**, 326 (1961)].

their attack on the functional groups, including the CH group bearing them, could be prevented.

We found that by *protonating* glycine (0.5 mole) by dissolving it in 1.5 moles of 100% sulfuric acid, it became protected against the action of chlorine atoms, as it was recovered in better than 90% yield after passing chlorine through this solution for 2 hr. at 65°, while being irradiated with a powerful ultraviolet light source.[5,6] Other strong acids, such as chlorosulfonic acid, trifluoroacetic acid, and concentrated hydrochloric acid, provided similar protection. These results suggested the attempt to C-chlorinate the amino acids in strong acid solution. After discovering the proper conditions, surprisingly selective reactions were achieved.

D,L-Ornithine hydrochloride (0.25 mole) dissolved in 150.4 g. of 90% sulfuric acid (1.25 moles; chlorosulfonic acid or trifluoroacetic acid can be substituted) was irradiated by ultraviolet light[7] while chlorine gas was introduced under vigorous stirring for a period of 1 hr. at 75–80°. After degassing *in vacuo*, the product was hydrolyzed in water containing silver sulfate. After removal of the Ag^+ ion, a sample was analyzed by the Beckman Spinco automatic amino acid analyzer (Spackman–Moore–Stein method).[8] This showed, in addition to 35% of unreacted ornithine, the presence of γ-hydroxyornithine (II, 45% yield, based on ornithine transformed). Benzoylation (Schotten–Bauman), followed by lactonization, gave N,N′-dibenzoyl-γ-hydroxy-DL-ornithine lactone, m.p. 232–233°, infrared (pyridine) γ-lactone carbonyl at 1778 $cm.^{-1}$.[9] *Anal.* for $C_{19}H_{18}N_2O_4$. Found: C, 67.44; H, 5.64; N, 8.05.

L-Lysine hydrochloride (1 mole), dissolved in concentrated hydrochloric acid (600 ml.) was chlorinated at 70° for 2 hr. (ultraviolet irradiation). At 80% conversion, the yield of γ-chloro-L-lysine was 74% of theory (on the basis of the Beckman Spinco analysis of the hydrolyzed product). γ-Chloro-L-lysine dihydrochloride (III, 48 g.) crystallized directly from the chlorination mixture, and a further 20 g. was recovered from the mother liquors, m.p. 198–202° dec., $[\alpha]_D$ +23° (*c* 2, 6 *N* HCl). *Anal.* for $C_6H_{15}N_2O_2Cl_3$. Found: C, 28.59; H, 5.70; N, 10.83; Cl, 41.84. No detectable amount of the diastereoisomeric chloroamino acids was formed either in the case of ornithine or lysine. Hydrolysis of III (silver acetate) gave 66% of γ-hydroxy-L-lysine (IV), a new hydroxydiaminomonocarboxylic acid,[10] HCl salt, m.p. 203–204° dec., $[\alpha]_D$ −6.6° (*c* 2, H_2O). *Anal.* for $C_6H_{15}N_2O_3Cl$. Found: C, 36.34; H, 7.24; N, 14.04; Cl, 17.78. The proton magnetic resonance spectrum of IV agreed with the assigned structure. Alanine, on chlorination in 100% sulfuric acid, gave β-chloroalanine in 78% yield (conversion 55%). In concentrated hydrochloric acid, this amino acid is completely unreactive to chlorination. In contrast, α-aminobutyric acid, dissolved in concentrated hydrochloric acid, was rapidly chlorinated to a mixture of β- and γ-chloro derivatives, in the ratio of 1:3. Analytically pure γ-chloro-α-aminobutyric acid hydrochloride[11] crystallized from the reaction mixture in a yield of 40%; acid hydrolysis gave homoserine.

TABLE I

DIRECTIVE EFFECTS ON THE CHLORINATION OF L-GLUTAMIC ACID (GA)

Solvent per mole of GA	β-Chloro-GA, yield, %[a,b]	γ-Chloro-GA, yield, %[a,c]
3 moles of 90% H_2SO_4	49	38
10 moles of 100% H_2SO_4	70	21
6 moles of $ClSO_3H$	71	25
GA anhydride in 3 moles of $ClSO_3H$	8	82

[a] Conversion of GA 50–80%. [b] On the basis of analysis by the Beckman Spinco automatic amino acid analyzer, corroborated by specific chemical assay and isolation. [c] Based on Beckman Spinco analysis, after hydrolysis to γ-hydroxy-L-glutamic acid (both the *erythro* and *threo* isomers were formed).[12]

Table I lists the results obtained on ultraviolet light-catalyzed chlorination of L-glutamic acid; these results show new ways for influencing the selectivity of free radical chlorinations. β-Chloro-L-glutamic acid (V), m.p. 141° dec., $[\alpha]_D$ +17° (*c* 2, 6 *N* HCl). *Anal.* for $C_5H_8NO_4Cl$. Found: C, 33.51; H, 4.78; N, 7.45; Cl, 19.48. On ammonolysis, V gave a new diaminodicarboxylic acid, β-amino-L-glutamic acid (VI), m.p. 235° dec., $[\alpha]_D$ +43° (*c* 1, 6 *N* HCl). *Anal.* for $C_5H_{10}N_2O_4 \cdot H_2O$. Found: C, 33.55; H, 6.40; N, 15.21. Proton magnetic resonance spectra of V and VI conformed with the assigned structures.[13]

The selectivities observed in these chlorinations are explainable by polar and novel solvent effects,[14] or by a combination of both.

Analogous transformations were carried out with other amino acids. Since many amino acids are commercially available, the above-described transformations open a route to the simple preparation of hundreds of new or known C-substituted amino acid derivatives. Up to this time, these types of compounds had to be synthesized by laborious methods which also required an optical resolution.[15] The ready availability of the C-derivatized amino acids offers a new opportunity for the correlation of biochemical, pharmacological, and nutritional properties of amino acids with their chemical structure.[16]

Further applications of these methods are being pursued.

(5) High-pressure mercury arc lamps (450 w., Hanovia 59A 36) were used throughout this work. The lamps (2) were mounted in the focus of paraboloid reflectors. Quartz flasks were used for the irradiations (in Pyrex the reaction rates were lower).

(6) In the first paper of this series[1] we showed that similar protonation exerted a protecting action on the pyridine and thiazole nuclei.

(7) In some of the cases studied, catalysis by 2–4% azobisisobutyronitrile or azobisisobutyroamidinium hydrochloride gave identical results.

(8) The authors thank Mr. R. M. Redfield of these Laboratories for performing the analyses.

(9) N. Izumiya and B. Witkop, *J. Am. Chem. Soc.*, **85**, 1835 (1963); B. Witkop and T. Beiler, *ibid.*, **78**, 2882 (1956).

(10) Concerning its naturally-occurring relative, γ-hydroxy-L-homoarginine see E. A. Bell, *Nature*, **199**, 70 (1963).

(11) M. Frankel and Y. Knobler, *J. Am. Chem. Soc.*, **80**, 3147 (1958).

(12) L. Benoiton, M. Winitz, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **79**, 6192 (1957); E. E. Dekker, "Biochemical Preparations," M. J. Coon, Ed., Vol. 9, John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 69, 74; E. Adams and A. Goldstone, *Biochim. Biophys. Acta*, **77**, 133 (1963).

(13) The authors thank Mr. B. Arison and Dr. N. Trenner for the p.m.r. spectra.

(14) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 2977 (1957); **80**, 4987, 4997, 5002 (1958).

(15) No sign of racemization was detected in the chlorinated amino acids.

(16) For reviews discussing hydroxylated and other C-derivatized amino acids see: ref. 3; B. Tscierch and K. Mothes, "Comparative Biochemistry," Florkin and Mason, Ed., Vol. V, Part C, Academic Press, New York, N. Y., 1963, pp. 1–90; Th. Wieland, *Angew. Chem.*, **72**, 892 (1960); W. Shive and C. G. Skinner, "Metabolic Inhibitors," R. M. Hochster and J. H. Quastel, Ed., Vol. I, Academic Press, New York, N. Y., 1963, pp. 2–73.

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