TABLE I

PHYSICAL DATA FOR AMINOBENZO[a]CYCLOALKANO[f]-QUINOLIZINIUM PERCHLORATES VI–VIII

Compd	VI	VII	VIII
Mp, °C	239 dec	252–254 dec	259–260 dec
λ_{max}^{EtOH}, mμ (ε)	346 (17,850)	353 (17,600)	353 (16,590)
λ^{Nujol}, μ	2.95, 3.07, 6.00, 6.13, 6.54	2.95, 3.08, 6.02, 6.29, 6.68	2.95, 3.03, 6.03, 6.22, 6.68
% yield	65	95	55
C, %			
Calcd	54.21	55.28	56.27
Found	53.93	55.07	56.42
H, %			
Calcd	5.81	6.10	6.38
Found	5.93	6.28	6.45
N, %			
Calcd	7.02	6.78	6.56
Found	7.03	6.89	6.58
Cl, %			
Calcd	8.89	8.59	8.30
Found	8.89	8.48	8.08

gathered by hydrolysis to the known enamino ketones (IX–XI).

Experimental Section

All melting points are corrected. Infrared and ultraviolet spectra were taken on Beckman IR-5 and DB instruments, respectively. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-(Cyanomethyl)-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II). A. N-(2,3-Dimethoxyphenethyl)cyanacetamide.—A solution of 24.5 g of 2-(2,3-dimethoxyphenyl)ethylamine[8] and 90 ml of ethyl cyanacetate was heated at 115–120° for 20 hr under a slow stream of nitrogen. The excess cyanoacetic ester was removed *in vacuo* leaving a crystalline residue. Recrystallization from ether–chloroform gave 27 g (80%) of the amide: mp 94–95°; λ^{CHCl_3} 2.88, 2.96, 4.42, 5.93, 6.32, 6.60, 6.78, 6.94 μ; nmr ($CDCl_3$), τ 2.83–3.35, (multiplet, aromatic and amide, 4 H), 6.15 (singlet, methoxyls, 6 H), 6.35–6.75 (multiplet, CH_2NHCO-CH_2CN, 4 H), 7.0–7.30 (triplet, benzylic, 2 H).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.72; H, 6.65; N, 11.50.

B. 1-(Cyanomethyl)-5,6-dimethoxy-3,4-dihydroisoquinoline.—To a refluxing solution of 27 g of N-(2,3-dimethoxyphenethyl)-cyanoacetamide in 450 ml of dry toluene was added, in three portions, 90 g of phosphorus pentoxide. The reaction mixture was stirred and refluxed for 1.5 hr after which it was cooled to −10° and decomposed with 750 ml of ice water. The aqueous layer was separated and the organic layer was extracted several times with dilute hydrochloric acid. The acid solution was neutralized with 40% sodium hydroxide and the solvent was removed to yield 10 g (40%) of the dihydroisoquinoline: mp 200–202°; λ_{max}^{EtOH} 329, 272 mμ; λ^{CHCl_3} 2.90, 4.56, 6.20, 6.40, 6.85 μ. A neutral portion on evaporation gave 14 g of the starting cyanoacetamide mp 93–94°.

C. 1-(Cyanomethyl)-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline.—A solution of 10 g of the above dihydroisoquinolinenitrile in 130 ml of acetic acid, containing 300 mg of platinum oxide was hydrogenated at 53 psi at room temperature for 20 hr. The catalyst was removed and the residue was dissolved in ice water, neutralized with potassium carbonate, and extracted with chloroform. The chloroform extract was washed with water and dried (sodium sulfate) and the solvent was removed to give a dark oil. The latter was dissolved in chloroform–ether (1:4) and filtered through alumina (30 g). Removal of solvent gave a solid which was recrystallized from dry ether as white flakes: yield, 6.8 g; nmr ($CDCl_3$), τ 3.18 (singlet, aromatic, 2 H), 5.50–5.82 (triplet, CHNH, 1 H), 6.18, 6.21 (singlets, methoxy, 3 H each), 6.77–7.30 (multiplet, methylenes, 6 H), 8.0 (broad singlet, NH, 1 H) exchangeable with D_2O.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.02; H, 6.87; N, 12.18.

(8) A. Lindenmann, *Helv. Chim. Acta*, **32**, 69 (1949).

7-Amino-3′,4′-dimethoxybenzo[a]cycloalkano[f]-1,5,6,9-tetrahydroquinolizinium Perchlorates VI–VIII.—A solution of 5 mmoles of the isoquinolinyl acetonitrile (II) in a tenfold excess of cycloalkanone and 20 ml of toluene containing a few crystals of *p*-toluenesulfonic acid was treated with 5.5 mmoles of anhydrous magnesium perchlorate and the mixture was refluxed under nitrogen for 40 hr. At the end of this period the crystalline magnesium perchlorate was transformed to an amorphous powder. The cold reaction mixture was shaken with 15 ml of a saturated solution of ammonium chloride and 5 ml of 40% sodium hydroxide solution at which time either a crystalline or a gummy solid separated. The solid was washed thoroughly with water and then with chloroform and dried. The crude product was recrystallized from anhydrous methanol.

Benzo[a]cycloalkano[f]quinolizinones IX–XI.—A mixture of 0.5 mmole of the 7-aminobenzo[a]cycloalkano[f]-1,5,6,9-tetrahydroquinolizinium perchlorates (VI–VIII) and 10 ml of 10% aqueous methanolic (1:3) sodium hydroxide solution was refluxed for 1.5–2.0 hr at which time a clear solution was obtained. Methanol was evaporated under reduced pressure and the residue was diluted with water, filtered, and washed thoroughly with water and dried. The product was sufficiently pure that, on admixture with authentic samples,[4] melting points were undepressed. The yields of IX–XI were 85–91%.

Registry No.—N-(2,3-Dimethoxyphenethyl)cyanacetamide, 7634-84-6; 1-(cyanomethyl)-5,6-dimethoxy-3,4-dihydroisoquinoline, 7634-85-7; II, 7634-86-8; VI, 7634-87-9; VII, 7634-88-0; VIII, 7634-89-1.

An Intramolecular Curtius Reaction of Some Hydroxy Amino Acids

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A well-known complication in the synthesis of serine peptides from carbobenzoxyserine azide is the rearrangement of the azide to an oxazolidinone (I) through the intermediate isocyanate.[1,2] This undesirable side reaction is usually avoided by maintaining adequate cooling during the formation and subsequent initial reaction of the azide with an amine function. It became of interest to us to determine if the carbobenzoxy group could be removed from this compound and the resulting unknown 4-amino-2-oxazolidinone isolated and identified.

Cyclization was readily performed by allowing an ethyl acetate solution of carbobenzoxyserine azide to stand at room temperature for a few hours. Catalytic hydrogenation of the resulting oxazolidinone in ethanol solution using palladium on carbon rapidly removed the carbobenzoxy group and on standing the solution developed a strong odor of ammonia. A crystalline solid was isolated which gave strong bands at 1030, 1736, and 3356 cm^{-1} in the infrared. The absence of a band at 1550 cm^{-1} supported the view that the oxazolidinone structure was still intact.[3,4] Analysis indicated a condensation product minus 1 mole of ammonia. The structure postulated for the product, 4,4′-iminodi-2-oxazolidinone (II), was supported by the

(1) J. S. Fruton, *J. Biol. Chem.*, **146**, 463 (1942).

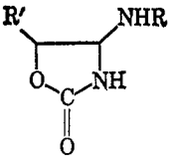
(2) E. Baer, J. Maurukas, and D. D. Clarke, *Can. J. Chem.*, **34**, 1182 (1956).

(3) S. Pinchas and D. Ben-Ishai, *Bull. Res. Council Israel Sect. A*, **6**, 166 (1957).

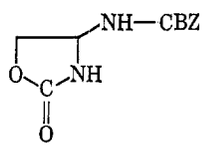
(4) H. K. Hall, Jr. and R. Zbinden, *J. Am. Chem. Soc.*, **80**, 6428 (1958).

TABLE I

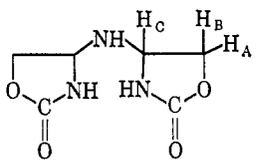
4-AMINO-2-OXAZOLIDINONES



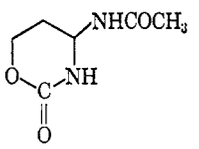
R	R′	Formula	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	CH_3	$C_4H_8N_2O_2 \cdot HCl$	141–145	81	31.48	5.95	18.37	31.91	6.02	18.08
Acetyl	H	$C_5H_8N_2O_3$	220	46	41.66	5.60	19.44	41.95	5.59	19.16
Acetyl	CH_3	$C_6H_{10}N_2O_3$	210–211	10	45.55	6.37	17.71	45.85	6.27	17.86
Carbobenzoxy	CH_3	$C_{12}H_{14}N_2O_4$	141–142	75	57.59	5.64	11.20	57.86	5.55	11.12
Carbobenzoxy		$C_{17}H_{16}N_2O_4$	164–165	89	65.41	5.17	8.97	65.35	5.10	8.90
Dichloroacetyl		$C_{11}H_{10}N_2O_3Cl_2$	219–220	68	45.70	3.47	9.69	45.85	3.65	9.66
Benzoyl		$C_{16}H_{14}N_2O_3$	215–216	85	68.07	5.00	9.92	68.29	5.09	10.11
Acetyl		$C_{11}H_{12}N_2O_3$	158–160	65	60.00	5.49	12.72	59.98	5.73	12.35



I



II



III

nmr spectrum. In deuteriodimethyl sulfoxide a poorly resolved series of bands between δ 3.9 and 5.1 was obtained. Addition of a small amount of deuterium oxide then gave a typical ABC pattern. The H_A proton was a quartet at about δ 4.05, two bands being obscured by the water peak. The H_B proton was a triplet at δ 4.5 and the H_C proton was a quartet at δ 4.95. The J_{AB} and J_{BC} coupling constant was about 8 cps and the J_{AC} coupling was 4 cps which was reasonable for this type of system. Incorporation of hydrogen chloride in the hydrogenation mixture of the carbobenzoxyoxazolidinone in an effort to stabilize the amine function was not successful. A white solid was obtained from the reaction mixture on standing which melted about 300° and was presumed to be ammonium chloride. The mother liquors yielded the condensation product previously isolated.

The stability of other 4-amino-2-oxazolidinones was investigated. Hydrogenolysis in ethanolic hydrogen chloride of the carbobenzoxy group from the oxazolidinone obtained from carbobenzoxy-DL-threonine azide gave 4-amino-5-methyl-2-oxazolidinone as its hydrochloride salt. The nmr spectrum gave a doublet at δ 1.55 and bands at 5.0, 5.15, 5.25, 5.35, and 5.45. This product was believed to be the *trans* isomer. During the preparation of the carbobenzoxy oxazolidinone two products were obtained. The high-melting isomer showed a doublet for the methyl group at δ 1.25 and a quartet at 4.7 for the proton split by the methyl protons. The low-melting isomer was found to be a mixture of isomers. Two doublets at δ 1.25 and 1.35 were obtained and a quartet at 4.50. Repeated recrystallization would not separate this mixture. The high-melting isomer was assigned the *trans* configuration because of its chemical characteristics and the downfield shift of the proton quartet. The pure isomer only was used in the hydrogenation study. It is probable that the *cis* isomer had it been obtained pure would not have been stable after hydrogenation even in the presence of hydrogen chloride. Hydrogenation of the *trans* isomer without incorporation of acid resulted in an oil which partially solidified on standing. From this mixture was isolated a small amount of white solid which analyzed for the condensation product 5,5′-dimethyl-4,4′-iminodi-2-oxazolidinone. Several other oxazolidinones which were prepared are listed in Table I.

Cyclization of acetyl-DL-homoserine azide was found to produce 4-acetamidotetrahydro-2H-1,3-oxazin-2-one (III) in poor yield. The infrared spectrum showed bands at 1740 and 1705 cm^{-1} for the cyclic carbamate structure.[4] γ-Hydroxy azides usually revert to the cyclic lactones through loss of hydrazoic acid.[5] The anticipated band at 1755 cm^{-1} for the 5-ring lactone was not observed in the product isolated but it is possible that the lactone was present in the by-products which were not investigated.

Experimental Section[6]

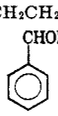
2-Oxo-4-oxazolidinecarbamic Acid Benzyl Ester.—To a cold solution (0°) of 20 g (0.08 mole) of carbobenzoxy-L-serine hydrazide in 12 ml of glacial acetic acid, 9 ml of concentrated HCl and 200 ml of water was slowly added 6 g of sodium nitrite in 20 ml of water. The mixture was extracted with 250 ml of cold ethyl acetate and the ethyl acetate solution was washed with ice–water and cold, 5% $NaHCO_3$ solution and dried. The solution was allowed to stand at 25° for 18 hr. During the first hour a large amount of gas was evolved. The solution was evaporated

(5) P. A. S. Smith in *Org. Reactions*, **3**, 351 (1946).

(6) Melting points were taken with a Thomas–Hoover capillary melting point apparatus and are corrected. The nmr spectra were obtained using a Varian A-60 with tetramethylsilane as an internal standard.

TABLE II
SUBSTITUTED HYDRAZIDES

R'CHCONHNH$_2$
|
NHR

R	R'	Formula	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Acetyl-L	CH_2OH	$C_5H_{11}N_3O_3$	178–179	68	37.26	6.88	26.08	37.39	6.92	26.08
Acetyl-DL	CHOH CH_3	$C_5H_{13}N_3O_3$	212–213	74	41.14	7.48	24.00	41.33	7.63	24.00
Acetyl	CH_2CH_2OH	$C_6H_{13}N_3O_3$	134–135	51	41.14	7.48	24.00	41.22	7.39	23.96
Dichloroacetyl[a]		$C_{11}H_{13}N_3O_3Cl_2$	181–182	60	43.16	4.28	13.73	43.17	4.57	13.55
Carbobenzoxy		$C_{17}H_{19}N_3O_4$	198–199	72	62.00	5.81	12.76	62.02	5.89	12.86
Benzoyl		$C_{16}H_{17}N_3O_3$	185–186	52	64.20	5.73	14.04	64.80	6.03	14.37
Acetyl		$C_{11}H_{15}N_3O_3$	202–203[b]	48	55.67	6.36	17.71	55.57	6.63	17.85

[a] The β-phenylserine used was DL-*threo*. [b] Reported mp 220°: G. Ehrhart, H. Nahm, and W. Seidel, U. S. Patent 2,745,875 (1956).

to one-third volume and ether was added giving white needles (13 g, 72%): mp 168–169° (lit.[1] mp 171°), $[\alpha]^{24}D$ −80° (*c* 2, ethanol).

4,4′-Iminodi-2-oxazolidinone.—A solution of 3 g (0.0127 mole) of the carbobenzoxy oxazolidinone in 200 ml of absolute ethanol was hydrogenated over 2 g of palladium on carbon for 2 hr. The catalyst was removed and the solution was allowed to stand at room temperature overnight. The odor of ammonia was evident. The solution was evaporated to a small volume and crystals appeared. Ether was added and the solid removed and dried (1 g, 42%), mp 136–137°.

Anal. Calcd for $C_6H_9N_3O_4$: C, 38.49; H, 4.85; N, 22.45. Found: C, 38.58; H, 4.96; N, 21.90.

2-Oxo-5-methyl-4-oxazolidinecarbamic Acid Benzyl Ester.—A solution of 17 g (0.0635 mole) of carbobenzoxy-DL-threonine hydrazide in 75 ml of glacial acetic acid and 34 ml of 2 *N* HCl was treated with 4.7 g (0.068 mole) of sodium nitrite in the manner described for carbobenzoxyserine hydrazide. The resulting ethyl acetate solution was allowed to stand at 25° overnight and was then concentrated to a small volume. Ether was added and 12 g of colorless solid was obtained. The solid was recrystallized from ethyl acetate–ether (7 g, 44%), mp 141–142°. The nmr spectrum in deuteriochloroform gave a doublet at δ 1.25, a quartet at 4.7, and single bands at 5.05 and 7.25.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.86; H, 5.55; N, 11.12.

The mother liquors from above were evaporated to a small volume and addition of petroleum ether (bp 35–60°) produced 5 g (31%) of colorless solid, mp 95–98°. Several recrystallizations from ethyl acetate–petroleum ether and ether–petroleum ether did not change the melting point. Thin layer chromatography on alumina using a variety of solvents gave one spot. The nmr spectrum in deuteriochloroform revealed a mixture to be present. Two doublets at δ 1.25 and 1.35 were found in addition to a quartet at 4.50 and single bands at 5.05 and 7.25.

Anal. Found: C, 57.69; H, 5.65; N, 11.25.

5,5′-Dimethyl-4,4′-iminodi-2-oxazolidinone.—A solution of 3 g (0.012 mole) of 2-oxo-5-methyl-4-oxazolidinecarbamic acid, benzyl ester, mp 141–142°, in 100 ml of absolute ethanol was hydrogenated over 1 g of palladium on carbon for 3 hr. The catalyst was removed and the filtrate was evaporated *in vacuo* below 20° to a clear oil. On standing overnight the oil partially solidified and trituration with methanol gave a white solid (0.5 g), mp 140–141°.

Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.59; H, 6.07; N, 19.71.

Preparation of Hydrazides.—For the preparation of the hydrazides listed in Table II, the following method was used. A suspension of 0.05 mole of the acyl or aroyl amino acid in 300 ml of methanol was saturated with HCl gas keeping the temperature below 30°. The resulting solution was allowed to stand for 18 hr and evaporated *in vacuo* to dryness, and the residue was re-treated with MeOH–HCl. The final residue was taken up in methanol, an excess of anhydrous hydrazine was added and the solution was allowed to stand overnight during which time a solid usually formed. The solid was removed, washed with water and dried.

Oxazolidinones.—The substituted oxazolidinones listed in Table I were prepared in the same manner as described for the 2-oxo-4-oxazolidinecarbamic acid benzyl ester.

4-Acetamidotetrahydro-2H-1,3-oxazin-2-one.—To a cold (0°) solution of 6 g (0.034 mole) of acetyl-DL-homoserine hydrazide in 25 ml of 2 *N* HCl was added 2.5 g of sodium nitrite in 5 ml of water. After 10 min the solution was extracted with cold ethyl acetate. The ethyl acetate solution was washed with ice–water and 5% $NaHCO_3$ solution and dried over $MgSO_4$. The filtered solution was kept at 25° overnight and then evaporated to an oil. Trituration with ether gave a white solid (1 g, 18.5%), mp 186–188°.

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.55; H, 6.37; N, 17.71. Found: C, 45.76; H, 6.25; N, 17.43.

Registry No.—$C_4H_8N_2 \cdot HCl$, 7705-80-8; $C_5H_8N_2O_3$, 7705-81-9; $C_6H_{10}N_2O_3$, 7705-82-0; $C_{12}H_{14}N_2O_4$; 7705-83-1; $C_{17}H_{16}N_2O_4$, 7705-84-2; $C_{11}H_{10}N_2O_3Cl_2$, 7705-85-3; $C_{16}H_{14}N_2O_3$, 7705-86-4; $C_{11}H_{12}N_2O_3$, 7705-87-5; $C_5H_{11}N_3O_3$, 7721-87-1; $C_6H_{13}N_3O_3$, 7705-75-1; $C_6H_{13}N_3O_3$, 7705-76-2; $C_{11}H_{13}N_3O_3Cl_2$, 7705-77-3; $C_{17}H_{19}N_3O_4$, 7705-78-4; $C_{16}H_{17}N_3O_3$, 7705-79-5; $C_{11}H_{15}N_3O_3$, 7721-88-2; 2-oxo-4-oxazolidinecarbamic acid benzyl ester, 7705-88-6; II, 7705-89-7; 2-oxo-5-methyl-4-oxazolidinecarbamic acid benzyl ester, 7705-90-0; 5,5′-dimethyl-4,4′-iminodi-2-oxazolidinone, 7721-89-3; III, 7705-91-1.

Acknowledgment.—The author is indebted to Mr. E. Schoeb and Mr. B. Scott for the infrared and nmr data and to Dr. G. Berchtold and Dr. Harry Crooks for many valuable discussions during the course of this investigation.