25787-55-7; **29**, 25787-56-8; **30**, 25787-57-9; **31**, 25791-57-5; **32**, 25791-58-6; **33**, 25791-59-7; **34**, 25791-60-0; 3-deoxy-3-methylamino-D-ribofuranose, 25791-61-1.

Acknowledgment.—We are indebted to Mr. Osborne P. Crews, Jr., and his staff for the large-scale preparation of intermediates and to Dr. Peter Lim and his staff for the spectra and paper chromatography.

2-Phenylaspartic Acid Derivatives from β-Lactams

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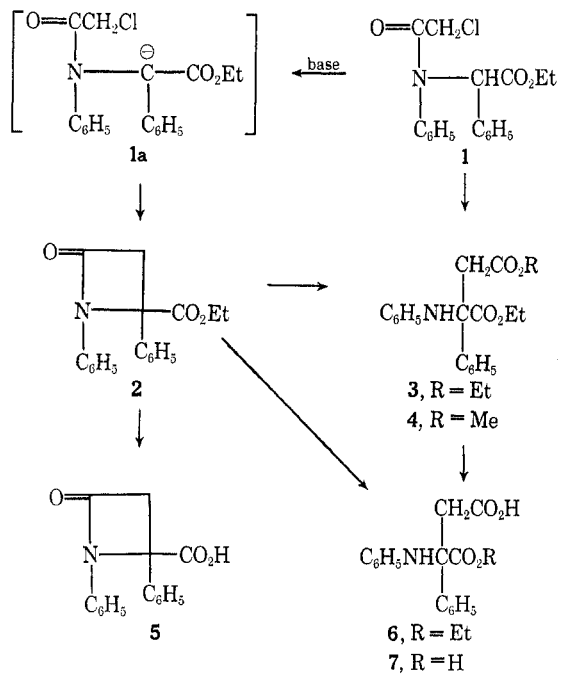
Received February 2, 1970

Intramolecular cyclization of an *N*-chloroacetyl-2-phenylglycine ethyl ester occurs in the presence of various bases to produce the corresponding 2-phenyl-4-oxoazetidine. A similar cyclization of the *N*-(3-chloropropionyl) homolog to an oxopyrrolidine has been observed. The facile ring cleavage of the oxoazetidines yielded a series of novel 2-phenylaspartic acid derivatives. Large geminal coupling constants from the pmr spectra of the *N*-phenyl- and *N*-benzyl-2-phenylaspartic acid derivatives support restricted rotational conformations for these compounds.

When *N*-chloroacetyl-*N*,2-diphenylglycine ethyl ester (**1**)[1] reacts with sodium cyanide, ethyl 4-oxo-1,2-diphenylazetidine-2-carboxylate (**2**)[2] is formed in good yield, rather than the *N*-cyanoacetyl derivative. Although **1** fails[1] to yield **2** in the presence of triethylamine, the reaction is successful[2] when carried out in the presence of basic anion exchange resin. Sheehan and Bose[3] report the intramolecular cyclization of diethyl *N*-arylhaloacetamidomalonates in the presence of triethylamine to 1-aryl-2,2-dicarbethoxy-4-oxoazetidines. Similarly, Deshpande, Mukerjee, and Dey[1,4] prepare 2,2-dicarbethoxy-1-phenyl-3-phthalimidomethyl-4-oxoazetidine from diethyl *N*-(3-phthalimido)-2-bromo-*N*-phenylpropionamidomalonate.

Sodium cyanide is apparently a strong enough base to form the carbanion (**1a**) which by intramolecular nucleophilic displacement of Cl gives **2**. Other bases (*e.g.*, NaH, NaOR, NaOAc, and NH_3) behave similarly, and may be preferred cyclization reagents (Scheme I).

SCHEME I



1,4-Diethyl *N*,2-diphenylaspartate (**3**) was obtained in 84% yield by the addition of an excess (1.3 equiv) of NaOEt to **1** in EtOH. When 1 equiv of NaOEt was added rapidly to **1**, compound **3** was the major reaction product. The localized excess of NaOEt presumably opens up the initially formed azetidine ring to give **3** and a lesser amount (26%) of **2**. As expected, when **2** was treated with NaOMe–MeOH the analogous ester, 1-ethyl 4-methyl *N*,2-diphenylaspartate (**4**), was obtained.

Mild hydrolysis[2-4] of **2** (1 equiv) at room temperature in a 0.5% solution of KOH (1 equiv) in 95% EtOH produced the azetidinecarboxylic acid **5**. When the reaction was repeated with MeOH as solvent, the chief product was the ring-opened diester **4** with only a minor amount of **5** being isolated. Refluxing **3** for 5 min in a 1.6% NaOH (2.4 equiv) aqueous EtOH solution allowed selective hydrolysis of the 4-carbethoxy group, giving an 80% yield of 1-ethyl *N*,2-diphenylaspartate (**6**). Compound **6** was prepared by: (a) selective hydrolysis of **3** with hot dilute H_2SO_4, or (b) the ring cleavage of **2** with concentrated H_2SO_4. More drastic hydrolysis of either **2** or **3** with excess NaOH in refluxing aqueous dioxane produced *N*,2-diphenylaspartic acid (**7**).

Other investigators[3] obtained *N*-phenylaspartic acid by hydrolysis of 2,2-dicarbethoxy-1-phenyl-4-oxoazetidine with KOH, followed by decarboxylation. The dimethyl ester was obtained[3] by treatment with diazomethane. α esters are less readily available than β or γ esters of monoaminodicarboxylic acids. Klieger and Gibian[5] found that benzyloxycarbonyl-L-glutamic acid anhydride reacts with ROH in the presence of dicyclohexylamine to produce the α ester dicyclohexylammonium salt. The α esters may also be prepared[6] by taking advantage of the difference in the dissociation constants of the α- and γ-carboxyl groups of *N*-acylglutamic acids. The reaction is carried out

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(1) A. K. Bose, B. N. G. Mazumdar, and B. G. Chatterjee, *J. Amer. Chem. Soc.*, **82**, 2382 (1960).

(2) B. G. Chatterjee, V. V. Rao, and B. N. G. Mazumdar, *J. Org. Chem.*, **30**, 4101 (1965).

(3) J. C. Sheehan and A. K. Bose, *J. Amer. Chem. Soc.*, **72**, 5158 (1950).

(4) S. M. Deshpande, A. K. Mukerjee, and P. M. Dey, *Indian J. Chem.*, **6**, 238 (1968).

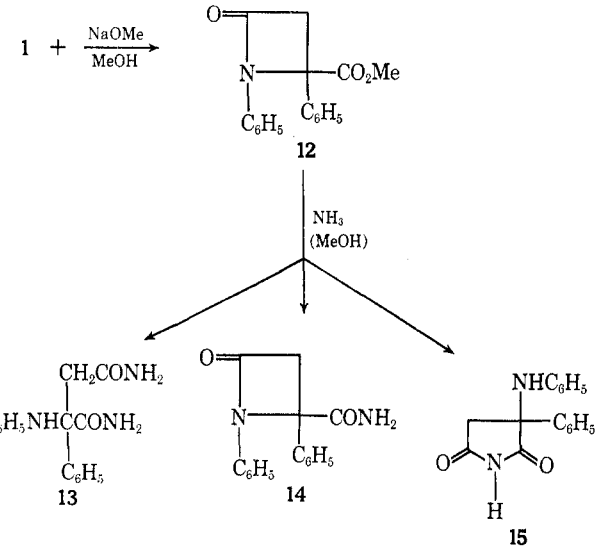
(5) E. Klieger and H. Gibian, *Justus Liebigs Ann. Chem.*, **655**, 195 (1962).

(6) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," G. A. Olah, Ed., Interscience, New York, N. Y., 1966, p 52.

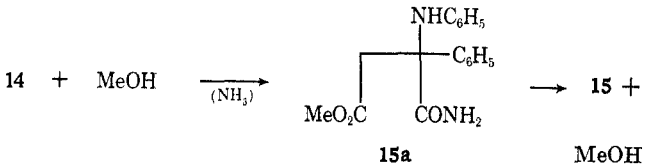
with RX in the presence of 1 equiv of a strong base. The mixed diesters can be obtained[6] from the α esters by several procedures.

The *N*-methyl and *N*-benzyl analogs of **1** were also prepared for cyclization to the corresponding oily oxoazetidines of type **2**. The crude oxoazetidines were treated with excess alkali in a manner similar to that used for the preparation of **7** from **2**. In both examples, however, the azetidine ring was more resistant to cleavage than **2** as shown by the isolation of azetidinecarboxylic acids **8** and **9** (Table I). The N-substituted 2-phenylaspartic acids **10** and **11** were obtained in lower yield.

During the intramolecular cyclization of **1** with NaOMe, transesterification also occurred giving **12**. The reaction of **12** with NH_3 in MeOH under pressure at room temperature gave three products: the succinamide **13**, the 4-oxoazetidine-2-carboxamide **14**, and the succinimide **15**. Compound **14** is believed to be the

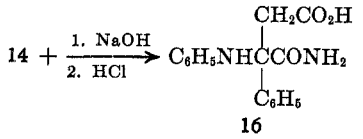


initial product of ammonolysis which reacts further with ammonia to produce the ring-cleavage product **13**. Pathways to **15** might include (a) ring cleavage of **14** with MeOH to yield an hypothetical intermediate **15a**, followed by the loss of MeOH, or (b) the intramolecular



rearrangement of **14**. Sheehan and Bose[3] prepared *N*,*N*′-dibenzyl-2-anilinosuccinamide by the action of benzylamine upon (a) *N*-phenylaspartic acid dimethyl ester or (b) 2-carbethoxy-2-carboxy-1-phenyl-4-oxoazetidine.

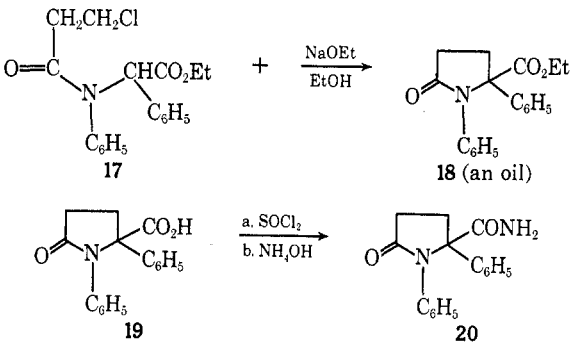
Ring cleavage of **14** with alkali has afforded a method for preparing the α amide, 3-anilino-3-phenylsuccinamic acid (**16**). A standard method[7] for preparing



(7) S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **75**, 1754 (1953).

3-aminosuccinamic acid has involved the reaction between *N*-phthaloylaspartic anhydride and ammonia. As ring opening of the anhydride may occur in two different ways, mixtures may result by this method.

Using *N*-(3-chloropropionyl)-*N*,2-diphenylglycine ethyl ester (**17**) as the intermediate, ethyl 5-oxo-1,2-



diphenylpyrrolidine-2-carboxylate (**18**) was prepared under conditions similar to those used for the preparation of **2**. Compound **18** (an oil) was readily hydrolyzed to the crystalline acid **19**, which was then converted to the amide **20**. Similarly, the cyclization of diethyl *N*-(3-bromopropionyl)anilinomalonate to 2,2-dicarbethoxy-1-phenyl-5-oxopyrrolidine is reported.[1,2]

A method[8] for the preparation of 2,5-dioxopiperazines by the action of NH_3 in MeOH upon α-haloacetyl derivatives of amino acid esters was applied to the chloroacyl intermediates **1** and **17**. However, the products isolated were compounds **14** and **21** (Table I), respectively, resulting from expected intramolecular cyclizations.

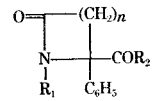
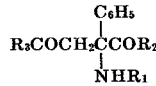
Pmr Spectra.—The proton magnetic resonance spectra of the substituted 4-oxoazetidines show marked magnetic nonequivalence of the two protons in position 3 caused by the asymmetric carbon atom 2 (Table II). The geminal coupling constants are in the normal range for methylene protons in four-membered ring compounds[9] having a planar configuration and one adjacent π bond.[10] No cross-ring coupling was observed in **8** or **9** between the hydrogens at position 3 and the methyl or benzylic protons as was reported by Barrow and Spotswood.[9] The two substituents at position 2 must force the N substituent into the plane of the ring thereby destroying the transoid pathway necessary for long-range coupling.

The absolute values of the geminal coupling constants observed for the *N*-phenyl- and *N*-benzyl-2-phenylaspartic acid derivatives are very large, especially for those spectra taken in trifluoroacetic acid solution. These values require a large population of restricted rotational conformations with the plane of the carbonyl group bisecting the H–C–H bonds of the methylene group.[10] Conformational restrictions imposed by rotational hindrance of the two benzene rings, and probably enhanced by intramolecular hydrogen bonding of the acidic hydrogen to the adjacent carbonyl group, allow a preferred conformation for the 2-phenylaspartic acid derivatives which approaches that of the cyclic compounds.

(8) Y. T. Pratt in *Heterocycl. Compounds*, **6**, 438 (1957).
(9) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, **37**, 3325 (1965).
(10) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).

TABLE I

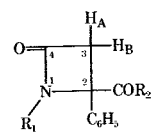
THE LACTAMS AND ASPARTIC ACID DERIVATIVES

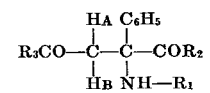
Compd no.	R_1	R_2	(n) or R_3	Prepn method (variation)[a]	Yield, %	Recrystn solvent[b]	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
														
2	C_6H_5	OEt	(1)	A, B, C	65, 93, 56	B	80–81.5	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	73.48	5.93	4.65
5	C_6H_5	OH	(1)	G	37	B	127.5–129	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.60	4.79	5.11
8	Me	OH	(1)	BH (1)	10	A	210.5–211 dec	...[a(1)]	62.89	6.50	11.28	63.19	6.40	11.30
9	$C_6H_5CH_2$	OH	(1)	BH (5)	77	C	145.5–146	$C_{17}H_{15}NO_3$	72.58	5.38	4.98	72.48	5.44	5.09
12	C_6H_5	OMe	(1)	B (2)	78	A	112–114	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.49	5.33	4.93
14	C_6H_5	NH_2	(1)	K, L	18, 31	A	197–198.5	$C_{16}H_{14}N_2O_2$	72.16	5.30	10.52	72.11	5.45	10.45
19	C_6H_5	OH	(2)	BH (3)	18	C	249–251 dec	$C_{17}H_{15}NO_3$	72.58	5.38	4.98	72.88	5.86	4.86
20	C_6H_5	NH_2	(2)	(4)	71	C, D	213–214.5	$C_{17}H_{16}N_2O_2$	72.83	5.75	10.00	72.62	5.76	9.99
21	C_6H_5	OMe	(2)	M	28	C	129–130	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	73.17	6.00	4.71
														
3	C_6H_5	OEt	OEt	D, E	84, 62	F	139.5–141.5	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.43	6.63	4.38
4	C_6H_5	OEt	OMe	E (2)	61	A	147–148	$C_{19}H_{21}NO_4$	69.70	6.46	4.28	69.79	6.19	4.59
6	C_6H_5	OEt	OH	F	80	C	190–191.5 dec	$C_{18}H_{19}NO_4$	68.90	6.11	4.47	68.92	5.89	4.65
7	C_6H_5	OH	OH	H	70, 56	B	180–180.5 dec	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	67.32	5.58	4.88
10	Me	OH	OH	H (6)	63	E	232[c]	$C_{11}H_{13}NO_4$	59.21	5.87	6.28	58.95	5.83	6.35
11	$C_6H_5CH_2$	OH	OH	H (7)	18	H	198.5 dec	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.22	5.72	4.61
13	C_6H_5	NH_2	NH_2	J	17	G	253.5–255.5 dec	$C_{16}H_{17}N_3O_2$	67.82	6.05	14.83	67.53	6.26	14.74
16	C_6H_5	NH_2	OH	N	70	C	160–161 dec	$C_{16}H_{16}NO_2O_3$	67.59	5.67	9.86	67.42	5.75	9.57

[a] See Experimental Section for the letters: (1) isolated from the EtOAc soluble fraction in method H as the piperazinium salt formula, $(C_{11}H_{11}NO_3)_2 \cdot C_4H_{10}N_2$; (2) MeOH was employed as the reaction solvent; (3) 75% aqueous 2-PrOH was used as the reaction solvent in method H; (4) prepared by the action of $SOCl_2$ on **19**, followed by treatment with NH_4OH; (5) concentration of the reaction mixture in method H, followed by solution of the residual oil in H_2O and adjusting pH to ~4–5 gave the solid; (6) precipitated by concentrating the aqueous layer from **8**; (7) H_2O soluble fraction from **9**. [b] A = MeOH, B = EtOAc–Skellysolve B, C = EtOH, D = DMF–MeOH, E = 50% aqueous MeOH, F = EtOAc–EtOH, G = DMF–H_2O, H = aqueous EtOH. [c] Indefinite.

TABLE II

PMR SPECTRAL DATA

Compd no.[a]	Solvent	Chemical shifts (ppm from TMS) R_1	H_A	H_B	$J_{A,B}$, cps
					
2	CCl_4	C_6H_5	3.05	3.77	15.2
8	CF_3COOH	CH_3, 3.17	3.62	3.91	15.5
9	CF_3COOH	$C_6H_5CH_2$, 4.74	3.62	3.90	16.0
12	CCl_4	C_6H_5	3.08	3.80	15.1
14	CF_3COOH	C_6H_5	3.80	4.04	15.7

Compd no.[a]	Solvent	Chemical shifts (ppm from TMS) R_1	H_A	H_B	$J_{A,B}$, cps
					
3	$CDCl_3$	C_6H_5	3.54	3.78	16.4
6	$CDCl_3$	C_6H_5	3.62	3.84	17.0
7	CF_3COOH	C_6H_5	3.58	3.90	18.9
10	CF_3COOH	CH_3, 2.79	3.98	3.98	None observed
11	CF_3COOH	$C_6H_5CH_2$, 4.20	3.87	4.05	18.7
13	CF_3COOH	C_6H_5	3.64	3.81	18.0
16	CF_3COOH	C_6H_5	3.75	3.92	19.0

[a] See Table I.

The coupling constants were obtained directly from the spectra, while the chemical shift values were adjusted using the formula[11] for the deviation from first-order treatment. The signs of the coupling constants were not determined, but the geminal coupling constants are probably negative.

Experimental Section

The ir spectra of all the described compounds are consistent with the assigned structures. The β-lactam carbonyl bands were in the expected range[2] of 5.65–5.75 μ. The pmr data were obtained from spectra taken with a Varian A-60A spectrometer, using TMS as internal reference. The melting points are corrected (Thomas–Hoover capillary apparatus).

The N-substituted 2-phenylglycine ethyl esters were prepared as described.[12,13] ***N*-Benzyl-2-phenylglycine ethyl ester·HCl** was obtained in a yield of 75%, mp 182.5–183.5° dec, after recrystallizing from anhydrous EtOH.

Anal. Calcd for $C_{17}H_{19}NO_2 \cdot HCl$: C, 66.77; H, 6.59; N, 4.58; Cl, 11.60. Found: C, 66.76; H, 6.72; N, 4.49; Cl, 11.77.

The *N*-chloroacyl derivatives were prepared in warm (50–60°) benzene solution according to a similar procedure.[14] ***N*-Chloroacetyl-*N*-methyl-2-phenylglycine ethyl ester** was obtained in a yield of 69%, mp 50–52°, after recrystallizing from EtOAc–Skellysolve B.

Anal. Calcd for $C_{13}H_{16}ClNO_3$: C, 57.88; H, 5.98; N, 5.19. Found: C, 57.77; H, 6.06; N, 5.22.

***N*-Benzyl-*N*-chloroacetyl-2-phenylglycine ethyl ester** was obtained in yield of 35%, mp 82.5–84.5°, after recrystallizing from EtOAc–Skellysolve B.

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05; Cl, 10.26. Found: C, 66.15; H, 5.90; N, 4.14; Cl, 9.85.

***N*-(3-Chloropropionyl)-*N*,2-diphenylglycine ethyl ester (17)** was obtained in a yield of 35%, mp 84.5–85.5°, after recrystallizing from EtOAc–Skellysolve B.

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; Cl, 10.26. Found: C, 65.79; H, 5.46; Cl, 10.32.

A. Ethyl 4-Oxo-1,2-diphenylazetidine-2-carboxylate (2).[2]—A suspension of 0.025 mol of the chloro intermediate 1,[1] 1.5 g (0.0306 mol) of NaCN, and 18 ml of dimethylformamide (DMF) was heated at 50–60° for 2 hr. After adding 10 ml of H_2O, the resulting solution was heated at 95–100° for 0.5 hr. The reaction mixture was diluted with H_2O to give an oil which crystallized from aqueous EtOH, yield 4.8 g (65%).

B.—A solution of 1 g (0.0435 g-atom) of Na dissolved in 60 ml of anhydrous EtOH was added slowly (10 min) to a stirred suspension of 14.4 g (0.0435 mol) of 1 in 80 ml of anhydrous EtOH. The reaction temperature increased from 25 to 30° during the addition. After slowly heating the mixture to reflux and maintaining this temperature for 1 hr, the neutral suspension was allowed to stand overnight. The solid (chiefly NaCl) was collected on a filter, washed with EtOH, and discarded. The filtrate was concentrated to a small volume and the resulting white solid was collected, yield 12 g (93%). When this reaction was repeated, omitting the heating step, a 79% yield was obtained. When the reaction was carried out under rapid addition of NaOEt, this compound was obtained in only 26% yield. The major product was ring-cleaved 1,4-diethyl *N*,2-diphenylaspartate (3).

C.—An equivalent of NaH (dispersion 54.3% in mineral oil) was added to a cold (3–5°) mixture of 8.3 g (0.025 mol) of 1 and 25 ml of DMF. After 3 hr at room temperature and 1 hr at 50–55°, the resulting neutral reaction mixture was diluted with 15% NaCl solution. The compound was isolated by extracting with C_6H_6, yield 4.1 g (56%).

D. 1,4-Diethyl *N*,2-Diphenylaspartate (3).—A solution of 100 ml of anhydrous EtOH containing 2.3 g (0.1 g-atom) of dissolved Na was added to a suspension of 25.5 g (0.077 mol) of 1 and 200 ml of anhydrous EtOH. The reaction temperature increased from 25 to 30°. The mixture was warmed at 35–40° for 0.5 hr and then heated under reflux for 1 hr. After standing overnight at room temperature, the solid was collected and washed first EtOH and then with H_2O, yield 22 g (84%) of white solid.

E.—A mixture of 2.5 g (0.0085 mol) of 2 and 50 ml of anhydrous EtOH containing 0.1 g (0.0044 g-atom) of dissolved Na was warmed slowly to 50° and the reaction temperature was maintained at 50–60° for 1 hr. During the heating time, solution resulted followed by precipitation of the product. After cooling, the white solid was collected and washed with EtOH, yield 1.8 g (62%).

F. 1-Ethyl *N*,2-Diphenylaspartate (6).—A mixture of 3.4 g (0.01 mol) of 3, 50 ml of EtOH, and 12 ml of 2 *N* NaOH was heated under reflux for 5 min. After cooling, the precipitate was collected and dried to give 1.2 g of white solid of mp >300°. It was dissolved in warm H_2O, and 5 ml of 1 *N* HCl was added to precipitate 6, yield 0.6 g. An additional quantity (1.9 g) was obtained by acidification of the original filtrate, total yield 2.5 g (80%).

Compound 6 was also prepared by acid hydrolysis from either compound 3 or 2. Compound 3 (6.5 g, 0.019 mol) was heated to 90° in 56 g of 65% H_2SO_4. The solution was poured onto ice water. The product was extracted with EtOAc to give 5 g (85%). Similarly, a solution of 3 g (0.01 mol) of 2 in 6 ml of concentrated H_2SO_4 was allowed to stand overnight, yield 1.4 g (45%).

G. 4-Oxo-1,2-diphenylazetidine-2-carboxylic Acid (5).—Hydrolysis[3] of the carbethoxy group in 2 was achieved by slowly adding 100 ml of 95% EtOH containing 1.1 g (0.020 mol) of KOH to a stirred suspension of 6 g (0.02 mol) of 2 in 100 ml of 95% EtOH. After 5 min, a complete solution resulted. The reaction mixture was allowed to stand overnight and concentrated to a white solid, yield 5.5 g (90%) of the K salt. A solution of this solid in 30 ml of H_2O was acidified. The product was isolated by extracting with Et_2O and concentrating the extract to give an oil. This material was slurried with EtOAc–Skellysolve B to give 2 g (73%) of product.

When this reaction was repeated using anhyd MeOH as the solvent, only 0.4 g (7%) of 5 was obtained. Compound 4 was isolated as the chief product (2.4 g, 37%).

H. *N*,2-Diphenylaspartic Acid (7).—A mixture of 15 g (0.05 mol) of 2 and 0.16 mol of NaOH in 230 ml of 65% aqueous dioxane was heated under reflux for 3 hr and then concentrated. After adding 160 ml of 1 *N* HCl, 10 g (70%) of 7 precipitated. When 3 was employed as the intermediate, a 56% yield of 7 was obtained.

J. 2-Anilino-2-phenylsuccinamide (13).—To 300 ml of MeOH saturated with NH_3 at 10° was added 11.7 g (0.041 mol) of 12. The cold suspension was stoppered and allowed to stand at room temperature for 4 days with careful agitation at the end of the first day to complete the solution. The flask was cooled and opened and the white solid was collected, yield 1.5 g (13%). A second crop was recovered from the filtrate by concentrating to one-half volume, slurrying the resulting solid with hot MeOH, total yield 2 g (17%).

K. 4-Oxo-1,2-diphenylazetidine-2-carboxamide (14).—The solid, which precipitated from the above methanolic filtrate, was recrystallized twice from MeOH to give 2 g (18%) of product.

2-Anilino-2-phenylsuccinimide (15).—A third crop (3.2 g) of crude material was obtained from the above filtrate (method K). Three recrystallizations from MeOH gave 1.2 g (11%) of purified solid. An additional recrystallization by dissolving the sample in 15 ml of DMF, followed by dilution with 5 ml of H_2O, gave 15 melting at 212.5–214°: λ_{max}^{KBr} 2.95, 5.58, 5.82, 6.24, 6.64, 13.32, 14.38 μ; $\delta^{(CF_3COOH)}$ 3.89, 4.08 (J = 18.8 cps), 10.08 (NH).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.18; H, 5.60; N, 10.36.

L.—Compound 14 was also obtained by bubbling NH_3 into a stirred mixture of 33.2 g (0.1 mol) of 1 and 300 ml of MeOH. The resulting solution was allowed to stand at room temperature for 5 days at the end of which time a solid had formed, yield 8.3 g (31%).

M. Methyl 5-Oxo-1,2-diphenylpyrrolidine-2-carboxylate (21).—Compound 17 (10.4 g, 0.03 mol) was added to 150 ml of MeOH saturated with NH_3 at 10°. After standing at room temperature for 10 days, the solution was concentrated to an oily solid. This material was slurried with EtOAc to give 1.5 g of NH_4Cl. The filtrate was diluted with Skellysolve B to precipitate 2.5 g (28%) of product. Its structure was further supported by hydrolysis to 19 as follows: A mixture of 0.1 g of 21, 1 ml of 2 *N* NaOH, and 2 ml of MeOH was warmed slightly for a few minutes and then allowed to stand for 3 hr. The carboxylic acid 19 was

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isolated by concentrating the reaction mixture to yield a solid, dissolving in H_2O, and acidifying, yield 0.1 g.

N. 3-Anilino-3-phenylsuccinamic Acid (16).—A solution of 2.7 g (0.01 mol) of **14** and 40 ml each of EtOH, dioxane, and 1 *N* NaOH was allowed to stand overnight. After neutralizing with 40 ml of 1 *N* HCl, the reaction mixture was concentrated, yield 2 g (70%).

Registry No.—**2**, 5634-62-8; **3**, 25791-42-8; **4**, 25791-43-9; **5**, 13327-23-6; **6**, 25791-45-1; **7**, 25791-46-2; **8** (piperazinium salt), 25791-47-3; **9**, 25791-48-4; **10**, 25791-49-5; **11**, 25791-50-8; **12**, 25791-51-9; **13**, 25791-52-0; **14**, 25791-53-1; **15**, 25791-54-2; **16**, 25791-55-3; **17**, 25834-64-4; **19**, 25791-56-4; **20**, 25791-62-2; **21**, 25791-63-3; *N*-benzyl-2-phenylglycine ethyl ester·HCl, 25791-64-4; *N*-chloroacetyl-*N*-methyl 2-phenylglycine ethyl ester, 25791-65-5; *N*-benzyl-*N*-chloroacetyl-2-phenylglycine ethyl ester, 25791-66-6.

Acknowledgment.—The authors are grateful to Mr. C. I. Kennedy and Mr. J. G. Schmidt for analytical and ir spectral data, and to Mr. D. H. Causey and Mr. W. F. Kavanaugh for technical assistance.

Synthesis of a Bicyclohydantoin

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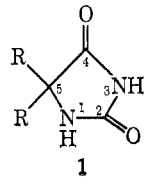
Received March 31, 1970

The preparation and intramolecular cyclizations of 5-phenyl-5-(3-hydroxypropyl)hydantoin tosylate, **4**, and 5-phenyl-5-(4-hydroxybutyl)hydantoin tosylate, **5**, are described. No products involving the imide nitrogen in the cyclizations could be obtained. Proof of structure of the compounds involving the amide nitrogen in the cyclization is discussed.

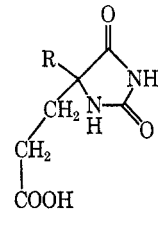
Previous reports have indicated that intermolecular alkylations of 5,5-disubstituted hydantoins, **1**, proceed exclusively at the imide nitrogen (N-3).[2] Amino-



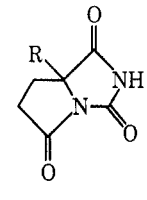
1

methylations utilizing formaldehyde,[3] aminoethylations with ethylenimine,[4] and Michael condensations[5] have also demonstrated a preference for the acidic imide function. Amide nitrogen (N-1) alkylations occur under more rigorous reaction conditions during which both nitrogens are alkylated. Mono N-1-alkylated hydantoins can be obtained by protecting the imide nitrogen with an aminomethyl group followed by alkylation of the amide nitrogen and then the removal of the protecting group by mild aqueous base hydrolysis.[6]

Intermolecular acylations have been reported to occur exclusively at the amide nitrogen and the intramolecular cyclization of the hydantoin propionic acids **2a**[7] and **2b**[8] yield only the amide cyclized products **3a** and **3b**, respectively.



2a, R = H
b, R = CH_3, C_6H_5



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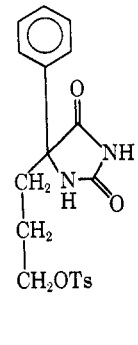
In these laboratories the base-catalyzed cyclizations of 5-phenyl-5-(3-hydroxypropyl)hydantoin tosylate, **4**, and 5-phenyl-5-(4-hydroxybutyl)hydantoin tosylate, **5**, produced only amide cyclized monomers. The synthesis of **4** and **5** and the proof of structure of the cyclized products are described below.



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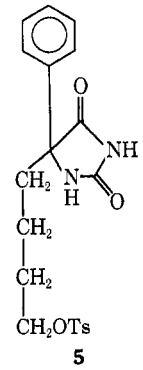

5

The conversion of 3-benzoylpropionic acid, **6a**, and 4-benzoylbutyric acid, **6b**, to 4-hydroxybutyrophenone, **8a**, and 5-hydroxyvalerophenone, **8b**, was performed by a lithium aluminum hydride reduction of the corresponding ethylene ketal monoethylene glycol esters **7a** and **7b** followed by acid hydrolysis according to the method of Pasto and Serve[9] (Scheme I).

The two keto alcohols, **8a** and **8b**, were converted to the 5-phenyl-5-(hydroxyalkyl)hydantoins, **9a** and **9b**,

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(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of The University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

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