

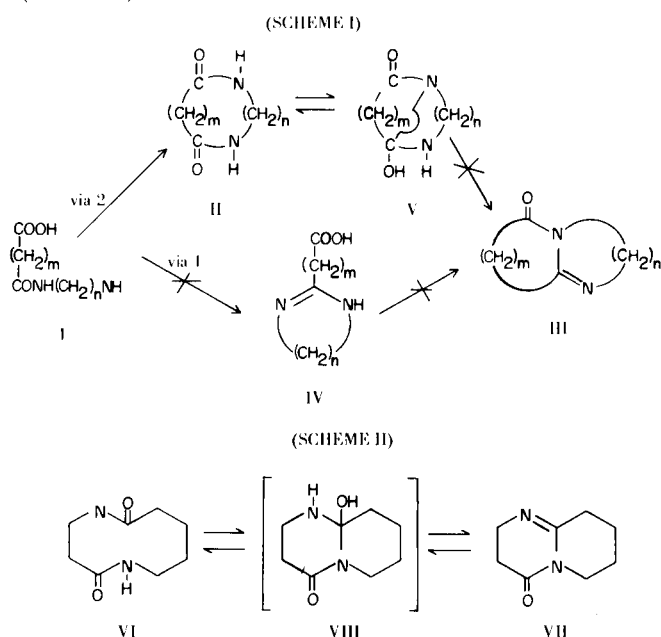
Heterocycles Derived from the Condensation of Aliphatic Diamines with Succinic and Glutaric Acid Derivatives

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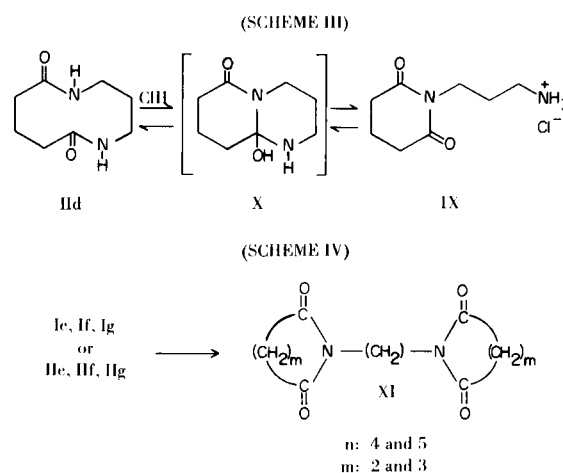
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Received December 11, 1974

In a previous report (1) we described the generation of heterocyclic compounds from the condensation of phthalic acid derivatives with 1,3-propanediamine. An interesting result was the intramolecular cyclization of *N*-(*o*-carboxybenzoyl)-1,3-propanediamine to a tetrahydropyrimidoisoindolone. In order to investigate the reaction in the aliphatic series, succinic and glutaric acid anhydrides were each condensed with ethylenediamine, 1,3-propanediamine, 1,4-butanediamine, or 1,5-pentanediamine to see if the type III heterocycles heretofore undescribed would result (Scheme I).



A priori the synthesis could proceed *via* two different routes. Possibility 1 (Scheme I) is supported by the reaction of phthalic anhydride with 1,8-diaminonaphthalene (2) or 1,3-propanediamine (1) whereas the most probable route 2 is indicated by several cases related to amide-amide interaction *via* a cyclol (3,4,5). Worthy of mention is the fact that the pyrimidopyridone VII (Scheme II) can be produced from the depsipeptide VI (4); an intermediate type VII cyclol being isolated in some cases. Moreover,



Glover *et al.*, (3) described the transformation of the lactam IIId into IX *via* the cyclol X closely related to our desired type of heterocycle (Scheme III).

The reaction of succinic and glutaric anhydrides with the diamines in ethanol solution afforded the expected amides Ia-Ih (Table I). Spectroscopic data (Tables II and III) supported the assigned structures. These compounds lost a molecule of water by heating above the melting point or by azeotropic distillation to form in varying yields IIa-IIg which are cyclic lactams. Compound Ih could not be cyclized. Compound IIId, the only one of the series previously synthesized by another method (3), was compared with our product and found to be identical in m.p., mixture m.p. and ir spectra.

The structure of the type II compounds were confirmed when they were also obtained, usually in lower yields, by aminolysis of the corresponding methyl esters. Elemental analysis, molecular weights, ir and uv spectrum (Table II), and nmr spectra (Table III) were in agreement with the assigned structures.

On the basis of Glover's results (3), ring contraction by dehydration was first attempted on IIId. The reaction was acid catalyzed to favor the formation of the intermediate cyclol and was carried out in toluene or xylene by azeotropic distillation. This procedure was repeated for the

Table I
Data of Compounds Prepared

Compound	m	n	Yield (%)	M.p. (°C)	Crystallization Solvent	Formula	Analysis (%)					
							Calculated			Found		
						C	H	N	C	H	N	
Ia	2	2	74	159-162	---	C ₆ H ₁₂ N ₂ O ₃	45.0	7.50	17.5	44.8	7.51	17.4
Ib	2	3	66	179-180	---	C ₇ H ₁₄ N ₂ O ₃	48.2	8.05	16.1	48.1	8.00	16.0
Ic	3	2	70	182-185	---	C ₇ H ₁₄ N ₂ O ₃	48.2	8.05	16.1	48.1	8.03	16.1
Id	3	3	85	247-250	---	C ₈ H ₁₇ ClN ₂ O ₃	42.7	7.57	12.4	42.7	7.56	12.4
Ie	2	4	69	169-172	---	C ₈ H ₁₆ N ₂ O ₃	51.0	8.56	14.9	50.9	8.58	14.8
If	2	5	82	175-178	---	C ₉ H ₁₈ N ₂ O ₃	53.4	8.91	13.8	53.3	8.90	13.7
Ig	3	4	56	180-183	---	C ₉ H ₁₈ N ₂ O ₃	53.4	8.91	13.8	53.5	8.92	13.8
Ih	3	5	86	242-245	---	C ₁₀ H ₂₁ ClN ₂ O ₃	47.3	8.28	11.0	47.2	8.26	10.9
Ila	2	2 (a)	21	259-261	Methanol-Acetic acid	C ₆ H ₁₀ N ₂ O ₂	50.7	7.09	19.7	50.6	7.07	19.7
Ilb	2	3 (a)	51	245-247	Methanol-Acetic acid	C ₇ H ₁₂ N ₂ O ₂	53.8	7.69	17.9	53.7	7.70	17.8
Ilc	3	2 (a)	16	287-289	Methanol-Acetic acid	C ₇ H ₁₂ N ₂ O ₂	53.8	7.69	17.9	53.7	7.69	17.9
Ild	3	3	30	234-237	Benzene	C ₈ H ₁₄ N ₂ O ₂	56.5	8.23	16.4	56.1	8.21	16.5
Ile	2	4 (a)	38	291-293	Methanol-Acetic acid	C ₈ H ₁₄ N ₂ O ₂	56.4	8.23	16.4	56.6	8.26	16.3
Ilf	2	5 (a)	29	235-238	Isopropanol-Benzene	C ₉ H ₁₆ N ₂ O ₂	58.7	8.69	15.2	58.5	8.72	15.3
Ilg	3	4 (a)	28	239-242	Methanol-Acetic acid	C ₉ H ₁₆ N ₂ O ₂	58.7	8.69	15.2	58.6	8.70	15.1
XIe	2	4	62	160-163	Benzene	C ₁₂ H ₁₆ N ₂ O ₄	57.1	6.34	11.1	57.0	6.36	11.2
XIf	2	5	61	59-62	Toluene-Cyclohexane	C ₁₃ H ₁₈ N ₂ O ₄	58.6	6.76	10.5	58.4	6.79	10.6
XIlg	3	4	59	173-176	Benzene	C ₁₄ H ₂₀ N ₂ O ₄	60.2	7.14	10.0	60.3	7.15	9.90

(a) By Method A. By Method B, yield %: Ila, 16; Ilb, 32; Ilc, 11; Ile, 23; Ilf, 18; Ilg, 14.

Table II
Spectral Data

Compound	NH	Infrared Spectra (cm ⁻¹)				Ultraviolet Spectra		Solvent
		I Band	II Band	COO ⁻	CO	λ max (nm)	log ε	
Ia	3400	1660	1560	1420, 1660	---	224	2.16	water
Ib	3380	1640	1530	1430, 1650	---	217	2.21	water
Ic	3370	1660	1560	1430, 1560	---	223	2.14	water
Id	3450	1630	1500	1440, 1630	---	208	2.16	water
Ie	3400	1660	1590	1400, 1500	---	213	2.14	water
If	3400	1660	1550	1430, 1560	---	218	2.12	water
Ig	3400	1660	1560	1460, 1400	---	213	2.15	water
Ih	3400	1660	1560	1420, 1560	---	216	2.17	water
Ila	3400	1720	1470	---	---	252	1.54	chloroform-acetic acid
Ilb	3400	1660	1560	---	---	262	2.29	water-DMF
Ilc	3370	1660	1570	---	---	253	2.75	acetic acid
Ild	3360	1660	1570	---	---	203	2.47	water
Ile	3400	1660	1540	---	---	244	1.47	acetic acid
Ilf	3400	1660	1550	---	---	257	2.54	acetic acid
Ilg	3400	1650	1550	---	---	250	1.47	acetic acid
XIe	---	---	---	---	1790, 1710	248	2.11	chloroform
XIf	---	---	---	---	1790, 1710	264	1.41	chloroform
XIlg	---	---	---	---	1740, 1670	264	1.63	chloroform

other type II compounds and their precursors I. These attempts were not successful and the reactants were recovered in over 85% yield except for the lactams Ile, Ilf, Ilg and their respective precursors Ie, If, and Ig, which rearranged to the symmetrical bisimides XIe, XIf, and XIg by elimination of water and diamine (Scheme IV).

Compounds XI display two typical succinimido or glutarimido bands in the ir spectra at 1770 (w) and 1770 cm⁻¹ (s) (6). Determination of molecular weight (see Experimental), elemental analysis (Table I) and nmr spectra (Table III) supported the assigned structures.

Table III
Nuclear Magnetic Resonance Data (δ , ppm)

Compound	O=C-NH	(CH ₂) _m	(CH ₂) _n
Ia (a)		2.48 (s, 4H)	3.31 (d, 4H)
Ib (a,b)		2.41 (s, 4H)	1.75 (m, 2H); 3.25 (m, 2H)
Ic (c,d)	7.55 (s, 1H)		3.65 (s, 2H)
Ie (a,e)		2.50 (s, 4H)	2.55 (m, 4H); 3.25 (m, 2H)
If (a,f)			1.35 (s, 6H); 3.11 (s, 2H); 2.55 (t, 2H)
Ig (a,g)			3.15 (s, 2H)
IIa (c,h)	9.79 (s, 2H)	2.98 (s, 4H)	3.90 (d, 4H)
IIb (c,h)	8.28 (s, 2H)	2.94 (s, 4H)	2.15 (m, 2H); 3.58 (s, 4H)
IIc (c,h)	8.25 (s, 2H)	2.35 (m, 2H); 2.90 (s, 4H)	3.85 (s, 4H)
IIf (c,h)	8.05 (s, 2H)	2.90 (s, 4H)	1.75 (s, 4H); 3.45 (s, 4H)
IIg (c,h)	8.32 (s, 2H)	2.75 (s, 4H)	1.33 (s, 6H); 3.10 (s, 2H); 2.65 (t, 2H)
XIe (i)	8.10 (s, 2H)	2.15 (s, 2H); 2.70 (s, 4H)	1.75 (s, 4H); 3.50 (s, 4H)
XIf (i)		2.65 (s, 8H)	1.51 (m, 4H); 3.48 (m, 4H)
XIg (i)		2.88 (s, 8H)	1.70 (m, 6H); 3.65 (t, 4H)
		1.45 (t, 4H); 2.58 (t, 8H)	1.88 (t, 4H); 3.68 (m, 4H)

(a) Solvent: deuterium oxide. (b) The protons CH₂-N< appear overlapped with the multiplet at $\delta = 1.75$. (c) Solvent TFA. (d) The protons (CH₂)_m and CH₂-N< appear as a no resolved multiplet at $\delta = 2.10$ -2.60. (e) The protons CH₂-N< appear as a no resolved system at $\delta = 2.3$. (f) The protons (CH₂)_m appear overlapped with the triplet at $\delta = 2.55$. (g) The remanent protons appear as two no resolved multiplets at $\delta = 2.0$ and $\delta = 4.6$. (h) The presence of the amide protons was confirmed by exchange with deuterium oxide. (i) Solvent: deuterium oxide.

EXPERIMENTAL

Melting points were determined on a Buchi capillary apparatus and are uncorrected. Ir spectra (potassium bromide) were obtained on a Perkin-Elmer 700A spectrophotometer. The nmr spectra were recorded on a 60 Mc Perkin-Elmer R-12 spectrometer and chemical shifts are reported in parts per million (δ) down-field from the TMS references. Uv spectra were determined in a Perkin-Elmer 350 spectrophotometer. Molecular weights of type II compounds were determined by the ebulloscopic method using acetic acid as solvent, molecular weights of type XI compounds were determined by the Rast method.

N-(Carboxysuccinoyl)- and *N*-(Carboxyglutaroyl)- α,ω -diamines (Ia, Ib, Ic, Id, Ie, If, Ig, and Ih).

To a suspension of succinic or glutaric anhydrides (0.09 mole) in ethanol (40 ml.) was added dropwise with stirring the corresponding diamine (0.09 mole) in ethanol (15 ml.); an exothermic reaction took place. The mixture was stirred for 45 minutes, allowed to cool, and the precipitate was collected and air-dried. No satisfactory recrystallization solvent could be found. Consequently, the solid was triturated thoroughly with dry chloroform and collected by filtration to give microcrystalline white products. Compounds Id and Ih resulted as non-crystalline yellow oils which were dissolved in absolute ethanol and allowed to react with ethereal hydrogen chloride to give the corresponding hydrochlorides. The hydrochlorides were washed with absolute ethanol and dried *in vacuo*. Dioxodiazacycloalkanes (IIa, IIb, IIc, IIf, and IIg).

Method A.

Type I compounds (0.034 mole) were heated in an oil bath with stirring at the melting point. The evolution of water was rapid and complete in a few minutes. The temperature was then lowered and with vigorous stirring, methanol was added. The suspension was filtered off and then the crystalline solid was recrystallized from the proper solvent (see Table I).

Method B.

A mixture of dimethyl succinate or dimethyl glutarate (0.064 mole), the corresponding diamine (0.064 mole) and a solution of sodium isopropoxide prepared from 40 ml. of isopropyl alcohol and 0.15 g. of sodium, was refluxed for 24 hours. The precipitate was collected and washed with isopropyl alcohol to give a white microcrystalline solid which was recrystallized from the proper solvent. The compounds obtained by this method were identical to those obtained by method A in all respects; molecular weight determinations: IIa: calculated: 142, found: 139, IIb: 156, (154); IIc: 156, (157); IId: 170, (172); IIf: 184, (181); IIg: 184, (182).

6,10-Dioxo-1,5-diazacyclodecane (IId).

The oily base of Id (20 g., 0.117 mole) was dehydrated by azeotropic distillation with toluene using methanesulfonic acid as catalyst. After 4 hours a yellow solid was obtained which was refluxed for 3 hours with absolute ethanol. The hot solution was filtered and then benzene was added. The clear solution was allowed to stand in the cold for 2 days to give a white solid, identical in m.p., mixed m.p., and ir with an authentic sample.

Attempts to Dehydrate type II Compounds.

Compounds IIa, IIb, IIc, and IId (0.008 mole) were azeotropically distilled with toluene and with 0.4 ml. of methanesulfonic acid as catalyst for 10 hours; no water distilled out at the end of this time. Cooling and filtering gave the starting material (identical in m.p., mixed m.p., and ir spectra with an authentic sample) in yields between 85% and 90%. The toluene solution evaporated *in vacuo* gave a mixture of unidentifiable products.

1,4-Disuccinimidobutane (XIe), 1,4-Diglutaramidobutane (XIg), and 1,5-Disuccinimidopentane (XIf).

Compounds IIf, or IIf, or IIg (0.008 mole) were azeotropically distilled with toluene and with 0.5 ml. of methanesulfonic acid as

catalyst until no more water distilled. Cooling crystallized the corresponding bisimides, which were recrystallized from the proper solvent; molecular weight determinations: XIe: calculated: 252, found: 250; XIg: 280, (278); XIh: 266, (268).

Acknowledgment.

We thank Dr. B. B. de Deferrari for microanalyses, Dr. B. Fernández for molecular weight determinations, and the Universidad de Buenos Aires and Consejo Nacional de Investigaciones Científicas y Técnicas for a research grant in support of this work.

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