Novel Heterotricyclic Systems: 2,6-Dioxa- and 2-Oxa-6-thia-10-azatricyclo-[5.2.1.$0^{4,10}$]decanes; 2,6-Dioxa-11-azatricyclo[5.3.1.$0^{4,11}$]undecane; and 9,13-Dioxa-14-azatetracyclo[6.5.1.$0^{2,7}$.$0^{11,14}$]tetradeca-2,4,6-triene (1a, b)

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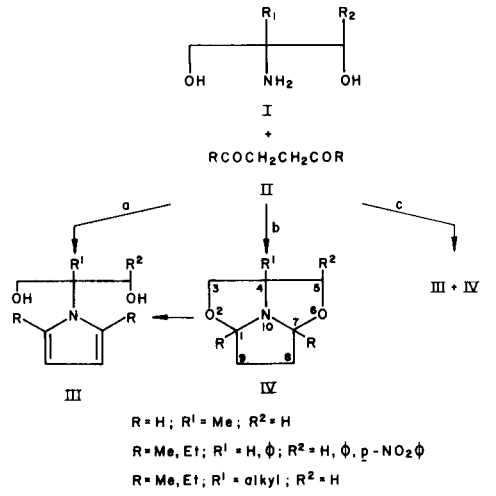
The acid-catalyzed condensation of 2-amino-1,3-propanediols and 1,4-diketones under water-azeotroping conditions has led to the first synthesis of the new tent-like, essentially strain-free heterotricyclic system, 2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane. Over thirty new compounds containing this system are reported. In cases where the aminodiol is unsubstituted or bears a phenyl substituent a mixture of the tricycle and the isomeric pyrrole resulted. These observations indicate alternative pathways in the Knorr-Paal condensation which lead to one, or the other, or both of these products. A scheme postulating common intermediates is presented. Examples of three additional, related, novel heteropolycyclic systems synthesized in analogous fashion are also reported.

J. Heterocyclic Chem., 13, 337 (1976).

The Knorr-Paal synthesis of pyrroles (3,4) and many of its modifications (5) are well-known; We have succeeded in synthesizing a number of highly sterically-crowded pyrroles by means of a Knorr-Paal type synthesis utilizing titanium tetrachloride in benzene as the condensation medium (6). However, the hydrogen-ion catalyzed condensation of the hindered amine, 2-amino-2-ethyl-1,3-propanediol with 2,5-hexanedione in a water-azeotroping solvent provided some novel and interesting results.

Figure 1

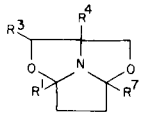


Instead of the expected pyrrole (path a, Fig. 1), a novel heterotricycle (path b, Fig. 1) was discovered, 1,7-dimethyl-4-ethyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]-decane (IV: R = Me, R^1 = Et, R^2 = H). Evidence ruled out any pyrrole character in the product: The compound formed a stable hydrochloride from which the free base could be recovered unchanged; it gave a negative test with bromine water and absorbed no hydrogen in attempted catalytic hydrogenation over platinum oxide. Infrared, proton magnetic resonance, and mass spectra and elemental analysis substantiated the fused tricyclic structure (IV, Fig. 1). Molecular models (Dreiding) show the new molecule to be tent-shaped, unstrained, but relatively rigid.

A considerable number of these tricyclic compounds have subsequently been prepared in these laboratories from various 2-amino-1,3-propanediols and 2,5-hexanedione or 3,6-octanedione. These compounds are presented in Table I.

In some cases, the tricycle was accompanied by the isomeric pyrrole (path c, Fig. 1). These pyrroles are listed in Table II. Especially interesting was the bright orange pyrrole derivative, 2-(2,5-dimethyl-1-pyrryl)-1-(*p*-nitrophenyl)-1,3-propanediol, which accompanied the colorless, isomeric tricycle 3-(*p*-nitrophenyl)-1,7-dimethyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane as a

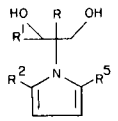
Table I



R^1, R^7	R_3	R^4	Procedure A reaction time (hours), solvent, acid catalyst	% Yield	B.p., °C/torr	M.p., °C	Analyses % C Calcd.	C Found	H Calcd.	H Found
CH_3-	H	H (a)	4, toluene, AcOH	19	29-31/0.05	132-133 dec. (b)	63.88	63.63	8.94	8.87
C_2H_5-	H	H (a)	5, toluene, TsOH	29	42-43/0.05		66.97	67.13	9.71	9.75
CH_3-	cyclohexyl	H	1, toluene, TsOH	77	60.5/0.01		71.67	71.86	10.03	10.14
CH_3-	*exo*-Ph	H (a)	1/4, toluene, TsOH	38	105-108/0.05	27-28	73.44	73.09	7.81	7.56
CH_3-	*endo*-Ph	H (a)	1/2, toluene, TsOH	41	82-83/0.05		73.44	73.63	7.81	7.84
CH_3-	*exo*-*p*-NO_2Ph	H (a)	3, toluene, AcOH	15		167-174 (b)	(b)			
CH_3-	H	CH_3	2, heptane, AcOH	50	68-70/15	56-58	65.64	65.34	9.35	9.47
CH_3-	H	C_2H_5	2, heptane, AcOH	50	83-84/6		66.97	67.03	9.71	9.55 (c)
CH_3-	H	*i*-C_3H_7	90, toluene, TsOH	22	47/0.05		58.12	58.29	8.88	8.98 (d)
CH_3-	H	Ph (a)	38, toluene, TsOH	43	90-92/0.05	73.5-75.5	73.44	73.32	7.81	7.84
CH_3-	H	CH_2OH	8, toluene, AcOH	63	153-156/20	80-82	(e)			
C_2H_5-	H	CH_3	120, toluene, TsOH	32	65-68/0.05		58.12	58.10	8.88	8.83 (d)
C_2H_5-	H	C_2H_5	60, toluene, TsOH	40 (d)	78-82/0.05	143-144 (d)	59.55	59.54	9.15	9.43
C_2H_5-	H	*i*-C_3H_7	72, cumene, TsOH	48 (d)	60-64/0.025	173-174 (d)	(f)			

(a) The isomeric pyrrole (Table II) was formed concurrently with the tricycle. (b) For the hydrochloride salt (See Experimental). (c) Calcd.: N, 7.10. Found: 7.19. (d) For the hydrochloride salt. (e) See Experimental. (f) For the hydrochloride salt. Calcd. for $C_{14}H_{26}ClNO_2$: Cl, 12.88; Found: Cl, 12.86.

Table II



R	R^1	R^2, R^5	% Yield	B.p., °C/torr or M.p., °C	C Calcd.	C Found	H Calcd.	H Found
H	H	CH_3	13	105-110/0.05	63.88	63.68	8.94	9.02
H	H	C_2H_5	36	135-140/0.05	66.97	66.81	9.71	9.74
H	Ph	CH_3	18	37-38	73.44	73.18	7.81	7.71
H	*p*-NO_2Ph	CH_3	15	151-151.5		(a)		
Ph	H	CH_3	8.5	77-87	73.44	73.36	7.81	7.84
CH_3	H	H	8	81-82		(a)		

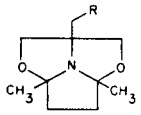
(a) *cf.* Experimental.

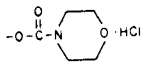
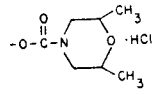
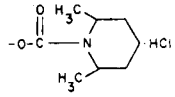
by-product in the reactions of L (+)-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and 2,5-hexanedione. Preliminary studies indicate that the pyrrole may exist as an intensely colored intramolecular charge-transfer complex.

Refluxing examples of the tricycles in 20% sulfuric acid resulted in complete hydrolysis to the starting materials, as would be expected from the ammonoketal structure. However, the system is stable to basic conditions and under such conditions several derivatives of 4-hydroxymethyl-1,7-dimethyl-2,6-dioxa-10-azatricyclo-[5.2.1.$0^{4,10}$]decane have been prepared. The 4-ethoxymethyl analog was prepared in 20% yield by the Williamson ether synthesis, and various esters of pharmacological interest were synthesized by ester interchange in refluxing heptane containing a catalytic amount of sodium. These compounds are presented in Table III.

All the fused cyclic compounds in this paper are named according to the von Baeyer bridge-type replacement system (Fig. 3) because of its simplicity and straightforwardness (7). For indexing purposes, at least, *Chemical Abstracts* prefers the Stelzner replacement-type name,

Table III



R	M.p., °C	B.p., °C/torr	% Yield	Proc.	Analyses, % Caled. C	Caled. H	Found N	Found C	Found H	Found N
-OC_2H_5·HCl	143 dec.		22		54.7	8.36	5.32	54.6	8.04	5.29
-O-C-CH_3 (O)		143/15	30		59.73	7.94	5.81	59.41	8.28	5.41
-O-C(O)-C(OH)-$(C_6H_5)_2$	116-116.5		60	B	70.40	6.65	3.42	70.52	6.55	3.40
-O-C(O)-C(OH)-$(C_6H_5)(C_6H_{11})$·HCl	140-150 dec.		67	B	63.7	7.51	3.10	63.4	7.60	2.85
-O-C(O)-C(OH)-$(C_6H_5)(C_5H_9)$·HCl	125-140 dec.		42	B	63.2	7.30	3.20	62.8	7.18	2.98
-O-C(O)-C(O)-C-CH_3 (C_6H_5)		176-180/4	8	C			3.90			4.12
-O-C(O)-C(OC_2H_5)-CH_3·HCl	125-135 dec.	245-250/20 (free base)	33	C	53.6	7.75	4.68	53.8	7.89	4.56
-O-C(O)-C(CH_3)-CH_3·HCl (CH_3)	120-130 dec.	176-178/20 (free base)	52	C	56.3	8.14	4.38	56.0	8.19	4.17
	125-135 dec.	245-250/20 (free base)	30	C	51.6	7.17	8.03	51.5	7.35	8.22
	120-134 dec.	235/13 (free base)	13	C	54.2	7.70		53.8	7.77	
-O-C(O)-N(H)-CH_2-CH_2-C_6H_5		dec.	43	C			8.09			7.80
	131-150 dec.	240-243/14 (free base)	48	C	57.7	8.02		57.5	8.11	

hexahydro-2*H*-1,4-dioxa-6b-azacyclopenta[*cd*]pentalene and the orientation shown (Fig. 3) rather than either the Hantzsch-Widman or von Baeyer systems (8,9).

Interesting variations in the tricyclic nucleus have also been achieved, (Fig. 2). 1,7-Dimethyl-2-oxa-6-thia-10-azatricyclo[5.2.1.$0^{4,10}$]decane was obtained by refluxing cysteinol and 2,5-hexanedione in a mixture of methylene chloride and ethanol. Use of 2,6-heptanedione or phthalaldehyde and 2-amino-1,3-propanediols resulted in compounds having the 2,6-dioxa-11-azatricyclo-[5.3.1.$0^{4,11}$]undecane and 9,13-dioxa-14-azatetracyclo-[6.5.1.$0^{2,7}0^{11,14}$]tetradeca-2,4,6-diene heterocyclic nuclei, respectively.

Figure 2

RING TYPES SYNTHESIZED

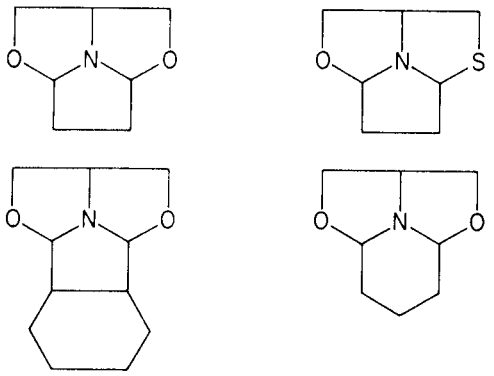
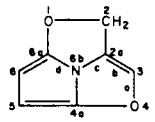


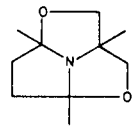
Figure 3

NOMENCLATURE

Stelzner Replacement Names

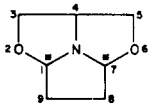


2H-1,4-Dioxa-6b-azacyclopenta-[cd]pentalene

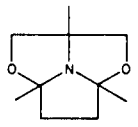


2a,4a,6a-Trimethylhexahydro-2H-1,4-dioxa-6b-azacyclopenta-[cd]pentalene

von Baeyer Bridge-type Replacement Names

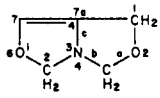


2,6-Dioxa-10-azatricyclo [5.2.1.0^{4,10}]decane

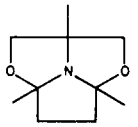


1,4,7-Trimethyl-2,6-dioxa-10-aza-tricyclo[5.2.1.0^{4,10}]decane

Hantzsch-Widman Fusion Names



1H,3H,5H-Oxazolo[3,4-c]oxazole



3,5,7a-Trimethyldihydro-3,5-ethano-1H,3H,5H-oxazolo[3,4-c] oxazole

Disucssion

The fused, tricyclic, tent-shaped and strain-free structure of these new compounds was substantiated by the infrared and nuclear magnetic resonance spectra of 1,7-dimethyl-4-hydroxymethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]-decane, obtained by refluxing an equimolar mixture of the readily available "THAM" (trishydroxymethylaminomethane) and 2,5-hexanedione (acetonylacetone) in toluene. The infrared spectrum was devoid of bands which could be attributed to a pyrrole nucleus and exhibited a characteristic triplet of bands between 1100 and 1000 cm^{-1} which appears to be typical of this tricyclic system. For this particular compound, these bands occur at 1035 (m), 1050 (s), and 1070 (s), cm^{-1} (potassium bromide). (In many instances the three bands also exhibited a shoulder or only partially resolved satellite band.) The assignments in the nmr spectrum are as follows (*cf.* Fig. 4): δ (deuteriochloroform): 1.36 (s, 6, CH_3), 1.95 (m, 4, J = 1.7, 10 Hz, A_2B_2), 3.00 (t, 1, d = 6, O*H*), 3.47 (d, 2, J = 6, CH_2OH), 3.72 (d, 2, J = 9 Hz, *A*B on C-3,5), 3.95 (d, 2, J = 9 Hz, A*B* on C-3,5) ppm. The band at δ 3.00 disappeared upon addition of deuterium oxide to the solution thus confirming it as being due to the -OH group.

Consideration of molecular models of the tricyclic nucleus shows that the methylene protons at C-8 (C-9) are non-equivalent and would be coupled with the adjacent methylene protons in a complex genuine A_2B_2 pattern in the nmr spectrum while the C-3 and C-5 protons would exhibit a pair of AB doublets. Confirmation of these predicted observations, together with the large geminal coupling constants (10 Hz and 9 Hz, respectively) verify the tent-like structure of the molecule. The nmr spectra of the 1,4,7-trimethyl analog, 1,4,7-trimethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane, and of the 1,4,7-trimethyl compound, and of the normethylbenzolog of the above tricycle, 11-hydroxymethyl-9,13-dioxa-14-azatetracyclo[6.5.1.0^{2,7}0^{11,14}]tetradeca-2,4,6-triene, particularly, were also useful in assigning chemical shifts (*cf.* Experimental).

The mass spectra were also consistent with the postulated tricycle structure and showed good molecular ion signals. Most remarkable of the major ionization fragments were those at m/e 98, 87, and 71. The first was exhibited by both the 1,4,7-trimethyl and the 1,7-dimethyl-4-hydroxymethyl compounds, probably due to the succinimidyl radical-ion and derived from C-1,7,8,9; O-2,6; and N-10. The peak at m/e 71, characteristic of the trimethyl compound, was probably due to the 2-methyl-2-methyleneoxiranyl radical-ion derived from C-3,4,5; Me at C-4; and O-2. The rather weaker signal at m/e 87, characteristic of the 1,7-dimethyl-4-hydroxymethyl compound, was probably due to the analogous 2-hydroxymethyl-2-methyleneoxiranyl radical-ion. (*cf.* Experimental).

The relatively rigid, tent-like shape of the tricycles causes groups in the 1, 4, and 7 positions to adopt a configuration in which they are thrust up above the "roof." In this configuration, these groups shield the nitrogen atom and its electron pair to such a degree that attempts to quaternize the 1,4,7-trimethylheterotricycle with methyl iodide failed. For this reason, several approaches for synthesizing the tricycle without alkyl

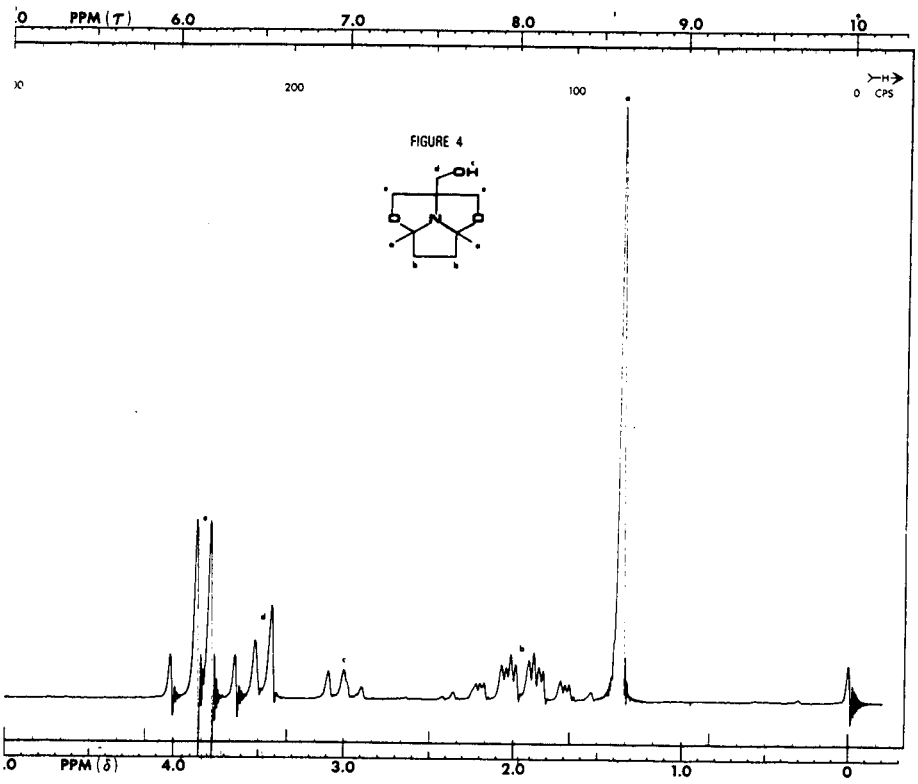


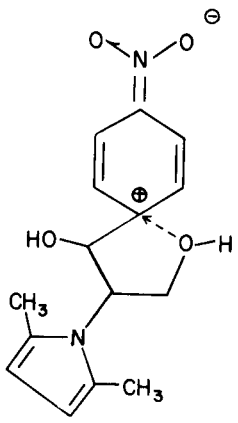
FIGURE 4

groups in the 1 and 7 positions were pursued, albeit unsuccessfully. The straight-forward synthesis with succinaldehyde was attempted, as was the *in situ* generation of succinaldehyde from 2,5-diethoxytetrahydrofuran. No heterotricycle was obtained due to polymerization of the succinaldehyde under the ensuing dehydrating reaction conditions. When 2-amino-2-methyl-1,3-propanediol was refluxed with 2,5-diethoxytetrahydrofuran in a mixture of 1:1 methanol-acetic acid, only 2-methyl-2-(1-pyrryl)-1,3-propanediol was obtained. There was no trace of the desired tricycle. The foregoing reaction conditions were repeated using 2,5-hexanedione in place of the 2,5-diethoxytetrahydrofuran, anticipating a mixture of the tricycle and the isomeric pyrrole, but this time only the tricycle was obtained.

These results suggest the existence of dual pathways in the Knorr-Paal condensation which may lead to the conventional pyrrole product or the newly discovered heterotricycle depending on kinetic and thermodynamic considerations. In support of this concept, we soon discovered six cases in which a mixture of the tricycle and isomeric pyrrole was produced from a given reaction. For instance, from the reaction of L (+)-*threo*-2-amino-1-*p*-nitrophenyl-1,3-propanediol (*cf.* Acknowledgments) with an equimolar amount of 2,5-hexanedione in toluene with acetic acid catalyst were isolated 1,7-dimethyl-*exo*-3-(*p*-nitrophenyl)-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]-decane and 2-(2,5-dimethyl-1-pyrryl)-1-*p*-nitrophenyl-1,3-propanediol in almost equal yields. The tricycle was a colorless, crystalline substance which easily formed a hydrochloride. The infrared spectrum was devoid of amine and hydroxyl stretching frequencies, and contained the three bands between 1100 and 1000 cm^{-1}, *e.g.*, 1075, 1059, 1035 cm^{-1}, which appear to be typical of the heterotricyclic system.

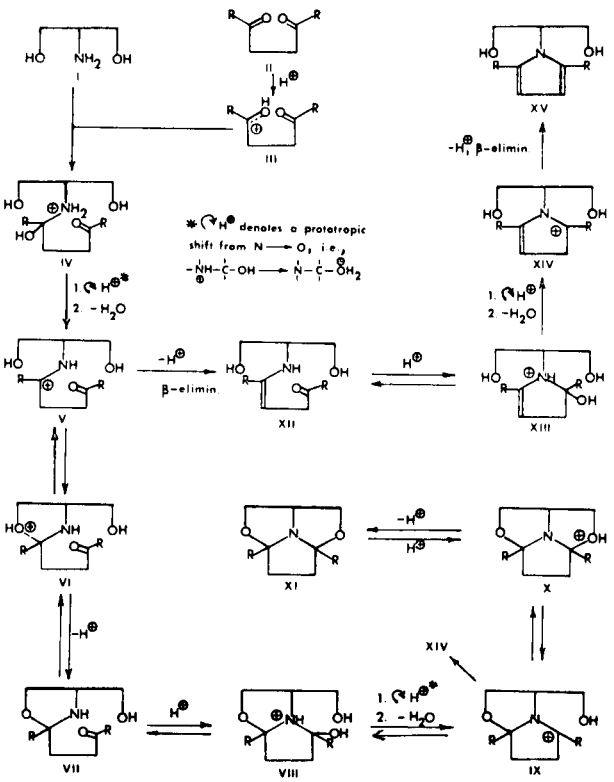
The pyrrole was isolated in the form of brilliant orange, ether-insoluble crystals, melting at 151°. The infrared spectrum of this compound exhibited a very strong, sharp OH stretching band at 3425 cm^{-1}. The methyl bending frequency occurred at 1395 cm^{-1}, a shift of +15 cm^{-1} from the methyl absorption of the tricycle, which would be expected if the methyl groups were attached to an aromatic ring. In addition, a strong band appeared at 749 cm^{-1} which is in the region attributed to out-of-plane deformation mode of the hydrogen atoms in the 3- and 4-positions of the pyrrole nucleus. The nmr spectra also support the indicated structures. A seemingly anomalous point in the structural evidence is the brilliant orange color of the compound. There appears to be no chromophore in the postulated structure that would lend such an intense color to the molecule. Careful purification did not alter its color, and only one spot appeared upon thin-layer chromatography thus negating the possibility of contamination by a highly-colored impurity. One possible

Figure 5



explanation of the orange color of the pyrrole is the formation of an intensely-colored charge-transfer complex formed between the *p*-nitrophenyl ring and the oxygen of the 3-hydroxy group or of the *p*-nitrophenyl ring and the π-excessive pyrrole moiety. While shown in Figure 5 as an σ-like complex, the compound more probably exists as a π-complex. Models emphasize the ease with which the oxygen of the 3-hydroxyl group can be drawn into position immediately beside the positively-charged carbon in the quinoid form of the *p-nitrophenyl* ring to give an unstrained, quasi five-membered ring. The quinoid form of the *p*-nitrophenyl system places a positive charge on the position *para* to the nitro group, lending partial carbonium ion character to the ring carbon atom which is most capable of bearing positive charge.

Figure 6



The mechanism for the concurrent production of the pyrrole and heterotricycle probably involves a common intermediate, V (Fig. 6). The most obvious explanation for the formation of two products from L (+)-*threo*-2-amino-*p*-nitrophenyl-1,3-propanediol is the decreased nucleophilicity of the 1-hydroxyl function due to electron withdrawal by the benzylic system. Thus the tendency of the intermediate, V, to undergo ring closure onto the tertiary carbonium ion is diminished and β-elimination of a proton occurs in place of cyclization, ultimately yielding the pyrrole rather than the tricycle.

Simultaneous production of a tricycle and the isomeric pyrrole was also observed in the reaction of 2,5-hexanedione with L (+)- and D (-)-*threo*-1-phenyl-, DL-*erythro*-1-phenyl-, 2-phenyl-2-amino-1,3-propanediols and 2-amino-1,3-propanediol, and in the reaction of 3,6-octanedione and 2-amino-1,3-propanediol. In contrast, no pyrrole was formed when 2-amino-1-cyclohexyl-1,3-propanediol was used as an example of an aminodiol bearing an electron-releasing group in the 1-position.

The possibility that pyrrole production could be accounted for by acid-catalyzed isomerization of tricycle to pyrrole (*i.e.*, XI → X → IX →→→ XV, Fig. 6) was investigated by refluxing a toluene solution of 1,7-dimethyl-*exo*-3-phenyltricycle with ten times the usual catalytic amount (0.3 molar equivalent) of acetic acid. Samples of the reaction mixture were periodically neutralized, extracted, dried, and examined by thin-layer chromatography and infrared spectrometry. The corresponding pyrrole was first detected in the six-hour sample. After 39 hours, the mixture exhibited much pyrrole and pyrrole polymer. These studies strongly suggest that the rates of formation of tricycle and pyrrole from postulated common intermediate V are faster (~ 1 hour) than isomerization (> 6 hours), at least for the *exo*-3-phenyl case, *i.e.*, routes V → XII →→→ XV and V → VI →→→ XI predominate over XI → X → IX →→→ XV and, therefore, that the pyrrole is the thermodynamically-controlled product and the tricycle is the kinetically-controlled product.

D (-)-*Threo*-2-amino-1-phenyl-1,3-propanediol and 2,5-hexanedione gave a tricyclic compound, 1,7-dimethyl-*exo*-3-phenyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane, the melting point, boiling point, and infrared spectrum of which were identical with those of the tricycle obtained from L (+)-*threo*-2-amino-1-phenyl-1,3-propanediol and 2,5-hexanedione. This was to be expected since the two

starting diols are simply enantiomers of one another. Optical rotations of the starting chiral aminodiols were $[\alpha]_D^{25}$ - 27° (c = 2.06 in methanol) and + 26.5° (c = 2 in methanol) for the D and L enatiomers, respectively. That the product tricycles are also enantiomers of one another was affirmed by measurement of the specific rotations of these compounds. The specific rotation of the heterotricyclic product obtained from the L (+)-*threo* isomer was $[\alpha]_D^{24}$ + 29.0° (c = 12.7 in ethanol). The product obtained from the D (-)-*threo* isomer had a specific rotation $[\alpha]_D^{24}$ = -28.8° (c = 2.2 in ethanol). That these two values are essentially equal in magnitude although opposite in sign demonstrates that racemization has not occurred during cyclization since it is extremely unlikely that if partial racemization had occurred that it would occur to precisely the same degree in the two synthetic procedures.

Molecular model manipulation according to the mechanism in Figure 6 also indicates that the heterotricycle prepared from L (+)- or D (-)-*threo*-2-amino-1-phenyl-1,3-propanediol has the 3-phenyl group located in the *exo* configuration and the heterotricycle prepared from D- or L-*erythro*-2-amino-1-phenyl-1,3-propanediol has the 3-phenyl group located in the *endo* configuration. Three items of experimental evidence substantiate this conclusion. First, the reactions, carried out under the same conditions of solvent, temperature and catalyst, were noticeably different in rate. The reaction in which L (+)-*threo*-2-amino-1-phenyl-1,3-propanediol was used required only one-half as long to go to completion (cessation of water production) as an identical reaction involving DL-*erythro*-2-amino-1-phenyl-1,3-propanediol. Such an observation would be expected if the *erythro* isomer of the starting aminodiol actually did give the *endo*-3-phenyl compound since this is a more hindered environment for phenyl group in step IX → X than in the *exo*-3-phenyl case. It is obvious from the reaction times listed in Table I that tricycle formation is very sensitive to the degree of steric hindrance in the product. The second observation leading to designation of one 3-phenyl tricycle as *endo* and the other *exo* was the difference in boiling point of the two compounds. The boiling point of the product obtained from DL-*erythro*-2-amino-1-phenyl-1,3-propanediol and 2,5-hexanedione (the *endo*-3-phenyl tricycle) was *ca.* thirty degrees lower than the tricycles obtained with the enantiomeric *threo*-aminodiols. The boiling point of the more spherical 1,7-dimethyl-*endo*-3-phenyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane would be expected to be lower than that of the *exo*-3-phenyl stereoisomer.

The third, and perhaps most compelling type of evidence, for the *exo*- and *endo*-assignments is furnished by their nmr spectra. The chemical shift of the singlet due to the methyl group closest to the phenyl group (at C-1 and C-3, respectively) is 0.20 ppm downfield of the singlet due to the other angular methyl group (at C-7) in the *exo*-3-phenyl tricycle whereas the corresponding difference is only 0.12 ppm in the *endo*-3-phenyl tricycle. This greater difference is attributed to the greater interaction of the 1-methyl group with the ring current of the *exo*-3-phenyl group (10). Similar influence of the phenyl group is apparent in the coupling pattern of the methylene protons at C-8 and C-9. In the *exo*-3-phenyl compound the spectrum shows the A_2B_2 pattern characteristic of the tricycles having no phenyl substituent. On the other hand, the *endo*-3-phenyl isomer displays a complex multiplet in the 1.5-2.5 ppm region: attributed to the nonequivalence of the two methylene proton pairs induced by the interaction of the closer of the two pairs with the phenyl ring, thereby causing a degeneration of teh A_2B_2 pattern to one more like ABCD pattern complexity.

EXPERIMENTAL

Elemental analyses were performed at B.Y.U. on a Coleman carbon, hydrogen and Coleman nitrogen analyzer of by MNW Laboratories, Garden City, Michigan. Infrared spectra were taken on Beckman IR-5, IR-7 or Perkin-Elmer 457 instruments. Nuclear magnetic resonance spectra were obtained on Varian A-60A and EM390 spectrometers. Melting points are uncorrected. Specific rotations were determined on a Rudolf Precision Model 80 polarimeter. Molecular weight determinations were made on a Mechrolab Model 301 vapor pressure osmometer. Distillations of small (*ca.*, 1 ml.) amounts of liquids were accomplished using the Craig concentric tube microdistillation apparatus (11).

Starting Materials.

2,6-Heptanedione was prepared by the reductive cleavage of 2,6-lutidine (12). Cysteinol was prepared by the reduction of ethyl cysteinate with lithium aluminum hydride (13).

1-Cyclohexyl-2-amino-1,3-propanediol.

L (+)-*Threo*-1-phenyl-2-amino-1,3-propanediol (16.7 g., 0.10 mole) and 4 g. 5% rhoduim on alumina in 150 ml. of glacial acetic acid were hydrogenated at *ca.* 50 psig. at room temperature for six days. During this time, the calculated amount of hydrogen was adsorbed. After filtration, most of the acid was removed by distillation, 50 ml. of saturated aqueous potassium carbonate and 50 ml. of concentrated aqueous potassium hydroxide were added to the residue, and the mixture was extracted continuously with ether for 24 hours. The product was recrystallized from ethyl acetate as colorless plates, 9.2 g. (53%), m.p. 105-105.5° (reported for DL-*threo* product, m.p. 112-113° (14); $[\alpha]_D^{24}$ = 0.0 (evidently racemization was complete); ir (potassium bromide); 3365(s), 3310(s), 2920(s), 2875(m), 2850(s), 1575(m), 1450(m), 1110(m), 1095(s), 1050(s) cm^{-1}; nmr very complex and poorly resolved but not inconsistent with structure proposed.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05. Found: C, 62.58; H, 11.30.

2-Amino-1,3-propanediol.

Paraformaldehyde was condensed with nitromethane to form 2-nitro-1,3-propanediol, which was then hydrogenated to the desired product over palladium-on-charcoal. (15).

2-Isopropyl-2-amino-1,3-propanediol.

Isobutyl alcohol (93 g., 1.25 moles) and powdered potassium iodide (415 g., 2.5 moles) were added to 372 g. of 95% phosphoric acid (prepared by mixing 82 g. of phosphorus pentoxide and 290 g. of commercial 85% orthophosphoric acid), and the mixture was refluxed 12 hours, cooled, diluted with 350 ml. of water and extracted twice with 250 ml. portions of ether. The combined extract was washed with 100 ml. of 10% aqueous sodium thiosulfate, then with 200 ml. of cold saturated brine, and dried over anhydrous magnesium sulfate. Filtration, evaporation, and distillation yielded 73.1 g. (32%) of isobutyl iodide boiling at 48-49°/55 torr.

Metathesis of the isobutyl iodide with silver nitrite gave a 73% yield of 2-methyl-1-nitropropane (16), from which 2-isopropyl-2-nitro-1,3-propanediol was obtained by condensation with formaldehyde (17). Finally, hydrogenation of the 2-isopropyl-2-nitro-1,3-propanediol in anhydrous ethanol over fresh W-2 Raney nickel at 1450 psig yielded 2-iospropyl-2-amino-1,3-propanediol, m.p. 70-72° (17).

2-Phenyl-2-amino-1.3-propanediol.

Phenylnitromethane was first prepared as per Organic Syntheses (18). Condensation with formaldehyde gave 2-phenyl-2-nitro-1,3-propanediol, 71% yield, m.p. 95-96° (19). Hydrogenation of the nitro compound dissolved in anhydrous ethanol over *freshly prepared* W-2 Raney nickel at 1200 psig for 1 hour followed by crystallization from toluene yielded 50-70% of 2-phenyl-2-amino-1.3-propanediol, m.p. 117.5-118.5° (20). The necessity of using *freshly prepared* Raney nickel is stressed, otherwise in our hands intractable mixtures of partly reduced material have resulted. The substitution of 5% palladium-on-charcoal as the hydrogenation catalyst leads to hydrogenolysis of the carbon-nitrogen bond resulting in the formation of 2-phenyl-1,3-propanediol, m.p. 46.5-48.5° [lit. m.p. 48.5-49° (21)].

Methyl mandelate was prepared in 61% yield by the method of Baer and Kates (22).

Methyl phenylglyoxalate.

This compound was prepared by *N*-bromosuccinimide oxidation of methyl mandelate (23). (The methanolysis of benzoyl cyanide yielded only methyl benzoate in our hands.) The 2,4-dinitrophenylhydrazone of methyl phenylglyoxalate, not previously reported, melts at 173-174° and 176-177° (polymorphic crystals).

Anal. Calcd. for $C_{15}H_{12}N_4O_6$: C, 52.33; H, 3.51; N, 16.28. Found: C, 52.79; H, 3.66; N, 16.12.

Methyl Cyclohexylphenylglycolate.

This compound was prepared in 23% yield from cyclohexylmagnesium bromide and methyl phenylglycolate by the procedure reported for ethyl cyclohexylphenyl glycolate (24), b.p. 161-163°/3.5 torr; ir (film): 3472(m), 3000(w), 2900(s), 2825(m), 1715(s), 1592(w), 1490(w), 1445(m), 1253(s), 1235(s), 1174(m), 1121(m), 730(s), 707(m), 696(m).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 62.37; H, 8.05.

Methyl cyclopentylphenylglycolate was prepared in the same manner as the cyclohexyl analog (24), b.p. 120-127°/0.25 torr.

4-Ethoxycarbonyl-2,6-dimethylmorpholine (25), 1-ethoxycarbonyl-2,6-dimethylpiperidine (26), and ethyl *N*-γ-phenethylcarbamate (27) were prepared according to the procedures cited.

Preparation of Heterotricycles.

Procedure A.

1,7-Dimethyl-4-hydroxymethyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]-decane.

A mixture of powdered 2-hydroxymethyl-2-amino-1,3-propanediol (121 g., 1.00 mole), 2,5-hexanedione (114 g., 1.00 mole) and glacial acetic acid (11.0 ml., 0.11 mole) in 250 ml. of toluene was refluxed in a one l. three-necked flask fitted with a stirrer and a Dean-Stark trap. (In some instances *p*-toluenesulfonic acid was used as the catalyst). After eight hours 38 ml. of water, 105 percent of the theoretical output (36 ml.), had been collected, and production of water had ceased.

Most of the toluene was removed by distillation, and the residue was neutralized with a minimum amount of saturated aqueous potassium carbonate (20 ml.). The organic layer was decanted from the aqueous phase, and the latter was extracted three times with ether. The combined organic fractions were dried over anhydrous potassium carbonate, filtered, and the ether evaporated. A brown oil was left which was vacuum distilled to yield 138 g. (69%) of colorless liquid, b.p. 153-156°/20 torr, wchich crystallized on standing, m.p. 73-74°. The m.p. was 80-82° after repeated recrystallization from hexane followed by sublimation; ir (film): 3470 (s, broad), 2975(s), 2930(m), 2870(s), 1470(w), 1447(w), 1380(s), 1330(m), 1290(m), 1260(s), 1230(m), 1167(m), 1135(s), 1108(s), 1070(s), 1050(s), 1035(m), 875(m), 843(m), 784(m), 736(m) 705(m), 660(m) plus numerous weaker bands in the "fingerprint" region; nmr, Fig. 4; mass spectrum: m/e, (ion) *199*(M), *184*(M-CH_3), 171, 170, 169(M-$(CH_3)_2$), 168(M-CH_2OH), 129, *98*(succinimidyl radical-ion), 87 (2-hydroxymethyl-2-methyleneoxiranyl radical-ion), 86, *43* (C_3H_7), 31 (CH_2OH). Strongest peaks are italicized.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.3; H, 8.6; N, 7.1.

The hydrochloride salt prepared in anhydrous ethereal hydrogen chloride melted at 206-208° dec.

Anal. Calcd. for $C_{10}H_{18}ClNO_3$: N, 5.94, Found: N, 5.82. Phenylurethane, m.p. 125-127°; 3,5-dinitrobenzoate, m.p. 169.5-170.5°.

1,4,7-Trimethyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane.

Ir (film): 2976(s), 2865(m), 1453(s), 1379(s), 1328(m), 1305(m), 1290(m), 1258(s), 1232(m), 1170(m), 1139(s), 1109(s), 1070(s), 1053(s), 863(s), 775(s), 638(s) cm^{-1}: nmr (deuteriochloroform): δ 1.29 (s, 3, Me at C-4), 1.37 (s, 6, Me at C-1,7), 1.92 (m, 4, A_2B_2 on C-8,9; J =1.7, 10 Hz), 3.72 (incipient AB pattern, 4,-CH_2- at C-3,5) ppm. (AB pattern at δ 3.72 was visible only with the higher resolution of a 90 MHz scan). Mass spectrum m/e (probable identity): *183*(M), 168(M-CH_3), *153*,(M-$(CH_3)_2$), 140, *138*, *113*, *112*, *98*, (succinimidyl radical-ion), *82*, *71* (2-methyl-2-methyleneoxiranyl radical-ion), 43 (C_3H_7), *42* (C_3H_6), *42* (C_3H_6), *29* (C_2H_5). Strongest peaks are italicized.

1,7-Dimethyl-2-oxa-6-thia-10-azatricyclo[5.2.1.$0^{4,10}$]decane.

Crude cysteinol prepared from 9.2 g. (0.062 mole) of ethyl cysteinate was refluxed for 36 hours with 2,5-hexanedione (3.4 g., 0.03 mole) in 50 ml. of absolute ethanol and 100 ml. of dichloromethane in a 250 ml. flask equipped with a modified Dean-Stark trap. Acetic acid (0.1 g., 0.0016 mole) was employed as catalyst. When water production had ceased, the solvents were removed by rotary evaporation, and the residue was treated as described in procedure A. Distillation of the crude product in an inert

atmosphere yielded one g. (18%) of colorless material, b.p. 50-55°/0.05 torr, which solidified in the condenser of the distillation apparatus, m.p. 28-30°; ir (capillary film): 2976(s), 2924(s), 2865(m), 1443(s), 1372(s), 1316(s), 1266(m), 1255(m), 1222(s), 1206(w), 1176(m), 1127(s), 1111(w), 1064(s), 1042(m), 1012(w), 947(m), 913(m), 880(w), 846(w), 816(m), 690(m), 661(m) cm^{-1}.

Anal. Calcd. for $C_9H_{15}NOS$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.23; H, 8.18; N, 7.76.

(+)-1,7-Dimethyl-*exo*-3-phenyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]-decane.

Prepared from L (+)-*threo*-2-amino-1-phenyl-1,3-propanediol($[\alpha]_D^{25}$ + 26.5° (c = 2 in methanol), optical purity 98%) by procedure A and separated from the accompanying pyrrole as described thereunder (*v.i.*). $[\alpha]_D^{24}$ + 29.0° (c = 12.7 in ethanol); ir (film): 3060(w), 3025(w), 2970(s), 2925(s), 2865(s), 1445(s), 1373(s), 1325(m), 1260(s), 1210(m), 1168(m), 1145(s), 1115(m), 1083(m), 1044(s), 1000(w), 978(w), 945(m), 858(s), 780(m), 755(s), 700(s), 670(m) cm^{-1}; nmr (deuteriochloroform): δ 1.34 (s, 3, CH_3 at C-7), 1.54 (s, 3, CH_3 at C-1), 2.0 (A_2B_2 pattern, 4, -CH_2CH_2- at C-8,9; J = 2.5, 8 Hz), 3.45 (d of t, 1, 4-H, J = 2.5,8) 3.96 (d, 2, 5-CH_2, J = 2.5), 4.56 (d, 1, 3-H, J = 8), 7.34 (s, 5, Ph) ppm.

(±)-1,7-Dimethyl-*endo*-3-phenyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]-decane.

Prepared from DL-*erythro*-2-amino-1-phenyl-1,3-propanediol by procedure A; ir (film): 3080(w), 3060(w), 3030(w), 2970(s), 2925(s), 2860(s), 1600(w), 1495(m), 1473(w), 1445(s), 1375(s), 1325(m), 1270(s), 1250(s), 1219(s), 1167(s), 1140(s), 1110(m), 1078(m), 1060(w), 1035(s), 1002(m), 998(m), 915(m), 878(m), 858(m), 831(s), 768(m), 701(s), 674(m) cm^{-1}; nmr (deuteriochloroform): δ 1.36 (s, 3, CH_3 at C-7), 1.48 (s, 3, CH_3 at C-1), 1.7-2.5 (m, 4, -CH_2CH_2- at C-8,9), 3.45 (m, 2, -CH_2- at C-5, J = 5.5, 8.5), 3.90 (q, 1, 4-H, J = 5.5), 5.40 (d, 1, 3-H, J = 5.5), 7.28 (s, 5, Ph) ppm.

1,7-Dimethyl-4-phenyl-2,6-dioxa-10-azaticyclo[5.2.1.$0^{4,10}$]decane.

Prepared from 2-amino-2-phenyl-1,3-propanediol by procedure A; ir (film): 3055(w), 3020(w), 2970(s), 2930(m), 2860(s), 1600(w), 1487(m), 1445(s), 1375(s), 1325(m), 1330(m), 1260(s), 1170(s), 1120(s), 1065(s), 1042(s), 1005(m), 860(s), 760(s), 700(s) cm^{-1}; nmr (deuteriochloroform): δ 1.37 (s, 6, CH_3 at C-1,7), 2.06 (A_2B_2, 4, -CH_2CH_2- at C-8,9; J = 1.6, 9 Hz), 3.95 (d, 2, *AB* pattern on C-3,5, J = 8.5), 4.16 (d, 2, A*B* pattern on C-3,5, J = 8.5), 7.32 (m, 5, phenyl) ppm.

1,7-Dimethyl-*exo*-3-(*p*-nitrophenyl)-2,6-dioxa-10-azatricyclo-[5.2.1.$0^{4,10}$]decane.

A mixture of L (+)-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (21.2 g., 0.100 mole), 2,5-hexanedione (12.5 g., 0.110 mole), and glacial acetic acid (2.0 ml.) in toluene (200 ml.) was refluxed for three hours in a 500 ml. round-bottomed flask equipped with a Dean-Stark trap. Total water evolution was 5.7 ml., 158% of the theoretical amount (3.6 ml.).

The solution was distilled carefully until 30 ml. of toluene remained. (Under no circumstances should the product mixture be heated or distilled since it has been found to decompose violently under these conditions.) The mixture was evaporated to a heavy oil on the rotary evaporator, treated with a saturated aqueous solution of potassium carbonate, and the organic layer was taken up in ether, dried over anhydrous potassium carbonate, and filtered.

After removal of the by-product pyrrole, treatment of the remaining ether solution with ethanolic hydrogen chloride gave a precipitate which was crystallized from ethanol to give 5.0 g. (15%) of tan crystals, m.p. 167-174°, which turned deep red and decomposed upon melting.

Conversion to the free base was accomplished by treating an aqueous soluiton of the hydrochloride with potassium carbonate to give a colorless crystalline product, which was recrystallized from anhydrous ethanol to yield 3.0 g. of colorless crystals, m.p. 107-107.5°; ir (potassium bromide-hydrochloride): 3106(w), 2933(m), 2857(m), 1605(m), 1511(vs), 1377(m), 1342(vs), 1144-(s), 1059(s), 1036(s), 945(m), 857(s), 845(s), 77(s), 747 (s), 706(m) cm^{-1}; nmr (DMSO-d_6): δ 1.29 (s, 3, CH_3 at C-7), 1.46 (s, 3, CH_3 at C-1), 2.00 (m, 4, -CH_2CH_2- at C-8,9), 3.36 (fused m, 2, -CH_2- at C-5) 4.06 (m, 1, CH at C-4, absorbed water peak overlays it), 4.76 (d, 1, CH at C-3) 7.76 and 8.28 (d of d, 4, *p*-phenylene, J = 7.5 Hz) ppm.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$·HCl: C, 55.2; H, 5.82; mol. wt. 290. Found: C, 55.0; H, 5.99; mol. wt. 279 (osmometry).

1,4,7-Trimethyl-1,6-dioxa-11-azatricydo[5.3.1.$0^{4,11}$]undecane.

2,6-Heptanedione (4.3 g., 0.034 mole), 2-amino-2-methyl-1,3-propanediol (3.5 g., 0.034 mole) and 0.1 g. of *p*-toluenesulfonic acid were mixed in 10 ml. of toluene refluxed six hours (1.1 ml. of water collected in the Dean-Stark trap), and then processed as described in Procedure A. Distillation yielded 1.8 g. (27%) of the tricycle, b.p. 68-70°/0.05 torr. This fraction was further purified by solution in ether, precipitation of the hydrochloride by addition of dry ethereal hydrogen chloride, and recrystallization of the hydrochloride from ethyl acetate followed by sublimation, m.p. 152-170° (sealed tube); ir (nujol): 2700(w), 2620(w), 2550(w), 2460(m), 1332(m), 1303(w), 1260(m), 1222(w), 1199(w), 1179-(w), 1179(w), 1162(w), 1067(s), 1039(w), 1020(w), 944(w), 905(m), 830(m), 800(m) cm.

Anal. Calcd. for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.63. Found: C, 56.61; H, 8.79.

11-Hydroxymethyl-9,13-dioxa-14-azatetracyclo[6.5.1.$0^{2,7}0^{11,14}$]-tetradeca-2,4,6-triene.

2-Hydroxymethyl-1,3-propanediol (2.5 g., 0.021 mole), *o*-phthalaldehyde (2.7 g., 0.021 mole), 0.1 g. of *p*-toluenesulfonic acid, and 40 ml. of toluene were refluxed in a 250 ml. round-bottom flask equipped with a Dean-Stark trap until water production ceased (0.7 ml. over a three-hour period). The product mixture was treated as in procedure A. Evaporation of the ether left a colorless, crystalline residue which was recrystallized from toluene and sublimed to yield 3.5 g. (80%) of crystalline compound, m.p. 125.5-126.5°; ir (potassium bromide): 3330 (s, broad), 3020(w), 2975(w), 2925(m), 2880(m), 2850(m), 1460(w), 1367(s), 1246(m), 1220(m), 1135(m), 1072(s), 1028(m), 955-(m), 863(m), 760(s) cm^{-1}; nmr (deuteriochloroform): δ 3.25 (broad s, 1, O*H*), 3.64 (s, 2, CH_2OH), 3.75 (d, 2, *AB* pattern on C-3,5, J = 9), 4.06 (d, 2, A*B* pattern on C-3,5, J = 9), 5.84 (s, 2, 3°H, α to O, N, Ph), 7.38 (s, 4, *o*-phenylene) ppm.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 65.97; H, 5.76.

11-Methyl-9,13-dioxa-14-azatetracyclo[6.5.1.$0^{2,7}0^{11,14}$]tetra-deca-2,4,6-triene.

o-Phthalaldehyde (1.34 g., 0.010 mole), 2-amino-2-methyl-1,3-propanediol (1.05 g., 0.010 mole), 1 drop of glacial acetic acid and 10 ml. of toluene were refluxed in a Dean-Stark trap-

equipped, small, round-bottom flask until no more water formation was evident (12 hours). The mixture was treated as in Procedure A, and the crude product distilled to yield 0.3 g. (18%) of the tricyclic compound, b.p. 87-90° torr, which solidified in the receiver, m.p. 55.5-56.5°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45. Found: C, 70.95; H, 6.52.

Hydrochloride salt (from ethyl acetate), m.p. 133.5-135.5°.

Isolation of Pyrroles.

1-(*p*-nitrophenyl)-2-(2,5-dimethylpyrryl)-1,3-propanediol.

As the last of the ether extract resulting from the preparation of 1,7-dimethyl-3-*exo*-(*p*-nitrophenyl)-2,6-dioxa-10-azatricyclo-[5.2.1.$0^{4,10}$]decane was being evaporated a red precipitate began to form. After removal of all the ether the small amount of residual toluene remaining in the flask was removed by blowing a stream of dry air into the flask while rotating it. When the product had reached the consistency of a red-brown sludge, 300 ml. of anhydrous ether was added, whereupon a dark red precipitate formed. This precipitate was separated by filtration and recrystallized from ethyl alcohol to yield 4.0 g. (14%) of bright orange product [2-(2,5-dimethyl-1-pyrryl)-1-*p*-nitrophenyl-1,3-propanediol)] which melted at 151-151.5° after recrystallization from anhydrous ethanol; ir (potassium bromide): 3436(s), 3106(w), 291(m), 2874(m), 1605(m), 1517(s), 1395(s), 1348(vs), 1292(m), 1193(m), 1972(m), 1047(s), 863(m), 827(m), 749(s), 734(m), 704(m), 697(m) cm^{-1}; nmr (DMSO-d_6): δ 1.76 (s, 3, CH_3), 2.42 (s, 3, CH_3), 3.4 (broad s, 1, OH), 3.80 (d, 2, -CH_2OH, J = 7.5 Hz), 4.21 (q, 1, H at C-2, J = 7.5), 5.14 (d, 1, H at C-1, J = 7.5), 4.4-6.1 (very broad, 1, OH), 5.50 and 5.64 (d of d, 2, H at C-3,4 of pyrrole moiety, J = 3) 7.53 and 8.10 (d of d, 4, *p*-phenylene, J = 9) ppm. Addition of deuterium oxide to the nmr sample caused disappearance of the broad OH peak plus a slight (>0.1 ppm) downfield shift of the remaining signals.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.21; N, 9.66; mol. wt. 290. Found: C, 61.9; H, 6.37; N, 9.50; mol. wt. 292.

2-Methyl-2-(1-pyrryl)-1,3-propanediol.

2-Amino-2-methyl-1,3-propanediol (2.63 g., 0.025 mole), 2,5-diethoxytetrahydrofuran (4.0 g., 0.025 mole), 2 ml. of acetic acid and 2 ml. of methanol were refluxed for six days. The mixture was then cooled, diluted with water and basified with potassium carbonate to *p*H 8-9. The brown oil which separated was taken up in ether, dried over anhydrous potassium carbonate, filtered, the ether evaporated off, and the residue distilled to yield 0.3 g. (8%), b.p. 190-194°/12 torr, of material which solidified on standing. Recrystallization from ethanol/petroleum ether gave white plates, m.p. 81-82°; ir (potassium bromide): 3257(s), 3086(w), 722.5(s) cm^{-1}; nmr (deuteriochloroform): δ 1.46 (s, 3, Me at C-2), 2.30 (broad s, 2, -OH), 3.81 (s, 4, -CH_2OH), 6.20 (m, 2, H at C-3,4 of pyrrole moiety), 6.88 (m, 2, H at C-2,5 of pyrrole moiety) ppm.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.92; H, 8.44; N, 9.03; mol. wt. 155. Found: C, 62.3; H, 8.53; N, 9.16; mol. wt. (osmometry) 158.

1-Phenyl-2-(2,5-dimethyl-1-pyrryl)-1,3-propanediol.

A portion of the residue left in the flask after distillation of 1,7-dimethyl-3-*exo*-phenyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]-decane was subjected to preparative thin-layer chromatography on 0.5 mm silica gel G plates, using 2:1 chloroform:ethyl acetate as the eluting solvent. The isomeric pyrrole, R_f = 0.60, was extracted from the silica gel and cooled to -20° at which temperature it solidified, m.p. 37-38°. Preparative thin-layer chromatography of 7% of the original mixture of the isomeric pyrrole and tricycle indicated an extrapolated yield of 18% of the pyrrole; ir (film): 3430 (s, broad), 3100(w), 3060(w), 3030(w), 2970(s), 2920(m), 2890(m), 1515(m), 1490(m), 1450(s), 1392(s), 1290(s), 1055(s), 1005(s), 758(s), 703(s) cm^{-1}.

2-Phenyl-2-(2,5-dimethyl-1-pyrryl)-1,3-propanediol.

This pyrrole was isolated from the residue left in the flask after distillation of the isomeric tricycle by preparative thin-layer chromatography on 0.5 mm silica gel G plates, eluting with a 1:1 mixture of chloroform and ethyl acetate, R_f = 0.50. Seventy mg. was isolated from 0.30 g. of the residue (total weight 1.35 g.) to give an extrapolated yield of 0.31 g. (9%). The product crystallized on cooling to -20°, m.p. 74-84°; m.p. 77-87° after sublimation; ir (potassium bromide): 3490(s), 3395(m), 3300(m), 2055(w), 2920(m), 1488(w), 1443(m), 1380(s), 1275(s), 1168(m), 1088(s), 1078(m), 1062(s), 1040(m), 1023(m), 983(s), 912(w), 897(w), 775(m), 761(s), 755(s), 700(s) cm^{-1}; nmr (deuteriochloroform): δ 1.51 (s, 6, CH_3 at C-2,5 of pyrrole moiety), 4.07 (d of d, 4, AB pattern of CH_2 OH, evidently restricted rotation around axis of C-1 to C-2 and C-2 to C-3 bonds), 5.92 (s, 2, H at C-3,4 of pyrrole moiety), 7.4 (m, 5, phenyl) ppm.

2-(2,5-Dimethyl-1-pyrryl)-1,3-propanediol.

Following distillation of the isomeric tricycle from the reaction mixture of 2-amino-1,3-propanediol and 2,5-hexanedione continued distillation gave 1.25 g. (9% of the pyrrole, b.p. 105-110°/-0.05 torr (bath temperature 190-205°). Thin-layer chromatography of the original mixture (R_f 0.80 and 0.65 for pyrrole and tricycle, respectively, on silica gel with acetone) gave an extrapolated yield of 1.8 g. (13%) of the pyrrole; ir (film): 3420(s), 3090(w), 2930(s), 1515(w), 1442(m), 1395(s), 1293(s), 1055(s), 1010(s), 758(s) cm^{-1}; nmr (deuteriochloroform): δ 2.22 (s, 6, Me at C-2,5 of pyrrole moiety), 2.93 (s, 2, -OH), 3.88 (d, 4, -CH_2OH, J = 7), 4.32 (quintet, 1, H at C-3, J = 7), 5.77 (s, 2, H at C-3,4 of pyrrole moiety) ppm.

2-(2,5-Diethyl-1-pyrryl)-1,3-propanediol.

This pyrrole was isolated in the same fashion as its 2,5-dimethyl counterpart eluting it from silica gel G with 1:1 chloroform-ethyl acetate, R_f 0.5.

Derivatives of 4-Hydroxymethyl-1,7-dimethyl-2,6-dioxa-10-azatricyclo[5.2.1.$0^{4,10}$]decane

1,7-Dimethyl-4-ethoxymethyl-2,6-dioxa-10-azatricylco[5.2.1.0-^{4,10}]decane.

1,7-Dimethyl-4-hydroxymethyl-2,6-dioxa-10-azatricyclo-[5.2.1.$0^{4,10}$]decane (20 g., 0.10 mole) and sodium metal (2.3 g., 0.10 mole) were stirred together for eight hours in anhydrous tetrahydrofuran and allowed to stand overnight. Stirring was then resumed and ethyl bromide (10.9 g., 0.10 mole) was added dropwise to the sodium alkoxide solution. After refluxing the mixture for one hour the excess alkoxide was destroyed by the additon of water (20 ml.) which caused an organic phase to separate as a supernatant layer.

The organic layer was dried over anhydrous potassium carbonate, diluted with ether, and redried. After filtration and evaporation of the ether, a brown oil remained, which was vacuum distilled to yield 5.0 g. (22%) of the free base. Conversion to the hydrochloride gave 5.0 g. (19%) of colorless crystals, m.p. 143°; ir (film): 2959(m), 2849(m), 1445(w), 1374(m), 1255(m), 1134-(m), 1109(s), 1066(s), 780(m) cm^{-1}.

4-Acetoxymethyl-1,7-dimethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane.

4-Hydroxymethyl-1,7-dimethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane (3.0 g., 0.015 mole) and acetyl chloride (1.25 g., 0.016 mole) were mixed in 50 ml. tetrahydrofuran, and triethylamine (1.5 g., 0.015 mole) was added dropwise with stirring. After stirring for one-half hour the solid material (triethylamine hydrochloride, 2.0 g.) was filtered off. The tetrahydrofuran was removed by rapid evaporation, and the residual yellow liquid was distilled to yield 1.2 g. (33%) of 4-acetoxymethyl-1,7-dimethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane, b.p. 143-144°/15 torr.

Procedure B

1,7-Dimethyl-4-cyclopentylphenylglycollyloxymethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane.

Sodium metal (0.2 g.) was added in small pieces to a refluxing solution of 1,7-dimethyl-4-hydroxymethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane (10.6 g., 0.053 mole) in heptane (100 ml.) which was contained in a three-necked flask fitted with a stirrer and Dean-Stark trap. When the sodium had reacted a 50% solution of methyl cyclopentylphenylglycollate (12.6 g., 0.053 mole) in heptane was added dropwise with vigorous stirring of the reaction mixture.

After one hour 1.7 ml. of methanol had collected in the trap (theoretical yield 2.2 ml.) and its formation had ceased. Seventy-five ml. of heptane was removed slowly by distillation over a period of one hour. The reaction was then cooled, diluted with water and the resulting brown supernatant layer was taken up in ether and separated from the aqueous phase. After drying over anhydrous potassium carbonate the ether solution was filtered, and the ether was evaporated leaving a brown oil, which solidified on cooling. Recrystallization from heptane followed by one washing with petroleum ether and vacuum drying yielded 9.0 g. (42%) of cream-colored crystals, m.p. 111-112°; ir (potassium bromide): 3521(m), 2959(m), 2857(m), 1712(s), 1247(vs), 1067(vs), 868(m), 699(m) cm^{-1}.

The free base was converted to the hydrochloride salt by dissolving in ether and adding ethanolic hydrogen chloride to give 8.0 g. of white crystals, m.p. 125-140°.

Procedure C.

1,7-Dimethyl-4-pivaloyloxymethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane.

Sodium metal (0.2 g.) was added slowly in small pieces to a refluxing solution of 1,7-dimethyl-4-hydroxymethyl-2,6-dioxa-10-azatricyclo[5.2.1.0^{4,10}]decane (10 g., 0.05 mole) in heptane (100 ml.) which was contained in a three-necked flask fitted with a stirrer and Dean-Stark trap.

When most of the sodium had reacted, ethyl pivalate (6.5 g., 0.05 mole) was added dropwise, and the product ethanol was removed from the reaction mixture *via* the heptane azeotrope. Since ethanol and heptane are miscible, unlike methanol and heptane, the distillate was allowed to drain continuously from the bottom of the trap, and the heptane solvent was replaced as needed. The progress of the reaction was followed by noting the evolution of hydrogen from a sample of the distillate when metallic sodium was added. When production of ethanol had ceased (about 6 hours) the remainder of the heptane was removed and the solution was cooled and treated with potassium carbonate solution. The brown supernatant layer was taken up in ether, dried over anhydrous potassium carbonate, and filtered. Evaporation of ether left a brown oil, which upon vacuum distillation yielded 7.4 g. (52%) of the colorless product, b.p. 168-178°/20 mm; ir (film): 2967(m), 2865(m), 1733(s), 1484(m), 1285(s), 1295(s), 1199(s), 1156(vs), 870(m), 779(m) cm^{-1}.

The compound was converted to the hydrochloride by the dropwise addition of ethanolic hydrogen chloride to an anhydrous ether solution of the free base. The product was recrystallized from ethyl acetate to give 6.0 g. of white crystals, m.p. 120-130°.

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