CYCLOHEXANE COMPOUNDS

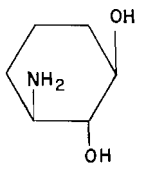
II. SYNTHESIS AND STRUCTURE OF TWO STEREOISOMERIC 3-AMINO-1,2-CYCLOHEXANEDIOLS[1,2]

R. A. B. BANNARD AND L. R. HAWKINS

ABSTRACT

The stereoisomeric 1-ethoxy-2,3-epoxycyclohexanes were prepared from 1-ethoxycyclohexene-2 via 1-ethoxycyclohexene-2 bromohydrin. Ammonolysis of the lower- and higher-boiling oxides furnished 1α-ethoxy-2β-hydroxy-3α-aminocyclohexane and 1α-ethoxy-2α-hydroxy-3β-aminocyclohexane respectively. In a similar manner, 1α-methoxy-2β-hydroxy-3α-aminocyclohexane and 1α-methoxy-2α-hydroxy-3β-aminocyclohexane were obtained from 1-methoxycyclohexene-2 via 1-methoxycyclohexene-2 bromohydrin and the stereoisomeric 1-methoxy-2,3-epoxycyclohexanes. Ether cleavage of 1α-ethoxy- and 1α-methoxy-2β-hydroxy-3α-aminocyclohexane gave 3α-amino-1α,2β-cyclohexanediol hydrobromide, from which the free base was obtained. 3β-Amino-1α,2α-cyclohexanediol was prepared similarly from 1α-ethoxy- and 1α-methoxy-2α-hydroxy-3β-aminocyclohexane. The stereochemistry of the 3-amino-1,2-cyclohexanediols, 1-alkoxy-2-hydroxy-3-aminocyclohexanes, and 1-alkoxy-2,3-epoxycyclohexanes has been elaborated.

In 1947 Mousseron and co-workers (1, 2, 3) prepared an ethoxyaminocyclohexanol of unknown structure by ammonolysis of 1-ethoxy-2,3-epoxycyclohexane, and in 1952, McCasland *et al.* (4) obtained a similar substance, m.p. 132–134°, in the same manner as Mousseron *et al.* (1, 2, 3). The compound was characterized as the N-*p*-nitrobenzoyl derivative, m.p. 201–203°, and was converted on ether cleavage with hydrobromic acid



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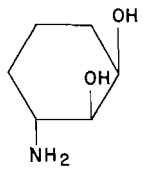

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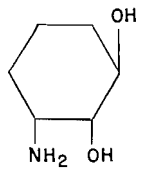

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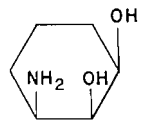

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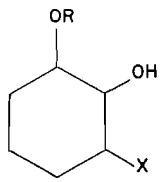

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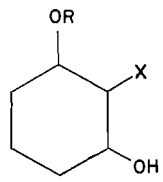

(VI)

[1]*Manuscript received April 15, 1958.*
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[2]*For Part I of this series see reference 12.*

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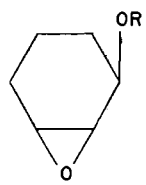
to an aminocyclohexanediol hydrobromide, m.p. 167–168°. The N-*p*-nitrobenzoyl derivative of the latter compound (m.p. 182–183°) rapidly consumed 1 mole of periodate, thus showing the aminediol to be a 3-amino-1,2-cyclohexanediol. McCasland *et al.* (4) did not assign a stereochemical structure to the substance but pointed out that of the four possible structures (I to IV) only I and II are probable, since oxide ring opening usually yields *trans*-oriented products (5, 6). The present communication describes the synthesis and assignment of structure to two isomeric 3-amino-1,2-cyclohexanediols and to the 1-alkoxy-2,3-epoxycyclohexanes and 1-alkoxy-2-hydroxy-3-aminocyclohexanes used as intermediates in their preparation.

Mousseron *et al.* (1, 2, 3) and McCasland *et al.* (4) had prepared 1-ethoxy-2,3-epoxycyclohexane, either by peracid oxidation of 1-ethoxycyclohexene-2, or by the action of aqueous alkali on 1-ethoxycyclohexene-2 chlorohydrin (V or VI; R = C_2H_5, X = Cl). The chlorohydrin, which was obtained (1, 3, 4) by interaction of monochlorourea (7, 8) and 1-ethoxycyclohexene-2, was considered by McCasland *et al.* (4) to possess structure VI (R = C_2H_5, X = Cl). No proof was submitted in support of this structure nor was it demonstrated that the chlorohydrin thus obtained consists of a mixture of isomers. In 1942 Moir (9), McRae (10), and co-workers studied the reaction between 1-methoxycyclohexene-2 and monochlorourea, and found that a mixture of isomeric chlorohydrins (V or VI; R = CH_3, X = Cl) was formed together with 1-methoxycyclohexene dichloride. It did not prove possible to separate the isomeric chlorohydrins from each other or completely from the dichloride by fractional distillation. The chlorohydrin mixture on treatment with aqueous alkali yielded a mixture of stereoisomeric 1-methoxy-2,3-epoxycyclohexanes (VII and VIII; R = CH_3), demonstrating the presence of at least two isomeric chlorohydrins in the mixture. Somewhat later, but prior to the work of Mousseron *et al.* (1, 3) and McCasland *et al.* (4), Fenton (11) showed that 1-ethoxycyclohexene-2 on treatment with monochlorourea led to a mixture of isomeric chlorohydrins (V or VI; R = C_2H_5, X = Cl) which in turn gave two stereoisomeric 1-ethoxy-2,3-epoxycyclohexanes (VII and VIII; R = C_2H_5). Fenton (11) did not make it clear whether or not 1-ethoxycyclohexene dichloride was present in the chlorohydrin mixture. Repetition of Fenton's work revealed that 1-ethoxycyclohexene dichloride is indeed present. Numerous attempts to separate the chlorohydrin–dichloride mixture by fractional distillation proved fruitless (see Table III).



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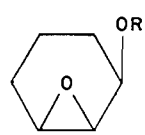


(VIII)

The presence of dichlorides in the 1-alkoxycyclohexene-2 chlorohydrins detracts from their usefulness for preparation of the corresponding oxides, since both the *trans*-, or lower-boiling, oxide (VII) and the *cis*-, or higher-boiling, oxide (VIII) were contaminated with chlorinated substances (10). Furthermore, the fact that the isomeric chlorohydrins are not readily separable makes them impractical as intermediates for preparation of

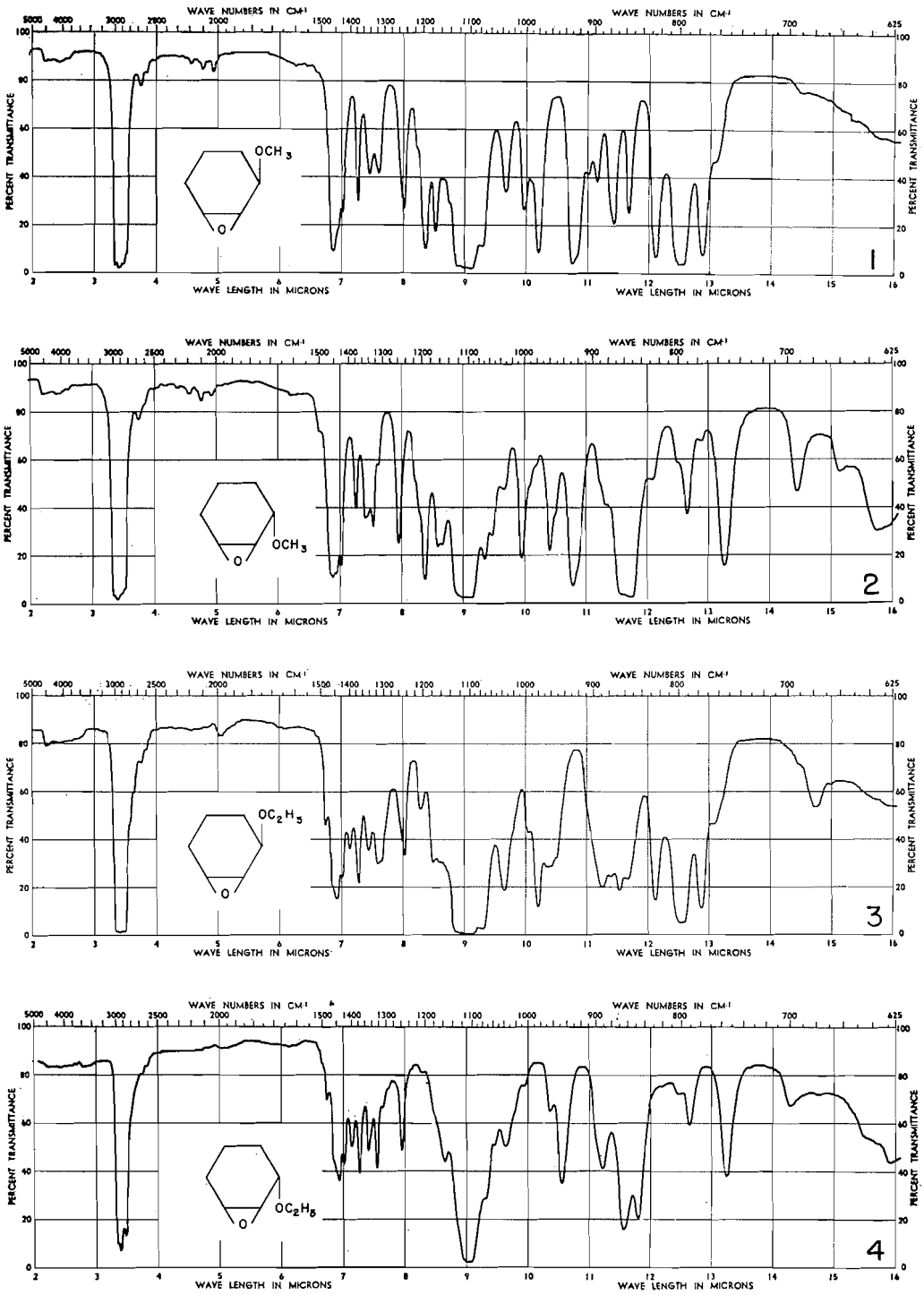
the 1-ethoxy-2-hydroxy-3-aminocyclohexanes by direct ammonolysis (12) because it has been found in the present investigation that separation of the resultant stereoisomeric amines is too laborious. Attention was therefore turned to preparation of the corresponding bromohydrins in the hope that either or both disadvantages characteristic of the chlorohydrins would be eliminated.

For many years the structures of the 1-methoxy-2,3-epoxycyclohexanes remained unassigned. Recently, however, it has been shown by Lemieux, Kullnig, and Moir (13) via proton magnetic resonance spectroscopy on the 1,3-dimethoxy-2-acetoxycyclohexanes resulting from acetylation of the products of methanolysis of the 1-methoxy-2,3-epoxycyclohexanes, that the lower-boiling isomer (the so-called α-isomer (10)) has the *trans*-configuration and the higher-boiling isomer (the so-called β-isomer (10)) the *cis*-configuration. This work, however, still left unsettled the configurations of Fenton's 1-ethoxy-2,3-epoxycyclohexanes. It will be demonstrated in the sequel that in this case also, the lower-boiling oxide is the *trans*-isomer and the higher-boiling oxide the *cis*-isomer.

1-Methoxy- and 1-ethoxycyclohexene-2 were prepared by modification of the method of Gogek *et al.* (14). 1-Methoxycyclohexene-2 on treatment with N-bromosuccinimide in aqueous suspension (cf. Guss and Rosenthal (15)) gave a mixture of isomeric 1-methoxycyclohexene-2 bromohydrins (V or VI; R = CH_3, X = Br) in 77% yield, uncontaminated with the corresponding dibromide. In a similar manner the mixed 1-ethoxycyclohexene-2 bromohydrins (V or VI; R = C_2H_5, X = Br) were obtained in 85% yield also free of dibromide. It did not prove possible to separate the isomeric bromohydrins by fractional distillation. However, the bromohydrin mixtures proved much superior to the chlorohydrin–dichloride mixtures as intermediates for preparation of the stereoisomeric 1-alkoxy-2,3-epoxycyclohexanes (VII and VIII).

1-Methoxycyclohexene-2 bromohydrin (V or VI; R = CH_3, X = Br) on treatment with aqueous sodium hydroxide gave an 84% yield of the stereoisomeric *dl*-1-methoxy-2,3-epoxycyclohexanes (VII and VIII; R = CH_3), which were readily separated by fractional distillation and were free of halogenated material (cf. McRae *et al.* (10)). On the basis of refractive index and infrared spectra of the various fractions (see Table V) it was estimated that the yield of *trans*-, or lower-boiling, oxide is 63% and that of the *cis*-, or higher-boiling, oxide is 19%. Thus, the percentages of *trans*- and *cis*-oxide in the mixture are 77% and 23% respectively, suggesting the same percentage composition for the 1-methoxycyclohexene-2 bromohydrin mixture. In a similar manner the stereoisomeric *dl*-1-ethoxy-2,3-epoxycyclohexanes (VII and VIII; R = C_2H_5) were obtained in 88% yield. The yield of *trans*-oxide was estimated to be 70.5% and that of the *cis*-oxide 17.5%, giving a distribution of 80% *trans*- and 20% *cis*-oxide in the mixture. It is evident from Table IV that fractionation of the 1-ethoxy-2,3-epoxycyclohexanes was not as clean cut as with the corresponding methoxy compounds. This result was unexpected in view of the difference in boiling points of the isomers and the high reflux ratio used.

The spectra of the 1-methoxy- and 1-ethoxy-2,3-epoxycyclohexanes are shown in Figs. 1 to 4. These substances give a strong band at 1100 cm^{-1} characteristic of the unsymmetrical C—O—C stretching vibration in aliphatic ethers (16). Absorption due to the symmetrical ring stretching vibration of the oxirane ring was observed in the characteristic 1250 cm^{-1} region (16). In each case, the *trans*-isomer showed a medium intensity band at 1245 cm^{-1} and the *cis*-isomer showed a similar band at 1255 cm^{-1}. It is possible to use the bands at 1245 and 1255 cm^{-1} as criteria of purity of the oxides but the change in intensity of these bands is not sufficiently great to permit accurate quantitative



FIGS. 1–4. Infrared spectra of the 1-alkoxy-2,3-epoxycyclohexanes.

estimation of the compositions of mixtures—the refractive index gives a more sensitive method. However, there are a number of bands in the region 690–1380 cm^{-1} which show great differences in intensity as the composition of mixtures of the *trans*- and *cis*-oxides change, some of which could undoubtedly be used for quantitative estimation by means of a suitable calibration curve. The *trans*-oxides show prominent characteristic bands at 775, 795, 800, 825, 980, 1200, and 1380 cm^{-1}, whereas the *cis*-oxides show prominent characteristic bands at 690, 755, 790, 845, 865, and 1325 cm^{-1}. The forerun of each oxide contained a trace of carbonyl impurity as shown by the appearance of a weak band at 1675 cm^{-1}. This carbonyl impurity could be due to the presence of a trace of *cis*-bromohydrin in the predominantly *trans*-oriented bromohydrin mixture (17), since the action of alkali on the former would lead to ketone rather than epoxide (18, 19).

Ammonolysis of *dl*-1β-methoxy-2α,3α-epoxycyclohexane* (VII; R = CH_3) with aqueous ethanolic ammonia by Hawkins and Bannard's method (12) gave *dl*-1α-methoxy-2β-hydroxy-3α-aminocyclohexane (IX; R = CH_3), m.p. 107–108°, in 84% yield, uncontaminated with its isomer X (R = CH_3), as shown by paper chromatography. In a similar manner, ammonolysis of *dl*-1α-methoxy-2α,3α-epoxycyclohexane (VIII; R = CH_3) produced *dl*-1α-methoxy-2α-hydroxy-3β-aminocyclohexane (X; R = CH_3), m.p. 94°, in 75% yield, uncontaminated with its isomer IX (R = CH_3). The two 1-methoxy-2-hydroxy-3-aminocyclohexanes (IX and X; R = CH_3) were shown to be distinctly different by comparison of their infrared spectra, paper chromatographic behavior (see Table VI), a mixed melting-point determination (m.p. 72–92°), and preparation of their hydrobromides, and N-acetyl, N-*p*-nitrobenzoyl, and N-phenylthiourea derivatives listed in Table I.

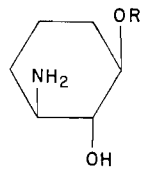
TABLE I

DERIVATIVES OF THE 1-ALKOXY-2-HYDROXY-3-AMINOCYCLOHEXANES

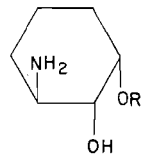
				Analysis									
				% C		% H		% N		% Br		% S	
Compound	Derivative	% Yield	M.p. (° C)	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
dl-1α-Methoxy-2β-hydroxy-3α-aminocyclohexane	Hydrobromide	80	206 –207	37.18	37.20	7.14	7.10	6.20	6.30	35.34	35.72		
	N-Acetyl	82	115.5–116.5	57.75	57.90	9.16	9.04	7.48	7.27				
	N-*p*-Nitrobenzoyl	85	178 –179.5	57.14	57.21	6.16	5.87	9.52	9.57				
	N-Phenylthiourea	77	135 –136	59.99	60.28	7.19	7.24	10.00	10.18			11.44	11.38
dl-1α-Methoxy-2α-hydroxy-3β-aminocyclohexane	Hydrobromide	81	203 –204	37.18	37.30	7.14	7.17	6.20	6.44	35.34	35.44		
	N-Acetyl	77	154.5–155	57.75	58.00	9.16	9.32	7.48	7.41				
	N-*p*-Nitrobenzoyl	85	238.5–239	57.14	57.14	6.16	6.28	9.52	9.68				
	N-Phenylthiourea	62	155 –156	59.99	60.06	7.19	7.09	10.00	10.12			11.44	11.60
dl-1α-Ethoxy-2β-hydroxy-3α aminocyclohexane	Hydrobromide	76	194.5–196	40.00	40.18	7.55	7.59	5.83	6.04	33.27	33.18		
	N-Acetyl	77	124	59.69	59.79	9.52	9.58	6.96	6.74				
	N-*p*-Nitrobenzoyl[a]	87	203 –204	58.45	58.34	6.54	6.43	9.09	9.07				
	N-Phenylthiourea	70	133 –134	61.17	61.28	7.53	7.67	9.52	9.55			10.89	11.07
dl-1α-Ethoxy-2α-hydroxy-3β-aminocyclohexane	Hydrobromide	79	179 –180	40.00	40.22	7.55	7.59	5.83	6.08	33.27	33.14		
	N-Acetyl	82	129 –129.5	59.69	59.77	9.52	9.55	6.96	6.66				
	N-*p*-Nitrobenzoyl	84	215.5–216	58.45	53.34	6.54	6.52	9.09	9.06				
	N-Phenylthiourea	76	143 –144	61.17	61.26	7.53	7.54	9.52	9.70			10.89	10.97

[a]McCasland *et al.* (4) report m.p. 201–203°.

**The system of nomenclature used to describe the configurations of the 1-alkoxy-2,3-epoxycyclohexanes and compounds obtained on scission of the oxirane ring conforms to that used by Lemieux, Kullnig, and Moir (13).*

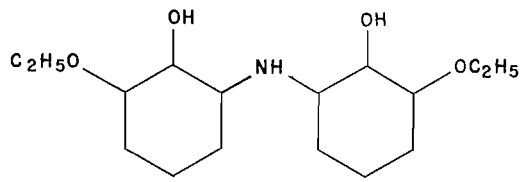


(IX)



(X)

Ammonolysis of *dl*-1β-ethoxy-2α,3α-epoxycyclohexane (VII; R = C_2H_5) gave *dl*-1α-ethoxy-2β-hydroxy-3α-aminocyclohexane (IX; R = C_2H_5), m.p. 134.5–135.5°, in 77% yield, uncontaminated with its isomer X (R = C_2H_5). In one experiment in which an ammonia/oxide ratio of less than 20:1 was used, a small amount of the secondary amine α,α-bis-(2β-hydroxy-3α-ethoxycyclohexyl)amine (XI) was obtained and isolated as the hydrobromide, m.p. 313–314° (cf. Hawkins and Bannard (12)). Ammonolysis of *dl*-1α-ethoxy-2α,3α-epoxycyclohexane (VIII; R = C_2H_5) furnished *dl*-1α-ethoxy-2α-hydroxy-3β-aminocyclohexane (X; R = C_2H_5), m.p. 133–134°, in 89% yield, uncontaminated with its isomer IX (R = C_2H_5). The two 1-ethoxy-2-hydroxy-3-aminocyclohexanes (IX and X; R = C_2H_5) were shown to differ from one another by comparison of infrared spectra, paper chromatographic behavior (see Table VI), a mixed melting-point determination (m.p. 116–118°), and preparation of their hydrobromides and N-acetyl, N-*p*-nitrobenzoyl, and N-phenylthiourea derivatives given in Table I.



(XI)

It is evident from the melting points of the N-*p*-nitrobenzoyl derivatives of the *dl*-1-ethoxy-2-hydroxy-3-aminocyclohexanes (Table I) that McCasland *et al.* (4) obtained *dl*-1α-ethoxy-2β-hydroxy-3α-aminocyclohexane (IX; R = C_2H_5). This result was anticipated in view of the fact that the *trans*-oxide greatly predominates in the mixture of stereoisomeric oxides resulting from the action of alkali on the 1-ethoxycyclohexene-2 bromohydrins, implying that a similar situation would prevail in the case of the corresponding chlorohydrins. A similar result (i.e. predomination of *trans*-oxide) would also be expected when the oxide is prepared by peracid oxidation of 1-methoxycyclohexene-2 (1, 2, 3, 4,), since Henbest and Wilson (20, 21) have found that peracid oxidation of cyclic allylic esters or ethers yields predominantly the *trans*-oxide. It thus seems certain that Mousseron *et al.* (1, 2, 3) obtained the same compound as McCasland *et al.* (4) but in a less pure condition.

Ether cleavage of *dl*-1α-methoxy-2β-hydroxy-3α-aminocyclohexane or *dl*-1α-ethoxy-2β-hydroxy-3α-aminocyclohexane (IX; R = CH_3 or C_2H_5) with 47% hydrobromic acid gave *dl*-3α-amino-1α,2β-cyclohexanediol hydrobromide, m.p. 168–169°, in 90% yield,

which was converted to the free base I, m.p. 151°, in 87% yield. In a similar manner, ether cleavage of *dl*-1α-methoxy-2α-hydroxy-3β-aminocyclohexane or *dl*-1α-ethoxy-2α-hydroxy-3β-aminocyclohexane (X; R = CH_3 or C_2H_5) gave *dl*-3β-amino-1α,2α-cyclohexanediol hydrobromide, m.p. 165.5–167°, in 70% yield, which was converted to the free base II, m.p. 104–105°, in 95% yield. The two aminediols were shown to be quite different by a mixed melting-point determination with their hydrobromides (m.p. 145–150°), comparison of their infrared spectra and paper chromatographic behavior (see Table VI), and preparation of the N-*p*-nitrobenzoyl, N-phenylthiourea, and triacetyl derivatives listed in Table II.

TABLE II

DERIVATIVES OF THE 3-AMINO-1,2-CYCLOHEXANEDIOLS

Compound	Derivative	% Yield	M.p. (° C)	Analysis							
				% C		% H		% N		% S	
				Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
dl-3α-Amino-1α,2β-cyclohexanediol	N-*p*-Nitrobenzoyl	74	185–187	55.71	55.39	5.75	5.77	10.00	9.89		
	N-Phenylthiourea*	98	115–117	57.65	57.06	7.74	7.70	8.97	8.81	10.26	10.31
	Triacetyl	80	193–194	56.02	56.02	7.44	7.39	5.44	5.57		
dl-3β-Amino-1α,2α-cyclohexanediol	N-*p*-Nitrobenzoyl	65	195–197	55.71	55.57	5.75	5.85	10.00	9.74		
	N-Phenylthiourea	80	151–152.5	58.61	58.66	6.81	6.86	10.52	10.84	12.03	11.88
	Triacetyl	59	148–149.5	56.02	55.80	7.44	7.56	5.44	5.22		

*Contains 1 molecule of ethanol of crystallization.

The data presented above establish the stereochemical identity of the 1-alkoxy-2-hydroxy-3-aminocyclohexanes (IX; R = CH_3 or C_2H_5) resulting from ammonolysis of the α- or lower-boiling 1-alkoxy-2,3-epoxycyclohexanes (VII; R = CH_3 or C_2H_5) and necessarily also show the stereochemical equivalence of the two oxides. Similarly the stereochemical identity of the 1-alkoxy-2-hydroxy-3-aminocyclohexanes (X; R = CH_3 or C_2H_5) resulting from ammonolysis of the β- or higher-boiling 1-alkoxy-2,3-epoxycyclohexanes (VIII; R = CH_3 or C_2H_5) has also been demonstrated and the stereochemical equivalence of the two oxides follows. Furthermore, it has been clearly shown that the α- and β-oxides differ from one another since they lead to distinctly different aminocyclohexanediols. The aminediols were shown to be 3-amino-1,2-cyclohexanediols, since the N-*p*-nitrobenzoyl derivative in each case rapidly consumed 1 mole of periodate at 25° (22). However, reaction was so rapid at this temperature that the relative rates of oxidation of the two isomers could not be observed with sufficient accuracy to permit stereochemical assignment to the diols. Repetition of the oxidation with sodium metaperiodate at 3°, however, gave the results shown in Fig. 5. Comparison of the $t_{\frac{1}{2}}$ values makes it clear that the diol group in the aminediol resulting from ammonolysis of the β-oxides must be assigned the *cis*-configuration II and the diol group in the aminediol from ammonolysis of the α-oxides must possess the *trans*-configuration I, since the N-*p*-nitrobenzoyl derivative of the former is oxidized 7.5 times more rapidly than that of the latter (23, 24, 25).

The N-phenylthiourea derivatives of the aminediols were prepared in the expectation that determination of relative rates of cleavage of the isomers with periodate would lead to confirmation of the structures assigned above. However, the periodate cleavage of these derivatives proved abnormal in that even the N-phenylthiourea derivative of

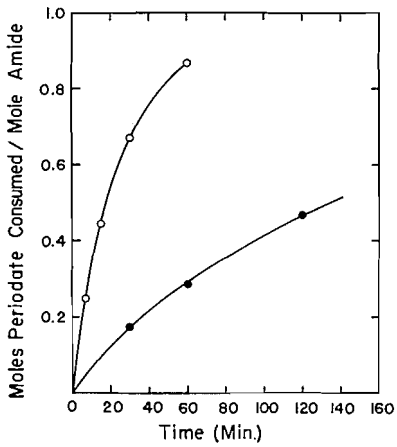


FIG. 5. Rate of periodate oxidation of the 3-*p*-nitrobenzamido-1,2-cyclohexanediols.
● 3α-*p*-Nitrobenzamido-1α,2β-cyclohexanediol
○ 3β-*p*-Nitrobenzamido-1α,2α-cyclohexanediol

trans-2-aminocyclohexanol reacted rapidly with periodate. Thus, these derivatives cannot be used to protect an amine function during diol scission with periodate.

Ionophoretic migration of *cis*-1,2-diols in borate buffer is generally considered to be associated with formation of ionized chelated complexes (25, 26) and has been used to deduce the structure of cyclitols (27). The ionophoretic mobilities of the N-*p*-nitrobenzoyl and N-phenylthiourea derivatives of the aminediols I and II in 0.1 *M* sodium tetraborate were determined. In each case (see Table VII) the derivative arising from the β- or higher-boiling 1-alkoxy-2,3-epoxycyclohexanes exhibited ionophoretic mobility, while the derivative obtained from the α- or lower-boiling 1-alkoxy-2,3-epoxycyclohexanes did not migrate, thus leading to the conclusion that derivatives obtained by oxide ring scission of the former compounds contain a *cis*-1,2-diol group (I), whereas derivatives obtained similarly from the latter compounds contain a *trans*-1,2-diol group (II). This result confirms the structural assignment made on the basis of relative rates of periodate cleavage of the aminediol N-*p*-nitrobenzoyl derivatives.

It is assumed throughout that opening of the oxirane ring under the basic conditions used is accompanied by Walden inversion at the reactive carbon atom (i.e. C_3) (4, 5, 6, 14, 28, 29), and that ether cleavage is not attended by Walden inversion (see Gogek *et al.* (14) and references there cited, also Lemieux, Kullnig, and Moir (13)). Assignment of structure I to the *trans*-diol leads to structure IX (R = CH_3 or C_2H_5) for the 3-amino-1-alkoxy-2-hydroxycyclohexanes derived from the α-oxides and hence to the *trans* structure VII (R = CH_3 or C_2H_5) for the latter, in agreement with the conclusion reached by Lemieux, Kullnig, and Moir (13) in the case of the α-methoxy oxide (VII; R = CH_3). In a similar manner, assignment of structure II to the *cis*-diol leads to structure X (R = CH_3 or C_2H_5) for the 3-amino-1-alkoxy-2-hydroxycyclohexanes derived from the β-oxides and hence to the *cis* structure VIII (R = CH_3 or C_2H_5) for the latter.

Lemieux, Kullnig, and Moir (13) have pointed out that both 1-methoxy-2,3-epoxycyclohexanes (VII and VIII; R = CH_3) show a preference for attack at position 3 by nucleophilic reagents and suggest that such preference is probably an electronic effect of the presence of the electronegative alkoxyl group, rather than a steric effect. This suggestion receives support from the results reported above on ammonolysis of the 1-methoxy- and 1-ethoxy-2,3-epoxycyclohexanes (VII and VIII; R = CH_3 or C_2H_5).

EXPERIMENTAL*, †

trans-1,2-Dibromocyclohexane

trans-1,2-Dibromocyclohexane was prepared by the method of Snyder and Brooks (30).

1-Methoxycyclohexene-2

1-Methoxycyclohexene-2 was prepared by the method of Gogek *et al.* (14), with the method of isolation modified as follows. After the solution of *trans*-1,2-dibromocyclohexane (3.88 g, 1.60 moles), sodium (90.0 g, 3.9 g-atoms), and absolute methanol (1100 ml) had been heated under reflux for 10 hours, the precipitated sodium bromide was collected by suction filtration and washed with anhydrous ether (6×50 ml). The filtrate and washings were distilled on the steam bath first at atmospheric pressure and finally at 25–30 mm pressure until a semisolid mushy residue remained. The residue was treated with water (200 ml) and the solution was extracted with ether (3×50 ml). The extracts were combined with the earlier distillates and the solution was fractionated slowly at atmospheric pressure using a 20-inch vacuum-jacketed Stedman column, yielding 134 g (74.8%) of 1-methoxycyclohexene-2 as a colorless mobile fragrant liquid, b.p. 138–139°, n_D^{25} 1.4513–1.4518. Gogek *et al.* (14) report a 60% yield of substance, b.p. 139°. Berlande (31) has reported n_D^{20} 1.4530.

1-Ethoxycyclohexene-2

1-Ethoxycyclohexene-2 was prepared by the same method as described above for 1-methoxycyclohexene-2. Yield, 58.5%, b.p. 153–154°, n_D^{25} 1.4490. Berlande (31) has reported b.p. 156°, and n_D^{20} 1.4585. Fenton (11) reported b.p. 153–153.5°.

1-Ethoxycyclohexene-2 Chlorohydrin

1-Ethoxycyclohexene-2 chlorohydrin was prepared by the method of Fenton (11) using monochlorourea as the source of hypochlorous acid. From 378 g (3.0 mole) of 1-ethoxycyclohexene-2, 358 g of colorless to pale yellow liquid, b.p. 108–113° at 11–13 mm pressure, n_D^{25} 1.4784–1.4794, was obtained. Fenton (11) reported b.p. 105–120° at 20 mm pressure and McCasland *et al.* (4) reported b.p. 110–117° at 12 mm. Refractionation at 1–2 mm pressure of 770 g of chlorohydrin prepared by the above method gave the fractions indicated in Table III.

TABLE III

FRACTIONATION OF 1-ETHOXYCYCLOHEXENE-2 CHLOROHYDRIN

Fraction No.	B.p. (° C)	Weight (g)	Refractive index n_D^{25}	Analysis[a]		
				% C	% H	% Cl
1	76 –77.5	249	1.4788	51.48	8.17	26.50
2	77.5–78	88	1.4789	52.02	7.98	25.24
3	78 –79.5	84	1.4792	52.43	8.11	24.56
4	79.5–81	92	1.4795	52.88	8.22	23.09
5	79.5–80	80	1.4798	53.23	8.48	22.15
6	80 –81	46	1.4798	53.35	8.46	21.23
7	83 –89	77	1.4800	52.38	8.21	21.10
8	Pot residue	34	1.4816	50.76	7.77	24.24

[a]Calc. for $C_8H_{15}O_2Cl$: C, 53.78; H, 8.46; Cl, 19.85%.
Calc. for $C_8H_{14}OCl_2$: C, 48.75; H, 7.16; Cl, 35.97%.

1-Ethoxycyclohexene-2 Bromohydrin

N-Bromosuccinimide (178 g, 1.00 mole), 1-ethoxycyclohexene-2 (132 g, 1.05 mole),

*All melting points and boiling points are uncorrected.
†Microanalyses by Micro-Tech Labs., Skokie, Ill., and J. G. Helie, of these laboratories.

and water (500 ml) were mixed at 25° in a 1-liter three-necked flask equipped with a "trubore" stirrer and thermometer (12). Stirring was continued until the N-bromosuccinimide dissolved (20 minutes) and a heavy colorless layer of bromohydrin separated, during which time the temperature rose to 75°. The two-phase system was allowed to cool to room temperature, the bromohydrin layer was separated, and the aqueous phase was extracted with ether (2×100 ml). The extracts and bromohydrin were combined and the ether removed by distillation *in vacuo*. The residue was kept overnight at 4°, after which the precipitated succinimide was removed by filtration. The filtrate was fractionated *in vacuo* yielding 190 g (85.2%) of 1-ethoxycyclohexene-2 bromohydrin as a colorless oil, b.p. 87.5–91.5° at 0.3 mm, n_D^{25} 1.5018–1.5025. Calc. for $C_8H_{15}O_2Br$: C, 43.07; H, 6.78; Br, 35.82%. Found: C, 42.95; H, 6.82; Br, 35.82%.

1-Methoxycyclohexene-2 Bromohydrin

1-Methoxycyclohexene-2 bromohydrin was prepared in exactly the same manner as described for 1-ethoxycyclohexene-2 bromohydrin. Yield, 161 g (77.0%) of colorless oil, b.p. 94–97° at 1 mm, n_D^{25} 1.5120–1.5131. Calc. for $C_7H_{13}O_2Br$: C, 40.22; H, 6.27; Br, 38.22%. Found: C, 40.08; H, 6.35; Br, 37.98%.

dl-1β-Ethoxy-2α,3α-epoxycyclohexane and dl-1-α-Ethoxy-2α,3α-epoxycyclohexane (VII and VIII; R = C_2H_5)

1-Ethoxycyclohexene-2 bromohydrin (234 g, 1.05 mole) was treated with aqueous sodium hydroxide (120 g, 2.94 moles, 300 ml) at 25° with mechanical stirring. The temperature rose to 35° and the lower bromohydrin layer was replaced by a supernatant layer of colorless oxide. The mixture was heated at 75° for 1 hour with continuous stirring, and cooled to room temperature; the oxide layer was then separated and the aqueous phase extracted with ether (3×100 ml). The combined oxide and ether extracts were dried over anhydrous magnesium sulphate, after which the ether was removed *in vacuo*. The colorless residue was fractionated at 10 mm pressure using a Podbielniak Whirling Heli-Band column, employing diphenylmethane as "chaser" during the final stage of fractionation, giving the results shown in Table IV.

TABLE IV

FRACTIONATION OF 1-ETHOXY-2,3-EPOXYCYCLOHEXANES

Fraction No.	B.p. (° C)	Refractive index n_D^{25}	Weight (g)	Analysis*	
				% C	% H
1	55.5–56.0	1.4484	84.2	67.52	10.01
2	56.0–56.5	1.4491	21.6	67.80	10.14
3	56.5–64.5	1.4520	2.3	67.63	9.91
4	64.5–65.5	1.4554	23.0	67.81	10.11
			131		

*Calc. for $C_8H_{14}O_2$: C, 67.58; H, 9.92%.

From Table IV it is clear that the 1-ethoxy-2,3-epoxycyclohexanes were obtained in 88.0% yield. Fraction 1 is pure *trans*-oxide, since the infrared spectrum of this compound showed the characteristic oxirane band at 1245 cm^{-1}, and fraction 4 is pure *cis*-oxide, since its infrared spectrum showed the characteristic oxirane band at 1255 cm^{-1}. Fractions 2 and 3 are mixtures of the two oxides, since both the above-mentioned bands were present in the infrared spectra. Mixtures of the pure oxides gave a linear relationship between refractive index and percentage composition and the yields of the two

oxides were estimated. The yield of *trans*-oxide is 105 g (70.4%) and that of *cis*-oxide is 26.3 g (17.6%), i.e. the mixture consists of 80% *trans*-oxide and 20% *cis*-oxide. Fenton (11) reported b.p. 82–84° at 20 mm for *trans*-oxide and 97–100° at 20 mm for *cis*-oxide. McCasland *et al.* (4) gave b.p. 79–82° at 15–16 mm and n_D^{25} 1.4530 for the oxide mixture resulting from peracid oxidation of 1-ethoxycyclohexene-2, and Mousseron *et al.* (3) gave b.p. 77–78° at 12 mm and n_D^{25} 1.4493 for a similar product.

dl-1β-Methoxy-2α,3α-epoxycyclohexane and dl-1α-Methoxy-2α,3α-epoxycyclohexane (VII and VIII; R = CH_3)

1-Methoxycyclohexene-2 bromohydrin (146 g, 0.70 mole) was treated with aqueous sodium hydroxide (84.0 g, 2.04 mole, 200 ml), as described for the preparation of the corresponding ethoxy compounds, yielding, after subsequent manipulation as described above, the fractions shown in Table V.

TABLE V

FRACTIONATION OF 1-METHOXY-2,3-EPOXYCYCLOHEXANES

Fraction No.	B.p. (° C)	Refractive index n_D^{25}	Weight (g)	Analysis*	
				% C	% H
1	54–55	1.4512	55.0	65.69	9.52
2	55–65	1.4520	0.7	65.82	9.57
3	65–69	1.4545	1.9	65.80	9.66
4	69–71	1.4585	17.4	65.71	9.56
			75		

*Calc. for $C_7H_{12}O_2$: C, 65.58; H, 9.44%.

From Table V it is evident that the yield of 1-methoxy-2,3-epoxycyclohexane mixture is 83.8%. Fraction 1 is pure *trans*-oxide and fraction 4 is pure *cis*-oxide, while fractions 2 and 3 are mixtures (infrared spectra). As in the case of the corresponding ethoxy compounds the composition of mixtures was estimated on the basis of refractive index. The yield of *trans*-oxide is thus 56.5 g (63.2%) and that of *cis*-oxide 17.4 g (19.4%), i.e. the mixture consists of approximately 77% *trans*-oxide and 23% *cis*-oxide. McRae *et al.* (10) have reported b.p. 67–69° at 15 mm and n_D^{20} 1.4532 for the *trans*-oxide and b.p. 75–85° at 12 mm and n_D^{20} 1.4603 for the *cis*-oxide.

dl-1α-Methoxy-2β-hydroxy-3α-aminocyclohexane (IX; R = CH_3)

dl-1β-Methoxy-2α,3α-epoxycyclohexane (12.8 g, 0.100 mole) was heated for 1 hour at 100° in a stainless-steel bomb with 28% aqueous ammonia (135 ml, 2 moles) and absolute ethanol (60 ml) (12). The solution was evaporated to dryness *in vacuo* and the resultant buff-colored amine was sublimed at 110–120° at 1 mm, yielding 12.1 g (83.5%) of colorless *dl*-1α-methoxy-2β-hydroxy-3α-aminocyclohexane, m.p. 107–108°. Calc. for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65%. Found: C, 57.52; H, 10.39; N, 9.58%.

dl-1α-Methoxy-2α-hydroxy-3β-aminocyclohexane (X; R = CH_3)

dl-1α-Methoxy-2α,3α-epoxycyclohexane (15.0 g, 0.117 mole) was ammonolyzed with aqueous ethanolic ammonia under the conditions described for 1β-methoxy-2α,3α-epoxycyclohexane, yielding 12.8 g (75.3%) of *dl*-1α-methoxy-2α-hydroxy-3β-aminocyclohexane as colorless feathery needles, m.p. 94°, after recrystallization from ethanol–ether. Calc. for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65%. Found: C, 57.47; H, 10.39; N, 9.58%.

dl-1α-Ethoxy-2β-hydroxy-3α-aminocyclohexane (IX; R = C_2H_5)

dl-1β-Ethoxy-2α,3α-epoxycyclohexane (31.1 g, 0.219 mole) was ammonolyzed with aqueous ethanolic ammonia under the conditions described for *dl*-1β-methoxy-2α,3α-epoxycyclohexane, yielding 26.8 g (77.0%) of *dl*-1α-ethoxy-2β-hydroxy-3α-aminocyclohexane as colorless platelets, m.p. 134.5–135.5°, after recrystallization from ethanol–ether. McCasland *et al.* (4) report m.p. 132–134° for this compound. Calc. for $C_8H_{17}O_2N$: C, 60.35; H, 10.76; N, 8.80%. Found: C, 60.67; H, 10.93; N, 8.72%.

In one experiment in which the ammonia–oxide ratio was less than 20:1 a small amount of α,α-bis-(2β-hydroxy-3α-ethoxycyclohexyl)amine was obtained, and isolated as the hydrobromide, m.p. 313–314°. Calc. for $C_{16}H_{32}O_4NBr$; C, 50.27; H, 8.44; N, 3.66; Br, 20.9%. Found: C, 50.36; H, 8.47; N, 4.12; Br, 20.93%.

dl-1α-Ethoxy-2α-hydroxy-3β-aminocyclohexane (X; R = C_2H_5)

dl-1α-Ethoxy-2α,3α-epoxycyclohexane (16.1 g, 0.113 mole) was ammonolyzed with aqueous ethanolic ammonia under the conditions described for *dl*-1β-methoxy-2α,3α-epoxycyclohexane, yielding 16.0 g (88.8%) of *dl*-1α-ethoxy-2α-hydroxy-3β-aminocyclohexane as fine colorless needles, m.p. 133–134°, after recrystallization from ethanol–ether. Calc. for $C_8H_{17}O_2N$: C, 60.35; H, 10.76; N, 8.80%. Found: C, 60.51; H, 10.83; N, 8.73%.

Derivatives of the dl-1-Alkoxy-2-hydroxy-3-aminocyclohexanes

The *dl*-1-alkoxy-2-hydroxy-3-aminocyclohexanes reported above were characterized as their hydrobromides and N-acetyl, N-*p*-nitrobenzoyl, and N-phenylthiourea derivatives. The hydrobromides and N-phenylthiourea derivatives were prepared by standard methods. The N-*p*-nitrobenzoyl derivatives were prepared by Leffler and Adams' procedure (32). The N-acetyl derivatives were obtained by treating the alkoxyaminocyclohexanols with a 10% excess of acetic anhydride at room temperature, followed by evaporation to dryness *in vacuo*, and recrystallization from ethanol–ether. Yields, melting points, and analytical data for the derivatives are given in Table I.

dl-3α-Amino-1α,2β-cyclohexanediol Hydrobromide

(*a*) *From dl-1α-Ethoxy-2β-hydroxy-3α-aminocyclohexane* (IX; R = C_2H_5)

dl-1α-Ethoxy-2β-hydroxy-3α-aminocyclohexane (60.0 g, 0.377 mole) was heated under reflux for 1½ hours with 48% hydrobromic acid (230 ml, 2.0 moles). Most of the excess acid was removed by distillation *in vacuo* but no attempt was made to distill to dryness (cf. McCasland *et al.* (4)). The residue was treated with ether (300 ml) and ethanol (75 ml) and evaporated *in vacuo* to small volume. This operation was repeated, after which 300 ml of ether was added, followed by just sufficient ethanol to produce a clear solution. When the solution was allowed to stand at 4°, *dl*-3α-amino-1α,2β-cyclohexanediol hydrobromide separated as colorless to light-grey rosettes. Yield, 73.1 g (91.4%), m.p. 168–169°. McCasland *et al.* (4) report m.p. 167–168°. Calc. for $C_6H_{14}O_2NBr$: C, 33.98; H, 6.65; N, 6.61; Br, 37.68%. Found: C, 33.89; H, 6.71; N, 6.66; Br, 37.64%.

(*b*) *From dl-1α-Methoxy-2β-hydroxy-3α-aminocyclohexane* (IX; R = CH_3)

dl-1α-Methoxy-2β-hydroxy-3α-aminocyclohexane (35.0 g, 0.241 mole) was subjected to ether cleavage under the conditions described above. Crystallization of the product from ethanol–ether furnished 46.3 g (90.5%) of *dl*-3α-amino-1α,2β-cyclohexanediol hydrobromide as colorless to light-grey rosettes, m.p. 167.5–169°. Admixture of this substance with that obtained in (*a*) above did not depress the melting point. The two samples gave identical infrared spectra, and moved with the same speed in paper chromatograms (R_F 0.40, see Table VI).

dl-3α-Amino-1α,2β-cyclohexanediol (I)

dl-3α-Amino-1α,2β-cyclohexanediol hydrobromide (60.0 g, 0.283 mole) was dissolved in a solution of sodium hydroxide (11.8 g, 0.286 mole in 100 ml water). Evaporation to dryness *in vacuo* gave a light-tan crystalline residue, which was sublimed at 140° at 0.5 mm to free it from inorganic material. Recrystallization of the sublimate from absolute ethanol yielded 32.4 g (87.4%) of *dl*-3α-amino-1α,2β-cyclohexanediol, m.p. 151°, as colorless prisms. Calc. for $C_6H_{13}O_2N$: C, 54.93; H, 9.99; N, 10.68%. Found: C, 55.05; H, 10.11; N, 10.71%.

dl-3β-Amino-1α,2α-cyclohexanediol Hydrobromide

(*a*) *From dl-1α-Ethoxy-2α-hydroxy-3β-aminocyclohexane* (X; R = C_2H_5)

dl-1α-Ethoxy-2α-hydroxy-3β-aminocyclohexane (14.0 g, 0.88 mole) was subjected to ether cleavage under the conditions described for its isomer. Crystallization from ethanol–ether gave 13.0 g (69.8%) of *dl*-3β-amino-1α,2α-cyclohexanediol hydrobomide as colorless rosettes, m.p. 165.5–167°. Calc. for $C_6H_{14}O_2NBr$: C, 33.98; H, 6.65; N, 6.61; Br, 37.68%. Found: C, 34.31; H, 6.86; N, 6.79; Br, 37.36%.

(*b*) *From dl-1α-Methoxy-2α-hydroxy-3β-aminocyclohexane* (X; R = CH_3)

dl-1α-Methoxy-2α-hydroxy-3β-aminocyclohexane (5.30 g, 0.0365 mole) was subjected to ether cleavage under the conditions described for *dl*-1α-ethoxy-2β-hydroxy-3α-aminocyclohexane. Crystallization from ethanol–ether gave 5.40 g (69.8%) of colorless rosettes, m.p. 165.5–167°. Admixture of this substance with the compound isolated from (*a*) above caused no depression in melting point. The two samples likewise gave identical infrared spectra and moved with the same speed in paper chromatograms (R_F 0.43, see Table VI).

dl-3β-Amino-1α,2α-cyclohexanediol (II)

dl-3β-Amino-1α,2α-cyclohexanediol hydrobromide (14.0 g, 0.066 mole) was converted to the free base by passing a 5% aqueous solution through Amberlite IRA-400 resin in the hydroxide form. Evaporation to dryness *in vacuo* followed by recrystallization from benezene gave 5.90 g (95.3%) of *dl*-3β-amino-1α,2α-cyclohexanediol, m.p. 104–105°, as colorless prisms. Calc. for $C_6H_{13}O_2N$: C, 54.93; H, 9.99; N, 10.68%. Found: C, 55.02; H, 10.00; N, 10.77%.

Derivatives of the dl-3-Amino-1,2-cyclohexanediols

The *dl*-3-amino-1,2-cyclohexanediols were characterized as their N-*p*-nitrobenzoyl, N-phenylthiourea, and triacetyl derivatives. The same methods were used as in preparation of derivatives of the 1-alkoxy-2-hydroxy-3-aminocyclohexanes, except that in preparation of the triacetyl compounds, a 10-fold excess of acetic anhydride was used. Yields, melting points, and analytical data for the derivatives are given in Table II.

N-Phenylthiourea Derivative of dl-trans-2-Aminocyclohexanol

The same method was used as for preparation of the N-phenylthiourea derivatives of the *dl*-1-alkoxy-2-hydroxy-3-aminocyclohexanes. Yield, 93%, m.p. 144.5°. Calc. for $C_{13}H_{18}N_2SO$: C, 62.37; H, 7.25; N, 11.19; S, 12.80%. Found: C, 62.09; H, 7.22; N, 11.29; S, 12.69%.

Paper Chromatography of the 3-Amino-1,2-cyclohexanediols and Derivatives

For paper chromatography 2% solutions of the compounds in water, ethanol, or acetone were applied to unwashed Whatman No. 1 paper (7.5 λ spots). The chromatograms were developed overnight in a glass tank by the descending technique using *n*-butanol – acetic acid – water (25:6:25) as developer. The air-dried chromatograms were sprayed with bromcresol green for detection of the free amines and with ammoniacal

TABLE VI

R_F VALUES OF 3-AMINO-1,2-CYCLOHEXANEDIOL DERIVATIVES IN *n*-BUTANOL – ACETIC ACID – WATER (25:6:25)

Compound	R_F
1α-Methoxy-2β-hydroxy-3α-aminocyclohexane	0.51
1α-Methoxy-2α-hydroxy-3β-aminocyclohexane	0.55
1α-Ethoxy-2β-hydroxy-3α-aminocyclohexane	0.60
1α-Ethoxy-2α-hydroxy-3β-aminocyclohexane	0.66
α,α-bis-(2β-Hydroxy-3α-ethoxycyclohexyl)amine	0.74
3α-Amino-1α,2β-cyclohexanediol	0.40
3β-Amino-1α,2α-cyclohexanediol	0.43
3α-N-*p*-Nitrobenzamido-1α,2β-cyclohexanediol	0.87
3β-N-*p*-Nitrobenzamido-1α,2α-cyclohexanediol	0.88
2β-Amino-1α-cyclohexanol	0.59

silver nitrate (33) for detection of the N-*p*-nitrobenzoyl derivatives of the aminediols. R_F values are given in Table VI.

Periodate Oxidation of dl-3α-p-Nitrobenzamido-2β,3α-cyclohexanediol and dl-3β-p-Nitrobenzamido-2α,3α-cyclohexanediol

(*a*) *At 25° C*

A 40-mg sample of each aminediol *p*-nitrobenzoyl derivative was treated with 0.1053 *N* paraperiodic acid (20.00 ml) at 25°. Iodometric titrations with sodium arsenite (22) revealed that 0.95 mole of paraperiodic acid was consumed per mole of *cis*-diol derivative in 60 minutes and 0.96 mole of paraperiodic acid was consumed per mole of *trans*-diol derivative in 90 minutes.

(*b*) *At 3° C*

A 20-mg sample of aminediol derivative was dissolved in 50 ml of water at room temperature and the solution was cooled to 3°. At time zero, sodium metaperiodate (10.00 ml, 0.0300 *N*) at 3° was pipetted into the solution, which was stirred constantly in a constant temperature bath at 3°±0.1°. The reaction was allowed to proceed for a specified length of time, after which further reaction was stopped by addition of sodium bicarbonate (2 g, A.R.), sodium arsenite (25.00 ml, 0.0200 *N*), and potassium iodide solution (1 ml, 20%). The consumption of periodate was determined by back-titration with 0.0100 *N* iodine (22) and the quantity of aminediol derivative oxidized calculated. Results are shown in Fig. 5.

Electrophoresis of 3-Amino-1,2-cyclohexanediol Derivatives on Glass Paper

The aminediol derivatives (1% solution in acetone) were spotted on 63×380 mm strips of glass fiber paper (H. Reeve Angel and Co., Inc.) together with D-glucose and 2,3,4,6-tetramethyl-D-glucose as reference compounds. The strips were placed in a water-cooled closed strip-type apparatus (E.C. Apparatus Co., Model No. 401) con-

TABLE VII

M_G VALUES OF 3-AMINO-1,2-CYCLOHEXANEDIOL DERIVATIVES

Compound		M_G
3α-Amino-1α,2β-cyclohexanediol	N-*p*-Nitrobenzoyl derivative	0.00
	N-Phenylthiourea derivative	0.00
3β-Amino-1α,2α-cyclohexanediol	N-*p*-Nitrobenzoyl derivative	0.34
	N-Phenylthiourea derivative	0.44

taining 0.1 *M* sodium tetraborate solution, and a voltage of 435 at 75 ma was applied for 1 hour. The strips were dried at 100° on a glass plate and sprayed with alkaline permanganate (34) giving yellow spots on a pink to greenish-pink background. The M_G values of the compounds studied are shown in Table VII.

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