Syntheses of Macrocyclic Enzyme Models. Part I. Preparation and Properties of [20]Paracyclophanes

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A series of [20]paracyclophane derivatives bearing a functional group or groups on the polymethylene bridge has been prepared, because of their novel enzyme-like functions in acyl-transfer reactions. An electrophilic substitution which introduces a carboxy-group into the benzene ring has been successfully used to afford a bifunctional paracyclophane. All the paracyclophanes have been characterised by ^{1}H and ^{13}C n.m.r. spectroscopy and by i.r. measurements. The major isomer of 11-amino[20]paracyclophan-10-ol (3), 2-aminocyclodecanol (13), and [20]paracyclophane-10,11-diol is in each case the *threo*-isomer, with synperiplanar conformation, as a result of energy gain due to intramolecular hydrogen bonding. The tendency towards hydrogen bonding is more pronounced for the hydrochloride forms of (3) and (13).

THE interest in the chemistry of macrocyclic compounds with a sizeable interior cavity lies in their ability to incorporate a suitably bulky substrate molecule, through hydrophobic interaction between ' host ' and ' guest '.[1-4] The binding behaviour has been occasionally compared to E–S complex formation in enzymic catalysis. An additional enzyme-like character might be expected for macrocycles in which a functional group is located close to the hydrophobic binding site. We have recently investigated the catalytic effects of the [20]paracyclophane oxime (2) on the release of *p*-nitrophenol from *p*-nitrophenyl carboxylates bearing a long alkyl chain.[2,3] The kinetic results were consistent with pre-equilibrium com-

[1] Y. Murakami, J. Sunamoto, and K. Kano, *Chem. Letters*, 1973, 223.
[2] Y. Murakami, J. Sunamoto, and K. Kano, *Bull. Chem. Soc. Japan*, 1974, **47**, 1238.
[3] Y. Murakami, J. Sunamoto, H. Okamoto, and K. Kawanami, *Bull. Chem. Soc. Japan*, 1975, **48**, 1537.
[4] (*a*) D. W. Griffith and M. L. Bender, *Adv. Catalysis*, 1973, **23**, 209; (*b*) J. H. Fendler and E. J. Fendler, ' Catalysis in Micellar and Macromolecular Systems,' Academic Press, New York, 1975.

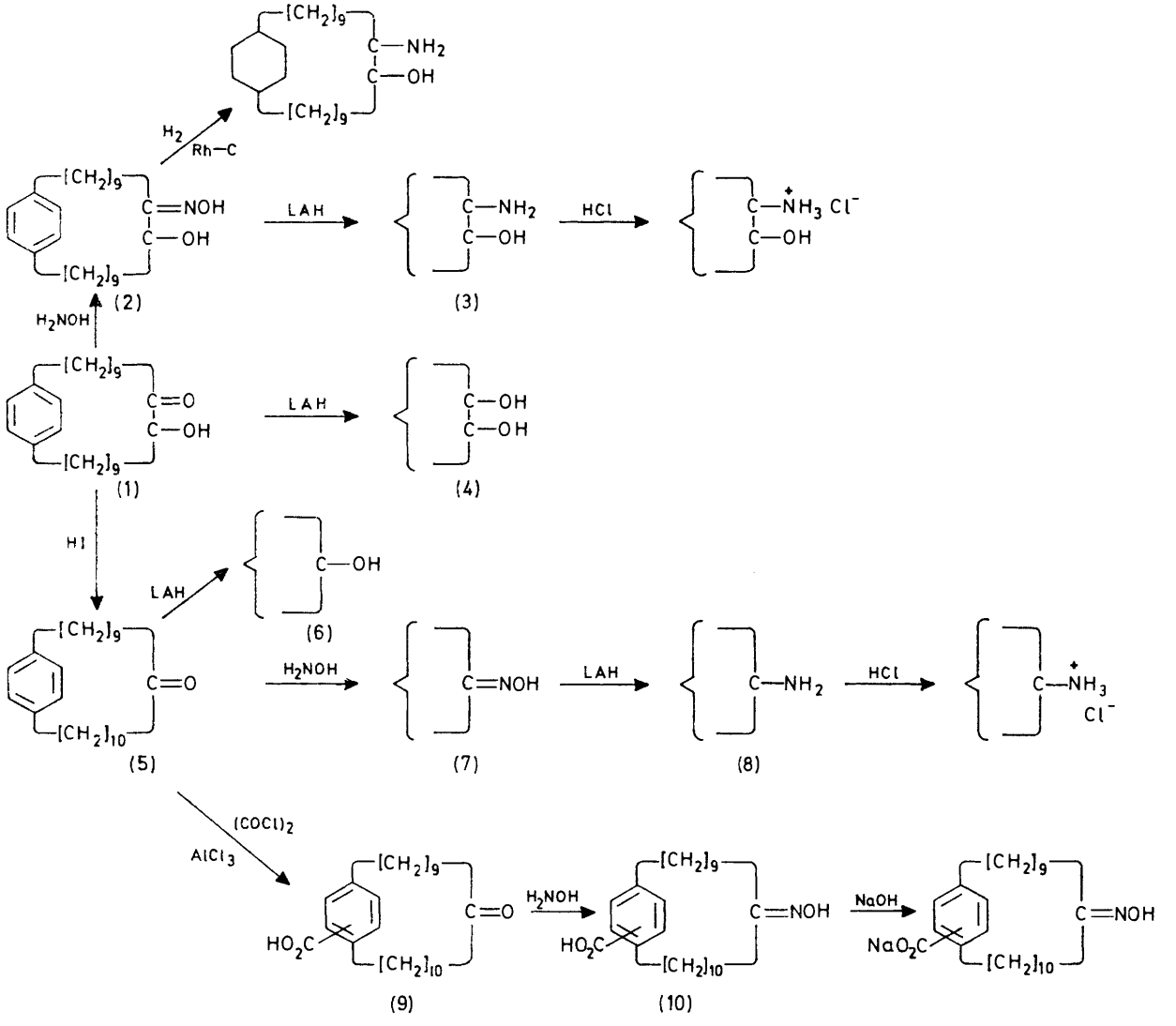
plex formation between substrate and paracyclophane, followed by pseudo-unimolecular acyl migration from the substrate to the oxime group of the paracyclophane.

These results tempted us to investigate a series of macrocyclic paracyclophanes having a functional group or groups, in the hope of developing macrocyclic systems of enzyme-like character.

Syntheses of paracyclophanes containing two,[5] three,[6] and four benzene rings [7] have been recently reported; in the products the functional groups are mostly located on the benzene rings. We report here the preparation of a unique series of [20]paracyclophanes in which the functional groups are on the polymethylene bridge. Their structural features are discussed with reference to those of the similarly substituted cycloalkanes.

RESULTS AND DISCUSSION

Preparation.— 11-Hydroxy[20]paracyclophan-10-one (1) was readily available by acyloin condensation of dimethyl 10,10′-*p*-phenylenedidecanoate.[2] [20]Paracyclophane derivatives obtained from the acyloin (1) are summarised in Scheme 1. The oxime (2), obtained by



SCHEME 1

treatment of (1) with hydroxylamine,[2] was reduced with lithium aluminium hydride (LAH) in ether to give a mixture of *erythro*- and *threo*-forms † of the amino-alcohol (3), which was converted into the corresponding hydrochloride with dry hydrogen chloride in ether. Reduction of the hydroxyimino-group in (2) to the amino-

† Although previous workers [8-10] cited the spatial configurations of the vicinal substituents as *cis* and *trans* rather than *erythro* and *threo*, respectively, we prefer the latter nomenclature.

[5] D. J. Cram and J. Abell, *J. Amer. Chem. Soc.*, 1954, **77**, 1179.
[6] I. Tabushi, H. Yamada, Z. Yoshida, and R. Oda, *Tetrahedron*, 1971, **27**, 4845.
[7] I. Tabushi, H. Yamada, K. Matsushita, Z. Yoshida, Y. Kuroda, and R. Oda, *Tetrahedron*, 1972, **28**, 3381.
[8] J. Sicher, M. Horak, and M. Svoboda, *Coll. Czech. Chem. Comm.*, 1959, **24**, 950.
[9] M. Svoboda, J. Jonas, and J. Sicher, *Coll. Czech. Chem. Comm.*, 1958, **23**, 1551.
[10] J. Sicher and M. Svoboda, *Coll. Czech. Chem. Comm.*, 1958, **23**, 1252.

group was also effected by catalytic hydrogenation at high temperature. However, hydrogenation of the benzene ring took place simultaneously and the major product was the cyclohexane derivative. Reduction of the parent acyloin (1) with LAH afforded the diol (4), high-speed liquid chromatographic analysis of which showed the presence of two isomers in the ratio 2.5 : 1. On the basis of the ^{13}C n.m.r. spectrum, the major isomer was identified as the *threo*- and the minor one as the *erythro*-form (see later). Several procedures for reduction of an acyloin to the corresponding monoketone have been reported.[11-13] Zinc–hydrogen chloride is a classical reagent of choice; however, its use for reduction of an acyloin may not be completely free from side reactions.[14] Under vigorous conditions, the resulting monoketone undergoes further reduction to yield the hydrocarbon. Reduction with hydriodic acid, originally examined by Reusch and LeMahieu,[15] seems a better method for obtaining the corresponding ketone. The acyloin (1) was in fact readily converted into [20]paracyclophan-10-one (5) with hydroiodic acid in refluxing acetic acid. The ketone (5) was reduced to the alcohol (6) by LAH, and was converted into the amine (8) and its hydrochloride *via* the oxime (7).

Electrophilic substitution on the benzene ring of the ketone (5) appeared to offer a readily accessible route to polyfunctional paracyclophanes. With oxalyl chloride and aluminium chloride in carbon disulphide, the ketone (5) was carboxylated to give the oxo-acid (9), which was converted into the oxime (10). As is often the case, a synthetic enzyme model suffers seriously from its poor solubility in water. The bifunctional paracyclophane (10) can be regarded as being composed of three parts: a hydrophobic cavity provided by the benzene ring and the long polymethylene chain, a nucleophilic centre at the hydroxyimino-group, and a hydrophilic carboxy-group which must enhance the solubility in alkali. In fact, the sodium salt of (10) shows an enhanced solubility in water (*ca.* 10^{-3} mol l^{-1}) in comparison with other cyclophanes lacking a carboxy-group. However it is still appreciably soluble in a hydrocarbon solvent.

the amino-alcohol (3) in CCl_4 and in CF_3CO_2H are shown in Figure 1. The hydroxymethylene ($>CH{\cdot}OH$) and aminomethylene proton ($>CH{\cdot}NH_2$) signals are shifted appreciably downfield in CF_3CO_2H relative to CCl_4, as a

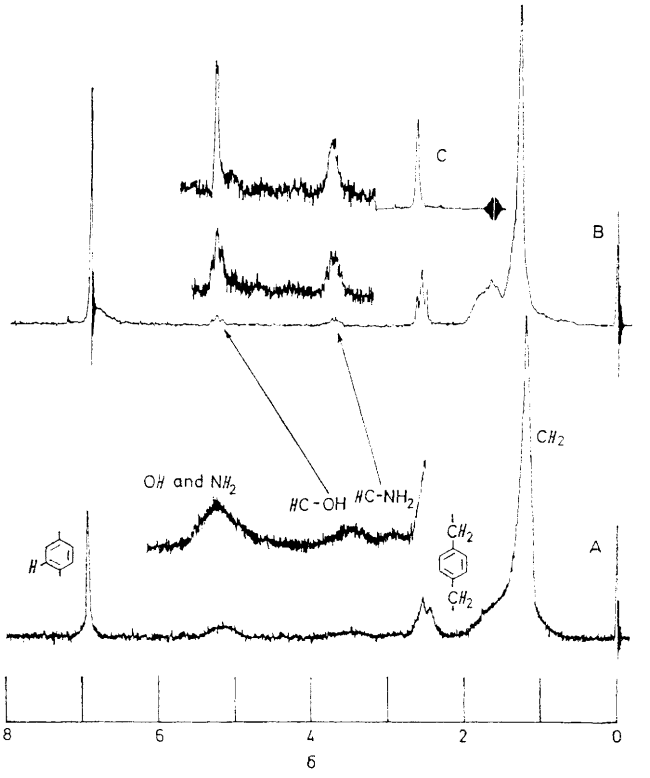
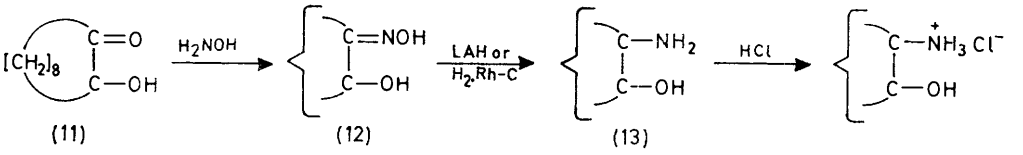


FIGURE 1 ^1H N.m.r. spectra of the hydroxy-amine (3): A, in CCl_4; B, in CF_3CO_2H; and C, in CF_3CO_2H after irradiation at the methylene frequency (δ 1.6)

result of protonation of the amino group. Irradiation at the frequency of the methylene signal (δ 1.6) in CF_3CO_2H gave a spin-decoupled spectrum in which the benzyl (δ 2.58) and hydroxymethylene proton (δ 5.27) peaks appeared as a singlet and doublet (J 2 Hz), respectively. Chemical shift data for the paracyclophanes and their cyclodecane analogues are summarised in Table 1. The



SCHEME 2

For comparison, some cyclodecanes were prepared from sebacoin (2-hydroxycyclodecanone) (11), as shown in Scheme 2. The reduction of 2-hydroxycyclodecanone oxime (12) gave a mixture of *erythro*- and *threo*-forms of the amino-alcohol (13).

^1H *N.m.r. and I.r. Spectra.*—The ^1H n.m.r. spectra of methylene proton signals of the disubstituted paracyclophanes are appreciably further upfield than those for the cyclodecane analogues. This may be attributable to a ring-current effect of the benzene ring in the paracyclophane derivatives; reduction of the amino-alcohol (3) to the cyclohexane analogue resulted in a downfield shift of the methylene signal by *ca.* 0.1 p.p.m. A hydrophobic

[11] A. C. Cope, J. W. Banthel, and R. D. Smith, *Org. Synth.* Coll. Vol. IV, 1963, p. 218.
[12] M. Stoll, *Helv. Chim. Acta*, 1947, **30**, 1837.
[13] V. Prelog, K. Schenker, and H. H. Gündhart, *Helv. Chim. Acta*, 1952, **35**, 1598.
[14] D. J. Cram and M. Cordon, *J. Amer. Chem. Soc.*, 1955, **77**, 1810.
[15] W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, 1964, **86**, 3068.

field effect (micro-solvent effect), provided by the macrocyclic paracyclophane skeleton, could be another cause of the downfield shift.

The amino-alcohol (3) shows only an unresolved broad singlet for the hydroxy- and amino-protons (Figure 1). Hydrogen bonding between these groups is likely, and may facilitate hydrogen exchange, resulting in line broadening as observed for 2-amino-3-pyridylmethanol, quinolin-8-ol, and 2-aminoethanol.[16] This result indicates that the vicinal hydroxy- and amino-groups of (3) are mainly in a synperiplanar conformation. The gain due to hydrogen bond formation in the synperiplanar conformation may be sufficient to cause the conformational change from synclinical to synperiplanar. The molecular strain associated with the *erythro*- and *threo*-configurations for disubstituted cyclic systems is reflected in the pK_a data for *erythro*- and *threo*-2-aminocyclanols measured in 80% methylcellosolve.[9] The pK_a values for five- to eight-membered aminocyclanols, with an appreciable molecular rigidity, depend on their stereochemistry, the *erythro*-isomers having the greater values. However the reverse relation was found for nine- to

TABLE 1

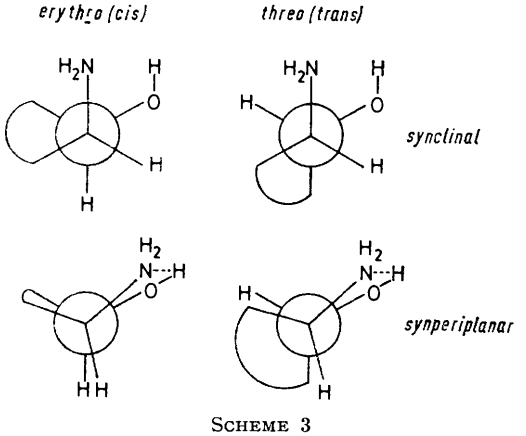
^{1}H N.m.r. chemical shifts [a]

		Chemical shift						
Compd.	Solvent	Aromatic	*H*C·OH	OH and/or NH_2	*H*C·NH_2	Benzyl [b]	H_2C–C=O or H_2C–C=NOH	Methylene
(1)	CCl_4	7.00	4.03	3.39		2.57	2.3	1.18
(2)	CCl_4	7.00	4.05	*d*		2.59	2.2	1.21
(12)	$CDCl_3$		4.33	*d*			2.5	1.41
(3)	CCl_4	6.96	3.62	5.24	2.97	2.56		1.19
	CF_3·CO_2H	6.93	5.27	6.9	3.72	2.58		1.27
(13)	$CDCl_3$		3.83	*d*	3.12			1.53
	CF_3·CO_2H		5.52	6.8	4.04			1.65
(4)	$CDCl_3$	7.03	3.56	1.90		2.57		1.23
(5)	CCl_4	7.02				2.57	2.25	1.20
(6)	$CDCl_3$	7.05	3.55	1.66		2.58		1.22
(7)	CCl_4	6.95		8.75		2.55	2.08	1.20
(8)	$CDCl_3$	7.05		2.4—2.8 [c]	*d*	2.57		1.20
(8) †	CCl_4	7.03		8.40	3.10	2.60		1.24
(9) [f]	CCl_4	7.79 (*o*) 7.13 (*m* and *p*)		11.20		3.02 (*o*) 2.62 (*m*)	2.25	1.20
(10) [f]	CCl_4	7.79 (*o*) 7.10 (*m* and *p*)		11.27		3.00 (*o*) 2.60 (*m*)	2.15	1.24

† Hydrochloride.

[a] δ Values (Me_4Si internal reference). [b] Triplet, *J ca.* 6.5 Hz. [c] Referred to the most intense peak. This peak is accompanied by a broad shoulder in the lower field region, which extends to δ 2.0. A separate broad peak was observed for (3) in trifluoroacetic acid. [d] Not observed as a definite peak. [e] Assigned on the basis of the spectral behaviour observed upon complete deuteriation of NH_2. [f] *o*, *m*, and *p* indicate the proton positions with reference to the carboxy-group.

flexibility of the polymethylene chain in compounds of the present type should be emphasised. There is good reason to expect a hydrogen-bonding interaction for both *threo*- and *erythro*- (3), on the basis of configurational



SCHEME 3

studies for 2-aminocyclanols by pK_a and i.r. measurements.[8,9] The hydrogen-bonding process may involve rotation around the C(10)–C(11) bond to give a synperiplanar conformation as shown in Scheme 3. The energy fifteen-membered systems. The difference in pK_a between *erythro*- and *threo*-isomers becomes negligible for the flexible aminocyclanols of sixteen or more members.

We considered that i.r. spectroscopy might throw more light on the stereochemistry of αβ-disubstituted paracyclophanes. The appropriate data are listed in Table 2, and the corresponding spectra in the OH and NH_2 stretching and bending regions are shown in Figure 2. The behaviour of the amino-alcohol (3) in the OH and NH_2 stretching regions is similar to that of the cyclodecane (13), showing OH vibrational modes at 3 635 and 3 481 cm^{-1} for the free and hydrogen-bonded forms, respectively, and the NH_2 vibration at 3 415 cm^{-1}. The diol (4) shows a similar set of OH stretching bands. The frequency of the free OH stretching mode, $\nu(OH)_{free}$, is reasonably constant (3 635—3 639 cm^{-1}) in the series mono-ol (6), diol (4), amino-alcohol (3); whereas the corresponding stretching mode for bonded OH, $\nu(OH)_{bonded}$, is dependent on the nature of the donor atoms. The differences between $\nu(OH)_{free}$ and $\nu(OH)_{bonded}$ [$\Delta\nu(OH)$] are 154 and 42 cm^{-1} for (3) and (4), respectively. The considerably greater

[16] Y. Murakami and J. Sunamoto, *J.C.S. Perkin II*, 1973, 1231.

Δν(OH) value for the amino-alcohol (3) is consistent with the generally accepted view that the O–H · · · N bond is stronger than the O–H · · · O bond. Sicher, Horak, and Svoboda have studied the i.r. spectra of a series of *erythro*- and *threo*-isomers of 2-aminocyclanols.[8] With rings of thirteen or more members, the Δν(OH) values were found to fall in the ranges 125—128 and 140—159 cm^{-1} for *erythro*- and *threo*-isomers, respectively. The observed Δν(OH) value for (3) (154 cm^{-1}) therefore seems to indicate that the predominant isomer of (3) is the *threo*-form. This does not exclude the presence of the *erythro*-isomer, since the hydrogen-bonded OH stretching mode due to this isomer as a minor component would be hidden by the intense and broad vibrational mode due to the *threo*-isomer. The hydrochlorides of compounds (3) and (13) show similar i.r. spectra in the OH stretching region, where a set of broad absorptions is observed below 3 400 cm^{-1}. No absorption attributable to the free OH stretching mode is apparent. These observations are consistent with more pronounced (than in the corresponding free base forms) hydrogen bonding of the H–O · · · H–$\overset{+}{N}H_2$ type.

TABLE 2

Stretching (ν) and bending (δ) vibrations of aminocyclanols and related compounds

Compd.	Frequenc (c m^{-1}) ν(OH)$_{free}$ [a]	ν(OH)$_{bonded}$ [a]	ν(NH_2) [a]	δ(NH_2) [b]	*asym*-δ($\overset{+}{N}H_3$) [b]	*sym*-δ($\overset{+}{N}H_3$) [b]	ν(C–O) [b]
(3)	3 635	3 481	3 415	1 617			1 050
				1 570			
(13)	3 625	3 479	3 389	1 600			1 018 [c]
				1 570			
(4)	3 639	3 597					
(6)	3 636						
(8)			3 290				
(3) †		*d*			1 607	1 497	1 017
					1 584		
(13) †		*d*			1 605	1 502	1 025
					1 587	1 482	
(8) †					1 611	1 510	
					1 578		

† Hydrochloride.

[a] In carbon tetrachloride. [b] KBr disc. [c] Most intense peak. [d] Not clearly assigned owing to broadness.

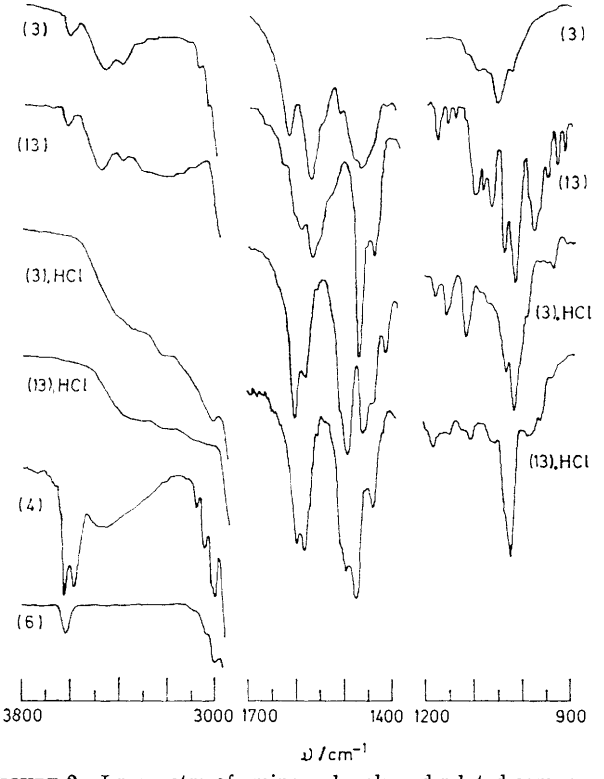


FIGURE 2 I.r. spectra of aminocyclanols and related compounds in CCl_4 (for the range 3 800—3 000 cm^{-1}) and in KBr disc (for the range 1 700—900 cm^{-1})

The NH_2 bending and C–O stretching modes are too complicated for complete analysis (Figure 2). Nevertheless, they deserve some comments: first, the symmetric NH_3^+ bending frequency [*sym*-δ($\overset{+}{N}H_3$)] of the amino-alcohol (3) hydrochloride is lower than that of the hydrochloride of the amine (8); secondly, the C–O stretching mode of (3) hydrochloride is significantly lower frequency in comparison with the free base (3). All these results support the existence of a strong interaction between NH_3^+ and OH in (3) hydrochloride.

It thus appears at this stage the paracyclophane amino-alcohol (3) assumes predominantly a synperiplanar conformation in the *threo*-form as a result of energy gain caused by intramolecular hydrogen bond formation. This hydrogen-bonding tendency seems to be pronounced in the corresponding hydrochloride.

^{13}C *N.m.r. Spectra.*—In the ^{13}C n.m.r. spectrum of the acyloin (1) (Figure 3) the resonance at 213.1 p.p.m. must be ascribed to the carbonyl carbon atom. The C-11 nucleus, bearing a hydroxy-group resonates at 75.9 p.p.m. Two sharp peaks between these signals should be ascribed to the aromatic carbon atoms: the less intense, lower field peak to those carrying the polymethylene chain, and the other to those bound directly to hydrogen nuclei. In the higher field region (20—40 p.p.m.), a set of absorptions composed of eleven peaks at least can be detected. Some of these may be assigned in the light of accumulated data on the ^{13}C shieldings for substituted hydrocarbons.[17] It is generally realized that

[17] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1973.

carbonyl and hydroxymethylene (>CH·OH) groups deshield adjacent carbon atoms by 12 and 7 p.p.m., respectively. The lowest field peak (37.1 p.p.m.) in this range may thus be most reasonably assigned to C-9, adjacent to the carbonyl group, and an absorption at 33.0 p.p.m. to C-12, adjacent to CH·OH. A relatively strong peak at 34.5 p.p.m. may be due to the benzylic carbon atoms, since the chemical shift is in a reasonable agreement with those for n-butyl-, n-pentyl-, and n-hexylbenzenes (36.0—36.4 p.p.m.).[17] These assignments are further supported by comparison with data for the diol (4) and ketone (5) (Figure 3 and Table 3). Apparently, the benzylic carbon atoms of all three compounds are shielded to the same extent. The chemical shifts for C-9 and C-12, α to CH·OH of (4), and those for C-9 and C-11, α to C=O of (5), are in excellent agreement with the values assigned to the corresponding carbon atoms of (1). The two α-carbon atoms (adjacent to C=O) of (5) are not equivalent, thus providing double signals. The carbonyl carbon atoms of (1) and (5) resonate at lowe field than those of macrocyclic ketones such as cyclohep tadecanone (208.5 p.p.m.).[17]

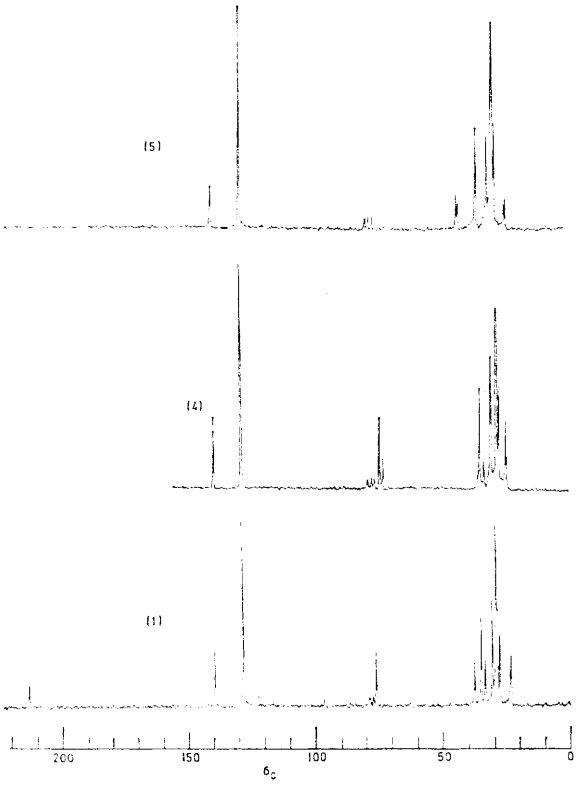


FIGURE 3 ^{13}C N.m.r. spectra of compounds (1), (4), and (5) in $CDCl_3$; a triplet signal at δ_C 77.1 is due to $CDCl_3$

The conclusion that the diol (4) is a mixture of *erythro*- and *threo*-isomers is substantiated by the observation of two separate peaks due to the equivalent C-10 and C-11 nuclei. Perlin and Koch found that C-1 and C-2 in *erythro*-cyclohexane-1,2-diol are more shielded (72.5 p.p.m.) than in the *threo*-isomer (76.8 p.p.m.).[18] Consequently, the more intense signal (73.9 p.p.m.) in the spectrum of (4) is attributed to the *threo*- and the other (72.8 p.p.m.) to the *erythro*-isomer; the major isomer is thus the *threo*-form.

EXPERIMENTAL

I.r. spectra were taken with a JASCO DS-403G grating spectrophotometer. ^1H N.m.r. spectra were obtained with either a Varian A-60 or a JEOL JNM-MH-100 spectrometer, equipped with a decoupling device; tetramethylsilane was used as an internal reference. ^{13}C N.m.r. spectra were recorded with a Bruker WH-90 FT spectrometer; deuteriochloroform was used as both a solvent and internal reference (δ_C 77.1 p.p.m.). High speed liquid chromatography was performed on a Hitachi 635 liquid chromatograph with Hitachi gel 3 010 and 3 019 for analytical and preparative purposes, respectively. Methanol was used as eluant and components eluted were detected by u.v. absorption at 254 nm.

11-Amino[20]*paracyclophan-10-ol* (3) *and its Hydrochloride*.—A mixture of 11-hydroxyimino[20]paracyclophan-10-ol [2] (2) (2.08 g) and lithium aluminium hydride (LAH) (2.02 g) in tetrahydrofuran (85 ml) saturated with LAH was refluxed with stirring for 4 h under nitrogen, and stirring was continued for another 1 h at room temperature. Then a small amount of water, aqueous Rochelle salt (20%; 30 ml), and aqueous sodium hydroxide (10%; 20 ml) were added. The resulting aluminium hydroxide was filtered off and washed with hot methanol (30 ml × 3) and ether (20 ml × 3). The combined filtrate and washings were extracted with ether (100 ml × 5). The extracts were dried ($CaSO_4$) and evaporated to dryness. The residue was recrystallised from n-pentane to give a white *solid* (3) (630 mg, 32%), m.p. 69.3—77.9° (Found: C, 77.3; H, 11.2; N, 3.4%; M^+, 387. $C_{26}H_{45}NO$ requires C, 77.0; H, 11.7; N, 3.45%; *M*, 387.6).

Into a solution of the amino-alcohol (3) in ether was introduced dry hydrogen chloride. The mixture was kept in a refrigerator and deposited the hydrochloride as white *needles*, m.p. 81—85°, softening at 71—74° (Found: C,

TABLE 3

^{13}C N.m.r. chemical shifts [a]

Compd.	Chemical shift						
	C=O	Aromatic	HC·OH	H_2C–C=O	Benzyl	H_2C·CHOH	Others
(1)	213.1	139.6, 128.1	75.9	37.1	34.5	33.0	30.1, 28.3, 27.1, 23.0
(4)		139.8, 128.9	73.9, 72.8		34.5	32.8	30.0, 28.2, 27.9, 26.9, 24.4, 24.0
(5)	212.3	139.6, 128.1		37.9, 37.2	34.5		30.4, 28.1, 27.4, 23.7, 23.0

[a] In [^2H]chloroform; δ values (from Me_4Si).

[18] A. S. Perlin and H. J. Koch, *Canad. J. Chem.*, 1970, **48**, 2639.

73.45; H, 11.15; N, 3.2. $C_{26}H_{45}NO$,HCl requires C, 73.65; H, 10.95; N, 3.3%).

Hydrogenation of the Oxime (2).—The oxime (2) (600 mg) dissolved in dry methanol (100 ml) was hydrogenated over 5% rhodium–carbon (400 mg) at 100 °C for 3.25 h (initial hydrogen pressure 60 kg cm^{-2}; autoclave of 300 ml capacity). The resulting oil was crystallised from n-pentane or methanol to give 12-*aminobicyclo*[20.2.2]*hexacosan*-11-*ol* as a white solid (100 mg), m.p. 68.8—72.3°; δ(CCl_4) 5.62 (OH and NH_2), 3.89 (*H*C·OH), 3.17 (*H*C·NH_2), and 1.30 (CH_2); $\nu_{max.}$ (KBr) 3 340 (NH), 3 190 (OH), 1 570 (NH), and 1 048 cm^{-1} (CN); M^+ 393.

[20]*Paracyclophane*-10,11-*diol* (4).—To a solution of the acyloin (1) (1.0 g) in ether (30 ml) was added LAH (0.3 g) with stirring, and the mixture was refluxed for 5 h. Water (3 ml) was added, and the mixture was poured into dilute hydrochloric acid (25 ml). The ethereal extract was dried (Na_2SO_4) and evaporated to give the *product* (0.9 g, 90%), m.p. 67—78° (Found: C, 80.3; H, 11.45. $C_{26}H_{44}O_2$ requires C, 80.35; H, 11.4%).

[20]*Paracyclophan*-10-*one* (5) *and* -10-*ol* (6).—A mixture of the hydroxy-ketone (1) (3.0 g) and 57% hydriodic acid (6.0 g) in acetic acid (30 ml) was refluxed for 2 h and allowed to cool to room temperature. It was then poured into aqueous 7M-sodium hydroxide (210 ml) containing sodium hydrogen sulphite (4.2 g) and extracted with ether (100 ml × 4). The combined extract was washed with aqueous 2% sodium hydrogen sulphite, aqueous 5% sodium hydroxide, and water, dried ($MgSO_4$), and evaporated to give the *ketone* (5) as an oil (2.2 g, 70%); $\nu_{max.}$ (neat) 1 717 cm^{-1} (C=O).

A solution of the ketone (5) (0.95 g) in ether (50 ml) was added dropwise to an ice-cooled suspension of LAH (0.70 g) in ether (50 ml). The mixture was refluxed for 3.5 h with stirring and then poured into ice–water. The organic layer was separated and the aqueous layer was extracted with chloroform. The organic layer and chloroform extract were combined and washed with water, dried (Na_2SO_4), and evaporated to afford the *alcohol* (6) as an oil (0.48 g, 51%); $\nu_{max.}$ (neat) 3 360 cm^{-1} (OH).

10-*Hydroxyimino*[20]*paracyclophane* (7), 10-*Amino*[20]-*paracyclophane* (8), *and the Hydrochloride of the Latter*.—A mixture of the ketone (5) (1.5 g), hydroxylamine hydrochloride (0.9 g), and powdered sodium hydroxide (1.6 g) in methanol (10 ml) was refluxed for 15 min with stirring. When cool the mixture was neutralised with 2M-hydrochloric acid and extracted with n-pentane (50 ml × 5). The combined extract was washed with water (50 ml × 5), dried (Na_2SO_4), and evaporated to give the *oxime* (7) as an oil (1.1 g, 64%); $\nu_{max.}$ (neat) 3 200 (OH) and 1 670 cm^{-1} (C=N) (Found: C, 80.65; H, 11.2; N, 3.45. $C_{26}H_{43}NO$ requires C, 81.0; H, 11.25; N, 3.65%).

To a suspension of LAH (1.0 g) in ether (50 ml) was added dropwise at room temperature a solution (50 ml) of the crude oxime (7) (1.1 g) in ether (50 ml) during 30 min. The mixture was refluxed with stirring for 3 h and then poured into ice–water (100 g). The organic layer was separated and the aqueous layer was extracted with ether (20 ml × 5). The organic layer and ethereal extracts were combined, washed with water (50 ml × 6), dried (Na_2SO_4), and evaporated to afford the *amine* (8) as an oil (680 mg, 65%); ninhydrin-positive; $\nu_{max.}$ (neat) 3 300 cm^{-1} (NH).

Dry hydrogen chloride gas was bubbled through a solution of the amine (8) (100 mg) in dry ether (20 ml) for 10 min. The mixture was concentrated to 2 ml and then set aside at −10 °C for 2 days. Crystalline material which separated was recrystallised from n-hexane to give the *hydrochloride* (90 mg, 83%), m.p. 131—133° (decomp.) (Found: C, 76.2; H, 11.4; N, 3.45. $C_{26}H_{45}N$,HCl requires C, 76.5; H, 11.35; N, 3.45%).

10(11)-*Oxo*[20]*paracyclophane*-22-*carboxylic Acid* (9), *its Oxime* (10), *and its Oxime Sodium Salt*.—A solution of the ketone (5) (1.0 g) in carbon disulphide (20 ml) was added to a mixture of anhydrous aluminium chloride (7.0 g) and oxalyl chloride (3.5 g) in dry carbon disulphide (30 ml) with vigorous stirring at 0 °C during 20 min. Stirring was continued for another 1 h at 0 °C and for a further 1 h at 15 °C. The mixture was poured with continuous stirring into ice–water (200 g) containing concentrated hydrochloric acid (20 ml), and extracted with ether (100 ml × 4). The extracts were washed three times with water, dried ($MgSO_4$), and evaporated to give a viscous oil; $\nu_{max.}$ (neat) 1 775 cm^{-1} (chlorocarbonyl C=O).

The oily product was heated at 50 °C in aqueous 10% sodium hydroxide (200 ml) for 30 min. The mixture was acidified with hydrochloric acid and extracted with ether. The usual work-up afforded the *acid* (9) as an oil (600 mg, 54%), $\nu_{max.}$ (neat) 1 720 (C=O) and 1 695 cm^{-1} (carboxy C=O). High-speed liquid chromatographic analysis showed only one peak.

A mixture of the acid (9) (600 mg), sodium hydroxide (900 mg), and hydroxylamine hydrochloride (450 mg) in methanol (90 ml) and water (90 ml) was heated at 80 °C for 30 min with stirring. Methanol was removed *in vacuo*, and water (100 ml) and a small amount of concentrated hydrochloric acid were added to the residue to neutralise it. The mixture was then extracted with ether (100 ml × 4). The extracts were washed with water, dried (Na_2SO_4), and refluxed (charcoal). Then the filtrate was evaporated to give the *oxime* (10) as a viscous oil (300 mg, 44%). A pure sample was obtained by a preparative liquid chromatography (methanol as eluant); $\nu_{max.}$ (neat) 3 260 (OH) and 1 695 cm^{-1} (C=O) (Found: C, 74.95; H, 10.0; N, 3.15. $C_{27}H_{43}NO_3$ requires C, 75.5; H, 10.1; N, 3.25%).

A small quantity of the crude oxime (10) dissolved in aqueous sodium hydroxide was repeatedly extracted with n-hexane. The extracts were dried (Na_2SO_4) and evaporated to give the *sodium salt* as an oil, which crystallised from n-hexane at liquid nitrogen temperature (Found: C, 70.95; H, 9.4; N, 2.75. $C_{27}H_{43}NaO_3$ requires C, 71.8; H, 9.35; N 3.1%).

2-*Aminocyclodecanol* (13) *and its Hydrochloride*.—2-Aminocyclodecanol was prepared from 2-hydroxycyclodecanone oxime (12) [2] by almost the same procedure as for the corresponding paracyclophane derivative (3); it had m.p. 79.0—92.2° (lit.,[10] *erythro* 98—99°; *threo* 94—95°) (Found: C, 70.15; H, 12.45; N, 8.2. $C_{10}H_{21}NO$ requires C, 70.1; H, 12,35; N, 8.15%). Catalytic hydrogenation of the oxime (12) also afforded the amine (13).

The amine (13) hydrochloride, prepared by a method similar to those for the paracyclophanes, had m.p. 140.3—142.1° (from methanol–ether).

This work was supported in part by a Scientific Research Grant from the Ministry of Education, Japan.

[5/2073 *Received*, 24*th October*, 1975]