Steric Interactions in Substituted cyclo*Hexadienes. Part I.* meso-*Substituted Dihydroanthracenes: Steric Effects in the Reactions of* cis- *and* trans-*Isomers.*

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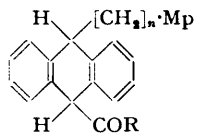
Stereoisomeric pairs of *meso*-substituted 9 : 10-dihydroanthracenes are prepared and their configurations elucidated. The interconversions and the differences in reactions and reactivities of the *cis*- and the *trans*-isomers are investigated.

The dihydroanthracenes are considered as substituted *cyclo*hexa-1 : 4-dienes;. conformational analysis is made, generalisations are formulated, and differences in properties of stereoisomers are explained in terms of conformations.

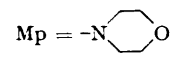
In an investigation of the stereochemical requirements of analgesics (cf., *e.g.*, Beckett and Casy, *J. Pharm. Pharmacol.*, 1954, **6**, 986), a few geometrically isomeric pairs of dihydroanthracenes (I) were required carrying aminoalkyl and acyl (or ester) *meso*-substituents.

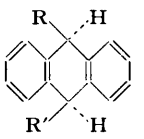
However, a wider interest was also involved. Dihydroanthracenes represent the parent structures of a type of compound which may be regarded as *cyclo*hexane-1 : 4-dienes existing in a " flattened boat " conformation with flat planar rings fused to its sides. The various probable geometrical arrangements of *meso*-groups relative to the planar rings in systems of this type raise interesting possibilities.

Isomeric 9 : 10-*Disubstituted* 9 : 10-*Dihydroanthracenes.*—The *cis*-diacid (II*a*) was obtained by acid hydrolysis of the *cis*-monoester (II*b*). Alkaline hydrolysis of the anhydride of the acid yielded the *trans*-diacid (III*a*). The configurations of these two isomers have been established by Mathieu [*Ann. Chim.* (*France*), 1945, **20**, 215] who showed that the *cis*-acid (II*a*) formed the anhydride readily with acetic anhydride whereas the *trans*-isomer (III*a*) more slowly gave the same anhydride.



(I)

Mp = 



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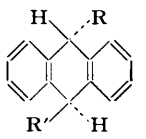

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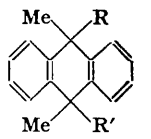


(IV)

	R	R′	R	R′
(*a*)	CO_2H	CO_2H	(*f*) CH_2·OAc	CH_2Mp
(*b*)	CO_2H	CO_2Me	(*g*) CH_2·OH	COMp
(*c*)	CO_2Me	COMp	(*h*) COEt	COMp
(*d*)	CO_2H	COMp	(*i*) CHEt·OH	CH_2Mp
(*e*)	CH_2·OH	CH_2Mp	(*j*) CHEt·OH	COMp

The *cis*-morpholide-ester (II*c*) was prepared by treating 9 : 10-dihydroanthracene-9 : 10-dicarboxylic anhydride (Beckett, Lingard, and Mulley, *J.*, 1953, 3328) with methyl alcohol to give the monoester (II*b*) and converting this into the acid chloride which was condensed with morpholine. The *trans*-isomer (III*c*) was obtained by converting the anhydride by morpholine into the morpholide-acid (III*d*) and esterifying this. The allocation of these configurations, and those of the intermediate compounds, rests upon the following observations.

(1) Ring opening of the anhydride with methyl alcohol would be expected to yield a *cis*-monoester, and hydrolysis of this ester yields the *cis*-diacid. [Separate experiments showed that the *trans*-diacid (III*a*) is not isomerised to the *cis*-diacid (II*a*) on comparable treatment, whereas the *cis*-diacid is *slowly* converted into *trans*-diacid on prolonged heating

with concentrated hydrochloric acid. The *cis*-diacid is rapidly isomerised by alkali to the *trans*-diacid. Consequently the results of acid, but not of alkaline, hydrolysis provide evidence of configuration. However, other supporting evidence is usually required because certain *trans*-isomers, other than diacids, are converted into *cis*-isomers by boiling concentrated hydrochloric acid (see below).]

(2) The above-mentioned morpholide-acid (III*d*) is isomeric with the *cis*-isomer (II*d*) obtained by acid hydrolysis of the *cis*-morpholide-ester (II*c*). The *trans*-morpholide-acid (III*d*) was inverted to this *cis*-isomer (II*d*) by boiling concentrated hydrochloric acid, a small amount of *trans*-diacid (III*a*) being also isolated.

(3) Treatment of the *trans*-morpholide-acid (III*d*) with diazomethane, which will give the corresponding methyl ester with retention of configuration, gave a product (III*c*) which was isomeric with the morpholide-ester obtained by treating the *cis*-monoester (II*b*) with thionyl chloride followed by morpholine. Esterification of the *trans*-morpholide-acid (III*d*) by the Fischer–Speier method yielded a mixture of the *cis*- and *trans*-esters (II*c* + III*c*), the latter predominating. The fact that alkaline hydrolysis of either of these morpholide-esters, or treatment of the *cis*-morpholide-acid with alkali, yields products which are identical with the morpholide-acid obtained by ring opening of the anhydride with morpholine provides further support for our allocation of configurations to these acids.

(4) 9 : 10-Dimethyl-9 : 10-dihydroanthracene-9 : 10-dicarboxylic anhydride, on treatment with methyl alcohol and with morpholine, yielded the acid-ester (IV*b*) and the morpholide-acid (IV*d*) respectively, both of the *cis*-configuration since epimerisation cannot occur. [The dimethyl anhydride yielded a *cis*-diacid (IV*a*) on hydrolysis with alkali and the morpholide-acid (IV*d*) was not inverted by alkali. Preliminary work had resulted in the isolation of isomeric diacids from the mixtures obtained by carbonating the sodio-derivative of 9 : 10-dimethylanthracene, and only one of these, to which the *cis*-configuration was allocated, was converted into an internal anhydride by hot acetic anhydride.] The *cis*-morpholide ester (IV*c*) was obtained stereochemically pure from *cis*-morpholide-acid by means of diazomethane or by the reaction of the *cis*-monoester (IV*b*) with thionyl chloride followed by morpholine. The amido- and ester-carbonyl stretching frequencies (see Table 1) of the *cis*-morpholide-ester (IV*c*) are identical with those of the non-methylated analogue (II*c*) to which, on chemical evidence, the *cis*-configuration had been assigned, but not with those of its stereoisomer; also the carbonyl frequencies of the *cis*-morpholide-acid (IV*d*) resembles that of the *cis*-analogue (II*d*) but not that of the *trans*-analogue (III*d*). (The infrared data are only regarded as supporting those obtained by the chemical interconversions, because of the dangers inherent in attempting to correlate infrared spectra obtained on solids.)

TABLE 1. *Carbonyl stretching frequencies of* meso-*substituted* 9 : 10-*dihydroanthracenes.*

	Subst.*	C=O stretching (cm.$^{-1}$) *cis*	*trans*	Band allocation
c	H ... COMp	1740	1734	Ester
	H ... CO_2Me	1637	1650	Amide
c	Me ... COMp	1740	- - -	Ester
	Me ... CO_2Me	1637	--	Amide
d	H .....COMp	1734	1722	Acid
	H ... CO_2H	1598	1593	Amide †
d	Me ... COMp	1731	—	Acid
	Me ... CO_2H	1598 (1608)	—	Amide †
a	H ... CO_2H	1708	1697	Acid
	H ... CO_2H	(1645)		

* Mp = morpholide residue. † Bonded.

The *cis*-amido-ester (II*c*) was reduced readily and almost quantitatively by lithium aluminium hydride to an amino-alcohol (II*e*) which has the *cis*-configuration since such reductions proceed with retention of configuration (Noyce and Denney, *J. Amer. Chem. Soc.*, 1950, **72**, 5743). With acetic anhydride this alcohol readily gave the acetate (II*f*). On the other hand, the *trans*-amido-ester (III*c*) gave only small amounts of *trans*-amino-alcohol, the main product being the *trans*-amido-alcohol (III*g*); and the *trans*-amino-alcohol was esterified only with difficulty.

A mixture of isomeric morpholino-ketones was obtained on treatment of the *trans*-morpholide-acid (III*d*) with thionyl chloride followed by diethylcadmium. One ketone

(A) was not inverted by acid, gave a stereochemically pure 2 : 4-dinitrophenylhydrazone under acid conditions, and was readily reduced with lithium aluminium hydride to an amino-alcohol which could be readily esterified with acetyl chloride. The other ketone (B) was partially inverted to ketone (A) by hot acid, gave a mixture of 2 : 4-dinitrodiphenylhydrazones (one identical with the product from ketone A), and was reduced, with great difficulty, mainly to an amido-alcohol. Therefore, by analogy, amido-ketone A and its derivatives are assigned the *cis*-configuration, and the B series the *trans*-configuration.

Some anomalies in melting points in these series require mention. The *cis*-diacid (II*a*) has been reported to melt at 294° (Schlenk and Bergmann, *Annalen*, 1928, **463**, 134) and 283° (block) (Mathieu, *loc. cit.*); our product, when placed in the heating block 10° below the melting point, partially melted at 265—266°, rapidly solidified, and then remelted at 301—302°. This is due to isomerisation; the *cis*- isomerised completely to the *trans*-isomer (identity confirmed by solubility and infrared absorption) when heated from 260° to 285° in 1 minute. Further, certain *trans*-derivatives can isomerise to *cis*-isomers when heated (see below), and decarboxylation has been found to occur with certain *meso*-dihydroanthracene acids (see Mathieu, *loc. cit.*); but, in our experience, reproducible melting points can be obtained if the compounds are placed in the heating block just below their melting points and the temperature raised at about 10° per minute. It is worthy of note that in this series, if the 9- and the 10-substituents are identical, the *trans*- have higher melting points than the *cis*-isomers, whereas the reverse is the case when the two substituents are not identical. The melting points of many pairs of isomers described in the literature follow the same rule (cf., *e.g.*, Mathieu, *loc. cit.*; Rigaudy, *Ann. Chim.* (*France*), 1950, **5**, 398).

In Table 2, certain inversions are summarised. Precise measurements have not yet been carried out, but infrared spectra, melting points, and solubilities indicate that the equilibria lie in the direction indicated in the Table. It is apparent that, in general, if an isomer is inverted by alkali, the *cis*-configuration can be assigned, whereas the *trans*-configuration can be assigned to an isomer which is inverted by acid. Rigaudy (*loc. cit.*) has observed similar interconversions in certain 9 : 10-diketones and keto-acids of 9 : 10-dihydroanthracene. The significance of the terms " *cis* " and " *trans* " will be considered below.

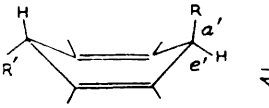
TABLE 2. *Inversions of* cis- *and* trans-*isomers of* 9 : 10-*disubstituted* 9 : 10-*dihydroanthracenes.*

9 : 10-Substituents *		*cis*	*trans*
CO_2H	CO_2H [a]	Aq. alkali → *trans* Acid → *trans* Heat → *trans*	Unchanged by heat alone or with acid or alkali
CO_2H	COMp [a]	Aq. alkali → *trans* Unchanged by heat alone or with acid	Heat → *cis* Acid → *cis*
CO_2Me	COMp [a]	Aq. alkali → *trans*-amido-acid Acid → *cis*-amido-acid	Aq. alkali → *trans*-amido-acid
COEt	COMp [a]	Unchanged by heat alone or with acid	Acid → *cis*
CO_2Me	CO_2Me [b]	—	Heat → *cis*
$CO{\cdot}C_6H_4Me$	$CO{\cdot}C_6H_4Me$ [c]	KOMe → *trans*	Acid → *cis*
CO_2H	$CO{\cdot}C_6H_4Me$ [c]	Aq. alkali → *trans*	Acid → *cis* Heat → *cis*
CO_2H	$CO{\cdot}C_6H_4{\cdot}OMe$ [d]	Aq. alkali → *trans*	—
$CO{\cdot}C_6H_4{\cdot}OMe$	$CO{\cdot}C_6H_4{\cdot}OMe$ [d]	KOMe → *trans*	—

[a] Present work. [b] Mathieu, *loc. cit.* [c] Rigaudy, *loc. cit.* [d] Rigaudy and Farthouat, *Compt. rend.*, 1952, **234**, 1064.
* Mp = morpholide residue.

Conformational Considerations.—The conformation of the central ring of 9 : 10-dihydroanthracene and its *meso*-substituents has been described in a preliminary communication (Beckett and Mulley, *Chem. and Ind.*, 1955, 146). In the 9 : 10-positions two geometrically

distinct types of bonds, now designated quasiequatorial (e') and quasiaxial (a'),* are present. The shallow boat conformation of the central ring (V) may be converted into conformation (VI) by " reverse folding " about the 9 : 10-axis, with the consequent interconversion of a' and e' bonds. Quasiequatorial groups are subjected to greater non-bonded interactions than the corresponding quasiaxial groups in this system. The preferred conformation of a 9 : 10-disubstituted dihydroanthracene will therefore be that which results in the quasiaxial form for the more bulky groups if there is no strong electrostatic repulsion between the two substituents, *e.g.*, a *trans*-dialkyl compound will have the conformation (VI) rather than (V) if R' is larger than R.

(V)  (VI)

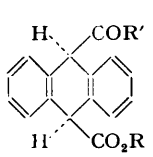
It has been shown (*e.g.*, by Barton and Schmeidler, *J.*, 1948, 1197; Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301) that strong electrostatic effects in *cyclo*hexane systems may result in exceptions to the generalisation that the thermodynamically most stable conformation is the one involving a minimum of non-bonded interactions. Consequently, when each *meso*-position of 9 : 10-dihydroanthracene is monosubstituted by groups such as RCO or CO_2H which can exert strong repulsive forces upon each other, especially under alkaline conditions, the allocation of " *cis* "- and " *trans* "-configurations to the pairs of isomers which have been obtained requires further consideration because the distance between the two substituents is in the order e'e' (*cis*) > e'a' (*trans*) > a'a' (*cis*). If isomer A is stable to alkali and isomer B is isomerised to A by treatment with alkali (or if isomer A is present in larger amounts than B in the equilibrated mixture), three possible allocations of configurations must be considered, *viz.*, (1) A as " *trans* " (e'a') with B " *cis* " (a'a'), (2) A as " *cis* " (e'e') with B " *trans* " (e'a'), and (3) A as " *cis* " (e'e') with B " *cis* " (a'a'). The last of these possible allocations can readily be rejected: for the strained " planar " dihydroanthracene conformation constitutes only a low energy barrier between the two forms of which one would be subject to considerable non-bonded interactions, and further, the inversion of B to A with alkali involves epimerisation, and only two isomers have been isolated from such systems whereas the allocation would require three isomers, namely, e'e', a'a', and e'a'. The second possibility allows of maximum group separation in the e'e' conformation, but, in such a conformation, both groups will be subject to considerable non-bonded interactions from the flanking aromatic ring substituents, whereas the first possibility will result in strong electrostatic repulsion between the groups but non-bonded interactions will be reduced to the minimum; the result is therefore mainly dependent upon the relative importance of the non-bonded interactions compared with the electrostatic repulsions. That the allocations should be made according to the first rather than the second possibility is indicated from the following observations: the 9 : 10-dihydroanthracene-9 : 10-dicarboxylic acid isomer which is isomerised with alkali (isomer B) is readily converted into the internal anhydride, whereas isomer A forms the *same* anhydride but only on more vigorous treatment, indicating that isomer B is unlikely to have the e'a' conformation; an approximate vectorial summation of moments indicates that the ratio of dipole moments of the A type [obtained from the diacid stable to alkali by Mathieu (*loc. cit.*)] to the B type (obtained from diacid which epimerises with alkali) isomers of dimethyl 9 : 10-dihydroanthracene-9 : 10-dicarboxylate will be approximately 0·7 if the A type is e'a' and the B type is a'a' but virtually zero if isomer A is e'e' and

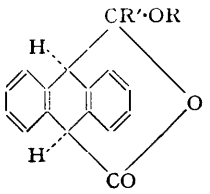
* Quasiequatorial and quasiaxial orientations were designated *lin* and *perp* in our previous communication for reasons there stated. The Referees consider the former terms to be preferable because the geometrical arrangement of the bonds at the " ends " of a 1 : 4-*cyclo*hexadiene boat may be related to the orientations of the bonds of *cyclo*hexane chairs (Barton, Hassel, Pitzer, and Prelog, *Nature*, 1953, **172**, 1096) and *cyclo*hexene " half chairs " (Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21). The relative compressions of the groups in these 1 : 4-*cyclo*hexadienes are consequently the reverse of those which obtain in the similarly designated groups in the *cyclo*hexenes.

B is e'a'—reported values (Bergman and Weizmann, *J. Amer. Chem. Soc.*, 1938, **60**, 1801) for the dipole moments of the two isomers give a ratio of approx. 0·65. "*trans*"-Isomers may therefore be regarded as existing in the e'a' and "*cis*"-isomers in the a'a' conformations.

There is a possibility that the interconversion of certain *trans*- and *cis*-isomers [*e.g.*, (VII); R = H or Me, R' = morpholino, etc.] when heated alone or in the presence of acid might be partly attributed to the existence of the latter as cyclic structures (VIII) in addition to the stabilisation effected by the reduction of non-bonded interactions. Similar

(VII)





(VIII)

cyclisations have been reported, *e.g.*, 8-benzoyl-1-naphthoic acid has been isolated in a "cyclic" and an "open" form (French and Kircher, *J. Amer. Chem. Soc.*, 1944, **66**, 298). Grove and Willis (*J.*, 1951, 877) showed that in δ- and γ-aldehydo- and -keto-acids the "open" form will have two C=O absorption bands in the C=O stretching region, whereas the cyclic forms will only exhibit one lactone C=O absorption. The presence of two carbonyl infrared bands (Table 1, first and third compound) for both *cis*- and *trans*-disubstituted 9 : 10-dihydroanthracenes indicates that the cyclic structure (VIII) does not contribute to the stability of the *cis*-isomer.

Consideration of molecular models indicates that bimolecular reactions involving an atom or group in the e' conformation will proceed only with great difficulty, although the possibility of "reverse folding" of the dihydroanthracene structure to convert an e' into an a' substituent will be possible, *e.g.*, when the a' group is more bulky than the e' group, bimolecular reaction involving the latter will necessitate "reverse folding" and reversed conformation; this change will constitute a considerable energy barrier to the reaction, since the group originally a' will have to be forced into a position of considerable non-bonded interactions and steric constraints.

The observed differences in the reactions and reactivities of certain *cis*- and *trans*-disubstituted 9 : 10-dihydroanthracenes can be explained in terms of the preferred conformations of the isomers.

The almost quantitative reduction of the *cis*-morpholide-ester (II*c*) into the *cis*-amino-alcohol (II*e*) by lithium aluminium hydride, in contrast to the reduction of the *trans*-isomer (III*c*) to yield only 10% of the *trans*-amino-alcohol and about 80% of the *trans*-amido-alcohol (III*g*) is explicable since the ester group, being more readily attacked by the reagent than the amido-group, will probably be attacked only when it is in the a' position, and the resulting bulky reduced complex causes the amido-group in the *trans*-isomer to remain in the hindered e' position where it is almost completely shielded; both ester and amido-group can be readily attacked in the *cis*-isomer in which they are both in the a' position. The fact that the *cis*-morpholide-ketone (II*h*) gives quantitative yields of the *cis*-amino-alcohol (II*i*) whereas the corresponding *trans*-ketone is reduced only with great difficulty to give poor yields of *trans*-amino-alcohol and large yields of *trans*-amido-alcohol (III*g*) can be accounted for similarly.

The following striking contrasts in the reactions of certain isomeric pairs of compounds can also be explained in terms of a hindered e' position for one substituent in the *trans*-isomer: the *trans*-amino-alcohol (III*e*) cannot be esterified under conditions which are successful for its *cis*-isomer; 9 : 10-dihydroanthracene-9 : 10-*trans*-dicarboxylic acid requires treatment with thionyl chloride for 5—20 hours to produce the *trans*-diacid chloride, whereas 15 minutes suffice for the *cis*-diacid (Mathieu, *loc. cit.*); *trans*-9 : 10-diacyl-9 : 10-dihydro-acids yield their acid chlorides with great difficulty and unchanged acids are always present, whereas the *cis*-isomers yield acid chlorides readily (Rigaudy,

loc. cit.); the 9 : 10-*cis*-diacid chloride reacts at room temperature with anisole in the presence of aluminium chloride to give a diketone, whereas the *trans*-diacid chloride requires heating at 80° (Rigaudy, *loc. cit.*).

It has been reported that *cis*-9 : 10-dihydro-9 : 10-dimethylanthracene is stable to aluminium chloride in benzene for 2 hours while the *trans*-isomer is dehydrogenated under similar conditions (Badger, Jones, and Pearce, *J.*, 1950, 1700). In the former, both *meso*-hydrogen atoms will be in e' positions whereas in the *trans*-isomer one hydrogen atom will be a' and thus susceptible to attack. (The assignment of the configurations was not rigidly established but, since both *meso*-groups are equal, the assignment of the *trans*-configuration to the higher-melting isomer is consistent with the empirical rule on p. 4161).

Rigaudy and Farthouat (*Compt. rend.*, 1953, **236**, 1173) have reported that *cis*-9-benzoyl-9 : 10-dihydroanthracene-10-carboxylic acid gives *cis*-9 : 10-dihydro-9-(hydroxydiphenylmethyl)anthracene-10-carboxylic acid with phenyl-lithium, whereas the *trans*-isomer yields the same *cis*-tertiary alcohol despite the fact that the *trans*- is thermodynamically more stable than the *cis*-acyl-acid, at least under alkaline conditions. Presumably, in the *trans*-isomer, the benzoyl group is e' and requires conversion into an a' conformation before reaction with the group can occur, and less energy is involved in the interconversion of *trans*- into the *cis*(*i.e.*, a'a')-configuration than would be involved in forcing the bulky carboxylate ion into the e' conformation.

The interconversions of the 9 : 10-disubstituted 9 : 10-dihydroanthracenes recorded in Table 2 can be explained in terms of the differences in the combined electrostatic and non-bonded flanking atom interactions obtaining in the a'a' and e'a' conformations. At least one group is present in these compounds to allow of incipient enolisation of a *meso*-hydrogen atom by which inversion can be realised. The inversion of the *trans*-amido-acid (Table 2, second compound) and the *trans*-diketone (Table 2, sixth compound) upon heating indicates that stabilisation of the molecule by reduction of non-bonded interactions is effected by the change of one e' (*trans*-isomer) to an a' group (*cis*-isomer), the other a' group being unchanged, despite the resultant increase in electrostatic repulsions between the groups. However, when the *cis*-isomers are heated in alkali, the acidic group is present as an anion, and the partial negative charge on the oxygen of the ketone group is increased, so that the electrostatic repulsions now become more significant than the non-bonded interactions of *one* of the groups in the e' position, with the result that the e'a' (greater group separation) is now more stable than the a'a' conformation (*i.e.*, *cis* → *trans*). The *cis*-diacid (Table 2, first compound) is inverted to the *trans*-isomer not only under alkaline conditions (two anionic groups present) but also by heat alone or in the presence of acid, indicating that the electrostatic repulsions even in the un-ionised molecule are sufficient to result in the e'a' conformation's being more stable than the a'a', despite the increased non-bonded interactions obtaining in the former. The other inversions recorded in Table 2 may be interpreted similarly.

The geometry of addition products from anthracenes and anthraquinones, and of substitution products of dihydroanthracenes, can be explained in similar terms. Three examples suffice for the present. *cis*-Diacids are the major products of carbonation of sodio-derivatives of anthracene and certain dialkylanthracenes (Beckett, Lingard, and Mulley, unpublished work) because the reaction occurs most readily if the entering carboxylate ion enters the a' position to yield an a'a' (*i.e.*, *cis*-)isomer, despite the fact that the *trans*-diacid (or dianion) is the thermodynamically more stable. Similarly there is *cis*-addition of chlorine to 1 : 5-dichloroanthracene and 9 : 10-diphenylanthracene (Bergmann and Weizmann, *loc. cit.*), and reaction of methyl iodide with the sodio-derivative of anthracene yields *cis*-9 : 10-dihydro-9 : 10-dimethylanthracene (Badger *et al.*, *loc. cit.*).

Experimental

Microanalyses were by Mr. Crouch, School of Pharmacy, London University. Equivalent weights of the bases were determined by titration with 0·02N-perchloric acid in glacial acetic acid with crystal-violet as indicator. Hydrochlorides were titrated similarly in the presence of mercuric acetate (see Pifer and Wollish, *J. Amer. Pharm. Assoc., Sci. Ed.*, 1951, **40**, 609). Infrared spectra were obtained on a Perkin-Elmer Model 21B double-beam automatic recording

spectrophotometer equipped with a rock-salt prism, the compounds being as solid mulls in Nujol. M. p.s were determined by introducing a capillary tube containing the sample into a heated block 10° below the m. p. and raising the temperature at about 5—10° per min.

9 : 10-*Dihydroanthracene*-9 : 10-cis-*dicarboxylic Anhydride*.—Prepared as described by Beckett *et al.* (*loc. cit.*) the anhydride had m. p. 194—195°. Mathieu and Rigaudy (*locc. cit.*) give m. p. 233—234° (block). Their anhydride, kindly supplied by Dr. Rigaudy, melted at 194—195° when the capillary-tube method was used; the m. p. did not vary significantly with the rate of heating.

Methyl cis-9-*Carboxy*-9 : 10-*dihydroanthracene*-10-*carboxylate* (II*b*).—Finely powdered anhydride (2 g.) was refluxed with methanol (8 ml.) and pyridine (15 drops) until dissolved. Ether (30 ml.) was added and the solution extracted with dilute hydrochloric acid. Evaporation of the solvent gave the monoester (2·25 g.), m. p. 165—170°, contaminated with about 10% of diester. The former was extracted with saturated sodium hydrogen carbonate solution and recrystallised from butyl ether, to give the *cis*-monoester, m. p. 182—184° (Found : equiv., 143. Calc. for $C_{17}H_{14}O_4$: equiv., 141). Rigaudy (*loc. cit.*) gave m. p. 184—185°; Beckett *et al.* (*loc. cit.*) reported m. p. 181—182°.

Alkaline hydrolysis. The ester was refluxed for 15 min. with dilute sodium hydroxide solution. Acidification of the solution gave the *trans*-diacid (III*a*), m. p. and mixed m. p. 309—310°.

Acid hydrolysis. This gave the *cis*-diacid (II*a*) only (no inversion; see preparation of the *cis*-diacid).

9 : 10-*Dihydroanthracene*-cis-9 : 10-*dicarboxylic Acid* (II*a*).—The *cis*-monomethyl ester (II*b*) (0·5 g.) was heated in acetone (5 ml.) and concentrated hydrochloric acid (10 ml.) at 120° for 1 hr. Water was added and the solid (0·34 g.) filtered off and washed with water and ether. Recrystallisation from glacial acetic acid (2 ml.) gave the *cis*-9 : 10-dicarboxylic acid as cubes (Found : C, 72·2; H, 4·8%; equiv., 130. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%; equiv., 134), which melted partially at 265—266° and then solidified and remelted at 301—302° (decomp.). Mathieu (*loc. cit.*) reported m. p. 283° (block) and Schlenk (*loc. cit.*) m. p. 294°.

Isomerisation. (*a*) This *cis*-diacid was heated with aqueous alkali to give the *trans*-diacid (III*a*) (cf. Mathieu, *loc. cit.*). (*b*) The *cis*-diacid, heated in a m. p. apparatus at 270° for 1 min., gave the *trans*-diacid (III*a*) (identified by m. p. 301—302° and infrared absorption). (*c*) The *cis*-diacid (54 mg.) was heated with concentrated hydrochloric acid (3 ml.) at 120° for 16 hr. A mixture of *cis*- (37 mg., cubes, m. p. 265—266°) and *trans*-diacid (9 mg., needles, m. p. 309—310°) was obtained.

9 : 10-*Dihydroanthracene*-trans-9 : 10-*dicarboxylic Acid* (III*a*).—Finely powdered anhydride (2 g.) was boiled with 5% sodium hydroxide solution (20 ml.) for 30 min. and the solution acidified, to give a solid (2·07 g.), m. p. 300°. Recrystallisation of this material (0·75 g.) from acetic acid (80 ml.) gave the 9 : 10-*trans*-acid (0·14 g.) as needles, m. p. 309—310° (decomp.) (Found : C, 70·9; H, 4·4%; equiv., 132·5). Mathieu (*loc. cit.*) reported m. p. 380° (block), Schlenk (*loc. cit.*) m. p. 286°, and Beyer and Fritsch (*Ber.*, 1941, **74**, 494) m. p. 305—307°.

Attempted isomerisation. (*a*) The *trans*-diacid was heated under the conditions described for the *cis*-isomer and gave unchanged material (m. p. and infrared spectrum unchanged). (*b*) Heating with concentrated hydrochloric acid (conditions as for the *cis*-isomer) gave unchanged material, m. p. 309—310° (decomp.).

9 : 10-*Dihydro*-9 : 10-*dimethylanthracene*-9 : 10-cis-*dicarboxylic Anhydride*.—Prepared by the method described by Beckett *et al.*, the anhydride had m. p. 215—216°. It gave *cis*-diacid only (no inversion; see preparation of the *cis*-diacid).

9 : 10-*Dihydro*-9 : 10-*dimethylanthracene*-cis-9 : 10-*dicarboxylic Acid* (IV*a*).—The foregoing anhydride (0·2 g.) was heated with dilute sodium hydroxide solution until dissolved. The acid was precipitated with dilute hydrochloric acid and recrystallised from glacial acetic acid to give cubes (0·15 g.) of the 9 : 10-cis-*diacid*, m. p. 310—312° (decomp.) (Found : C, 72·8; H, 5·5; equiv., 150. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%; equiv., 148).

The acid was stable when heated alone or with aqueous alkali. Heating the diacid with acetic anhydride regenerated the anhydride.

9 : 10-*Dihydro*-9 : 10-*dimethylanthracene*-trans-9 : 10-*dicarboxylic Acid* (IV*a*).—A mixture of crude acids (2·7 g.) prepared by carbonation of the sodium addition compound of dimethylanthracene (*idem*, *loc. cit.*) was heated with acetic anhydride (6 ml.), chloroform (20 ml.) was added, and the *trans*-diacid (50 mg.) extracted with saturated sodium hydrogen carbonate solution. Recrystallisation from glacial acetic acid gave the 9 : 10-trans-*diacid* as needles, m. p. 347—348° (decomp.; sealed capillary) (Found : C, 72·7; H, 5·5%).

Heating the *trans*-diacid with acetic anhydride [same conditions as for the *cis*-diacid (IV*a*)] gave unchanged diacid.

Methyl cis-9-*Carboxy*-9 : 10-*dihydro*-9 : 10-*dimethylanthracene*-10-*carboxylate* (IV*b*).—The dimethyl-anhydride (0·35 g.) was refluxed with methyl alcohol (3 ml.) and pyridine (6 drops) (as described for the parent anhydride) to give the *monomethyl ester* contaminated with about 10% of diester. The former recrystallised from butyl ether as solvated cubes, m. p. 157—158° (material for analysis was recrystallised from benzene; difficulties were experienced in obtaining consistent analytical figures owing to explosion during combustion) (Found: C, 72·5; H, 5·6. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·8%).

cis-9-*Carboxy*-9 : 10-*dihydroanthracene*-10-*carboxymorpholide* (II*d*).—The *cis*-amido-ester (II*c*) (0·22 g.), as a fine powder, was heated at 120° for 1 hr. with concentrated hydrochloric acid (5 ml.). The solid product was filtered off and recrystallised from glacial acetic acid to give cubic crystals of the *monomorpholide*, m. p. 266—269° (Found: C, 71·1; H, 5·4; N, 4·05%; equiv., 334. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6; N, 4·3%; equiv., 334).

The *cis*-amido-acid (17 mg.) was boiled for 30 min. with dilute sodium hydroxide solution, and the solution acidified to give the *trans*-isomer (6 mg.) (identified by the infrared spectrum and m. p. 225—226°). Heating the *cis*-amido-acid under the conditions described for the *trans*-isomer gave unchanged *cis*-amido-acid (infrared spectrum).

trans-9-*Carboxy*-9 : 10-*dihydroanthracene*-10-*carboxymorpholide* (III*d*).—The anhydride (14 g.) was heated with morpholine (32 ml.) until dissolved. The solution was then cooled and acidified, and the precipitated solid *morpholide* (18·7 g.) filtered off and recrystallised from butanol to give diamond-shaped crystals, m. p. 225—226° (Found: C, 71·4; H, 5·9; N, 4·3%; equiv., 333).

The *trans*-amido-acid was refluxed for 6 hr. with acetic acid (12·5 ml.) and concentrated hydrochloric acid (7·5 ml.). Upon cooling, crystals (0·15 g.) of the *cis*-amido-acid (identified by m. p. 266—269° and the infrared spectrum) were obtained; a second crop (0·42 g.), m. p. 225—226°, consisted mainly of unchanged *trans*-amido-acid. A few needle-shaped crystals of the *trans*-diacid, m. p. 305—310°, were hand-picked from this second crop.

The *trans*-amido-acid, when heated from 210° to 230° during 3½ min., gave the *cis*-amido-acid (infrared spectrum and m. p. 265°).

The *trans*-amido-acid was boiled for 30 min. with aqueous alkali and gave unchanged material, m. p. 225—226°.

cis-9-*Carboxy*-9 : 10-*dihydro*-9 : 10-*dimethylanthracene*-10-*carboxymorpholide* (IV*d*).—Prepared as described by Beckett *et al.* (*loc. cit.*) the amido-acid had m. p. 291—292°. This acid was unchanged when boiled with dilute sodium hydroxide solution for 30 min.

cis-9-*Methoxycarbonyl*-9 : 10-*dihydroanthracene*-10-*carboxymorpholide* (II*c*).—The *cis*-mono-ester (1·8 g.) was heated with thionyl chloride (3 ml.) until dissolved. Excess of thionyl chloride was removed under pressure, the residue dissolved in ether (25 ml.), morpholine (0·65 g.) in ether (5 ml.) added, and the precipitated solid (1·95 g.) filtered off. Three recrystallisations from butanol gave colourless needles of the cis-*ester-morpholide*, m. p. 212—214° (Found: C, 72·0; H, 5·8; N, 4·2%; equiv., 354. $C_{21}H_{21}O_4N$ requires C, 71·8; H, 6·0; N, 4·0%; equiv., 351).

The *cis*-amido-ester (61 mg.) was refluxed with 0·1N-sodium hydroxide for 5 min. Acidification of the solution gave the *trans*-amido-acid (53 mg., complete inversion) identified by m. p. 225—226° and the infrared spectrum. The *cis*-amido-ester was recovered unchanged (m. p. and infrared spectrum) when heated from 210° to 230° during 3½ min. Acid-hydrolysis gave the *cis*-amido-acid (no inversion; see preparation of the *cis*-amido-acid).

trans-9-*Methoxycarbonyl*-9 : 10-*dihydroanthracene*-10-*carboxymorpholide* (III*c*).—*Method A.* *trans*-Amido-acid (III*d*) (0·65 g.) was treated with a large excess of diazomethane in ether (50 ml.) at room temperature. A little insoluble material was filtered off and the ether removed. Recrystallisation from benzene gave colourless plates (0·34 g.) of trans-*ester-morpholide*, m. p. 161—162·5° (Found: C, 71·8; H, 6·2. $C_{21}H_{21}O_4N$ requires C, 71·8; H, 6·0%). *Method B.* The *trans*-amido-acid (0·77 g.) was refluxed with methanol (10 ml., containing 1% of hydrogen chloride) for 3 hr. Water (100 ml.) and benzene (60 ml.) were added and the separated aqueous layer was extracted with more benzene (20 ml.). The mixed benzene fractions were evaporated to give a solid, m. p. 156—158°, softening at 150°. Recrystallisation from butyl ether gave crystals of two types which were separated by hand-picking: colourless plates (0·62 g.) of the *trans*-amido-ester (III*c*), m. p. 161—162·5, and needles (80 mg.) of the *cis*-amido-ester, m. p. 212—214°.

The *trans*-amido-ester (50 mg.) was refluxed for 10 min. with 0·1N-sodium hydroxide.

Acidification of the solution gave the *trans*-amido-acid (40 mg.; no inversion), m. p. and mixed m. p. 225—226°. The *trans*-amido-ester was unchanged by heat (infrared spectrum).

trans-*Ethoxycarbonyl*-9 : 10-*dihydroanthracene*-10-*carboxymorpholide*.—Prepared from the *trans*-amido-acid (8·2 g.) as described for the methyl ester (method B), the *ethyl ester* (4 g.) had m. p. 118—118·5° (Found : C, 71·7; H, 6·5; N, 3·9. $C_{22}H_{23}O_4N$ requires C, 72·3; H, 6·3; N, 3·8%).

cis-9-*Methoxycarbonyl*-9 : 10-*dihydro*-9 : 10-*dimethylanthracene*-10-*carboxymorpholide* (IV*c*).—*Method A. cis*-Monomethyl ester (IV*b*) (0·13 g.) was refluxed with thionyl chloride (0·5 ml.) until dissolved and excess of reagent was removed under reduced pressure. The crude acid chloride in ether (5 ml.) was treated with morpholine (45 mg.) in ether (2 ml.), the mixture extracted with dilute acid, and the organic layer evaporated. Recrystallisation from butyl ether gave the cis-*ester-morpholide* (56 mg.), m. p. 157—158°, as plates (Found : C, 73·2; H, 6·4; N, 3·8. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·65; N, 3·7%). *Method B.* The *cis*-amido-acid (0·36 g.) was treated with excess of diazomethane in ether. The ether was removed and the ester recrystallised from butyl ether to give the *cis*-amido-ester (0·1 g.), m. p. 157—158°

9-*Acetyl*-9 : 10-*dihydroanthracene*-10-*carboxymorpholides* (II*h and* III*h*).—Powdered *trans*-amido-acid (III*d*) (2 g.) was refluxed with thionyl chloride (4 ml.) until dissolved. Excess of thionyl chloride was removed and the gummy acid chloride then run slowly in benzene (25 ml.), with vigorous stirring, into a solution of diethylcadmium (from 2·6 g. of anhydrous cadmium chloride, 0·68 g. of magnesium, and 3·06 g. of ethyl bromide) in ether (100 ml.) in a nitrogen atmosphere. An immediate precipitate changing to a gum was formed. The mixture was stirred and refluxed for 30 min., the complex decomposed with ice and dilute sulphuric acid, the organic layer separated, and the acidic layer extracted with benzene (20 ml.). The organic fractions were extracted with saturated sodium hydrogen carbonate solution, washed with water, dried, and evaporated, to give a gum (1·5 g.) (acidification of the sodium hydrogen carbonate solution gave 0·5 g. of unchanged *trans*-amido-acid, m. p. and mixed m. p. 225—226°). The gum was dissolved in benzene (3 ml.) and gave, on storage, colourless needles (0·16 g.), m. p. 214—215°. Recrystallisation from benzene gave the cis-*morpholido-ketone*, m. p. 219—220° (Found : C, 75·7; H, 6·6; N, 4·0. $C_{22}H_{23}O_3N$ requires C, 75·6; H, 6·6; N, 4·0%). Evaporation of the benzene mother-liquors gave a solid which, recrystallised from ethanol, gave colourless blades (0·35 g.) of trans-*morpholido-ketone*, m. p. 139—139·5°, containing ethanol of crystallisation (material for analysis was heated at 100° under reduced pressure for 30 min. : the m. p. was unchanged) (Found : C, 75·9; H, 6·9%).

The *cis*-amido-ketone (20 mg.) in ethanol (3 ml.) was boiled with 2 : 4-dinitrophenylhydrazine reagent (1 ml. of a 5% solution in ethanol–sulphuric acid), to give the 2 : 4-*dinitrophenylhydrazone*, yellow needles, m. p. 265—266° (decomp.) (Found : C, 63·9; H, 5·15; N, 13·4. $C_{28}H_{27}O_6N_5$ requires C, 63·5; H, 5·1; N, 13·4%).

The *trans*-amido-ketone (48·5 mg.) in ethanol (0·5 ml.), boiled with 2 : 4-dinitrophenylhydrazine reagent (2 ml.), gave a yellow solid (30 mg.), m. p. 185—200°. Recrystallisation from acetone gave yellow needles of the *cis*-2 : 4-dinitrophenylhydrazone (*i.e.*, partial isomerisation), m. p. and mixed m. p. 265—266°. Evaporation of the alcoholic mother-liquors gave material (27 mg.), m. p. 163—165°. Recrystallisation from ethanol gave the trans-2 : 4-*dinitrophenylhydrazone* (18·6 mg.) as yellow needles, m. p. 187—189° (Found : C, 63·9; H, 5·4; N, 13·2%).

Isomerisation of the cis- *and* trans-*Keto-morpholides*.—(*a*) The *trans*-compound (9 mg.) was heated at 120° for 1 hr. with concentrated hydrochloric acid (0·5 ml.). Water (2 ml.) was added and the precipitated solid recrystallised from ethanol (0·25 ml.), to give the *cis*-isomer (0·4 mg.), m. p. and mixed m. p. 215—216°. (*b*) The *cis*- and *trans*-ketones were heated from 210—230° during 3½ min. : the isomers were unchanged (m. p. and infrared spectra).

cis-9 : 10-*Dihydro*-9-*hydroxymethyl*-10-*morpholinomethylanthracene* (II*e*).—The *cis*-amido-ester (II*c*) (1·0 g.) in dry benzene (50 ml.) was added to excess of lithium aluminium hydride in dry ether, the mixture refluxed for 6 hr., and excess of reducing agent destroyed by the addition of water. The solvent was decanted through a filter, the inorganic material extracted with benzene, and the base extracted from the organic solvent with dilute acid. The base was precipitated with alkali and taken up in ether, and the ether evaporated, to give a solid (0·81 g.). Recrystallisation from ethanol gave colourless cis-*alcohol*, m. p. 118—119·5° (Found : C, 78·0; H, 7·4; N, 4·6%; equiv., 308·5. $C_{20}H_{23}O_2N$ requires C, 77·6; H, 7·5; N, 4·5%; equiv., 309·5). The *hydrochloride* had m. p. 279—282° (decomp.) (Found : C, 69·3; H, 6·6%; equiv., 344·5. $C_{20}H_{24}O_2NCl$ requires C, 69·4; H, 7·0%; equiv., 346), and the *picrate* m. p. 202—203° (decomp.) (Found : C, 58·4; H, 5·0; N, 10·7. $C_{20}H_{16}O_9N_4$ requires C, 58·0; H, 4·9; N, 10·4%).

A similar reaction in the *trans*-series gave the *trans*-alcohol (0·45 g. from 2·5 g.) as a gum which gave a *hydrochloride*, m. p. 280—282° (decomp.) (Found : C, 69·9; H, 6·9%; equiv., 348) [mixed m. p. with the *cis*-hydrochloride 269—270° (decomp.)], and a *picrate*, m. p. 202—204° (decomp.) (Found : C, 58·0; H, 5·1; N, 10·7%) [mixed m. p. with the *cis*-picrate 181—189° (decomp.)]. A non-basic compound (1·53 g.) was isolated from the organic solvent after extraction of the base and recrystallised from benzene, yielding trans-9 : 10-*dihydro*-9-*hydroxymethylanthracene*-10-*carboxymorpholide* (III*g*), m. p. 165—166° (Found : C, 74·8; H, 6·6; N, 4·3. $C_{20}H_{21}O_3N$ requires C, 74·3; H, 6·5; N, 4·3%).

cis-9 : 10-*Dihydro*-9-1′-*hydroxypropyl*-10-*morpholinomethylanthracene* (II*i*).—The *cis*-amido-ketone (II*h*) (0·6 g.) was reduced with lithium aluminium hydride (as previously described) to give the required *base* (0·54 g.), m. p. 113—114° (from ethanol) (Found : C, 78·5; H, 7·8; N, 4·2%; equiv., 333·5. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·1; N, 4·15%; equiv., 337·5).

The *trans*-amido-ketone (III*h*) (1·05 g.), when similarly reduced, gave a base as a gum (0·15 g.) and a non-basic substance (0·87 g.), trans -9 : 10-*dihydro*-9-1′-*hydroxypropylanthracene*-10-*carboxymorpholide* (III*j*), m. p. 151—153° (from benzene) (Found : C, 74·9; H, 7·2; N, 4·2. $C_{22}H_{25}O_3N$ requires C, 75·2; H, 7·2; N, 4·0%). Attempts to crystallise the basic gum, or to produce derivatives of the base, were unsuccessful.

cis-9-*Acetoxymethyl*-9 : 10-*dihydro*-10-*morpholinomethylanthracene* (II*f*).—The *cis*-amino-alcohol (II*e*) (0·3 g.) in dry ether (15 ml.) was added to ethylmagnesium iodide (from 0·1 g. of magnesium and 0·63 g. of ethyl iodide) in ether with vigorous stirring, and the mixture refluxed for 15 min. Acetic anhydride (2 ml.) in ether (10 ml.) was slowly added to the cooled suspension, and the mixture stirred overnight at room temperature (see Beckett and Linnell, *J. Pharm. Pharmacol.*, 1950, **2**, 430). Dilute hydrochloric acid was added, non-basic material extracted with ether, the solution made alkaline, and the precipitated base extracted with ether. Evaporation of the solvent gave the acetate (0·29 g.) as a gum, which afforded a *hydrochloride* (0·25 g.), m. p. 237—239° (decomp.) (Found : C, 68·3; H, 6·75; N, 3·5%; equiv., 389·5. $C_{22}H_{26}O_3NCl$ requires C, 68·1; H, 6·75; N, 3·6%; equiv., 387·5), and a *picrate*, m. p. 208—209° (decomp.) (Found : C, 57·6; H, 5·0; N, 9·6. $C_{28}H_{28}O_{10}N_4$ requires C, 57·9; H, 4·9; N, 9·6%). Acetylation of the *cis*-amino-alcohol with acetyl chloride in the presence of pyridine gave similar results.

The crude *trans*-amino-alcohol (III*e*) (0·39 g.) was treated with ethylmagnesium iodide and acetic anhydride (10 ml.) as above. The mixture was refluxed for 6 hr. and the base obtained as a gum. Part (22 mg.) of the gum in ethanol, with picric acid (19·5 mg.) in ethanol, gave a yellow solid (28·5 mg.), m. p. 167—170°; recrystallisation from ethanol gave crystals of two types which were separated by hand-picking and gave the *picrate* of the *trans*-acetate as clusters of needles, m. p. 181—182° (decomp.) (11 mg.; from acetone–ethanol) (Found : C, 58·4; H, 5·0; N, 9·4%), and discrete needles, m. p. 202—204° (decomp.), of unacetylated amino-alcohol picrate.

The *trans*-amino-ester picrate (23·5 mg.) in acetone (3 ml.) was decomposed with 5% lithium hydroxide solution, and the base extracted with ether. Evaporation of the solvent gave the base (11 mg.) which formed the trans-*amino-acetate hydrochloride*, needles, m. p. 256—257° (decomp.) (from ethanol–ether).

cis-9-1′-*Acetoxypropyl*-9 : 10-*dihydro*-10-*morpholinomethylanthracene*.—The *cis*-amino-alcohol (II*i*) (0·4 g.) was refluxed with acetyl chloride (2 ml.), and the reagent then removed under reduced pressure to give the required base. This was treated with picric acid to give the *ester picrate*, m. p. 178—179° (Found : C, 58·8; H, 5·4; N, 9·1. $C_{30}H_{32}O_{10}N_4$ requires C, 59·2; H, 5·4; N, 9·2%). The base formed a *hydrochloride*, m. p. 187—190° (Found : C, 68·7; H, 6·7%; equiv., 420. $C_{24}H_{30}O_3NCl$ requires C, 69·3; H, 7·3%; equiv., 416).

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