Tetrahedron, 1963, Vol. 19, pp. 545 to 556. Pergamon Press Ltd. Printed in Northern Ireland

STERIC INTERACTIONS IN SUBSTITUTED CYCLOHEXADIENES—II

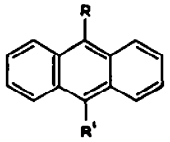
MESO-SUBSTITUTED DIHYDROANTHRACENES: STERIC EFFECTS IN THE REACTIONS OF *CIS*- AND *TRANS*- ISOMERS

A. H. BECKETT and J. WALKER
School of Pharmacy, Chelsea College of Science and Technology, London

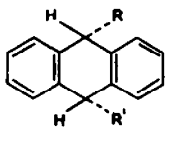
(*Received* 17 *October* 1962)

Abstract—A series of *meso*- substituted 9,10-dihydroanthracenes has been prepared, their configurations assigned and the stereochemical course of certain reactions explained in terms of the steric requirements of the *meso*- carbon atoms of 9,10-dihydroanthracene.

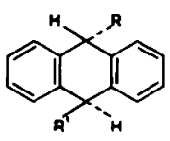
A REPORT[1] that 1,4-bis-diethylaminomethyl naphthalene possessed analgesic activity comparable to that of pethidine prompted the attempted preparation of 9,10-bis-(diethylaminomethyl) anthracene and the morpholino and piperidino analogues (I a, b, c.), together with the *cis*- and *trans*- forms of 9,10-dihydro-9,10-bis-(alkylaminomethyl)-anthracenes (II and III a, b, c). 9,10-bis-(Chloromethyl)-anthracene with



I



II



III

	R	R′
(a)	·$CH_2N(Et)_2$	·$CH_2N(Et)_2$
(b)	·$CH_2NC_4H_8O$	·$CH_2NC_4H_8O$
(c)	·$CH_2NC_5H_{10}$	·$CH_2NC_5H_{10}$
(d)	·COCl	·COCl
(e)	·CO_2H	·$CON(Et)_2$
(f)	·CO_2H	·$CON(Me)_2$
(g)	·CO_2Me	·$CON(Et)_2$
(h)	·CH_2OH	·$CH_2N(Et)_2$
(i)	·CH_2OH	·$CON(Et)_2$

	R	R′
(j)	·$CON(Et)_2$	·$CON(Et)_2$
(k)	·$CONC_4H_5O$	·$CONC_4H_8O$
(l)	·$CONH_2$	·$CONH_2$
(m)	·CONHMe	·CONHMe
(n)	·$CONHCH(Me)_2$	·$CONHCH(Me)_2$
(p)	·$CON(Me)_2$	·$CON(Me)_2$
(r)	·$CONH_2$	·$CONC_4H_8O$
(s)	·$CONHCH(Me)_2$	·$CON(Et)_2$

the appropriate secondary amines gave the tertiary bases (I a, b, c) in good yields. The following attempts to reduce the bis-(diethylaminomethyl)-compound (Ia) to the required dihydro derivative (IIa and/or IIIa) were unsuccessful: sodium in ethanol, (cf. reduction of 9,10-dimethylanthracene to the 9,10-dihydro analogue[2]) and red phosphorus and hydrogen iodide (cf. reduction of 9-benzyl-10-benzoyl[3a]-, 9-acyl- and 9-aminoacylanthracenes[3b]) gave starting material while sodium in ether followed by

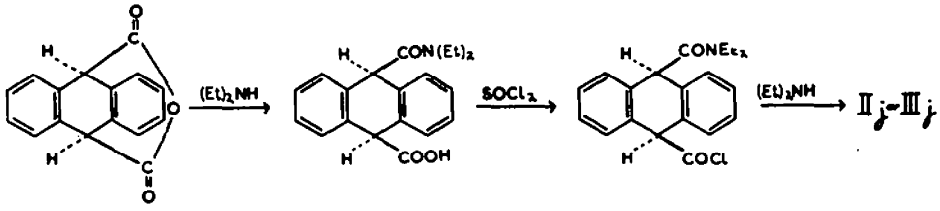
[1] G. M. Badger, J. W. Cook, G. M. S. Donald, J. M. P. Graham and T. Walker, *Nature, Lond.* **162,** 21 (1948).

[2] K. Sisido and T. Isida, *J. Amer. Chem. Soc.* **70,** 1289 (1948); D. D. Phillips and J. Cason, *ibid.* **74,** 2934 (1952); G. M. Badger, M. L. Jones and R. S. Pearce, *J. Chem. Soc.* 1700 (1950).

[3a] J. W. Cook, *J. Chem. Soc.* 2160 (1926);

[b] E. L. May and E. Mossettig, *J. Amer. Chem. Soc.* **70,** 686 (1948).

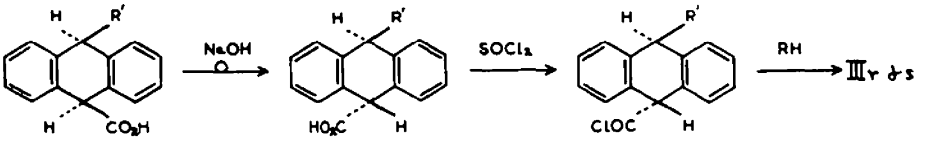
solvolysis with ethanol[4] gave a yellow insoluble amorphous non-basic solid of indefinite melting point. A route via lithium aluminium hydride reduction of some *meso*- amides of dihydroanthracene was therefore attempted. The action of diethylamine, or aqueous diethylamine on *cis*- (route A) and *trans*- (route B) 9,10-dihydroanthracene-9,10-dicarboxylic acid chloride gave the same isomeric bis-amide (IIj or IIIj) as did route C.



ROUTE C.

Analogous products (II k or III k) were obtained by all routes when diethylamine was replaced by morpholine.

Assignment of configuration to the single isomer rests on the following considerations. A predominating influence of steric factors in the reaction would result in the formation of the *cis*- isomer with both *meso*- substituents in the less hindered quasi-axial conformation.[5a,b] However, forces of repulsion between the amide groups might result in the formation of the *trans*- isomer with greater group separation, despite the attendant increase in non-bonded interactions between the quasiequatorial group and the flanking 1,8-hydrogen atoms.[5a,b] The influence of the steric factor on the formation and stability of possible isomeric pairs was investigated by preparing a series of amides with 9,10-substituents of increasing size (II and III l, m, n, p) via routes A or C, and B, using the appropriate amines. The *cis*-forms of 9-carboxamido-9,10-dihydroanthracene-10-carboxymorpholide (II r) and 9-carboxyisopropylamido-9,10-dihydroanthracene-10-carboxydiethylamide (II s) were also prepared by a suitable modification of route C, and the corresponding *trans*- isomers (III r and s) by route D.



IV

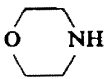
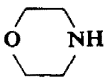
r). R' = ·CO·NC4H8O ; R = ·NH2

s). R' = ·CO·N[Et]2 ; R = ·NHCH[Me]2

ROUTE D.

[4] W. Schlenk and E. Bergmann, *Liebigs Ann.* **463**, 98 (1928); M. D. Scott, U.S.P.2, 183, 847/1939.
[5a] A. H. Beckett and B. A. Mulley, *Chem. & Ind.* 146 (1955);
[b] A. H. Beckett and B. A. Mulley, *J. Chem. Soc.* 4159 (1955).

TABLE 1

Amine used	p*Ka*	Route*	Reaction product	Equilibration reaction: Starting material	Equilibration reaction: Product composition % *Cis*	Equilibration reaction: Product composition % *Trans*
NH_3 (0·880)	9·26[6]	C	*cis* (II l)	*cis* (II l)	56	15
		B	*trans* (III l)	*trans* (III l)	59	9
CH_3NH_2 (aqueous)	10·64[6]	A	*cis* (II m)	*cis* (II m)	57	23
		B	*trans* (III m)	*trans* (III m)	72	14
$(CH_3)_2CHNH_2$	10·63[6]	A	*cis* (II n)	*cis* (II n)	30	60
		B	*trans* (III n)	*trans* (III n)	37·5	50
$(CH_3)_2NH$ (aqueous)	10·71[6]	C	*trans* (III p)	*trans* (III p)		57
		B	*trans* (III p)			(+15% of aromatized material)
$(C_2H_5)_2NH$	11·1[6]	A, C	*trans* (III j)	*trans* (III j)		77·5
		B	*trans* (III j)			
$(C_2H_5)_2NH$ (aqueous)		A	*trans* (III j)			
		B	*trans* (III j)			
	8·36[7]	A, C	*trans* (III k)	*trans* (III k)	78·5% of (I k)	
		B	*trans* (III k)			
(a) 		C	*cis* (II r)	*cis* (II r)	63	
(b) NH_3 (0·880)		D	*trans* (III r)	*trans* (III r)	61 + 11% of (I r)	
(a) $(C_2H_5)_2NH$		C	*cis* (II s)	*cis* (II s)	75	
(b) $(CH_3)_2CHNH_2$		D	*trans* (III s)	*trans* (III s)	72·5	

* For routes, see text.

[6] Lange, *Handbook of Chemistry* (9th Edition) p. 1202 Handbook Publishers (1956).
[7] N. F. Hall, *J. Amer. Chem. Soc.* **78**, 2570 (1956).

The resulting amides were equilibrated by means of ethanolic sodium ethoxide solution (with the exception of (II l and III l) which, because of their insolubility in ethanol, were equilibrated by means of triethylamine in nitrobenzene) and the products isolated (See Table 1).

Ammonia, methylamine and isopropylamine used in preparative routes A or C gave different isomers respectively from those resulting from route B. *cis*-9-chlorocarbonyl-9, 10-dihydroanthracene-10-carboxymorpholide and diethylamide when treated with ammonia and isopropylamine respectively (modified route C) gave different respective isomeric amides from those resulting when *trans*-9-chlorocarbonyl-9, 10-dihydroanthracene-10-carboxymorpholide or diethylamide (IV r or s) were treated with the same amines (Route D).

Dimethylamine, diethylamine and morpholine furnished one isomer only, irrespective of the route used and these compounds (III p, j, k) have been assigned a *trans*-configuration from the following considerations.

1. In compounds obtained in two isomeric forms (II and III, l, m, n), equilibration experiments result in a larger proportion of the *trans*-isomer (*trans*-configuration assigned by identity with product from route B) as the size of the substituent group increases (Table 1). This is to be expected on the grounds that the effect of non-bonded interactions between the alkyl chains in the *cis*-amido groups will increase with increase in size of these groups. With further increase in size of substituent, these forces of repulsion will become greater than those exerted by the 1:8 hydrogen atoms upon *one* group in the quasiequatorial position: the exclusive adoption of a *trans*-configuration (III p, j, k) therefore occurs.

2. The adoption of the quasiequatorial position by one group is also facilitated by the fact that the planar C=O portion of the substituent can be accommodated with minimum interactions at a 9- or 10-position in a plane perpendicular to the general plane of the molecule. This is supported by the fact that 9,10-dibenzoyl-[8] and 9,10-diphenyl-9,10-dihydroanthracene exist in both *cis*- and *trans*- forms whereas 9,10-dibenzyl-9,10-dihydroanthracene possessing a bulky CH_2- group exists in the *cis*- form only (see later).

3. A potential stabilising intramolecular >NH/carbonyl hydrogen bond is present in all those compounds (II l, m, n, r, s) shown to exist in *cis*- as well as *trans*- forms.

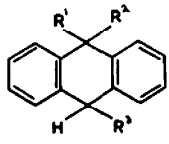
Attempts to reduce the amides (III j and k) to the corresponding amines (III a and b) with lithium aluminium hydride resulted in aromatization with production of the *meso*-anthracene derivatives (I a and b). Whether this was due to instability resulting from a bulky alumino-hydride complex at the carbonyl oxygens or to the prolonged reaction time necessitated by the ether-insolubility of the amides has not been established. The latter explanation is supported by the facts that *cis*-9-methoxycarbonyl-9,10-dihydroanthracene-10-carboxydiethylamide (II g) gave *cis*-9,10-dihydro-9-hydroxymethyl-10-diethylaminomethylanthracene (II h) with lithium aluminium hydride and attempts to equilibrate the amides (III j and k) with sodium ethoxide in ethanol resulted in appreciable aromatization.

The suggested conformational requirements at the *meso*-carbon atoms of 9,10-disubstituted-9,10-dihydroanthracenes described in earlier publications[5a,b] have

[8] J. Rigaudy, *Ann. Chim.* **5**, 398 (1950).

received support from the behaviour of further examples of such compounds described in recent literature. Dufraisse *et al.*[9] report that the lithium aluminium hydride reduction of anthraquinone gives a mixture of *cis*- and *trans*- 9,10-dihydroanthracene 9,10-diols (V a) in which the *cis*-isomer predominates.

The addition of benzyl radicals to anthracene gives among other products, the same isomeric form of 9,10-dibenzyl-9,10-dihydroanthracene (V b) as is obtained by the reduction of 9,10-dibenzylanthracene with sodium in liquid ammonia[10], sodium in ether followed by ethanol[11] or sodium in pentanol.[10,11] This compound (presumably the *cis*-isomer) could not be isomerized by means of sodium hydride or sodamide[10] and no other isomer appears to have been reported in the literature.



V

(a) $R' = H$; $R^2 = R^3 = OH$
(b) $R' = H$; $R^2 = R^3 = C_6H_5CH_2\cdot$
(c) $R' = H$; $R^2 = R^3 = C_6H_5\cdot$
(d) $R' = H$; $R^2 = R^3 = (CH_3)_2(CN)C\cdot$
(e) $R' = CH_3$; $R^2 = R^3 = (CH_3)_2(CN)C\cdot$
(f) $R' = CH_3O$; $R^2 = R^3 = (CH_3)_2(CN)C\cdot$
(g) $R' =$ Cl or Br; $R^2 = R^3 = (CH_3)_2(CN)C\cdot$
(h) $R' = H$; $R^2 = (CH_3)(C_6H_5)(OH)C\cdot$
$R^3 = \cdot CO_2H$
(i) $R' = H$; $R^2 = (CH_3)(C_6H_5)CH\cdot$
$R^3 = \cdot CO_2CH_3$
(j) $R' = H$; $R^2 = CH_3(C_6H_5)CH\cdot$
$R^3 = \cdot CO_2H$

9,10-Diphenylanthracene treated with sodium in liquid ammonia followed by hydrolysis gives 9,10-diphenyl-9,10-dihydroanthracene (V c) m.p. 227°[12] while reduction by means of sodium or lithium in ether with subsequent alcoholysis results in an isomeric form of (V c) m.p. 199°[4a] and reduction with sodium amalgam[11,15a] and sodium in ethanol or pentanol yields a mixture of isomers[4a,13,15a] in which the higher melting isomer (presumably the *cis*-form) predominates.[14] The different products obtained by the first two methods can be explained in terms of a greater stabilization of the carbanion intermediate in the presence of the ionizing solvent ammonia resulting in thermodynamic control of the reaction, and a predominance of kinetic influences in the case of reduction by lithium or sodium in ether. In other systems the first method of reduction has been shown to give the thermodynamically more stable product.[16]

That (V c) exists in a *trans*- as well as in a *cis*-form can be ascribed to the adoption

[9] C. Dufraisse, G. Rio and Y. Lepage, *C.R. Acad. Sci. Paris*, **247**, 1928 (1958).
[10] A. L. Beckwith and W. A. Waters, *J. Chem. Soc.* 1001 (1957).
[11] E. Bergmann and S. Fujisse, *Liebigs Ann.* 480, 188 (1930).
[12] C. K. Ingold and P. G. Marshall, *J. Chem. Soc.* 3080 (1926).
[13] E. de B. Barnett, J. W. Cook and I. G. Nixon, *J. Chem. Soc.* 505 (1927).
[14] E. Haack, *Ber. Dtsch. Chem. Ges.* **62**, 1771 (1929).
[15a] A. Haller and M. A. Guyot, *Bull. Soc. Chim. Fr.* **31**, 795 (1904); [b] **33**, 375 (1905).
[16] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.* 3045 (1954).

by the relatively planar phenyl groups of an orientation perpendicular to the plane of the central ring of the 9,10-dihydroanthracene nucleus thus reducing to a minimum the effects of non-bonded interactions of the one quasiequatorial phenyl group in the *trans*-compound. The presence of the methylene groups in 9,10-dibenzyl substituents results in an increase in bulk sufficient to prohibit the adoption of a quasiequatorial conformation and leads to the exclusive formation of the *cis*-diquasiaxial form of (V b). The production of a mixture of isomers by reduction of 9,10 bis(*p*-chlorophenyl) anthracene with sodium amalgam[12] and of one isomer only by reducing 9,10 dibenzal-9,10-dihydroanthracene with sodium in pentanol[11b] can be explained similarly.

The foregoing examples supplement those discussed in earlier communications[5a,b] and indicate the general applicability of the arguments put forward therein. These facts and the recently established configurations of the two 9,10-dimethyl-9,10-dihydroanthracenes[18] raise doubts concerning the configurational assignments made by Kooyman *et al.*[17a] to a series of meso-substituted-9,10-dihydroanthracenes. They found that the addition of 2-cyano-2-propyl radicals to anthracene gave two isomeric forms of 9,10-di-2-cyano-2-propyl-9,10-dihydroanthracene (V d) and assigned the *trans*-configuration to the isomer predominating in the reaction mixture and also (with reference to the 2-cyano-2-propyl groups) to the 9-methyl-, 9-methoxy- and 9-halo-9,10-di-2-cyano-2-propyl-9,10-dihydroanthracenes (V e, f and g respectively) isolated in yields of 90% or more when 9-methyl-, 9-methoxy- and 9-halo-anthracenes were allowed to react with 2-cyano-2-propyl radicals. The assignments were based on a consideration of the possible reaction mechanism and by similarities of their U.V. absorption spectra to those of the isomeric 9,10-dimethyl-9,10-dihydroanthracenes.[17b]

From conformational arguments it would appear that the configurations allotted to this series of compounds should be reversed, and support for this comes from the following evidence. (1) The configurations of the two isomeric forms of 9,10-dimethyl-9,10-dihydroanthracene have recently been shown to be the reverse of those originally assigned*.[18] (2) Phenyl magnesium bromide reacts with anthraquinone to give a mixture of *cis*- and *trans*- 9,10-diphenyl-9,10-dihydroanthracene-9,10-diols,[19] the predominating higher melting isomer again being the *cis*-form. Treatment of the diols with ethanol, 2-phenylethanol or ethylene glycol in the presence of a trace of sulphuric acid gives isomeric forms of the diethers different from those obtained by solvolysis with the same three alcohols of 9,10-dichloro-9,10-diphenyl-9,10-dihydroanthracene, the only known form of which has been shown to be the *cis*-compound.[21] *cis*- and *trans*-9,10-Dihydro-9,10-dihydroxy-9,10-dimethylanthracene also give the same diether

* *Note added in proof*—L. M. Jackman and J. W. Lown (*J. Chem. Soc.* 3776 (1962)) have presented evidence that the isomer m.p. 100–101° is not *trans* 9,10 dimethyl-9,10-dihydroanthracene as reported[18] (cf. also Badger *et al.*, *J. Chem. Soc.* **18** (1945)), although it possessed the same m.p. as the authentic isomer and gave a correct analysis. Found: C, 92·0; H, 7·70. Calc. for $C_{16}H_{16}$: C, 92·3; H, 8·0%. (R. G. Lingard Private communication). This does not invalidate the above arguments however, as the configuration of the *cis*-isomer is established.

[17a] A. F. Bickel and E. C. Kooyman, *Rec. Trav. Chim.* **71**, 1137 (1952); J. W. Engelsma, E. Farenhorst, and A. F. Bickel, *ibid.* **73**, 878 (1954);

[b] C. La Lau, *Ibid.* **73**, 931 (1954).

[18] A. H. Beckett and R. G. Lingard, *J. Chem. Soc.* 2409 (1959).

[19] C. Dufraisse and J. Le Bras, *Bull. Soc. Chim. Fr.* 1037 (1937).

[20a] C. Pinazzi, *C.R. Acad. Sci. Paris*, **223**, 1150 (1946); [b] *Ibid.* **225**, 503 (1947).

[21] E. Bergmann and A. Weizmann, *J. Amer. Chem. Soc.* **60**, 1801 (1938).

when treated with methanol–benzene in the presence of a trace of hydrochloric acid.[22] The acid catalysed removal of the tertiary OH group leaves a carbonium ion stabilized by the aromatic rings of the dihydroanthracene nucleus; the sterically favoured *cis*-dialkyl ethers are therefore expected from the above reaction. Therefore solvolysis of *cis*-9,10-dichloro-9,10-diphenyl-9,10-dihydroanthracene must give the *trans*-diethers. That the reaction of 9,10-diphenyl-9,10-dihydroxy-9,10-dihydroanthracene with N,N-dimethyl- or diethylaniline gives two isomeric forms of 9,10-diphenyl-9,10-*p*-dimethyl- (or *p*-diethyl-) aminophenyl-9,10-dihydroanthracene in equal amounts[15b] is not inconsistent with the foregoing explanations since no appreciable difference in the thermodynamic stabilities of the *cis*- or *trans*- forms of these compounds would be expected. The observation of Kooyman *et al.*[17a] that solvolysis of the 9-halo derivatives (V g) with methanol gave a different form of the ether (V f) than the one obtained by the action of 2-cyano-2-propyl radicals on 9-methoxyanthracene can also be explained in terms of an operative nucleophilic substitution mechanism in the former instance giving *trans*-isomers as solvolysis products, whereas the free radical addition product gives the *cis*-form.

Rigaudy and Kha-Vang-Thang[23] prepared the *cis*- and *trans*- forms of 9-(α-hydroxy-α-phenylethyl)-10-carboxy-9,10-dihydroanthracene (V h) and have explained the Saytzeff type dehydration of the former and the Hofmann type dehydration of the latter isomer in terms of their conformational requirements, together with the inversions of *trans*- (V i) to *cis*- (V j).

It seems reasonable therefore to explain certain reactions of meso-substituted dihydroanthracenes in terms of the adoption of a non-planar form by the reacting molecules although it has recently been shown that crystalline *trans*-dimethyl-9,10-dihydroanthracene 9,10-dicarboxylate exists in a planar form.[24]

EXPERIMENTAL

Microanalyses are by Mr. Crouch of the School of Pharmacy, London University and Drs. Weiler and Strauss of Oxford.

9,10-*bis*-(*Diethylaminomethyl*) *anthracene* (I a). 9,10-bis-(Chloromethyl) anthracene[25] (20 g) was dissolved in benzene (150 ml) and to it was slowly added, with stirring, a solution of diethylamine (20 g) in benzene (25 ml). When the addition was complete the solution was boiled under reflux for 3 hr, cooled, extracted with dil hydrochloric acid, the acid solution separated, made alkaline with dil sodium hydroxide solution and the precipitated base recrystallized from ethanol to give 9,10-*bis*-(*diethylaminomethyl*) *anthracene* (25·5 g, 94·5%) as fine lemon yellow needles, m.p. 131–132° (Found: C, 81·7; H, 9·3; N, 7·9; equiv., 174·6. $C_{24}H_{32}N_2$ requires: C, 82·7; H, 9·3; N, 8·0%; equiv., 174·2). *Hydrochloride* m.p. 270–275° (dec.). (Found: C, 68·1; H, 8·3; equiv., 211·4. $C_{24}H_{34}Cl_2N_2$ requires: C, 68·4; H, 8·1%; equiv., 210·7).

9,10-*bis*-(*Morpholinomethyl*) *anthracene* (I b) was prepared from 9,10-bis-(chloromethyl) anthracene (20 g) and morpholine (20 g) as described above. The resulting base recrystallized from ethanol gave 9,10-*bis*-(*morpholinomethyl*) anthracene (26·4 g, 96·7%) as yellow plates m.p. 243° (dec). (Found: C, 76·7; H, 7·5; N, 7·5; equiv., 190·3. $C_{24}H_{28}O_2N_2$ requires: C, 76·6; H, 7·5; N, 7·4%; equiv., 188·3). *Hydrochloride* m.p. 273–275° (dec). Found: C, 63·7; H, 7·1; equiv., 225·6. $C_{24}H_{30}O_2Cl_2N_2$ requires: C, 63·9; H, 7·1%; equiv., 224·7).

9,10-*bis*-(*Piperidinomethyl*) anthracene (I c) prepared from 9,10-bis-(chloromethyl) anthracene (20 g) and piperidine (20 g) in the same manner as for the two previous compounds and recrystallized

[22] A. H. Beckett and R. G. Lingard, *J. Chem. Soc.* 588 (1961).
[23] J. Rigaudy and Kha-Vang-Thang, *Bull. Soc. Chim. Fr.* 1628 (1959).
[24] R. P. Ferrier, J. Iball, and K. J. H. Mackay, *Acta Cryst.* **13**, 277 (1960).
[25] M. W. Miller, R. Amidon and P. O. Tawney, *J. Amer. Chem. Soc.* **77**, 2845 (1955).

from benzene gave pale yellow silky needles (23·7 g, 89·4%) m.p. 197·5–198°. (Found: C, 83·4; H, 8·5; N, 7·5; $C_{36}H_{32}N_2$ requires: C, 83·8; H, 8·7; N, 7·5%).

9,10-*Dihydroanthracene*-cis-9,10-*dicarboxylic acid.* 9,10-Dihydroanthracene-9,10-*cis*-dicarboxylic anhydride[26] (10 g) was finely powdered and added to a boiling solution of 0·5 N NaOH (170 ml) diluted to 600 ml with water. When most of the anhydride had dissolved (7 min) the solution was rapidly cooled, filtered and acidified with dil hydrochloric acid. The precipitated 9,10-dihydroanthracene-*cis*-9,10-dicarboxylic acid (9·8 g, 91·5%) melted at 265–268° resolidified and melted at 306–308°. (Beckett and Mulley[5b] reported m.p. 265–266° remelting at 301–302°).

9,10-*Dihydranthracene*-trans-9,10-*dicarboxylic acid.* Prepared from 9,10-dihydroanthracene-9,10-*cis*-dicarboxylic anhydride (10 g) according to the method described by Beckett and Mulley.[5b] Yield of recrystallized acid 9·1 g (85%) m.p. 306–308° (dec.) (Beckett and Mulley reported m.p. 305–307° dec.)

9,10-*Dihydroanthracene*-cis-9,10-*dicarboxylic acid chloride* (II d). 9,10-Dihydroanthracene-*cis*-9,10-dicarboxylic acid (10 g) was finely powdered and added to purified thionyl chloride (30 ml). A vigorous reaction occurred in the cold and when this had subsided the suspension was heated gently under reflux until all the solid material was in solution (15 min). The solution, on cooling, deposited fine white needles which were washed free from thionyl chloride with dry ether to give 9,10-dihydroanthracene-*cis*-9,10-dicarboxylic acid chloride (6·1 g, 54%) m.p. 156–158°. Mathieu[27] reported m.p. 155–156°.

9,10-*Dihydroanthracene*-trans-9,10-*dicarboxylic acid chloride* (III d). 9,10-Dihydroanthracene *trans*-9,10-dicarboxylic acid (10 g) was finely powdered and heated under reflux with purified thionyl chloride (100 ml) until it had dissolved completely (9 hr). Approximately 50 ml of thionyl chloride were then removed by distillation, and the remaining solution on cooling yielded large yellow prisms of 9,10-dihydroanthracene-*trans*-9,10-dicarboxylic acid chloride (8·3 g, 73%) which when washed free from thionyl chloride with dry ether gave m.p. 167–168°. Mathieu[27] reported m.p. 167–168°.

cis-9-*Carboxy*-9,10-*dihydroanthracene*-10-*carboxydiethylamide* (II e). 9,10-Dihydroanthracene-*cis*-9,10-dicarboxylic anhydride (5·0 g) was finely powdered and added to an aqueous solution of diethylamine (10% w/v 100 ml) with stirring. As soon as the anhydride had dissolved the solution was filtered, acidified with dil hydrochloric acid and the resulting precipitate on recrystallization from ethanol gave colourless needles of cis-9-*carboxy*-9,10-*dihydroanthracene*-10-*carboxydiethylamide* (5·4 g, 84%). m.p. 207–208° (dec.). (Found: C, 74·5; H, 6·6; N, 4·6; $C_{20}H_{21}O_3N$ requires: C, 74·3; H, 6·5; N, 4·3%).

trans-9-*Carboxy*-9,10-*dihydroanthracene*-10-*carboxydiethylamide* (III e). *cis*-9-Carboxy-9,10-dihydroanthracene-10-carboxydiethylamide (6·0 g) was finely powdered and boiled with 10% aqueous sodium hydroxide solution (30 ml) for 20 min under reflux. The solution was cooled, acidified with dil hydrochloric acid and the precipitated solid (5·7 g, 95%) on recrystallization from ethanol gave colourless prisms of trans-9-*carboxy*-9,10-*dihydroanthracene*-10-*carboxydiethylamide*, m.p. 222–224°. (Found: C, 74·7; H, 6·8; N, 4·1; $C_{20}H_{21}O_3N$ requires: C, 74·3; H, 6·5; N, 4·1%).

cis-9-*Carboxy*-9,10-*dihydroanthracene*-10-*carboxydimethylamide* (II f). This compound was prepared from the *cis*-9,10-dicarboxylic anhydride (5·0 g) and 10% w/v aqueous dimethylamine (100 ml) in a manner similar to that described for the *cis*-diethylamide. The crude product (6·2 g, 88%) gave cis-9-*carboxy*-9,10-*dihydroanthracene*-10-*carboxydimethylamide* 215–216° as colourless plates on recrystallization from ethanol. (Found: C, 73·2; H, 5·4; N, 4·8; $C_{18}H_{17}O_3N$ requires: C, 73·2; H, 5·8; N, 4·7%).

cis-9-*Methoxycarbonyl*-9,10-*dihydroanthracene*-10-*carboxydiethylamide* (II g). *cis*-9-Carboxy-9,10-dihydroanthracene-10-carboxydiethylamide (2·8 g) was finely powdered and added in small portions to an ethereal solution of diazomethane (1 g approx. in 150 ml). The amide dissolved with effervescence and after 24 hr the excess of diazomethane and ether were removed under red press. The semi-solid residue (3·1 g) on recrystallization from ethanol gave colourless cubic crystals of cis-9-*methoxycarbonyl*-9,10-*dihydroanthracene*-10-*carboxydiethylamide* (2·2 g, 74%) m.p. 141–142°. (Found: C, 74·85; H, 6·8; N, 4·25; $C_{21}H_{23}NO_3$ requires; C, 74·75; H, 6·9; N, 4·15%).

Reduction of cis-9-*methoxycarbonyl*-9,10-*dihydroanthracene*-10-*carboxydiethylamide.* The amide (1·8 g) was finely powdered, suspended in dry ether (25 ml) and slowly added to a stirred suspension

[26] A. H. Beckett, R. G. Lingard and B. A. Mulley, *J. Chem. Soc.* 3328 (1953).
[27] J. Mathieu, *Ann. Chim.* **20**, 215 (1945).

of lithium aluminium hydride (0·2 g) in dry ether (25 ml). During the course of the addition the suspension turned greenish yellow in colour and, when all the amide had been added, stirring was continued for 3 hr at room temp and the reaction product finally refluxed for 1 hr. The resulting complex was then decomposed by the dropwise addition of water until a granular precipitate formed, which was removed by filtration. The ethereal filtrate (A) was extracted with dil hydrochloric acid, the acid solution made alkaline with ammonia and extracted with ether to give a yellowish oil (0·8 g, 52%) which furnished cis-9,10-*dihydro*-9-*hydroxymethyl*-10-*diethylaminomethylanthracene hydrochloride* (IIh) m.p. 271–272° (dec.) as colourless cubes from ethanolic HCl–ether solution. (Found: C, 72·2; H, 7·85; Cl, 10·65; $C_{20}H_{27}OClN$ requires: C, 72·4; H, 7·9; Cl, 10·7%). The original ether solution (A) on evaporation yielded a neutral component (0·35 g, 21%) which on recrystallization from benzene gave fine white needles of cis-9-*hydroxymethyl*-9,10-*dihydroanthracene*-10-*carboxydiethylamide* (IIi) m.p. 196–198°. (Found: C, 77·6; H, 7·4; N, 4·7; $C_{20}H_{23}O_2N$ requires: C, 77·6; H, 7·5; N, 4·5%).

Preparation of the amides

Route A. 9,10-Dihydroanthracene-*cis*-9,10-dicarboxylic acid chloride (IId, 1–2 g) was finely powdered and suspended in dry benzene (20–30 ml). To the cooled suspension an excess of the appropriate amine was added dropwise with shaking. In cases where aqueous solutions of ammonia or amines were used, these were added directly to the finely powdered acid chloride. When the addition of the amine was complete, the flask was stoppered, the reaction mixture allowed to stand at room temp for 3 hr and the solvent removed under red press. The residue was washed with water to remove amine hydrochloride and recrystallized from a suitable solvent.

Route B. 9,10-Dihydroanthracene-*trans*-9,10-dicarboxylic acid chloride (IIId) (1–2 g) was treated in an exactly similar manner to that described under route A.

Routes C *and* D. These routes, starting from 9,10-dihydroanthracene-*cis*-9,10-dicarboxylic anhydride were modified in individual instances and are described in detail in each case.

trans-9,10-*Dihydroanthracene*-9,10-*bis-carboxydiethylamide* (III j)

Route A. *cis*-Acid chloride (IId, 1·0 g). The residue, recrystallized from benzene gave *trans*-9,10-dihydroanthracene-9,10-bis-carboxydiethylamide (0·8 g, 66%) as colourless cubes m.p. 196–197° undepressed on admixture with the amide produced via route B.

Route B. 9,10-Dihydroanthracene-*trans*-9,10-dicarboxylic acid chloride (IIId, 0·8 g). The residue on recrystallization from benzene gave trans-9,10-*dihydroanthracene*-9,10-*bis-carboxydiethylamide* (0·72 g, 75%) as colourless cubes m.p. 196–197°. (Found: C, 76·2; H, 8·0; N, 7·4; $C_{24}H_{30}O_2N_2$ requires: C, 76·1; H, 8·0; N, 7·4%). When aqueous diethylamine (50% w/v. 10 ml) was substituted for the pure amine in routes A and B the same amide was again obtained in good yields (78% and 88% respectively).

Route C. Finely powdered *cis*-9-carboxy-9,10-dihydroanthracene-10-carboxydiethylamide (IIe; 1·0 g) was treated with purified thionyl chloride (10 ml) heated carefully to b.p., and the thionyl chloride removed under red press. The product was dissolved in benzene (25 ml), the solution cooled in an ice bath, diethylamine (10 ml) added dropwise, and the reaction mixture allowed to stand for 3 hr with occasional shaking. A white solid separated which was filtered off, washed with a little water, and dried, yield 0·87 g, 71·5% m.p. 190–196°. Recrystallization from benzene gave colourless cubes of *trans*-9,10-dihydroanthracene-9,10-bis-carboxydiethylamide (0·66 g) m.p. 196–197° undepressed on admixture with the compounds obtained via routes A and B.

trans-9,10-*Dihydroanthracene*-9,10-*bis-carboxymorpholide* (III k)

Route A. *cis*-Acid chloride (IId; 1·0 g) and morpholine gave a residue (1·25 g, 96%) m.p. 269–272° which on recrystallization from ethanol furnished small white prisms of trans-9,10-*dihydroanthracene-bis-carboxymorpholide* m.p. 273–275°, (Found: C, 70·9; H, 6·5; N, 7·0; $C_{24}H_{26}O_4N_2$ requires: C, 70·9; H, 6·45; N, 6·9%).

Route B. *trans*-Acid chloride (IIId, 1·0 g) and morpholine gave a residue 1·2 g, 92%) m.p. 268–272° which on recrystallization from ethanol gave *trans*-9,10-dihydroanthracene-bis-carboxymorpholide m.p. 273–274° which was not depressed on admixture with the compound produced via route A.

Route C. *cis*-9-Carboxy-9,10-dihydroanthracene-10-carboxymorpholide m.p. 266–268° (20 g) prepared from 9,10-dihydroanthracene-*cis*-9,10-dicarboxylic anhydride[26] was finely powdered,

warmed with purified thionyl chloride (20 ml) until solution was complete, boiled under reflux for 5 min, cooled, and the excess thionyl chloride removed under red press. The resulting solid was dissolved in dry benzene (25 ml) and morpholine (10 ml) added dropwise to the cooled solution. The reaction mixture was allowed to stand for 3 hr at room temp, the precipitated solid removed, washed with a little water and dried, to give *trans*-9,10-dihydroanthracene-9,10-bis-carboxymorpholide (2·15 g, 86%) m.p. 274°–275° on recrystallization from ethanol, undepressed on admixture with the products obtained via routes A and B. (Found: C, 70·8; H, 6·3; N, 7·0; $C_{24}H_{26}O_4N_2$ requires: C, 70·9; H, 6·45; N, 6·9%).

cis-9,10-*Dihydroanthracene*-9,10-*bis-carboxamide* (II l)

Route C. Finely powdered *cis*-9-carboxy 9,10-dihydroanthracene-10-carboxamide (4·0 g) m.p. 261–263° (Mathieu[27] reported m.p. 264°) was boiled under reflux for 5 min with purified thionyl chloride (20 ml). The product was finely powdered and added in small portions to cooled 0·880 ammonia solution (20 ml). The flask and contents were allowed to attain room temp and stand overnight. The solid material was then removed, washed with a little water and dried (3·9 g, 97·5% m.p. 279–283°). Recrystallization from dimethylformamide gave *cis*-9,10-dihydroanthracene 9,10-bis-carboxamide (3·0 g) as colourless rectangular prisms m.p. 282–284° (dec). Mathieu[27] reported instantaneous m.p. 302–304°. (Found: C, 72·3; H, 5·3; N, 11·0; Calc. for $C_{16}H_{14}O_2N_2$: C, 72·1; H, 5·3; N, 10·5%).

trans-9,10-*Dihydroanthracene*-9,10-*bis-carboxamide* (III l)

Route B. 9,10-Dihydroanthracene-*trans*-9,10-dicarboxylic acid chloride (III d; 1·4 g) when allowed to react with ice cold 0·880 ammonia solution (20 ml) according to the general procedure previously described gave a white product (1·2 g, 100% m.p. 326–330°) which on recrystallization from dimethylformamide furnished *trans*-9,10-dihydroanthracene-9,10-carboxamide (0·9 g) as a fine white powder m.p. 329–331° (dec. darkens at 320°). Mathieu[27] reported instantaneous m.p. 424–426°. (Found: C, 71·6; H, 5·3; N, 10·3; Calc. for $C_{16}H_{14}O_2N_2$: C, 72·1; H, 5·3; N, 10·5%).

cis-9,10-*Dihydroanthracene*-9,10-*bis-carboxymethylamide* (II m)

Route A. *cis*-Acid-chloride (II d; 2·0 g) and 40% v/v aqueous diethylamine (20 ml) yielded a crude product as a white solid (1·75 g, 92·0%). Recrystallization from ethanol gave colourless crystals of cis-9,10-*dihydroanthracene*-9,10-*bis-carboxymethylamide* (1·4 g) m.p. 278–280°. (Found: C, 73·3; H, 6·25; N, 9·4; $C_{18}H_{18}O_2N_2$ requires: C,73·5; H, 6·2; N, 9·5%).

trans-9,10-*Dihydroanthracene*-9,10-*bis-carboxymethylamide* (III m)

Route B. *trans*-Acid chloride (III d; 1·7 g) and 40% v/v aqueous methylamine (20 ml) gave trans-9,10-*dihydroanthracene*-9,10-*bis-carboxymethylamide* (1·5 g, 93·5%) crystallizing from dimethylformamide as colourless prisms m.p. 340–341° (dec. inserted at 335°). (Found: C, 73·55; H, 6·2; N, 9·25; $C_{18}H_{18}O_2N_2$ requires: C, 73·5; H, 6·2; N, 9·5%).

cis-9,10-*Dihydroanthracene*-9,10-*bis-carboxyisopropylamide* (II n)

Route A. *cis*-Acid chloride (II d; 1·1 g) and isopropylamine gave a product (1·24 g, 96% m.p. 266–270°) which on recrystallization from ethanol gave colourless prisms of cis-9,10-*dihydroanthracene*-9,10-*bis-carboxyisopropylamide* (0·96 g) m.p. 268–271°. Found: C, 75·6; H, 7·4; O, 9·0; N, 8·5; $C_{22}H_{26}O_2N_2$ requires: C, 75·4; H, 7·5; O, 9·1; N, 8·0%).

trans-9,10-*Dihydroanthracene*-9,10-*bis-carboxyisopropylamide* (III n)

Route B. *trans*-Acid chloride (III d; 1·4 g) and isopropylamine gave trans-9,10-*dihydroanthracene*-9,10-*bis-carboxyisopropylamide* (1·6 g, 100%), which recrystallized from dimethylformamide as white microcrystals (1·4 g) m.p. 331–332·5° (dec. darkens at 320°). (Found: C, 75·7; H, 7·7; N, 8·2; $C_{22}H_{26}O_2N_2$ requires: C, 75·4; H, 7·5; N, 8·0%).

trans-9,10-*Dihydroanthracene*-9,10-*bis-carboxydimethylamide* (III p)

Route C. Finely powdered *cis*-9-carboxy-9,10-dihydroanthracene-10-carboxydimethylamide was suspended in dry benzene (25 ml), and purified thionyl chloride (10 ml) was added dropwise. The reaction mixture, protected from moisture, was allowed to stand with occasional shaking, until all the

amide had dissolved and the evolution of hydrogen chloride had subsided. The solvent was then removed under red press at room temp. A cooled solution of 20% w/v aqueous dimethylamine (25 ml) was added to the residue and the mixture slowly allowed to reach room temp.

After 3 hr the solvent was removed under red press and the residue, washed with water and dried, gave trans-9,10-*dihydroanthracene*-9,10-*bis-carboxydimethylamide* (1 g, 91%) crystallizing as colourless cubes from benzene, m.p. 230–232° (dec). (Found: C, 74·95; H, 6·9; N, 8·55; $C_{20}H_{22}N_2O_2$ requires: C, 74·5; H, 6·9; N, 8·6%).

Route B. 9,10-Dihydroanthracene-*trans*-9,10-dicarboxylic acid chloride (III d; 1·5 g) with 20% w/v aqueous dimethylamine (25 ml) gave *trans*-9,10-dihydroanthracene-9,10-bis-carboxydimethylamide (1·55 g, 94%) as colourless cubes m.p. 131–132° (dec) from ethanol, m.p. undepressed on admixture with compound prepared via route C. (Found: C, 74·9; H, 7·2; N, 8·4; $C_{20}H_{22}O_2N_2$ requires: C, 74·5; H, 6·9; N, 8·6%).

cis-9-*Carboxamido*-9,10-*dihydroanthracene*-10-*carboxymorpholide* (II r)

Route C. *cis*-9-Carboxy-9,10-dihydroanthracene-10-carboxymorpholide[22] (4·7 g) finely powdered, was suspended in dry benzene (15 ml) and purified thionyl chloride added dropwise with gentle heating until the suspended amide-acid dissolved. The solution was cooled and *cis*-9-chlorocarbonyl-9,10-dihydroanthracene-10-carboxymorpholide crystallized; yield 1·6 g, m.p. 165–168°. The acid chloride (1·6 g) was finely powdered and treated with cooled 0·880 ammonia solution (10 ml). After 3 hr the solid was removed by filtration and gave cis-9-*carboxamido*-9,10-*dihydroanthracene*-10-*carboxymorpholide* (1·35 g, 91% based on acid chloride), m.p. 282–285° (dec). Recrystallization from ethanol gave small colourless prisms m.p. 287–289° (dec) with "½ a molecule" of ethanol of crystallization. (Found: C, 70·1; H, 6·5; N, 8·1; O, 15·3; $C_{20}H_{20}O_3N_2 \cdot \frac{1}{2}C_2H_5OH$ requires: C, 70·2; H, 6·45; N, 7·8; O, 15·55%).

trans-9-*Carboxamido*-9,10-*dihydroanthracene*-10-*carboxymorpholide* (III r)

trans-9-Carboxy-9,10-dihydroanthracene-10-carboxymorpholide[5b] (4·7 g) m.p. 224–226° was treated with thionyl chloride as above. The solution was diluted with dry ether (20 ml) and a small crop of the *cis*-acid chloride m.p. 163–166° was obtained. This was removed, the mother liquors were evaporated to small bulk (4–5 ml), benzene (2 ml) and ether (10 ml) added and the solution set aside in a refrigerator. Clusters of *trans*-9-chlorocarbonyl-9,10-dihydroanthracene-10-carboxymorpholide were deposited overnight as white crystals; yield 3·5 g m.p. 127–130° (dec). The dried, finely powdered product was treated with cooled 0·880 ammonia solution (25 ml) and after 3 hr, the solid (3·1 g) was removed. Recrystallization from ethanol gave trans-9-*carboxamido*-9,10-*dihydroanthracene*-10-*carboxymorpholide* as a white microcrystalline powder m.p. 199–201°. (Found: C, 70·0; H, 6·5; N, 7·5: $C_{20}H_{20}O_3N_2 \cdot \frac{1}{2}C_2H_5OH$ requires; C, 70·2; H, 6·45; N, 7·8%).

cis-9,10-*Dihydroanthracene*-9-*carboxydiethylamide*-10-*carboxyisopropylamide* (II s)

Route C. Finely powdered *cis*-9-carboxy-9,10-dihydroanthracene-10-carboxydiethylamide (II e) (3·0 g) was suspended in dry benzene (10 ml), the suspension warmed under reflux and purified thionyl chloride was added dropwise until the solid had dissolved. On cooling, yellowish crystals separated, which on recrystallization from benzene gave *cis*-9-chlorocarbonyl-9,10-dihydroanthracene-10-carboxydiethylamide (0·8 g, 26%) m.p. 119–121°. This acid chloride (0·5 g) was dissolved in dry benzene (25 ml) cooled by means of crushed ice, treated with isopropylamine (5 ml) in benzene (10 ml) allowed to stand for 12 hr, the solvent removed under red press, the residual solid washed with water and dried, gave cis-9,10-*dihydroanthracene*-9-*carboxydiethylamido*-10-*carboxyisopropylamide* (0·51 g, 98% m.p. 131–136°) which crystallized from ethanol as colourless prisms (0·4 g) m.p. 134–137°. (Found: C, 74·5; H, 7·75; N, 7·4; $C_{23}H_{28}O_3N_2 \cdot \frac{1}{2}C_2H_5OH$ requires: C, 74·4; H, 8·1; N, 7·2%).

trans-9,10-*Dihydroanthracene*-9-*carboxydiethylamido*-10-*carboxyisopropylamide* (III s)

Route D. *trans*-9-Carboxy-9,10-dihydroanthracene-10-carboxydiethylamide (III e; 1·5 g) was converted to the corresponding acid chloride by treatment with thionyl chloride in a manner similar to that described for the preparation of the *cis*-isomer (II s). Yield 0·5 g (32%) m.p. 125–127°. This, dissolved in dry benzene (15 ml) and treated with isopropylamine (5 ml) gave a whitish solid (0·5 g,

96% m.p. 189–194°) which on recrystallization from ethanol gave colourless crystals of trans-9,10-*Dihydro-anthracene*-9-*carboxydiethylamido*-10-*carboxyisopropylamide* m.p. 193–195°. (Found: C, 75·5; H, 7·9; N, 7·7; $C_{33}H_{38}O_2N_2$ requires: C, 75·8; H, 7·7; N, 7·5%).

Alkaline equilibration of the amides

(a) With the exception of *cis*- and *trans*-9,10-dihydroanthracene-9,10-bis-carboxamide, equilibration was carried out by the following general method. A sample of the amide (approx 0·2 g) was finely powdered, weighed and boiled under reflux for 0·5 hr with N/20 sodium ethoxide solution (20 ml). The solution was then cooled, diluted with water (10 ml) neutralized with dil hydrochloric acid, the solvent removed under red press, the residue washed, dried, weighed and the isomers separated by fractional crystallizations. The results are tabulated in Table I. *trans*-9,10-Dihydroanthracene-9,10-bis-carboxymorpholide (IIIk) was largely aromatized by this treatment and gave *anthracene*-9,10-*bis-carboxymorpholide* (Ik). m.p. 319–321° (dec.) log E_{max} 5·38 at 256 mμ (ethanol). Found: C, 71·4; H, 6·5; N, 7·0; $C_{24}H_{24}O_4N_2$ requires: C, 71·3; H, 6·0; N, 6·9%).

trans-9-Carboxamido-9,10-dihydroanthracene-10-carboxymorpholide (III r) also gave 11% of *anthracene*-9-*carboxamido*-10-*carboxymorpholide* (I r) m.p. 329–331° (dec); log E_{max} 4·87 at 256 mμ, (ethanol). (Found: C, 71·85; H, 5·8; N, 8·15; $C_{20}H_{18}O_3N_2$ requires: C, 71·9; H, 5·3; N, 8·4%). The *trans*-9,10-bis-carboxydimethylamide (III g) also furnished a small amount (15%) of yellow crystalline neutral material with an U.V. spectrum characteristic of an anthracene derivative; log $E^{1\%}_{cm}$ 420 at 256·5 mμ (ethanol), but which could not be purified sufficiently to give a sharp m.p. or consistent analyses.

(b) *cis*- and *trans*-9,10-Dihydroanthracene-9,10-bis-carboxamides (II l and III l) owing to their insolubility in ethanol were suspended in nitrobenzene (25 ml), and triethylamine (5 ml) added; the suspension was boiled under reflux until solution was complete (15 min approx) and for a further 15 min. Most of the nitrobenzene was removed by steam distillation, the residue removed by filtration and fractionally crystallized from dimethylformamide giving the percentages of each isomer shown in Table I.