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DIASTEREOISOMERIC FORMS OF α,α'-DIPHENYL-SUBSTITUTED ADIPONITRILES

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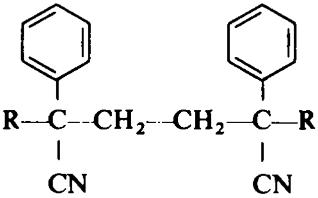
Abstract—The preparation of some adiponitriles with two equivalent asymmetric carbon atoms in the α and α' positions is described. The two diastereoisomeric forms isolated for each of them are assigned *meso* and *dl* configurations on the basis of a detailed analysis of the NMR signals of the —CH_2—CH_2— groups, which constitute an AA'BB' spin–spin coupling system. The differences in physical properties of the *meso* and *dl* forms are examined, and some partial and total hydrolysis reactions are described.

IN THIS PAPER, which is part of research carried out on dinitrile and trinitrile compounds,[1–6] we have turned our attention to the study of a series of adipic dinitriles with different, albeit paired, substituents in the α and α' positions with a view to isolating their diastereoisomeric forms, assigning to them the configurations *meso* and *dl* and studying their reactivity.

Examples of α-α'-diphenyl-substituted adiponitriles are already present in the literature, but the opportunity to study their stereoisomerism has never been taken. Already known are, for example, α,α'-tetraphenyl-adiponitrile[7] and α,α'-diphenyladiponitrile (Ia), the latter obtained as a secondary product together with 1-cyano-1-phenylcyclopropane from phenyl-acetonitrile and 1,2-dibromoethane.[8]

We prepared compounds corresponding to the following structures and isolated the diastereoisomeric forms I and II:



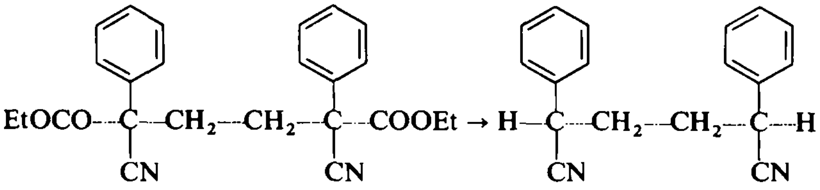
I and II

where

R = —H — Ia and IIa
—COOEt — Ib and IIb
—Me — Ic and IIc
—Et — Id and IId

The isomeric pairs with R = —COOEt (Ib and IIb), —Me (Ic and IIc) and —Et (Id and IId) were obtained with a very common type of reaction (ethylene bromide alkylation of the carbanion of the appropriate α-substituted phenylacetonitrile).

The isomeric pair with R = H (Ia and IIa) which was barely attainable by the same route[8] was obtained by acid or basic cleavage of compounds Ib and IIb:

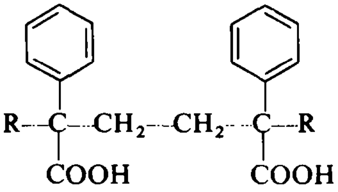


Ib, IIb Ia, IIa

In this reaction, however, there is a change of configuration which leads to the same reaction mixture starting from either of the two diastereoisomers Ib and IIb: only one of the two isomers (Ia) is isolated in high yield from this mixture, the other (IIa) being present only in small amounts.

Furthermore, compound IIa is seen to isomerize easily, being transformed into Ia merely by heating in EtOH. These observations indicate that the two stereoisomers Ia and IIa containing H atoms in α relative to the —CN groups may reach equilibrium at a higher temperature, or in the presence of a base or an acid; and that the equilibrium itself is noticeably shifted towards the more stable of the two (Ia).[*]

In any case, this reaction pattern prevented us from using complete hydrolysis in assigning configurations to compounds Ia, IIa and Ib, IIb, on the bases of a correlation with the corresponding diastereoisomeric bicarboxylic acids IIIa and IVa, known in the literature[9] and obtained by a different route.[10]



where R = —H IIIa and IVa
—Me IIIc and IVc
—Et IIId and IVd

III and IV

As expected, hydrolysis of the dinitriles Ic, IIc and Id, IId with quaternary carbon atoms in α and α′ was very difficult: refluxing HCl proved ineffective: ethanolic KOH and conc. H_2SO_4 produced only partial hydrolysis on compound Id; only KOH in ethylene glycol at 180° for a long period and with initial help of H_2O_2 was able to produce complete hydrolysis on the four compounds and lead to the corresponding bicarboxylic acids IIIc, IVc and IIId, IVd, with retention of configuration.

Of these the pair IIIc, IVc was already cited in the literature with doubtful configurational assignment[9] and with m.ps that do not correspond with those found by us.

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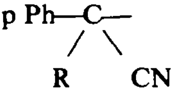
[*] The catalytic action of bases might be interpreted in terms of the formation of a resonance stabilized planar carbanion, and that of acids in terms of the intermediate formation of a ketenimine, with the loss of configurational identity in both cases.

Conclusive assignment of the *meso* and *dl* configurations to the diastereoisomeric pairs Ia and IIa, Ib and IIb, Ic and IIc, Id and IId was made possible by a detailed study of their NMR spectra and in particular of the signals from the —CH_2—CH_2— groups.

In the case of Ib a singlet is observed, while in the case of IIb, Ic and IIc, Id and IId the ethylene group gives an AA'BB'-type multiplet, which may be analyzed using the LAOCN3 program.*

The resultant spectral parameters are reported in Table 1. In accordance with the findings of Jung and Bothner-By[11] they enable us to assign the configurations *meso* and *dl* to the single pairs of diastereoisomers,† bearing in mind the possible conformations represented in Fig. 1, in which G_R and G_S refer to the two opposite configurations of the group



$Ph{-}\underset{R\quad CN}{\overset{}{C}}{-}$

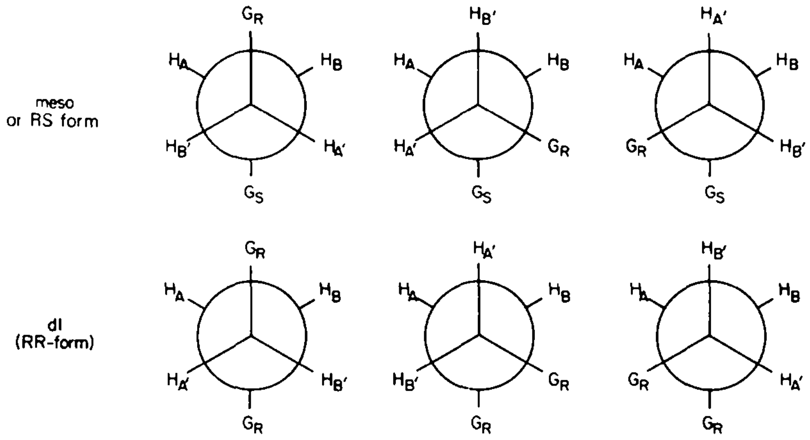
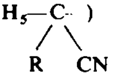


FIG 1. Conformations and equivalence relationships between the hydrogen atoms of the —CH_2—CH_2— groups, for *meso* and *dl* configurations. (G =



$C_6H_5{-}\underset{R\quad CN}{C}{-}$)

Indeed, because of the notable steric hindrance of the G_R and G_S groups, the *anti* conformations should be the most populated, and since the J_{HH} *trans* are larger than the *gauche*[13] one should obtain a greater value for $J_{AB'}$ in the *dl* form and for $J_{AA'}$ in the *meso* form.

The results contained in Table 1, at least in the case of IIb, Ic and IIc, Id and IId seem also to indicate, on the basis of standard values[11] of J_g and J_t, that the *anti* conformation should be over 90% populated.

The spectra of compounds Ia and IIa prove to be more complicated because of

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* Program kindly supplied by Dr. S. Castellano, Mellon Institute, Pittsburg USA.

† The presence of the singlet in the Ib derivative may be related to the NMR spectra of the two diastereoisomers of 2,5-dithiahexane-2,5-dioxide[12] in which the —CH_2—CH_2— group gives a singlet in the *meso* form and an AA'BB' signal in the *dl* form. We wonder whether the presence of the singlet in situations of this type may or may not always be associated with the *meso* form.

TABLE 1. NMR PARAMETERS FOR *meso* AND *dl* FORMS (I AND II), EXPRESSED IN HZ.

Derivative	δ_ν	$J_{AA'} = J_{BB'}$	$J_{AB'} = J_{A'B}$	$J_{AB} = J_{A'B'}$	Assignment
Ia[a]	~0				*meso*
IIa[b]	~0	4·8	11·8		*dl*
Ib	~0				*meso*
IIb	21·28 ± 0·09	3·90 ± 0·17	13·15 ± 0·12	−13·52 ± 0·12	*dl*
Ic	19·92 ± 0·03	13·19 ± 0·26	4·10 ± 0·04	−13·64 ± 0·05	*meso*
IIc	23·30 ± 0·12	4·80 ± 0·24	11·80 ± 0·16	−13·30 ± 0·16	*dl*
Id	22·00 ± 0·03	13·12 ± 0·19	4·20 ± 0·03	−13·50 ± 0·04	*meso*
IId	29·40 ± 0·13	4·69 ± 0·17	11·87 ± 0·22	−13·58 ± 0·19	*dl*

[a] Two different vicinal coupling constants are observed, $J_{CH_2-CH} = 7{\cdot}8$ and 3·3 Hz, and one long range coupling constant of about 1 Hz.

[b] The vicinal coupling constants are equal to each other, $J_{CH_2-CH} = 6{\cdot}7$ Hz, as are the long range coupling constants[13] $J_{CH_2-CH} = 1{\cdot}5$ Hz.

the coupling of the protons of each of the methylene groups with the proton on the neighbouring asymmetric carbon atom.

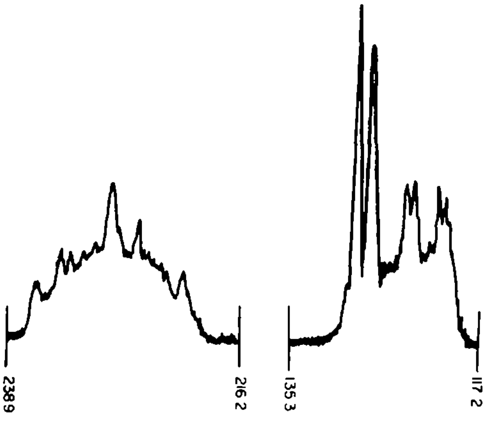
The spectra of these two compounds are shown schematically in Fig. 2.

When the CH multiplet (at 228 Hz and 230 Hz in the Ia and IIa compounds, respectively) is irradiated the fine structure of the methylene protons collapses to a singlet, with band width of about 4 Hz in the first case and 3·4 Hz in the second case. The opposite chirality of the two asymmetric centers might be related to a different coupling of the methylene CH_2's with the vicinal CH as it is found in compound Ia. One may therefore propose the *meso* configuration for this derivative. The spectroscopic parameters of IIa are in turn consistent with a *dl* configuration.

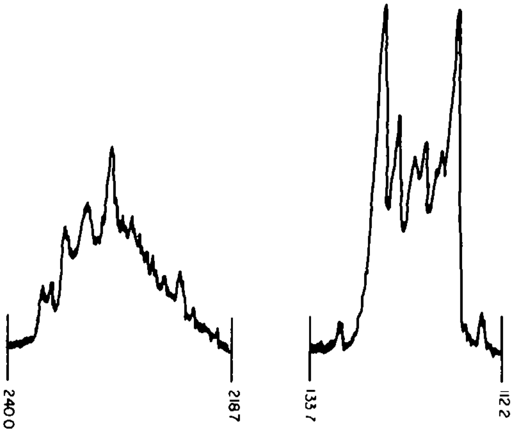
The assignment of configurations to the diastereoisomeric pair Ia and IIa, which is the one which proved most difficult by means of the NMR data, is confirmed by the great difference in stability between the two diastereoisomeric forms, the *meso* form (Ia) being much more stable[14] that the *dl* form (IIa); this is also reflected in the yield ratio in which the two products are obtained (Table 2). The yield differences for the

TABLE 2. COMPARISON OF M.PS, R_f VALUES AND YIELD RATIOS FOR THE *meso* AND *dl* FORMS.

	m.p.	R_f	yield ratio *meso*/*dl*
Ia (*meso*)	173–5°	0·36	9:1
IIa (*dl*)	103–5°	0·34	
Ib (*meso*)	131–3°	0·37	2:1
IIb (*dl*)	98–100°	0·36	
Ic (*meso*)	128–9°	0·45	5:6
IIc (*dl*)	124–6°	0·40	
Id (*meso*)	107–9°	0·50	4:3
IId (*dl*)	107–8	0·41	



Ia



IIa

FIG 2. NMR signals of —CH—CH$_2$—CH$_2$—CH group for compounds Ia (*meso*) and IIa (*dl*)

other stereoisomeric pairs are less marked. Table 2 and the data in the experimental part for the diacids also show that the assignment of configuration on the basis of the differences in m.ps[9] is not generally completely reliable; the same Table shows, however, that the chromatographic R_f values might be useful to this end, the value always being greater for the *meso* form, which may in fact assume a less polar centro-symmetrical conformation (*anti-meso*, Fig. 1).

EXPERIMENTAL

M.ps (determined on a Büchi apparatus) are uncorrected; anhyd. Na_2SO_4 was used as drying agent; for TLC, plates of silica gel, GF 254 Merck, 0·25 mm, were employed, C_6H_6 being used as eluent: the R_f values are shown in Table 2 together with the yield ratios of the stereoisomeric pairs. The IR spectra (Perkin-Elmer mod. 257) and the NMR spectra (Jeol JNM-MH-60 Minimar) are all in agreement with the proposed structures. More accurate NMR spectra for iterative analysis were recorded at 60 MHz using a Jeol JNM-C60-HL, $CDCl_3$ as a solvent and TMS as internal reference. The spectra were calculated on a CDC 6600 computer.

Preparation of the α,α′-disubstituted-α,α′-diphenyl-adiponitriles (I *and* II, *cases* b, c, d). The appropriate phenylacetonitrile (ethylphenylcyanoacetate[15] for b: α-phenyl-propionitrile[16] for c: α-phenyl-butyronitrile[17] for d) was added whilst stirring and cooling to one mole of base (b: NaOEt/EtOH; c and d: $NaNH_2$ suspended in C_6H_6) in a stream of nitrogen: to this mixture ethylene dibromide (0·5 mol) was slowly added whilst cooling and stirring. The mixture was left a few hours at room temp. and then boiled for 2 to 8 hr; the mixtures were processed in the usual way and the crude oily products obtained treated as follows:

Case (b): the oily product partly crystallized: the solid, crystallized from EtOH, had a m.p. 131–3° (Ib), yield 16·5%, (Found: C, 71·40: H, 6·09: N, 6·82. $C_{24}H_{24}O_4N_2$ requires: C, 71·27; H, 5·98; N, 6·93%), configuration *meso*. The crystallization liquids gave a second crop of crystals which were purified from EtOH, m.p. 98–100° (IIb), yield 8·2%. (Found: C, 71·21: H, 5·82: N, 6·99%) configuration *dl* (racemic). The residual oil subjected to column chromatography, gave only a mixed crystalline fraction, which was further separated into Ib and IIb by crystallization.

Cases (c) and (d): the oily product was made free from a most volatile fraction (which contained some unsaturated components) by distillation at about 100°/0·2 mm. The distillation residue was chromatographed on a column of silica gel (0·05–0·2 mm, eluent C_6H_6). Apart from a head oily fraction containing bromine, two crystalline fractions were separated in both cases (c) and (d):

Ic: first crystalline fraction, crystallized from cyclohexane, m.p. 128–9°, yield 15·8%. (Found: C, 83·34: H, 6·71: N, 9·68. $C_{20}H_{20}N_2$ requires: C, 83·29: H, 6·99: N, 9·71%), configuration *meso*. IIc: second crystalline fraction, crystallized from n-hexane, m.p. 124–6°, yield 19·0%. (Found: C, 83·40: H, 6·92: N, 9·67%) (required as above), configuration *dl* (racemic).

Id: first crystalline fraction, crystallized from ligroin, m.p. 107–9°, yield 25·3%. (Found: C, 83·57: H, 7·63: N, 8·89%. $C_{22}H_{24}N_2$ requires: C, 83·50: H, 7·64: N, 8·85%), configuration *meso*. IId: second crystalline fraction, crystallized from n-hexane, m.p. 107–9°, yield 19·0%. (Found: C, 83·80: H, 7·20: N, 8·59%) (required figures as above), configuration *dl* (racemic).

The pair of isomers Ib, IIb could be equilibrated at room temp. by a catalytic amount of KOH: on the contrary, both pairs of isomers Ic, IIc and Id, IId proved to be stable in these conditions and also by refluxing in conc. HCl.

Partial hydrolysis reactions. (1) Preparation of the α,α′-diphenyl-adiponitriles (Ia, IIa):

One millimole of either stereoisomeric form (Ib or IIb) of α,α′-diphenyl-α,α′-dicarbethoxy-adiponitrile was suspended in a solution of four millimoles of KOH in 20 ml of EtOH and the mixture left at room temp. for 24 hr: the solid was filtered and washed with water in order to eliminate K_2CO_3: crystallization from EtOH yielded Ia, m.p. 173–5°. (Found: C, 83·13: H, 6·30: N, 10·78%. $C_{18}H_{16}N_2$ requires: C, 83·04: H, 6·20: N, 10·76%), configuration *meso*. Vacuum evaporation of the crystallization liquids yielded a small amount of solid which was crystallized from ether, m.p. 103–5° (IIa); the compound isomerized to Ia by boiling in EtOH. (Found: C, 83·26: H, 6·02: N, 10·84%) (required as above), configuration *dl* (racemic).

The same mixture as from the above basic conditions was obtained when Ib or IIb was subjected to partial hydrolysis in acid (refluxing 3 hr in a 2:1 mixture of glacial AcOH and conc HCl.)

For the substance already reported in the literature[8] as α,α′-diphenyl-adiponitrile a m.p. of 194–5° is cited: we repeated this, isolating a small amount of compound identical to Ia (m.p. 173–5°), but were unable to detect the presence of IIa.

When compound Ia was alkylated with an excess of $NaNH_2$ and EtBr in C_6H_6 it gave a mixture of approximately equal amounts of the two stereoisomers Id and IId, thus with a partial configuration change.

(2) *Partial hydrolysis of* Id.

1·5 millimoles of *meso*-α,α′-diphenyl-α,α′-diethyladiponitrile (Id) were dissolved in 20 ml of EtOH, an excess of sat. KOH aq in EtOH was added and the solution refluxed for 3 days: $CHCl_3$ extraction gave no acidic fractions, but a neutral one, which, when crystallized from EtOAc gave a solid m.p. 196–8° (*meso* α,α′-diphenyl-α,α′-diethyl-adipammide, Vd). (Found: C, 74·90: H, 8·35: N, 7·84%. $C_{22}H_{28}O_2N_2$ requires: C, 74·96: H, 8·01: N, 7·95%). By evaporating the crystallization liquids a residue was obtained which, when crystallized from ligroin, had a m.p. 115–8° (2,5-diphenyl-2-ethyl-5-cyano-heptaneamide, VId). (Found: C, 79·10: H, 8·24: N, 8·24%. $C_{22}H_{26}ON_2$ requires: C, 79·00: H, 7·84: N, 8·38%).

The same mixture was obtained by leaving one millimole of Id and 3 ml of H_2SO_4 (97%) at room temp. for 3 days.

Complete hydrolysis reactions.

(1) Hydrolysis of Ia to give *meso*-α,α′-diphenyl-adipic acid: (IIIa):

One millimole of *meso*-α,α′-diphenyl-adiponitrile (Ia) was refluxed 48 hr in 25 ml of a 2:3 mixture of glacial AcOH and conc. HCl; on cooling, a solid precipitate which, when recrystallized from AcOH had m.p. 255–60°. The analytical data fit with the structure of α,α'-diphenyl-adipic acid, and comparison of the m.p. observed by us with the values reported in the literature[9] for the *meso* and *dl* forms (266–7° and 208° respectively) confirms its *meso* configuration (IIIa).

(2) Hydrolysis of Ic, IIc, and Id, IId: α,α'-disubstituted α,α'-diphenyl-adipic acids.

One millimole of each compound was added to a solution obtained by diluting 20 millimoles of KOH (dissolved in one ml of H_2O) in 7 ml of ethylene glycol; one ml of H_2O_2 (120 vols.) was then added, the mixture heated to 100° for 3 hr and then to 180° for 100–150 hr in a nickel capsule. After dilution with H_2O and $CHCl_3$ extraction of the basic solution, acidification with 2 N HCl produced a nitrogen free precipitate in all four cases, which crystallized from EtOH-H_2O.

Meso-α,α'-diphenyl-α,α'-dimethyl-adipic acid (IIIa) had a m.p. 227–9°; the *dl*-form (IVc) a m.p. 232–4°; the m.p. values reported in the literature[9] for this pair of acids (190–214°, and 247–9° respectively) do not correspond with those found by us; however our analytical data for IIIc and IVc are in accordance with the proposed structures.

Meso-α,α'-diphenyl-α,α'-diethyl-adipic acid (IIId) had a m.p. 232–4°. (Found: C, 74·31; H, 6·99. $C_{22}H_{26}O_4$ requires: C, 74·55; H, 7·39%).

dl-α,α'-diphenyl-α,α'-diethyl adipic acid (IVd) had a m.p. 212–19°. (Found: C, 74·25; H, 7·19%) (required as above).

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