Studies on the *meso*, Racemic, and Optically Active Forms of 3,6-Bis-[1-hydroxy-1-(4-methylphenyl)ethyl]-1,2,4,5-tetrazines and Related Systems along with the Corresponding 3,5-Disubstituted 1,2,4-Triazoles, their 4-Amino-derivatives and 2,5-Disubstituted 1,3,4-Oxadiazoles including their Circular Dichroism Spectra

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The stereoisomeric title compounds (II)—(VI) were prepared by the action of hydrazine hydrate on (±)-, (+)-, and (−)-amidinium chlorides (I). The initial products, the dihydrotetrazines (II), were readily oxidised to the tetrazines (III) or could undergo rearrangement in methanolic hydrogen chloride to give the corresponding 4-amino-1,2,4-triazoles (IV) which by deamination with nitrous acid yielded the 1,2,4-triazoles (VI). The 1,3,4-oxadiazoles (V) were most easily prepared by the action of 40% peracetic acid on the tetrazines (III), other methods tending to give diacylhydrazines (VII). A study was made of the c.d. curves of the optically active forms of compounds (II)—(VI) including studies in both acid and neutral solutions for the triazoles (IV) and (VI).

AMIDINES (I) have been shown to be useful precursors in the synthesis of 1,2-dihydro-1,2,4,5-tetrazines (II) symmetrically [1] or unsymmetrically [2] substituted in the 3,6-positions. We have previously reported [1] the formation of the stereoisomeric forms of the tetrazines (IIIb and c), prepared from the corresponding amidines (Ib and c) and more recently [2] the diastereomeric forms of the tetrazine (IIIa), obtained as a byproduct in the synthesis of 3,6-unsymmetrically-disubstituted-1,2,4,5-tetrazines. We now report various other heterocycles (IV—VIa, b, and c) derived from these systems, including some of their optically active forms.

The diastereomeric forms of the tetrazine (IIIa), previously separated by crystallisation [2] have now also been separated by t.l.c. It was earlier [2] assumed on the basis of work on centrosymmetric molecules,[1-4] that the higher melting isomer would have the *meso*-structure and that the lower melting isomer was the (±)-tetrazine (IIIa). This has now been confirmed by a mixed m.p. determination on the lower melting isomer and the product obtained on recrystallisation of approximately equal amounts of (+)- and (−)-tetrazine (IIIa) (see later). This assignment has permitted us to derive the stereochemistry of the compounds (IIa) and (IV—VIIa) derived from the diastereomeric tetrazines (IIIa),

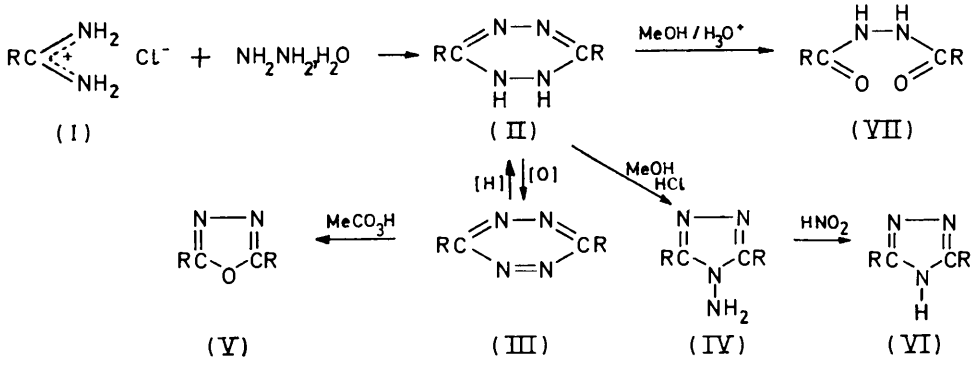
[1] J. L. Fahey, P. A. Foster, D. G. Neilson, K. M. Watson, J. L. Brokenshire, and D. A. V. Peters, *J. Chem. Soc.* (*C*), 1970, 719.

[2] R. A. Bowie, M. D. Gardner, D. G. Neilson, K. M. Watson, S. Mahmood, and V. Ridd, *J.C.S. Perkin I*, 1972, 2395.

[3] R. Stern, J. English, jun., and H. G. Cassidy, *J. Amer. Chem. Soc.*, 1957, **79**, 5797.

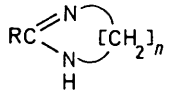
[4] R. A. Carboni and R. V. Lindsey, jun., *J. Amer. Chem. Soc.*, 1958, **80**, 5793.

(Table 1). The individual tetrazines (IIIa) were reduced with sodium dithionite [1,2,5] to their dihydroderivatives (IIa). Dihydrotetrazines are normally readily isomerised by heat or by acid [6] to give the corresponding 4-amino-1,2,4-triazoles (IV). Our attempts to prepare these aminotriazoles (IVa) by isomerisation that the diacylhydrazine (VIIa) arose from the oxadiazole (Va), oxadiazoles having been recognised as byproducts [6] of the isomerisation reaction (II) ⟶ (IV). In addition, oxadiazoles are known to cleave in acid media to diacylhydrazines, the ease of hydrolysis depending markedly on the substituents present.[7] Pure



(I) (II) (VII) (V) (III) (IV) (VI)

a; R = 4-MeC$_6$H$_4$C(OH)Me
b; R = PhC(OH)Me
c; R = PhC(OH)Et



(VIII)

TABLE 1

M.p.s (°C) of compounds (II)—(VII)

R	4-MeC$_6$H$_4$C(OH)Me			PhC(OH)Me			PhC(OH)Et		
	meso	(±)	Opt. act.	*meso*	(±)	Opt. act.	*meso*	(±)	Opt. act.
Tetrazine (III)	166—167	139—141	117—118	186—187*	133—134*	121—121·5*	161—162*	101·5—102*	109—110*
Dihydrotetrazine (II)	174—176	188—190	139—141	180—182*	154—155*	122—123*	159—160*	107·5—108·5*	118—119*
Aminotriazole (IV)	203—204	205—206	207		202—203†	194—197		189—190†	163—164
Oxadiazole (V)		193—195	198—199	135—138	187—189	182—183	137—139	190—193	174—175
Triazole (VI)	157—160	169—171	174—175						
Diacylhydrazine (VII)	228—229	162—164	185—188						

* See ref. 1. † Prepared from a mixture of diastereoisomers.

TABLE 2

Rotations [a] of compounds (I)—(VII) in methanol at 546·1 nm

R	4-MeC$_6$H$_4$C(OH)Me	PhC(OH)Me	PhC(OH)Et
R-(−)-Amidinium chloride (I)	−60·0 (H_2O)	−46·2 (H_2O) (E) *	−50·0 (H_2O) (E) *
R,R-(+)-Dihydrotetrazine (II)	+244·6	+165 (E) *	(+227·3 (E) *
R,R-(+)-Tetrazine (III)	†	†	†
R,R-(+)- or (−)-Aminotriazole (IV) ‡	−51·3	+10·2 (E)	+13·3 (E)
R,R-(−)-Oxadiazole (V)	−85·6 (E)	−59·3 (E)	−24·4 (E)
R,R-(+)-Triazole (VI)	+85·7		
R,R-(+)-Diacylhydrazine (VII)	+106·6		

[a] In degrees.
E, Compound handled was the enantiomer.

* Ref. 1. † Accurate values unobtainable due to strong colour of solutions. ‡ Sign of rotation can be + or − at 546·1 nm depending on the system.

of the dihydrotetrazines in aqueous acid gave mainly the diacylhydrazines (VIIa). It was finally found that a methanolic hydrogen chloride solution of (IIa) kept *ca.* 15 h at 0—5 °C gave the aminotriazole (IVa) whereas higher temperatures and/or aqueous conditions led to the open chain compound (VIIa). It seems very likely samples of the diastereomeric oxadiazoles (Va) were best prepared by the action of 40% peracetic acid [8] on the tetrazines (IIIa). The 4-aminotriazoles (IVa) could be deaminated by the action of nitrous acid [9]

[5] P. Truitt and L. T. Creagh, *J. Org. Chem.*, 1963, **28**, 1910.
[6] V. P. Wystrach, 'Heterocyclic Compounds,' ed., R. C. Elderfield, Wiley, New York, 1967, vol. 8, p. 105.
[7] A. Hetzheim and K. Möckel, 'Advances in Heterocyclic Chemistry,' eds. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1966, vol. 7, p. 183.
[8] J. Allegretti, J. Hancock, and R. S. Knutson, *J. Org. Chem.*, 1962, **27**, 1463.
[9] J. F. Geldard and F. Lions, *J. Org. Chem.*, 1965, **30**, 318.

to the parent triazoles (VIa). In every case other than that of the 4-aminotriazoles (IVa) the m.p.s of the diastereoisomers differed considerably (see Table 1).

TABLE 3

C.d. measurements

Compound	Solvent	Δε	λ/nm
Amidinium chloride			
(*R*)-(−)-(Ia)	MeOH	+4·09m	224
		−6·14!	207
(*R*)-(−)-(Ib)	MeOH	+6·24m	219
		0·0!	212
R-(−)-(Ic)	MeOH	+3·88m	219
		−3·37!	208
Tetrazine			
(*R*,*R*)-(+)-(IIIa) (E)	MeOH	+6·29m	272
		0	238
		−8·92m	217
		−2·5!	210
(*R*,*R*)-(+)-(IIIc)	MeOH	−0·12m	539
		+5·1m	270
		−10·9!	217
4-Aminotriazoles			
(*R*,*R*)-(−)-(IVa)	MeOH	+0·33m	272
		+0·28m	264
		+0·07m	258
		+0·12sh	254
		−45·0	222
		−68·0!	200
	MeOH–HCl	+0·32m	272
		+0·30m	265
		−6·5m	222
		−17·8!	200
(*R*,*R*)-(+)-(IVc) (E)	MeOH	+0·57m	267
		+0·55m	260
		+0·29m	254
		+0·05m	248
		−51·2m	217
	MeOH–HCl	−6·18m	218
		−7·90m	210
		−8·57!	206
Oxadiazoles			
(*R*,*R*)-(−)-(Va) (E)	MeOH	+0·16m	272
		−0·03m	268
		+0·07m	264
		−0·07m	260
		−0·12sh	252
		−27·1m	222
		−27·8!	206
(*R*,*R*)-(−)-(Vb) (E)	MeOH	+0·21m	266
		+0·17m	259
		+0·08m	253
		−0·06m	249
		−0·08sh	243
		−28·9m	216
		−26·3m	206
(*R*,*R*)-(−)-(Vc) (E)	MeOH	+0·28m	266
		+0·24m	259
		+0·13m	252
		−0·07sh	242
		−26·3m	217
		−20·4!	207
Triazoles			
(*R*,*R*)-(+)-(VIa)	MeOH	+0·18m	270
		+0·22m	263
		+0·16m	259
		−2·56m	222
		~0·0!	210
	MeOH–HCl	+0·16m	272
		+0·13m	265
		−9·87m	224
		−14·6!	203

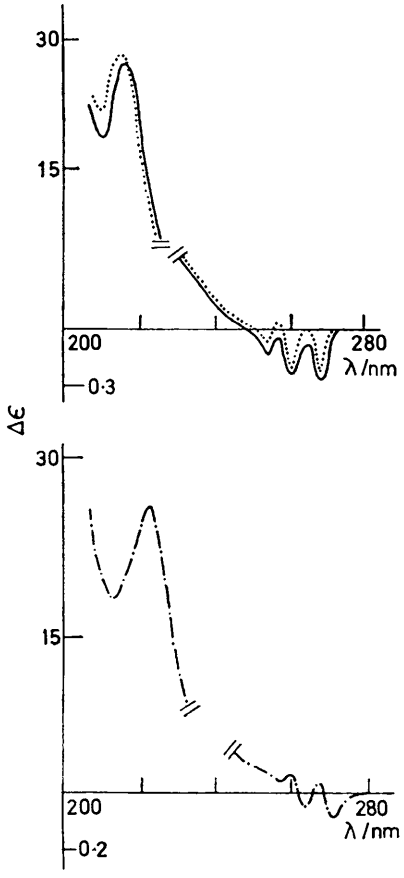
(E) = Run as the enantiomer; m = maximum value; ! = lowest wavelength measured.

From the known,[1] related tetrazines (IIIb and c) and dihydrotetrazines (IIb and c) we have obtained by a corresponding series of reactions, the (±)- and *meso*-oxadiazoles (Vb and c) and, as a mixture of stereoisomers, the 4-aminotriazoles (IVb and c) (see Table 1).

A similar reaction sequence (Ia) ⟶ (Va) was carried out starting from either (+)- or (−)-4-methylatrolactamidinium chloride [10] (Ia) and Table 2 shows the stereochemical relationships of the products so obtained. The configuration of the 4-methylatrolactic system does not appear to have been determined but the close relationship of the c.d. curves of the 4-methylatrolactic system (Ia *etc.*) to those of the parent system (Ib *etc.*) and to those of the related α-hydroxy-α-phenylbutyric system (Ic *etc.*), both of which have the *R*-(−)-configuration for the amidinium chlorides [11] (Ib and c), leads to the conclusion that 4-methylatrolactamidinium chloride (Ia) is also of the *R*-(−)-series. Unlike the tetrazines (IIIb and c) which exhibit weak maxima in the visible region,[1] the tetrazine (IIIa) appears featureless in this region. The c.d. curves of the triazoles (VI) and their 4-amino-derivatives (IV) were run in methanol and methanol containing hydrochloric acid. For the (*R*,*R*)-(−)-disubstituted triazole (VIa) there is a marked negative shift in the low wavelength maxima and a less defined negative shift in the longer wavelength aromatic region (250—270 nm) on protonation. This negative shift on protonation is typical [10,12] of the *R*-series for the closely related imidazolines (VIII; $n = 2$), tetrahydropyrimidines (VIII; $n = 2$) and for the ephedrines.[13] By contrast, the 4-aminotriazoles (IVa and c), derived from the *R*-(−)-amidinium chlorides (Ia and c), show marked positive shifts of the low wavelength region (200—225 nm) on protonation; the higher wavelength region being little affected apart from loss of fine structure. The 4-aminotriazole structure has two distinct sites for protonation, the amino-group and/or the triazole ring, but it is not possible to say whether these ' against the rule ' changes [12] in rotation can be attributed to conformational changes or to change in the electronic state of the chromophore due to protonation of the amino-group. Indeed little is known about any aryl amino-group's contribution to c.d. or o.r.d. spectra.[14,15] The c.d. curves of the oxadiazoles (Va, b, and c) (Figure) are more akin to those of the corresponding 4-aminotriazoles (IVa and c) than to those of the parent triazole system (VIa) but somewhat less intense. The close identity of these

[10] D. F. Ewing and D. G. Neilson, *J. Chem. Soc.*, 1965, 770.
[11] T. R. Emerson, D. F. Ewing, W. Klyne, D. G. Neilson, D. A. V. Peters, L. H. Roach, and R. J. Swan, *J. Chem. Soc.*, 1965, 4007.
[12] D. G. Neilson, ' Some Newer Physical Methods in Structural Chemistry,' eds. R. Bonnett and J. G. Davis, United Trade Press, London, 1967, p. 186.
[13] I. P. Dirkx and Th. J. de Boer, *Rec. Trav. chim.*, 1964, **83**, 535.
[14] P. Crabbé, ' An Introduction to the Chiroptical Methods in Chemistry,' Impresos Offsali-G, S. A. Mexico, 1971, p. 57.
[15] P. Crabbé and A. C. Parker, ' Techniques of Chemistry, Part IIIC: Polarimetry,' eds. A. Weissberger and B. W. Rossiter, Wiley–Interscience, New York, 1972, p. 237.

curves (Va, b, and c) helps to confirm the (*R*)-configuration of the (−)-amidinium chloride (Ia) and hence of the related (−)-4-methylatrolactic acid.[10] As our



C.d. curves of oxadiazoles (Va) (— · — · —) ($\lambda_{max.}$ 275infl., 272, 263, 257, 252, and 220 nm); (Vb) (· · · ·) ($\lambda_{max.}$ 266infl., 263, 257, 251, 248, and 220 nm); (Vc) (——) ($\lambda_{max.}$) 267infl., 263, 257, 251, 247, and 218 nm)

compounds have multiple chromophores (phenyl, heterocyclic, and hydroxy-groups) it is not possible to allocate bands and there is a need for simpler reference heterocyclic compounds.

EXPERIMENTAL

All rotations are quoted at 546·1 nm for methanol solutions unless otherwise stated.

(±)-, (+)-, *and* (−)-4-*Methylatrolactamidinium Chlorides* (Ia).—4-Methylacetophenone was converted into the (±)-amidinium chloride (Ia) which was resolved by means of sodium (+)- or (−)-mandelate according to the published procedure.[10] Compound (+)-(Ia) had [α] +62·2° (water), m.p. 164—165°, [lit.,[10] [α] +62·1° (water); m.p. 164—165°] and (−)-(Ia) had [α] −60·0° (water), m.p. 163—165°.

Preparation of Diastereomeric Tetrazines (IIIa).—The (±)-amidinium chloride (Ia) (4·6 g) and hydrazine hydrate (99%; 3 g) were refluxed together under nitrogen in methanol (50 ml) for 3 h.[1,2] Water (150 ml) was then added to the cooled solution yielding a precipitate (IIa) (2·8 g), m.p. 141—144°, and further dilution yielded more solid (0·16 g), m.p. 172—174°. [The m.p. of the diastereomeric mixture of dihydrotetrazines (IIa) varied in subsequent experiments, the highest m.p. being 184—185°.] The dihydrotetrazine (IIa) (2·8 g), m.p. 141—144° was dissolved in ethanol (50 ml) to which was added gradually [1] sodium nitrite (9·4 g) and sulphuric acid (70 ml; 1M).[16] Addition of ice–water (250 g) yielded the red diastereomeric tetrazines (IIIa) (1·9 g), m.p. 140—144°. These could be separated by fractional crystallisation from aqueous methanol [2] or by t.l.c. using silica gel G and eluting with ethyl acetate–cyclohexane (1 : 4). The plate was removed 4 or 5 times, dried, and replaced in the solvent to achieve a good separation. The separated red bands were extracted with ether or acetone and the tetrazines (IIIa) were recrystallised from aqueous methanol. The upper band gave (±)-(IIIa), m.p., 139—141° and the lower band *meso*-(IIIa), m.p. 166—167° (lit.,[2] m.p. 139—144 and 166—167° respectively).

Similarly the (+)-amidinium chloride (Ia) (3·6 g), [α] +62·2° (water) gave (−)-3,6-*bis*-[1-*hydroxy*-1-(4-*methylphenyl*)*ethyl*]-1,2,4,5-*tetrazine* (IIIa) (1 g), m.p. 117—118° (from aqueous methanol) (Found: C, 68·6; H, 6·3; N, 16·2. $C_{20}H_{24}N_4O_2$ requires C, 68·7; H, 6·3; N, 16·0%) and (−)-amidinium chloride (Ia) (2·5 g), [α] −60·0° (water) gave the (+)-*isomer* (IIIa) (1·4 g), m.p. 114—116° (Found: C, 68·6; H, 6·3; N, 16·2%). The intense red colour of the tetrazines precluded *any* accurate measurement of their rotations.

Approximately equal weights of (+)- and (−)-tetrazines (IIIa) were recrystallised together from aqueous methanol. The (±)-tetrazine so obtained gave no depression with the lower melting isomer confirming our assumed assignment of the (±)-structure.[2]

Preparation of Diastereomeric Dihydrotetrazines (IIa).—Solid sodium dithionite was added slowly to a pure tetrazine stereoisomer (IIIa) (1 g) dissolved in aqueous ethanol (20 ml; 1 : 1) and the mixture was stirred for a few minutes until the red colour disappeared.[1,2,5] The mixture was then added to water (80 ml), the dihydrotetrazine precipitate (0·9 g) was filtered off, and recrystallised from n-hexane–ethyl acetate. (±)-1,2-*Dihydro*-3,6-*bis*-[1-*hydroxy*-1-(4-*methylphenyl*)*ethyl*]-1,2,4,5-*tetrazine* (IIa) had m.p. 188—190° (Found: C, 67·9; H, 6·7; N, 16·2. $C_{20}H_{24}N_4O_2$ requires C, 68·2; H, 6·8; N, 16·0%), the meso-*isomer* (IIa) had m.p. 174—176° (Found: C, 68·1; H, 6·6; N, 16·2%). The optically active tetrazines (IIIa) as above similarly yielded respectively (−)-(IIa), m.p. 139—141°, [α] −246·5° and (+)-(IIa), m.p. 139—143°, [α] +244·6°. The rotations may not be highly accurate as the dihydrotetrazines show signs of oxidation in methanol.

Preparation of Diastereoisomeric 4-*Aminotriazoles* (IVa).—The dihydrotetrazine (IIa; mixture of isomers) (2·5 g) was dissolved in dry methanol and dry hydrogen chloride was passed into the solution for 10 min at 0°. The mixture was kept at 0—5° for 24 h and the solvent was removed on a rotary evaporator yielding the aminotriazole hydrochloride (1·7 g). Basification with ammonia (*d* 0·88) liberated the aminotriazole (IVa) (1·5 g). (±)-Dihydrotetrazine gave (±)-4-*amino*-3,5-*bis*-[1-*hydroxy*-1-(4-*methylphenyl*)*ethyl*]-1,2,4-*triazole* (IVa), m.p. 205—206°. [This isomer was not precipitated and so was extracted with ether, then recrystallised from ethyl acetate (Found: C, 67·8; H, 6·7; N, 15·6. $C_{20}H_{24}N_4O_2$ requires C, 68·2; H, 6·8; N, 15·9%).] The *meso*-dihydrotetrazine gave the meso-*isomer* (IVa), m.p. 203—204°, which precipitated and was recrystallised from aqueous ethanol (Found: C, 67·4;

[16] R. Huisgen, J. Sauer, and M. Seidel, *Annalen*, 1962, **654**, 146.

H, 6·8; N, 15·8%). The (−)-dihydrotetrazine (IIa), [α] −246·5°, gave similarly the (+)-*isomer* (IVa), m.p. 206—207°, [α] +49·1° after crystallisation from ethyl acetate (Found: C, 68·1; H, 6·7; N, 16·1%), and the (+)-dihydrotetrazine [α] +244·6° gave the (−)-*isomer* (IVa), m.p. 207°, [α] −51·3° (Found: M^+, 352·1904. $C_{20}H_{24}N_4O_2$ requires M, 352·1899) after crystallisation from aqueous methanol.

Preparation of 4-*Aminotriazoles* (IVb).—The dihydrotetrazine [1] (IIb) (2·3 g) (mixed isomers treated as above) yielded, on basification, solid 4-*amino*-3,5-*bis*-(1-*hydroxy*-1-*phenylethyl*)-1,2,4-*triazole* (IVb) (1·0 g), m.p. 202—203° (from aqueous ethanol) (Found: C, 66·9; H, 6·2; N, 17·4. $C_{18}H_{20}N_4O_2$ requires C, 66·7; H, 6·1; N, 17·3%). Similarly, (−)-dihydrotetrazine [1] (IIb) (0·35 g; [α] −165°) (lit.,[1] [α] −165°) gave the (−)-4-*aminotriazole* (IVb) (0·02 g), m.p. 194—197°, [α] −10·2° (Found: M^+, 324·1588. $C_{18}H_{20}N_4O_2$ requires M, 324·1586).

Preparation of 4-*Aminotriazoles* (IVc).—The dihydrotetrazine [1] (IIc) (1·5 g), as a mixture of isomers, was treated as above. An ether extract of the basic solution yielded 4-*amino*-3,5-*bis*-(1-*hydroxy*-1-*phenylpropyl*)-1,2,4-*triazole* (IVc) (0·15 g), m.p. 189—190° (Found: C, 68·2; H, 7·1; N, 16·0. $C_{20}H_{24}N_4O_2$ requires C, 68·2; H, 6·8; N, 15·9%). Similarly (−)-dihydrotetrazine [1] (IIc) (0·05 g; [α] −227·4°; m.p. 117—118°) (lit.,[1] [α] −227·4°; m.p. 117—118°), yielded a precipitate of the (−)-4-*aminotriazole* (IVc), [α] −13·3°, m.p. 163—164° (from aqueous ethanol) (Found: C, 68·1; H, 6·9; N, 16·0%).

Preparation of Diastereoisomeric Triazoles (VIa).—The 4-aminotriazole (IVa) (1 g) was dissolved in glacial acetic acid (10 ml) by heating. The solution was cooled, aqueous sodium nitrite (4 g in 8 ml) was added, and the mixture left for *ca.* 20 min.[9] It was then boiled for 5 min, cooled, and made alkaline with ammonia (*d* 0·88) yielding triazole (0·5 g). (±)-3,5-*Bis*-[1-*hydroxy*-1-(4-*methylphenyl*)*ethyl*]-1,2,4-*triazole* (VIa) had m.p. 169—171° (from benzene) (Found: C, 70·4; H, 6·6; N, 13·2%; M^+, 337·1785. $C_{20}H_{23}N_3O_2$ requires C, 71·2; H, 6·8; N, 12·5; M, 337·1790) and the meso-*triazole* (VIa) had m.p. 157—160° (from benzene) (Found: C, 71·0; H, 6·7; N, 12·7%). The (−)-4-aminotriazole (IVa), [α] −51·3° gave similarly the (+)-*triazole* (VIa), m.p. 174—175° (from aqueous ethanol), [α] +85·7° (Found: M^+, 337·1782).

Preparation of Diastereoisomeric Oxadiazoles (Va).—*Method A.* To the tetrazine (IIIa) [1 g; mixture of (±)- and *meso*-forms] was added peracetic acid (10 ml; 40%) which had been buffered to pH 5 with sodium acetate [8] and the mixture was stirred at 50—60°. After 24 h the red colour of the tetrazine had disappeared and dilution of the mixture with water gave 2,5-*bis*-[1-*hydroxy*-1-(4-*methylphenyl*)*ethyl*]-1,3,4-*oxadiazole* (Va) (0·7 g), m.p. 193—195° (from aqueous ethanol) (Found: C, 70·8; H, 6·4; N, 8·3. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·5; N, 8·3%).

Method B. The dihydrotetrazine (IIc) [1 g; mixture of (±)- and *meso*-forms], m.p. 141—144°, was dissolved in the minimum of ethanol. Hydrochloric acid (30 ml; 6M) was added and the solution was stirred for 24 h at room temperature under nitrogen. Reduction of solvent in a rotatory evaporator and extraction with ether led to the isolation of oxadiazole (0·7 g) identical to that above. Similarly, (−)-dihydrotetrazine (IIa) from (+)-amidinium chloride, [α] +55·5° yielded the (+)-2,5-*bis*-[1-*hydroxy*-1-(4-*methylphenyl*)*ethyl*]-1,3,4-*oxadiazole* (Va), m.p. 198—199°, [α] +106·6° (Found: C, 70·8; H, 6·5; N, 8·3%). Attempts to repeat these experiments (Method B) however, yielded the diacylhydrazines (VIIa).

Preparation of Diastereomeric Oxadiazoles (Vb).—*Method A.* Similarly [8] the (±)-tetrazine (IIIb) (0·05 g) yielded (±)-2,5-*bis*-(1-*hydroxy*-1-*phenylethyl*)-1,3,4-*oxadiazole* (Vb) (0·02 g), m.p. 187—189° (from aqueous ethanol) (Found: C, 70·1; H, 5·9; N, 9·2. $C_{18}H_{18}N_2O_3$ requires C, 69·7; H, 5·8; N, 9·0%) and *meso*-tetrazine (0·1 g), the meso-*oxadiazole* (Vb) (0·05 g), m.p. 135—138° (from aqueous ethanol) (Found: C, 70·1; H, 5·8; N, 9·1%). Also (−)-tetrazine (IIIb) [0·05 g; m.p. 121°; from amidinium chloride (Ib); [α] +46·2° (H_2O)] yielded the (+)-*oxadiazole* (Vb) (0·03 g), m.p. 182—183°, [α] +59·3° (from aqueous ethanol) (Found: M^+, 310·1295. $C_{18}H_{18}N_2O_3$ requires M^+, 310·1317).

Preparation of Diastereomeric Oxadiazoles (Vc).—*Method A.* The (±)- and *meso*-tetrazines (IIIc) (0·1 g) yielded as above [8] (±)-2,5-*bis*-(1-*hydroxy*-1-*phenylpropyl*)-1,3,4-*oxodiazole* (Vc) (0·08 g), m.p. 190—193° (Found: C, 70·9; H, 6·4; N, 8·5. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·5; N, 8·3%) and the meso-*oxadiazole* (Vc) (0·08 g), m.p. 137—139° (Found: C, 71·1; H, 6·6; N, 8·6%). The (−)-tetrazine (IIIc) {0·1 g; m.p. 109—110°; from amidinium chloride (Ib); [α] +50° (H_2O)} after a more prolonged reaction time (72 h) gave the (+)-*oxadiazole* (Vc), m.p. 174—175°, [α] +24·4° (Found: C, 70·5; H, 6·8; N, 8·0%).

Preparation of Diastereoisomeric Diacylhydrazines (VIIa).—The dihydrotetrazine (IIa) (1 g) was dissolved in ethanolic hydrochloric acid and treated as in Method B (see above). The dried extracts yielded, not the expected oxadiazoles (Va), but the diacylhydrazines which were recrystallised from aqueous ethanol. (±)-*Di*-4-*methylatrolactoylhydrazine* (VIIa) had m.p. 162—164° (Found: C, 67·4; H, 6·8; N, 8·0; $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·7; N, 7·9%) and meso-*isomer* (VIIa) had m.p. 228—229° (Found: C, 67·1; H, 6·6; N, 7·7%). The (+)-dihydrotetrazine (IIa), [α] 244·6°, gave the (+)-isomer (VIIa), m.p. 193—195°, [α] +106·6° (confirmed by similarity of i.r. spectrum to diastereoisomers). I.r. spectra of diacyl hydrazines (VIIa) showed (±), 5·98 and 6·13 μm; *meso*, 6·17 μm; and (+), 5·95 and 6·05 μm.

The specific rotations were measured on a Perkin-Elmer polarimeter, model 141. The c.d. measurements were made at 20—25° in the concentration range 0·2—1·0 mg ml^{-1} with a Roussel-Jouan dichrograph at Westfield College, London.

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