Formation of Optically Active 1,2,4-Triazoles from the Reactions of Optically Active *N*-Arylmandelamidrazones with Trialkyl Ortho Esters or Aldehydes

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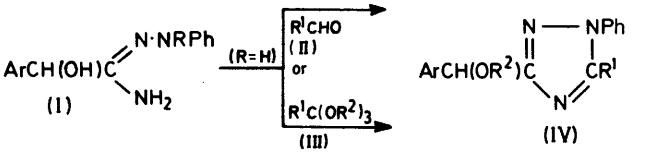
A series of optically active *N*-arylmandelamidrazones has been prepared, either by the action of a substituted hydrazine on ethyl (−)-mandelimidate hydrochloride or by direct resolution of the (±)-amidrazone *via* the (+)- and (−)-mandelic acids. Reactions of these amidrazones with trialkyl ortho esters led to optically active 1,3-disubstituted and 1,3,5-trisubstituted 1,2,4-triazoles. The reaction of *N*-arylmandelamidrazone salts with ortho esters is, however, more complex, the 1,2,4-triazole products either being identical with those formed from the amidrazone bases or having undergone *O*-alkylation along with racemisation to the benzylic centre. A mechanism is proposed for this alkylation process. The reaction of optically active amidrazones with aldehydes is also complex, aliphatic aldehydes apparently yielding optically active 1,2,4-triazoles but aromatic aldehydes giving either optically active or racemised products, depending on the amidrazone used. Absolute configurations have been assigned to both amidrazones and triazoles by chemical means and also, tentatively, by comparison of c.d. spectra.

AMIDRAZONES possess skeletal structures which make them useful intermediates in the synthesis of 1,2,4-triazoles (Scheme 1) by carbon insertion reactions involving, among other species, aldehydes or ortho esters;[1-5] we have recently described reactions of this type[6] based on (±)-mandelamidrazones (I). This paper describes an extension of our work on optically active nitrogen bases, *e.g.* amidines,[7,8] tetrahydropyrimidines,[9] and imidazolines,[10] into the field of optically active amidrazones and 1,2,4-triazoles. To date, only a brief mention of optically active amidrazones has appeared in the literature,[11] although optically active 3,5-disubstituted 1,2,4-triazoles have been synthesised from 3,6-disubstituted 1,2,4,5-tetrazines.[12]

Optically active mandelamidrazones (I; Ar = Ph) can be synthesized by the action of substituted hydrazines on ethyl (−)-mandelimidate hydrochloride[10] prepared from amygdalin, and optically active *N*-phenyl- (Ia), *N*-methyl-*N*-phenyl- (Ib), and *NN*-diphenylmandelamidrazones or their salts have been obtained in this way without any apparent problems of racemisation. Alternatively, when the aryl group [Ar of structure (I)] carried a substituent, direct resolution of the (±)-amidrazone was required and the (+)- and (−)-mandelic acids[13] were found to be useful reagents in this respect. The amidrazones (Id and e) were resolved in this way.

The availability of chiral amidrazones opens a way to optically active 1,3-disubstituted and 1,3,5-trisubstituted triazoles by interaction with ortho esters. Our earlier work[6] has shown that whereas (±)-mandelamidrazone bases (I; R = H) react generally to give (±)-triazol-3-ylbenzyl alcohols (IV; R^2 = H), their hydrochlorides lead in certain cases to *O*-alkylated products (IV; R^2 = alkyl) (see Scheme 2). Analagously, the (+)-amidrazone (Ia) reacted with triethyl orthoformate to give the (+)-triazole (IVa), and with orthoacetate to give the (+)-triazole (IVb); likewise with this latter reagent (−)-*N*-phenyl-2-chloromandelamidrazone (Id) yielded the (−)-triazole (IVc) (the benzylic hydroxy-group is unaffected



a; Ar = Ph, R = H
b; Ar = Ph, R = Me
c; Ar = R = Ph
d; Ar = 2—ClC_6H_4, R = H
e; Ar = 2—$MeO{\cdot}C_6H_4$, R = H

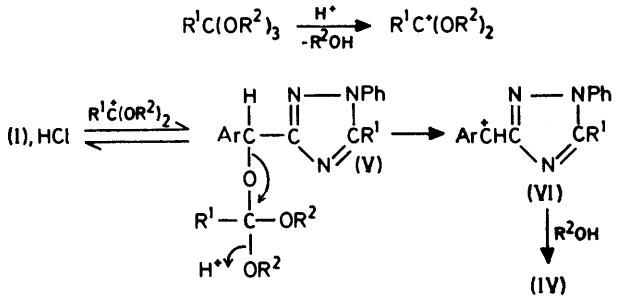
a; Ar = Ph, R^1 = H, R^2 = H
b; Ar = Ph, R^1 = Me, R^2 = H
c; Ar = 2—ClC_6H_4, R^1 = Me, R^2 = H
d; Ar = Ph, R^1 = H, R^2 = Et
e; Ar = 2—ClC_6H_4, R^1 = R^2 = H
f; Ar = Ph, R^1 = 4—HO—3—$MeO{\cdot}C_6H_3$, R^2 = H
g; Ar = Ph, R^1 = 4—$MeO{\cdot}C_6H_4$, R^2 = H
h; Ar = Ph, R^1 = Pr^n, R^2 = H
i; Ar = 2—$MeO{\cdot}C_6H_4$, R^1 = Pr^n, R^2 = H
j; Ar = 2—ClC_6H_4, R^1 = 4—$MeO{\cdot}C_6H_4$, R^2 = H
h; Ar = R^1 = Ph, R^2 = H

SCHEME 1

in these cases). When, however, (−)-*N*-phenylmandelamidrazone hydrochloride [(Ia), HCl] was treated with triethyl orthoformate, the resultant triazole (IVd) was found to have undergone both alkylation and racemisation at the benzylic centre. This finding provides

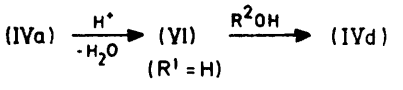
[1] D. G. Neilson, R. Roger, J. W. M. Heatlie, and L. R. Newlands, *Chem. Rev.*, 1970, **70**, 151.
[2] K. M. Watson and D. G. Neilson, ' The Chemistry of Amidines and Imidates,' ed. S. Patai, Wiley, New York, 1975, pp. 385 and 491.
[3] A. W. Nineham, *Chem. Rev.*, 1955, **55**, 355.
[4] K. T. Potts, *Chem. Rev.*, 1961, **61**, 87.
[5] J. H. Boyer, ' Heterocyclic Compounds,' vol. 7, ed. R. C. Elderfield, Wiley, New York, 1961, p. 384.
[6] J. K. Fraser, D. G. Neilson, L. R. Newlands, K. M. Watson, and M. I. Butt, *J.C.S. Perkin I*, 1975, 2280.
[7] D. G. Neilson and D. A. V. Peters, *J. Chem. Soc.*, 1963, 4455.
[8] D. G. Neilson and L. H. Roach, *J. Chem. Soc.*, 1965, 1658.
[9] D. G. Neilson, I. A. Khan, and R. S. Whitehead, *J. Chem. Soc.* (*C*), 1968, 1853.
[10] D. G. Neilson, D. A. V. Peters, and L. H. Roach, *J. Chem. Soc.*, 1962, 2272.
[11] D. G. Neilson, ' Some Newer Physical Methods in Structural Chemistry,' eds. R. Bonnett and J. G. Davis, United Trade Press Ltd., London, 1967, p. 186.
[12] D. G. Neilson, S. Mahmood, and K. M. Watson, *J.C.S. Perkin I*, 1973, 335.
[13] R. Roger, *J. Chem. Soc.*, 1935, 1544.

further evidence for our previously proposed reaction scheme (Scheme 2), which involves a carbocation intermediate (VI) leading to racemised product, *e.g.* the triazole (IVd). Evidence to support the intermediacy of the complex ortho ester (V) is based on the characterisation of related compounds, *e.g.* $PhCH[OCH(OR)_2]CO{\cdot}NH_2$



SCHEME 2

(R = Me or Et), from the interaction of mandelamide with ortho esters,[6] and secondly on the fact that treatment of the (+)-triazolyl-benzyl alcohol (IVa) with triethyl orthoformate in acid solution leads to the (±)-*O*-alkyltriazole (IVd), alkylation having taken place along with racemisation. An alternative route (Scheme 3) for the formation of the carbocation (VI) and the alkylated product (IV) by simple protonation of the benzylic group, loss of water, and attack by alcohol can be shown to be not the main reaction pathway. Thus the (+)-triazole (IVa), on heating in ethanol–acid for a time equivalent to that of the ortho ester–triazole racemisation experiment, lost less than 20% of its activity owing to the formation of alkylated product (IVd); hence this alternative route (Scheme 3), although accounting for some alkylated product, is secondary to that in Scheme 2.



SCHEME 3

In the case of (±)-2-chloromandelamidrazone hydrochloride [(Id), HCl], it has already been reported [6] that treatment with orthoformate leads to the (±)-triazole (IVe), *i.e.* no alkylation takes place at the benzylic centre; however it was not known whether this was a steric or electronic effect of halogen, or even a combination of both. Similarly the (+)- and (−)-2-chloromandelamidrazone hydrochlorides (Id) gave, respectively, the (−)- and (+)-triazoles (IVe) with free benzylic hydroxy-groups, and these triazoles were optically stable even under prolonged reaction conditions. In addition when the (+)-triazole (IVe) was treated with ethanol–acid no *O*-alkylation took place [*cf.* compound (IVa)]. Failure of this latter protonation reaction (Scheme 3) might be construed as evidence for an electronic rather than a steric effect of the 2-chloro-substituent but this is by no means conclusive.

The reaction of aldehydes with amidrazones (Scheme 1) presents an alternative pathway to 1,2,4-triazoles.[2,6] When the (+)-amidrazone (Ia) was treated with either vanillin or anisaldehyde, the resultant triazoles (IVf and g) were found to be racemic, although there was some evidence in the latter case that the crude product had initially some optical activity of opposite sign to that of the starting material. This loss of activity was not due to optical instability of the starting material, the amidrazone (Ia) or its hydrochloride, as these lost only a small fraction of their optical purity on heating for several hours or storage for some days in solution. Indeed, this small loss of activity was shown to be attributable to the formation of (*N*-phenyl)phenylglyoxylamidrazone [$PhCO{\cdot}C(NH_2){:}N{\cdot}NHPh$]. The optical stability of the starting material (Ia) is further supported by the fact that n-butyraldehyde smoothly converts the (+)-amidrazone (Ia) and also its (−)-2-methoxy-derivative (Ie) into optically active triazoles (IVh and i, respectively). Although at first sight this might point to the nature of the 5-substituent of the 1,2,4-triazole having a surprisingly marked effect on its optical stability, *i.e.* optically stable if the 5-substituent (R^1) is aliphatic but unstable if aromatic, the matter is further complicated by the finding that the (−)-2-chloromandelamidrazone (Id) reacts with anisaldehyde to give an optically stable (+)-triazole (IVj). In an attempt to clarify these findings *N*-phenylmandelamidrazone (Ia) was treated with trimethyl orthobenzoate in the hope of synthesising a 5-aryltriazole (IVk) by this alternative route; however, *N*-phenylmandelohydrazide was the only product characterised. Thus, at present, the nature of the effect of the 5-substituent on the optical stability of the 1,2,4-triazoles remains unclear.

Ethyl (−)-mandelimidate hydrochloride, prepared from amygdalin, is known to have the *R*-configuration,[10,14] and hence (+)-*N*-phenylmandelamidrazone (Ia), its (−)-hydrochloride [(Ia), HCl], (+)-*N*-methyl-*N*-phenylmandelamidrazone (Ib), and (−)-*NN*-diphenylmandelamidrazone (Ic) also all belong to the *R*-series, being directly synthesised from the imidate. In addition the (+)-triazoles (IVa, b, and h) prepared from (+)-(*R*)-*N*-phenylmandelamidrazone (Ia) by reaction with the appropriate aldehyde or ortho ester must also belong to the *R*-series. The availability of these chemically correlated substances permitted the use of c.d. studies to determine the configurations of compounds based on the 2-chloro- and 2-methoxy-mandelo systems (Id and e).*

The c.d. curves of the triazoles (IVa—c, e, and h—j) were run in methanolic solution and then in methanol containing a drop of concentrated hydrochloric acid (see Figures 1 and 2). Exceptionally, the (+)-triazole (IVj), with a 1,3,5-triaryl substitution pattern, gave no detectable c.d. spectrum, and the (+)-compound (IIh) had a cut-off at 238 nm in neutral solution; these effects are due to high absorption. Comparison of the other c.d.

* C.d. data for the mandelamidrazones (Ia, b, d, and e) and for the triazoles (IVa—c, e, and h—j) are available as Supplementary Publication No. SUP 21971 (6 pp.), which also contains Table 3 and Figures 3 and 4. (For details of Supplementary Publications, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.)

[14] S. Reid, Ph.D. Thesis, University of St. Andrews, 1949.

curves (Figures 1 and 2) showed that at *ca.* 225 nm there was a positive maximum in each case for compounds

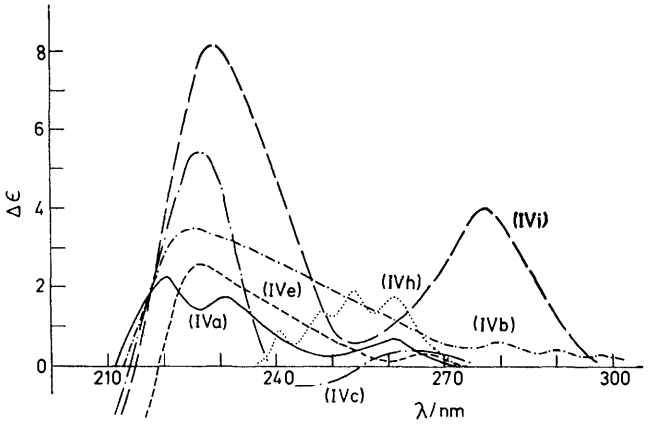


FIGURE 1 C.d. spectra of (*R*)-1,2,4-triazoles in methanol

(+)-(IVa), (+)-(IVb), (+)-(IVi), (−)-(IVc), and (+)-(IVe). As the (+)-triazoles (IVa and b), derived from amygdalin, belong to the *R*-series (see above), the triazoles (+)-(IVi), (−)-(IVc), and (−)-(IVe) are also tentatively assigned to the *R*-series. As the triazoles (+)-(IVj), (−)IVc), and (−)-(IVe) have a common precursor, *viz.* (−)-2-chloromandelamidrazone (Id), the triazole (+)-(IVj) has also been assigned the *R*-configuration. Application of the rule of shift [15] by comparison of the rotations of the triazoles (IV) at 5 461 Å in neutral and acidic solutions (Table 3) * helps to confirm the c.d. assignments: apart from compound (+)-(IVi), all other triazoles assigned the *R*-configuration above show a marked positive shift on protonation. It is well established [16,17] that conformational rigidity has a marked effect on the c.d. (or o.r.d.) spectra of compounds and hence on the rotations at higher wavelength. Thus in the case of *N*-phenyl-2-methoxymandelamidrazone (IVi) there could well be a high population of the hydrogen-bonded conformer (VII) in neutral solution. This however would be destroyed on addition of acid and could thus account for the anomalous results observed for compound (IVi), this form of hydrogen bonding being denied by nature of their structures to all the other triazoles.

It is also of interest that the triazole (IVi) has a high intensity ^1L_b Cotton effect (*ca.* 274 nm), supporting the idea of hydrogen bonding as depicted in structure (VII). Korver [18] has suggested that the ^1L_b Cotton effect of the aromatic chromophore is positive for unsubstituted and negative for 2-arylsubstituted mandelic acids (and their esters) of the *R*-series, results which are paralleled by our own work on mandelamidines [19] (VIII). The present results on the ^1L_b Cotton effects of the triazoles do not appear to tie in with these earlier findings, but the triazoles (IV) have in fact three aromatic chromophores, and indeed Korver's observations on the mandelic acids do not appear to hold for the closely related α-amino-acids.[20]

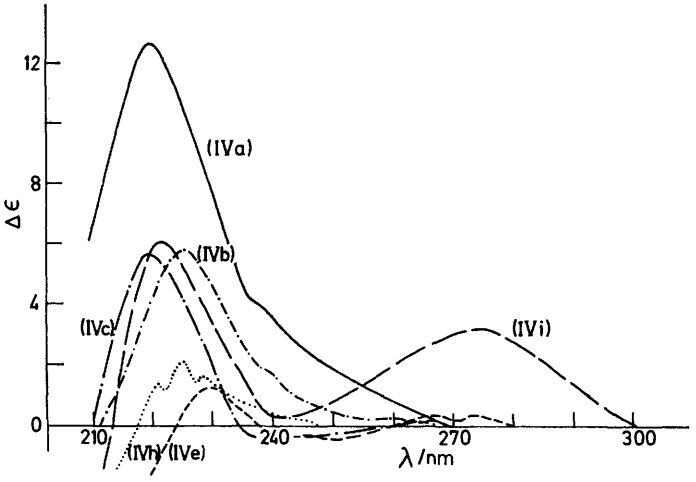
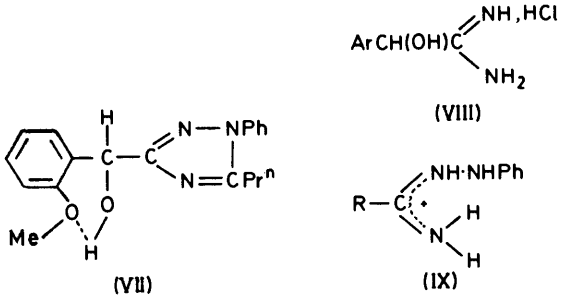


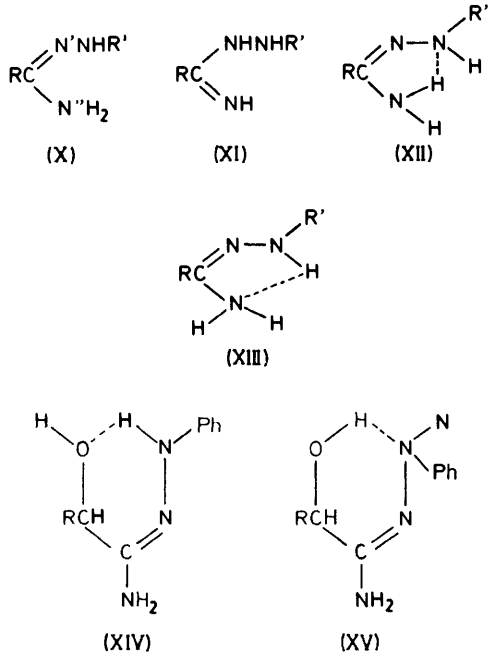
FIGURE 2 C.d. spectra of (*R*)-1,2,4-triazoles in methanolic hydrochloric acid



* In the Supplementary Publication.

[15] K. Freudenberg, *Ber.*, 1933, **66**, 177.
[16] G. G. Lyle and W. Lacroix, *J. Org. Chem.*, 1963, **28**, 900.
[17] L. Verbit, S. Mitsui, and Y. Senda, *Tetrahedron*, 1966, **22**, 750.
[18] O. Korver, *Tetrahedron*, 1970, **26**, 5507.
[19] 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.
[20] G. Snatzke, M. Kajtár, and F. Snatzke, 'Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism,' eds. F. Ciardelli and P. Salvadori, Heyden, London, 1973, pp. 162—169.

The c.d. curves of the amidrazones (Ia, b, d, and e) are complex both in neutral (Figure 3) † and acidic solutions (Figure 4).* The amidrazones (Ia, d, and e) show distinct maxima in the region 300—315 nm (C=N); these bands disappear on protonation of the amidrazones owing to charge delocalisation (IX), but the complexity of the curves makes assignments of configuration almost impossible. However, (+)-2-methoxy- (Ie) and (−)-2-chloro-mandelamidrazones (Id) are both tentatively assigned the *R*-configuration on the basis of the triazole assignments above. Studies [21-24] based on physical methods have shown that amidrazones exist preferentially in the amide hydrazone (X) rather than the hydrazide imide structure (XI). In addition the preferred configuration [21] is *syn* to the amino-group (*N*″) with internal hydrogen bonding linking *N* and *N*″ [(XII) and (XIII)]. However, for compounds of type (I), our n.m.r. evidence points to conformations of the type (XIV) or



(XV) with *anti*-configurations caused by hydrogen bonds between the benzylic hydroxy-group and the hydrazine residue. For example, the n.m.r. spectrum of compound (Ia) [in $(CD_3)_2SO$] includes two singlets at δ 7.9 (1 H) and 5.6 (2 H), respectively, which collapse on addition of D_2O. Similarly, compound (Ib) has a singlet at δ 6.0 (2 H), suggesting that the two protons on N″ (X) are equivalent in each of these compounds. In structures (XII) and (XIII) the two protons on N″ should be non-equivalent owing to rigidity imposed by the hydrogen bonding. The hydrochloride of the amidrazone (Ia) exhibits four singlets at δ 8.5, 9.1, 9.6, and 11.7 (each 1 H), supporting the belief that protonation takes place at N′ (X), causing non-equivalence of the two protons on N″ owing to an amidinium type charge delocalisation as depicted by structure (IX). Such different possibilities for conformations [(VII) and (XII)—(XV)] could help to explain the complexity of the c.d. curves.

* In the Supplementary Publication.

[21] H. C. Brown and D. Pilipovich, *J. Amer. Chem. Soc.*, 1960, **82**, 4700.

EXPERIMENTAL

N.m.r. spectra were determined with a Varian A60 instrument (tetramethylsilane as internal reference). C.d. measurements were made with a Roussel-Jouan dichrograph at Westfield College, London. Specific rotations were measured with a Perkin-Elmer **141** polarimeter, and are recorded at 546.1 nm for ethanolic solutions unless otherwise stated.

Solvents used in the crystallisation of amidrazones and their salts were ' boiled out '.

Ethyl (−)-*Mandelimidate Hydrochloride*.—Prepared by the literature method, this had m.p. 106—108°, [α] −167.3° (lit.,[10] m.p. 106—108°; [α] −171°).

(−)-N-*Phenylmandelamidrazone* (Ia) *Hydrochloride*.—The above (−)-imidate salt (14.2 g) in dry ethanol (60 ml) was stirred with phenylhydrazine (7.1 g) for 24 h at room temperature. Ammonium chloride was then filtered off, concentrated hydrochloric acid (2 ml) was added, and the solution was evaporated. Addition of ether to the residue yielded a solid which was purified by dissolution in alcohol and reprecipitation with ether. The (−)-*amidrazone* (Ia) *hydrochloride* (8.9 g) had m.p. 193—194°, [α] −43.2° (Found: C, 60.2; H, 5.8; N, 15.0. $C_{14}H_{16}ClN_3O$ requires C, 60.5; H, 5.8; N, 15.1%).

(+)-N-*Phenylmandelamidrazone* (Ia).—To the (−)-amidrazone (Ia) hydrochloride (3.3 g) in aqueous solution was added a solution of sodium carbonate (0.63 g) in water at 0 °C. The (+)-amidrazone (Ia) (2.4 g) had m.p. 147—148° (from aqueous ethanol), [α] +160.1° (Found: C, 69.0; H, 6.2; N, 16.9. $C_{14}H_{15}N_3O$ requires C, 69.7; H, 6.2; N, 17.5%).

(+)-N-*Methyl*-N-*phenylmandelamidrazone* (Ib).—Prepared as for compound (Ia) but by using methylphenylhydrazine, the (+)-*amidrazone* (Ib) (47%) (from ethanol) had m.p. 160—161°, [α] +32.0° (Found: C, 70.6; H, 6.7; N, 16.4. $C_{15}H_{17}N_3O$ requires C, 70.6; H, 6.7; N, 16.5%). Attempts to isolate the hydrochloride yielded only oils. Addition of one drop of concentrated hydrochloric acid to the rotation sample [*i.e.* formation of (Ib) hydrochloride *in situ*] gave [α] −41.4°.

(−)-NN-*Diphenylmandelamidrazone* (Ic) *Hydrochloride*.—Prepared as for compound (Ia) except that the imidate salt and diphenylhydrazine were left in contact for 7 days, the grey *amidrazone* (Ic) *hydrochloride* (25%) had m.p. 197—199° (Found: C, 67.7; H, 5.9; N, 11.7. $C_{20}H_{20}ClN_3O$ requires C, 67.9%; H, 5.7; N, 11.9%), and the free *base* (Ic) m.p. 152—153° (Found: N, 13.2. $C_{20}H_{19}N_3O$ requires N, 13.2%). Samples were too small and coloured to allow measurements of rotation and the sign allotted to (Ic) hydrochloride is based on an o.r.d. trace.

Resolution of (±)-N-*Phenyl*-2-*chloromandelamidrazone* (Id).—(±)-*N*-Phenyl-2-chloromandelamidrazone [6] (12.5 g) and (−)-mandelic acid [13] (6.9 g), [α] > −180° (in acetone), were warmed together in ethanol (50 ml). Solid obtained on cooling was recrystallised three times from methanol giving the (+)-amidrazone (Id) (−)-mandelate (6.6 g),

[22] W. Walter and H. Weiss, *Annalen*, 1972, **758**, 162.

[23] W. Walter and H. Weiss, *Tetrahedron Letters*, 1974, 3009.

[24] R. E. Smith, D. S. Johnson, C. L. Hyde, T. C. Rosenthal, and A. C. Bates, *J. Org. Chem.*, 1971, **36**, 1155.

m.p. 167—168°, [α] −24.4° (in methanol) (constant rotation). Hydrogen chloride gas was passed through a solution in methanol of the mandelate salt kept at 0 °C. Removal of the solvent yielded a solid which was taken up in hot ethanol and precipitated with ether. The (+)-*amidrazone* (Id) *hydrochloride* (4.6 g) had m.p. 183—184°, [α] +29.7° (Found: C, 53.3; H, 4.9; N, 13.3. $C_{14}H_{15}Cl_2N_3O$ requires C, 53.8; H, 4.8; N, 13.4%).

The (−)-*amidrazone* (Id) *hydrochloride* prepared similarly from (+)-mandelic acid had m.p. 184—185°, [α] −29.4° (Found: C, 53.9; H, 4.8; N, 13.4%).

Treatment of the (+)-amidrazone (Id) hydrochloride (4.7 g) in aqueous solution with a slight excess of aqueous sodium carbonate, dropwise at 0° yielded an oil which slowly solidified. The (−)-*amidrazone* (Id) (3.7 g) had m.p. 97—99°, [α] −45.5° (Found: C, 59.7; H, 5.4; N, 14.8. $C_{14}H_{14}ClN_3O$, 0.25 H_2O requires C, 60.0; H, 5.2; N, 15.0%) (the analysis remained consistent after prolonged drying *in vacuo*).

Resolution of (±)-N-*Phenyl*-2-*methoxymandelamidrazone* (Ie).—The (±)-amidrazone [6] (Ie) (7.0 g) and (+)-mandelic acid [13] (3.9 g), [α] ⩾ +180.0° (in acetone), were dissolved in ethanol (20 ml). Solid which precipitated out after a few days was recrystallised three times from ethanol to give the (−)-amidrazone (+)-mandelate (2.5 g), m.p. 148—150°, [α] −7.3°. Further crystallisation did not change this rotation. The mandelate was dissolved in ethanol (50 ml) and hydrogen chloride bubbled through the cooled solution. Removal of the solvent yielded solid which was dissolved in ethanol and precipitated with ether. The (−)-*amidrazone* (Ie) *hydrochloride* (1.8 g) had m.p. 161—162°, [α] −71.1° (Found: C, 58.6; H, 6.0; N, 13.5. $C_{15}H_{16}ClN_3O_2$ requires, C, 58.5; H, 5.9; N, 13.7%). The (+)-*amidrazone* (Ie) *hydrochloride*, prepared in the same way but from (−)-mandelic acid, [α] ⩾ −180° (in acetone), had m.p. 159—161°, [α] +69.9° (Found: C, 58.4; H, 5.9; N, 13.5%).

The (−)-amidrazone (Ie) hydrochloride (3.0 g), [α] −71.1° was dissolved in water and a slight excess of aqueous sodium carbonate was added dropwise at 0 °C. The resultant oil soon solidified giving the (−)-*amidrazone* (IIe) (2.3 g), m.p. 95—97°, [α] −75.0° (from aqueous methanol) (Found: C, 64.0; H, 6.5; N, 15.0. $C_{15}H_{17}N_3O_2$, $0.5H_2O$ requires C, 64.5; H, 6.4; N, 15.0%).

Interaction of Ortho Esters with Amidrazones and their Salts.—Various 1-aryl-3-(α-hydroxybenzyl)-1,2,4-triazoles were prepared according to our published procedures [6] (see Table 1).

Reaction of (+)-3-(α-*Hydroxybenzyl*)-1-*phenyl*-1,2,4-*triazole* (IVa) *with Triethyl Orthoformate under Acidic Conditions.*—The (+)-triazole (IVa) (0.065 g) in ethanol (10 ml) was refluxed with triethyl orthoformate containing one drop of concentrated hydrochloric acid. The rotation of this solution fell to zero in 72 h, by which time the initial triazole (IVa) had undergone alkylation with racemisation to give the (±)-triazole (IVd).

Reaction of (+)-3-(α-*Hydroxybenzyl*)-1-*phenyl*-1,2,4-*triazole* (IVa) *with Ethanol under Acidic Conditions.*—The (+)-triazole (IVa) in ethanol (10 ml) was refluxed for 70 h with one drop of concentrated hydrochloric acid. Examination of the resultant solution showed 82% of the original rotation to be retained. T.l.c. [ether–petroleum (4 : 1)] showed an intense spot corresponding to starting material (IVa) and a much less intense spot corresponding to alkylated triazole (IVd).

Reaction of (+)-3-(2-*Chloro*-α-*hydroxybenzyl*)-1-*phenyl*-1,2,4-*triazole* (IVe) *with Ethanol under Acidic Conditions.*—The (+)-triazole (IVe) was treated as above. The rotation of the sample increased slightly (owing to solvent evapor-

TABLE 1

Triazoles from ortho esters with amidrazones

Product (IV)	Reagents (III)	Reagents (I), [α] (°)	M.p. (°C)	[α] (°)	Recryst. from	Found (%)	Required (%)	Yield (%)
(+)-(IVa)	R^1 = H, R^2 = Et	(Ia), +161.9	148—149	+24.9	H_2O–EtOH	C, 71.4; H, 5.2; N, 16.7	C, 71.7; H, 5.2; N, 16.7	56
(+)-(IVb)	R^1 = Me, R^2 = Et	(Ia), +158.0	128—130	+28.0	EtOH–petrol	C, 72.9; H, 5.7; N, 15.9	C, 72.5; H, 5.7; N, 15.9	50
(−)-(IVc)	R^1 = Me, R^2 = Et	(Id), −45.9	129—131	−4.9	EtOH–petrol	C, 64.2; H, 4.8; N, 14.0	C, 64.1; H, 4.7; N, 14.1	44
(±)-(IVd)	R^1 = H, R^2 = Et	(Ia), HCl, −43.2	96—98	0	EtOH–petrol	Ref. 6		46
(−)-(IVe)	R^1 = H, R^2 = Et	(Id), HCl, +27.8	139—141	−13.6	EtOH	C, 63.0; H, 4.2; N, 14.8	C, 63.0 H, 4.2; N, 14.7	50

TABLE 2

Triazoles from aldehydes with amidrazones

Product (IV)	Reagents (II); R^1 =	Reagents (I), [α] (°)	Reaction time (h)	M.p. (°C)	[α] (°)	Recryst. solvent	Found (%)	Required (%)	Yield (%)
(±)-(IVf)	4-HO-3-MeO·C_6H_3	(Ia), +156.7	2	171—173	0	MeOH	Ref. 6		56
(±)-(IVg)	4-MeO·C_6H_4	(Ia), +151.8	3	149—151	0	EtOH	Ref. 6		46
(+)-(IVh)	Pr^n	(Ia), +152.3	4	114—116	+14.1	EtOH–petrol	C, 73.2; H, 6.5; N, 14.2	C, 73.7; H, 6.5; N, 14.4	62
(−)-(IVi)	Pr^n	(Ie), −71.3	5	104—106	−57.6	EtOH–petrol	C, 70.5; H, 6.6; N, 12.9	C, 70.6; H, 6.5; N, 13.0	33
(+)-(IVj)	4-MeO·C_6H_4	(Id), −45.9	7	164—165	+6.0	EtOH	C, 67.3; H, 4.6; N, 10.6	C, 67.5; H, 4.6; N, 10.7	50

ation) and t.l.c. showed only one spot, corresponding to starting material.

Reaction of (+)-N-*Phenylmandelamidrazone* (Ia) *with Anisaldehyde*.—The (+)-amidrazone (Ia) (1.1 g), [α] +151.8°, in ethanol (10 ml) was refluxed for 3 h with anisaldehyde (1.8 g). Evaporation yielded a solid which was washed with ether. This crude solid had [α] −30.9° but lost activity within a few hours or on work-up. T.l.c., mixed m.p., and i.r. spectra showed the final product, m.p. 149—151°, to be identical with the (±)-triazole (IVg). Other triazoles (IVf and h—j) prepared similarly are detailed in Table 2.

Optical Stability of (+)-N-*Phenylmandelamidrazone*.—The (+)-amidrazone (Ia), [α] +152°, was refluxed in ethanol for 2 h. The solution became yellow and on cooling had [α] +149°. The (+)-amidrazone (Ia), [α] +160°, was left in ethanolic solution for 4 days in the dark. The solution then had [α] +140.7°, which value had fallen to +120.9° after 12 days (*i.e.* 76% retention of activity). The yellow decomposition product was shown to be (*N*-phenyl)phenylglyoxylamidrazone [6] by comparison with authentic material.

The (−)-amidrazone (Ia) hydrochloride was optically stable over at least 6 days in alcoholic solution at room temperature.

Optical Stability of the (+)-*Triazole* (IVa).—The (+)-triazole (IVa), [α] +17.9°, in ethanol was almost unchanged in rotation after 18 h at room temperature or refluxing for 3 h.

Reaction of N-*Phenylmandelamidrazone* (Ia) *with Trimethyl Orthobenzoate*.—The (±)-amidrazone (Ia) (1.4 g) in ethanol (15 ml) was refluxed with trimethyl orthobenzoate (3.2 g) for 4.5 h. Evaporation yielded, as the sole crystalline product, *N*-phenylmandelohydrazide (0.4 g), m.p. 184—186° (lit.,[25] 182°), identical with authentic material.

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