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

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A series of *N*-arylmandelamidrazones has been prepared from the corresponding imidate hydrochlorides and mono- and unsymmetrically di-substituted hydrazines. The amidrazones were converted directly into 1,3,5-trisubstituted 1,2,4-triazoles by reaction with aldehydes, the more commonly reported triazolines and Schiff's bases not being observed. The triazole structure was confirmed by comparison with the products from reactions of the amidrazones with aliphatic trialkyl ortho esters. However, when, in place of the corresponding base, an amidrazone hydrochloride was treated with an ortho ester, alkylation of the benzylic hydroxy-group took place in some instances. A mechanism for this alkylation is proposed based on an intermediate isolated in a related reaction involving mandelamide.

IMIDATE HYDROCHLORIDES (I) react at room temperature with equimolar proportions of monosubstituted hydrazines [1,2] to give *N*-substituted amidrazone hydrochlorides (II). Use of an excess of the hydrazine [1-3] and more prolonged treatment leads to the formazans (III). Amidrazones (II) possess skeletal structures which make them useful intermediates in the synthesis of 1,3,5-trisubstituted and 1,3-disubstituted 1,2,4-triazoles by carbon insertion reactions involving reagents such as acyl halides, ortho esters, and aldehydes (after oxidation of the intermediate dihydro-derivative).[1-5] This paper describes work based on *N*-substituted mandelamidrazones.

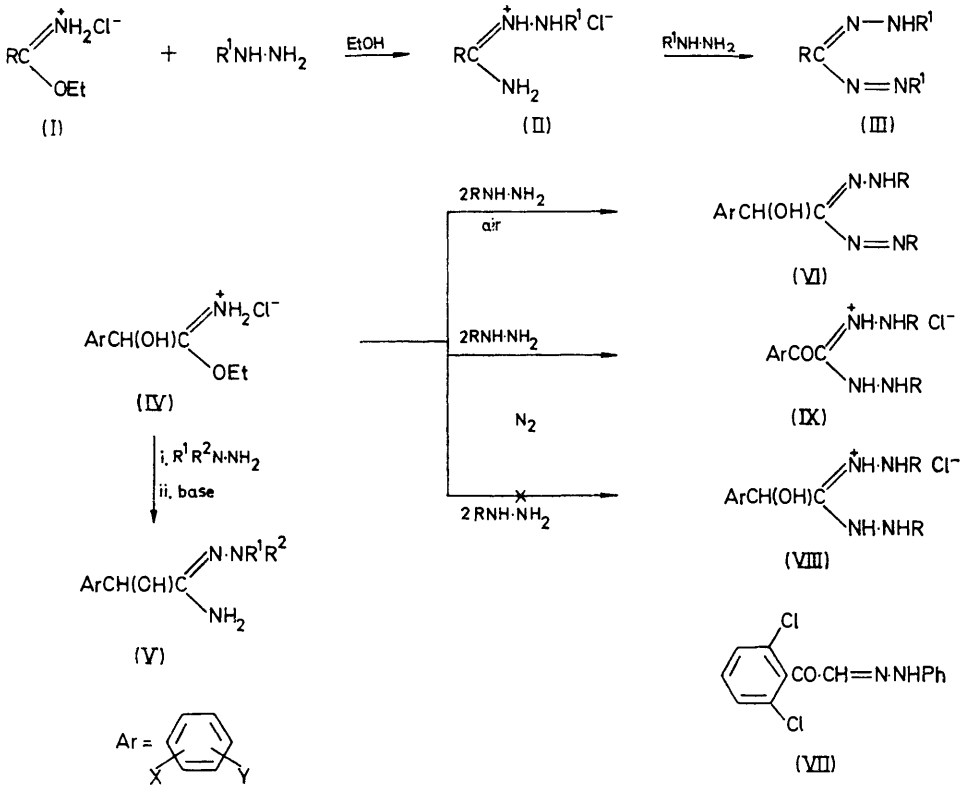
Ethyl mandelimidate hydrochlorides (IV) reacted smoothly with various arylhydrazines to give the corresponding *N*-arylmandelamidrazone hydrochlorides [(V), HCl; R^1 = H, R^2 = aryl], or, after basification the amidrazones. Exceptionally in the case of 4-nitrophenylhydrazine, the main product of reaction with compound (IV; Ar = Ph) was the formazan (VI; Ar = Ph, R = *p*-$O_2N{\cdot}C_6H_4$), and ethyl 2,6-dichloromandelimidate hydrochloride (IV; Ar = 2,6-$Cl_2C_6H_3$) with phenylhydrazine gave 2,6-dichlorophenylglyoxal phenylhydrazone (VII) as a major product. Scale models indicate severe crowding at the benzylic centres in compounds (IV; Ar = 2,6-$Cl_2C_6H_3$) and (Vi.) A further example of the susceptibility to oxidation of the benzylic centre in compounds of this type is seen in the reaction of ethyl mandelimidate hydrochloride (IV; Ar = Ph) with an excess of phenylhydrazine under nitrogen, which afforded the hydrochloride not of the expected α-hydroxybenzylhydrazidine (VIII; Ar = R = Ph) but of the benzoylhydrazidine (IX; Ar = R = Ph). The corresponding reaction in which the reagents were left exposed to the atmosphere yielded the formazan (VI; Ar = R = Ph), the benzylic centre being apparently unaffected. Hydrazines are known to react either as reducing or oxidising agents, and Henle [6] has reported the formation of aldehyde hydrazones from imidates in the presence of hydrazines; however, these reactions were carried out under reductive conditions, *e.g.* in the presence of sodium amalgam. In the above oxidation reactions, the mechanistic pathways are far from clear.

Unsymmetrically disubstituted hydrazines reacted similarly with ethyl mandelimidate hydrochloride (IV; Ar = Ph) to yield *NN*-disubstituted mandelamidrazone salts [(V), HCl; R^1 and R^2 = Ph or Me].

Products, usually coloured, which have been isolated from the action of both aliphatic and aromatic aldehydes on amidrazones have been variously described [2,7-10] as Schiff's bases (X) and/or triazolines (XI), but spectroscopic evidence [8,9] presented to distinguish between these

[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] F. Henle, *Ber.*, 1902, **35**, 3039; 1905, **38**, 1362.
[7] J. A. Bladin, *Ber.*, 1889, **22**, 796; 1892, **25**, 183.
[8] B.-G. Baccar and F. Mathis, *Compt. rend.*, 1964, 6470.
[9] B.-G. Baccar, R. Mathis, A. Secches, J. Barrans, and F. Mathis, *J. Mol. Structure*, 1971, **7**, 369.
[10] N. N. Vereshchagina, G. S. Melkozerova, N. N. Frolova, A. V. Bedrin, and I. Y. A. Postovskii, *Khim-Farm. Zhur.*, 1973, **7**, 18 (*Chem. Abs.*, 1973, **79**, 92,107x).

structures is far from conclusive and at times even confusing. Only cyano-*N*-phenylformamidrazone (II; R = CN, R^1 = Ph) has been reported [7] to give a 1,2,4-triazole by direct interaction with an aldehyde, and that along with its dihydro-derivative (X or XI; R = CN); in all other cases the intermediate dihydro-compounds condensation of *N*-substituted mandelamidrazones (V) with ketones failed. In order to confirm the triazole structure (XII), physical methods were used (see Experimental sections) and alternative syntheses were sought. Scheme 1 illustrates the first of these, starting from **3**-benzoyl-1,5-diphenylformazan [11] (III; R = PhCO, R^1 =

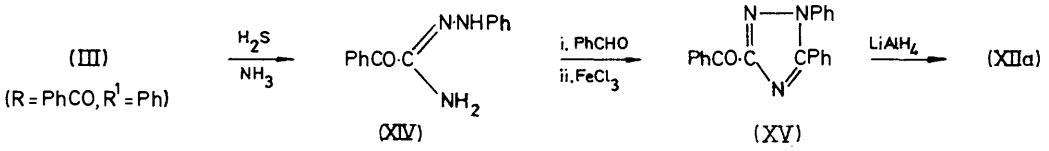


(V),HCl	X	Y	R^1	R^2
a;	H	H	H	Ph
b;	H	H	H	2 – MeC_6H_4
c;	H	H	H	3 – MeC_6H_4
d;	H	H	H	4 – MeC_6H_4
e;	H	H	H	4 – $NO_2C_6H_4$
f;	2 – MeO	H	H	Ph
g;	2 – Cl	H	H	Ph
h;	4 – Cl	H	H	Ph
i;	2 – Cl	6 – Cl	H	Ph
j;	H	H	Ph	Ph
k;	H	H	Me	Ph
l;	H	H	Me	Me

which were isolated required oxidation (*e.g.* with $FeCl_3$) for conversion into the corresponding triazoles. However, in this present work, when ethanolic solutions of *N*-arylmandelamidrazones (V; R^1 = H, R^2 = Ar) were refluxed with aliphatic or aromatic aldehydes, **1,3,5**-trisubstituted 1,2,4-triazoles (XII) were obtained directly in good yields. At no time was any intermediate isolated and all attempts to form Schiff's bases (XIII) from the Ph). *N*-Phenylphenylglyoxylamidrazone (XIV) gave the corresponding triazole (XV) with benzaldehyde only after oxidation of the reaction intermediate with $FeCl_3$. The final product (XIIa) of Scheme 1 was identical with that formed directly by the action of benzaldehyde on *N*-phenylmandelamidrazone.

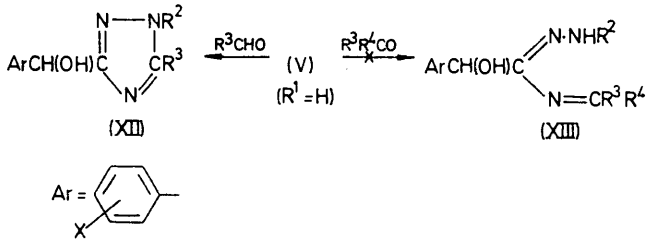
[11] E. Bamberger and H. Witter, *Ber.*, 1893, **26**, 2786; *J. prakt. Chem.*, 1902, **65**, 142.

In Scheme 2, trialkyl ortho esters (XVI; R^3 = H, Me, or Et) were treated with *N*-phenylmandelamidrazone bases (V; R^1 = H) to form the corresponding 1,3-disubstituted and 1,3,5-trisubstituted 1,2,4-triazoles (XVII; R^3 = H, Me, or Et, R^4 = H). Compound



SCHEME 1

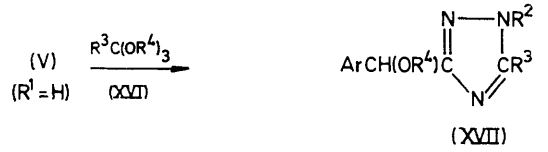
(XVIIc) formed in this way was identical with that from the reaction of the amidrazone (Va) and propionaldehyde. Surprisingly, however, when the hydrochlorides rather than the free bases of either *N*-phenylmandelamidrazone (Va) or its 2-methoxy-derivative (Vf) were treated with trimethyl or triethyl orthoformate under reflux, alkylation of the benzylic hydroxy-group took place along with ring closure, yielding triazoles of type (XVII; R^4 = alkyl). On the other hand, both 2-chloromandelamidrazone (Vg) and its hydrochloride reacted to give a non-alkylated product (XVII; R^3 = R^4 = H). Ortho esters are known to alkylate acidic hydroxy-groups such as those in enols or phenols, but normally undergo transesterification reactions with

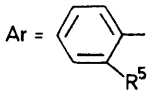


	X	R^2	R^3
a;	H	Ph	Ph
b;	H	4-MeC_6H_4	Ph
c;	H	Ph	4-MeC_6H_4
d;	H	Ph	2-HO·C_6H_4
e;	H	Ph	4-HO·C_6H_4
f;	H	Ph	4-MeO·C_6H_4
g;	H	Ph	4-HO-3-MeO-C_6H_3
h;	H	Ph	2,6-$Cl_2C_6H_3$
i;	H	Ph	Et
j;	H	Ph	Pr^n
k;	H	Ph	2-pyridyl
l;	H	Ph	2-furyl
m;	2-MeO	Ph	Et
n;	2-MeO	Ph	Pr^n
o;	Cl	Ph	Pr^n

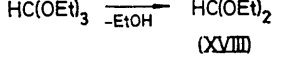
alcohols under mild conditions,[12] although exceptionally 3β-hydroxy-Δ^5-steroids have been shown to undergo alkylation on reaction with ortho esters in concentrated perchloric acid solutions.[13] Hence this alkylation reaction was unexpected in view of the mild conditions employed.

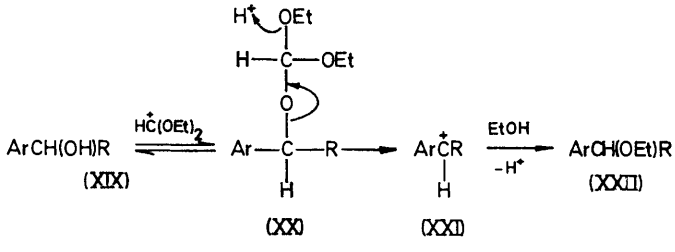
One possible pathway to the alkoxy-products (XVII; R^4 = alkyl) involves direct interaction of the benzylic hydroxy-group of the amidrazone or triazole with alcohol





	R^3	R^4	R^5
a;	H	H	H
b;	Me	H	H
c;	Et	H	H
d;	H	H	Cl
e;	Me	H	Cl
f;	H	Me	H
g;	H	Et	H
h;	H	Me	MeO
i;	H	Et	MeO





SCHEME 2

formed by breakdown of ortho ester in the presence of acid. However, although amidrazone salts are formed in alcohol–acid solution [(I) ⟶ (II)], no trace of *O*-alkylmandelamidrazones has been observed. Similarly, refluxing the triazole (XVIIa) in ethanol–acid yielded only a small amount of alkylated product (XVIIg). By contrast, when the triazole (XVIIa) was treated with triethyl orthoformate in the presence of acid

[12] R. H. De Wolfe, 'Carboxylic Ortho Acid Derivatives,' Academic Press, New York, 1970.

[13] J. P. Dusza, J. P. Joseph, and S. Bernstein, *Steroids*, 1966, **8**, 495.

for a similar time, an almost quantitative yield of the α-ethoxybenzyltriazole (XVIIg) was obtained. Hence the mechanistic route for the alkylation process could involve the formation from the ortho ester,[12] under acidic conditions, of a dialkoxycarbocation (XVIII), which could then react with a benzylic hydroxy-group to give a complex ortho ester (XX). This could then undergo nucleophilic substitution either by direct attack of alcohol at the benzylic carbon atom or *via* a carbocation (XXI) to yield the product (XXII). Support for this scheme can be found in the isolation of a product of type (XX; Ar = Ph, R = $CO{\cdot}NH_2$) from the reaction of triethyl orthoformate and mandelamide (XIX; Ar = Ph, R = $CO{\cdot}NH_2$) and a corresponding product from trimethyl orthoformate. However, compound (XX; Ar = Ph, R = $CO{\cdot}NH_2$) breaks down in protic solvents, re-forming mandelamide, and does not undergo the alkylation reactions exhibited by the triazoles [(XX) ⟶ (XXII); R = triazolyl]. Thus the failure of the 2-chloromandelamidrazone system to undergo alkylation during or subsequent to triazole formation may be accounted for either (*a*) by failure of the mixed ortho ester (XX; Ar = 2-ClC_6H_4) to be formed for steric reasons, or (*b*) by formation of the ortho ester (XX) which then breaks down in protic conditions by a route akin to that followed by the mandelamide derivative (XX; Ar = Ph, R = $CO{\cdot}NH_2$). Treatment of phenylacetamide with triethyl orthoformate yields the compound $HC(NH{\cdot}CO{\cdot}CH_2Ph)_3$, in keeping with the structure now assigned to the products of the reaction of ortho esters with related amides.[2,14]

EXPERIMENTAL

Details of i.r. and n.m.r. spectra, mass spectral molecular weights, and elemental analyses, as indicated by asterisks, are contained in Supplementary Publication No. SUP 21541 (10 pp., 1 microfiche),† which also contains Tables 1—4.

Amidrazones (V).—The substituted hydrazine ($R^1R^2N{\cdot}NH_2$) was added to the imidate hydrochloride [15-18] (1 mol. equiv.) in ethanol. After 24—28 h at room temperature the red mixture was filtered, to remove ammonium chloride and any formazan. Concentrated hydrochloric acid (100 ml mol^{-1}) was added and ethanol removed under reduced pressure. Addition of ether precipitated the crude *amidrazone* (V) *hydrochloride*, which was purified by dissolution in ethanol, filtration to remove ammonium chloride, and reprecipitation with ether. The *amidrazone* was obtained by basification of the aqueous solution of its hydrochloride at 0 °C with 2M-sodium hydroxide, saturated aqueous sodium carbonate, or ammonia (*d* 0.88) (see Tables 1 and 2).*

Exceptionally, 4-nitrophenylhydrazine reacted with ethyl mandelimidate hydrochloride to give the orange *formazan* * (VI; R = 4-$O_2NC_6H_4$, Ar = Ph), m.p. 155—156° (analysis),* as well as the *amidrazone* (Ve) *hydrochloride** On the other hand, phenylhydrazine and ethyl 2,6-dichloromandelimidate hydrochloride yielded 2,6-*dichlorophenylglyoxal phenylhydrazone*,* m.p. 217—218°, $\lambda_{max.}$,* M^+,* analysis.*

Action of Phenylhydrazine on Ethyl Mandelimidate Hydrochloride under Nitrogen.—The imidate hydrochloride (IV; Ar = Ph) (4.3 g) was added to phenylhydrazine (4.3 g) dissolved in ethanol (20 ml) and the solution was kept under nitrogen at room temperature for several weeks. Concentrated hydrochloric acid (5 ml) was added, and the solution was then exposed to the atmosphere. Ammonium chloride was filtered off and the filtrate treated with dry ether to yield a semi-solid which on recrystallisation (hot filtration) yielded N^2,N^4-*diphenylphenylglyoxylohydrazidine hydrochloride* (IX; Ar = R = Ph), which yellowed at 120°, softened at 130—150° and finally decomposed at 225° (Found: C, 64.0; H, 5.8; Cl, 8.3. $C_{22}H_{25}ClN_4O_2$ requires C, 64.0; H, 6.1; Cl, 8.6%).

1,3,5-*Trisubstituted* 1,2,4-*Triazoles* (XII) *from Aldehydes.*—An amidrazone (V) was dissolved in ethanol and the aldehyde was added (molar ratios 1 : 1 or 1 : 3). In some cases catalytic amounts of hydrochloric acid were added. The solutions were refluxed for 2—12 h. Usually oils formed from which *crystals* separated after a few days; these were washed with ether and recrystallised (see Table 3).*

3-*Benzoyl*-1,5-*diphenylformazan* (III; R = PhCO, R^1 = Ph) *and* N-*Phenylphenylglyoxylamidrazone* (XIV).—These were prepared from ethyl benzoylacetate and benzenediazonium chloride by the method of Bamberger and Witter; [11] m.p.s agreed with literature values.

3-*Benzoyl*-1,5-*diphenyl*-1,2,4-*triazole* (XV).—*N*-Phenylphenylglyoxylamidrazone (XIV) (2.4 g) and benzaldehyde (1.0 g) were dissolved in ethanol (10 ml) and concentrated hydrochloric acid (2 drops) was added. The mixture was heated to boiling and the dark red needles (m.p. 170—172°) which formed immediately were filtered off after cooling. Alcoholic iron(III) chloride was added to a suspension of the product in ethanol. After heating the mixture for a short time, water was added to the cooled solution to precipitate 3-*benzoyl*-1,5-*diphenyl*-1,2,4-*triazole* (XV) (1.7 g), m.p. 158—159° (from ethanol) (Found: C, 77.1; H, 4.7; N, 13.1. $C_{21}H_{15}N_3O$ requires C, 77.5; H, 4.6; N, 12.9%).

Reduction of 3-*Benzoyl*-1,5-*diphenyl*-1,2,4-*triazole* (XV).—Lithium aluminium hydride (0.3 g) was suspended in ether (150 ml) and the triazole (XV) (1.3 g) was added *via* a Soxhlet thimble (*ca.* 6 h). Addition of water, then sulphuric acid (2.5M; 50 ml), caused precipitation of a solid which was collected. The ether and acid layers were separated and the acid layer was further extracted with ether. Removal of ether left a solid which was combined with the solid already collected. Recrystallisation from ethanol gave starting material and 3-(α-*hydroxybenzyl*)-1,5-*diphenyl*-1,2,4-*triazole* (XIIa),* m.p. 148—149°, identical (mixed m.p.) with the product of condensation of benzaldehyde with *N*-phenylmandelamidrazone. Another high melting product was obtained but was not further investigated.

3-(α-*Hydroxybenzyl*)-1-*phenyl*-1,2,4-*triazoles* (XVII; R^3 = H or alkyl, R^4 = H) *from Ortho Esters.*—In a representative preparation, *N*-phenylmandelamidrazone (Va) (1.7 g) was heated under reflux at 100 °C for 4 h with triethyl orthoacetate (5.7 g) and ethanol (10 ml). The crude yellow solid

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[14] H. Bredereck, R. Gompper, F. Effenberger, H. Keck, and H. Heise, *Chem. Ber.*, 1960, **93**, 1398.

[15] F. E. King, T. J. King, and I. H. M. Muir, *J. Chem. Soc.*, 1946, 5.

[16] N. W. Bristow, *J. Chem. Soc.*, 1957, 513.

[17] D. G. Neilson and D. A. V. Peters, *J. Chem. Soc.*, 1963, 4455.

[18] D. G. Neilson and D. A. V. Peters, *J. Chem. Soc.*, 1962, 1309.

which resulted yielded, after crystallisation from ethanol–petroleum (b.p. 60—80°), the white *triazole* (XVIIb) * (1.0 g), m.p. 101—103°.

Compounds (XVIIa, c, d, and e) were prepared similarly from the appropriate reagents (see Table 4).*

3-(α-*Alkoxybenzyl*)-1-*phenyl*-1,2,4-*triazoles* (XVII; R^3 = H, R^4 = alkyl).—*N*-Phenyl-*o*-methoxymandelamidrazone (Vf) hydrochloride (2.0 g) and trimethyl orthoformate (10.4 g g) were refluxed together at 90 °C for 48 h. Evaporation of the solution produced an oil which solidified. The solid was filtered off, washed with a little ether, and recrystallised (charcoal) from ethanol–petroleum (b.p. 60—80°) giving the *triazole* (XVIIh) (0.8 g), m.p. 97—99°. *Compounds* (XVIIf, g, and i) were prepared similarly from related reagents (see Table 4).* Similar treatment of *N*-phenyl-*o*-chloromandelamidrazone (Vg) hydrochloride yielded, not the alkylated product, but the *unalkylated triazole* (XVIId).

Interaction of Mandelamide and Triethyl Orthoformate.—Mandelamide (3.0 g) was heated for 20 h at 140—145 °C with triethyl orthoformate (20 ml). The excess of orthoformate was removed *in vacuo* and the resultant solid recrystallised from cyclohexane containing some triethyl orthoformate to give O-*diethoxymethylmandelamide* (XX; R = CO·NH_2, Ar = Ph), m.p. 92—93°, in 60% yield (Found: C, 61.4; H, 7.2; N, 5.7. $C_{13}H_{19}NO_4$ requires C, 61.6; H, 7.6; N, 5.5%). Treatment of the product with protic solvents caused quantitative regeneration of mandelamide. The n.m.r. spectrum (60 MHz) showed δ($CDCl_3$) 7.4 (s, 5 aromatic H), 6.8br (2 H, s, NH_2), 5.1—5.2 (2 H, two s, methines), 3.3—3.8 (4 H, q, 2 × CH_2), and 0.9—1.3 (6 H, t, 2 × Me). The triplet and quartet showed fine splitting due to the presence of the benzylic asymmetric centre. A spectrum of an impure sample (containing mandelamide) run in $(CD_3)_2SO$ showed clearly two singlets at δ 4.8 and 5.1 due to the two methine protons in compound (XX; Ar = Ph, R = $CONH_2$) and, in addition, two doublets centred around δ 4.6 and 5.75 due to H,OH coupling in the mandelamide impurity. A spectrum of pure mandelamide in $(CD_3)_2SO$ showed these doublets, the lower field one vanishing and the higher field one collapsing to a singlet on addition of D_2O. This is taken as good evidence for alkylation at oxygen, rather than at nitrogen.

Interaction of Mandelamide and Trimethyl Orthoformate.—Mandelamide (2 g) was heated for 22 h under reflux with trimethyl orthoformate. Solid (2.1 g) which precipitated on cooling was recrystallised from trimethyl orthoformate and cyclohexane to give O-*dimethoxymethylmandelamide*, m.p. 92—94° (Found: C, 59.1; H, 6.6; N, 6.2. $C_{11}H_{15}NO_4$ requires C, 58.7; H, 6.7; N, 6.2%).

Reaction of 3-(α-*Hydroxybenzyl*)-1-*phenyl*-1,2,4-*triazole* (XVIIa) *with Triethyl Orthoformate under Acidic Conditions.*—Triethyl orthoformate (7.4 g) was added to the triazole (XVIIa) (1.25 g) and concentrated hydrochloric acid (0.5 g). The solution was heated (*ca.* 100 °C) for 24 h and the alkoxybenzyltriazole (XVIIg) (1.3 g), identical with that prepared from the amidrazone hydrochloride and triethyl orthoformate, was obtained.

Reaction of 3-(α-*Hydroxybenzyl*)-1-*phenyl*-1,2,4-*triazole with Ethanol under Acidic Conditions.*—The triazole (XVIIa) (1.25 g) in ethanol (20 ml) containing hydrochloric acid (0.5 g) was refluxed for 24 h. T.l.c. (ether) showed a minor spot corresponding to the alkylated triazole (XVIIg), the major spot running with starting material (XIIa). Removal of the solvent yielded a mixture of starting material (*ca.* 83%) and alkylated triazole (*ca.* 17%).

NN'N''-*Methylidynetris*(*phenylacetamide*).— Phenylacetamide (2.7 g) and trimethyl orthoformate (7.4 g) were refluxed for 12 h to yield solid which was recrystallised from *NN*-dimethylformamide to give the *product* (0.75 g), m.p. 229—231° (Found: C, 72.0; H, 6.1; N, 10.2. $C_{25}H_{25}N_3O_3$ requires C, 72.3; H, 6.0; N, 10.1%).

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