The Preparation of 3-Benzyl-6-(α-methylbenzyl)- and 3,6-Bis(α-methylbenzyl)-*s*-tetrazines by Alkylation of 3,6-Dibenzyl-*s*-tetrazine and a Study of their Rearrangements to Imidazo[1,2-*b*]-*s*-tetrazines in Alkali

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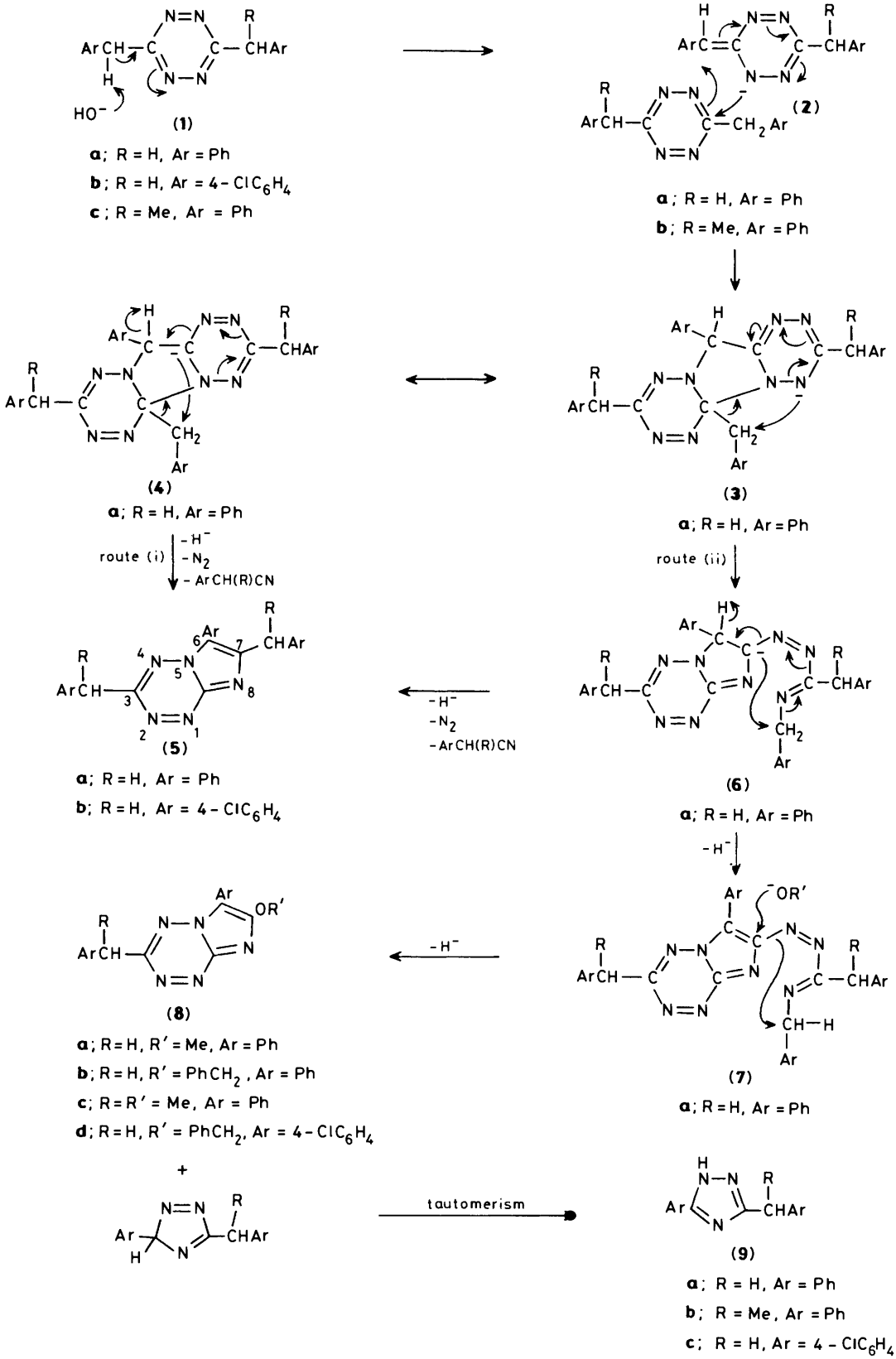
3,6-Dibenzyl-*s*-tetrazine (**1a**) can be alkylated with methyl iodide after treatment with LDA in tetrahydrofuran to give a mixture of 3-benzyl-6-(α-methylbenzyl)- and 3,6-bis(α-methylbenzyl)-*s*-tetrazines (**1c**) and (**18**) separable by chromatography. 3,6-Dibenzyl-*s*-tetrazine on treatment with potassium hydroxide in benzyl alcohol yields, among other products, 3-benzyl-7-benzyloxy- and 3,7-dibenzyl-6-phenylimidazo[1,2-*b*]-*s*-tetrazines (**8b**) and (**5a**), the 7-benzyloxy group being generated from the solvent but the 7-benzyl group having the parent tetrazine (**1a**) as its precursor. Similar treatment of 3-benzyl-6-(α-methylbenzyl)-*s*-tetrazine (**1c**) but with methanol as solvent yields the related 7-methoxy-3-(α-methylbenzyl)-6-phenylimidazo[1,2-*b*]-*s*-tetrazine (**8c**) along with a novel compound assigned the structure of a substituted 1,2,4-triazolo[1′,5′:4,5]pyrazino[1,2-*b*]-*s*-tetrazine (**15**). 3,6-Bis(α-methylbenzyl)-*s*-tetrazine (**18**) is stable to alkali except when prolonged reaction times are employed when it breaks down to acetophenone, by way of an alkylidene hydrazide intermediate (**19**). Mechanisms are proposed for each of these reactions.

In our earlier work,[1] attempts were made to alkylate the benzyl group of 3,6-dibenzyl-*s*-tetrazine (**1a**) with methyl iodide under alkaline conditions. However, when for example potassium hydroxide in methanol was used, no trace of alkylated tetrazine was found but the identified products included 3-benzyl-7-methoxy-6-phenylimidazo[1,2-*b*]-*s*-tetrazine (**8a**), 3-benzyl-5-phenyl-1,2,4-triazole (**9a**) and 2,5-dibenzyl-1,3,4-oxadiazole (**17a**) among others.[1,2] A dark red product obtained in very small quantities remained unidentified. When the reaction was carried out under different conditions, *e.g.*, potassium t-butoxide in t-butyl alcohol or even potassium hydroxide in ethanol, the reaction took completely different courses and the multiplicity of products precluded their separation and identification.

Rearrangement of 3,6-*Dibenzyl*-s-*tetrazine in Benzyl Alcohol.*—In the present work rearrangement of 3,6-dibenzyl-*s*-tetrazine (**1a**) induced by potassium hydroxide in benzyl alcohol has lead to the isolation of higher proportions of the previously unidentified red product along with the expected, but novel, 3-benzyl-7-benzyloxy-6-phenylimidazo[1,2-*b*]-*s*-tetrazine (**8b**) and the triazole (**9a**). N.m.r. comparisons of the imidazo-*s*-tetrazines (**8a**) and (**8b**) with the spectrum of the red compound pointed to the structure 3,7-dibenzyl-6-phenylimidazo[1,2-*b*]-*s*-tetrazine (**5a**). In order to confirm that the 7-benzyl group of compound (**5a**) arose from its precursor (**1a**) and not from the benzyl alcohol as did the 7-benzyloxy group of the related compound (**8b**), 3,6-bis(4-chlorobenzyl)-*s*-tetrazine (**1b**) was treated with alkali in benzyl alcohol. The rearranged product was identified as 3,7-bis(4-chlorobenzyl)-6-(4-chlorophenyl)-imidazo[1,2-*b*]-*s*-tetrazine (**5b**) showing clearly that the 7-benzyl substituent of compound (**5a**) also comes from the parent *s*-tetrazine (**1a**) and not from the solvent. A possible mechanism for the formation of compound (**5a**) is given in Scheme 1 and is based on our earlier work.[1,2] The anion (**2a**) formed by loss of a benzylic proton from the tetrazine attacks a second molecule of tetrazine (**1a**) at ring carbon. The two, illustrated, canonical forms of the tricyclic anion (**4a**) and (**3a**) thus formed could then undergo 1,3-benzyl shifts—route (i) would give the observed 7-benzylimidazo-tetrazine (**5a**) directly by elimination of nitrogen, phenylacetonitrile and hydride ion (tetrazines are known to be acceptors of hydride ion[2,3]). Route (ii) would lead to a further bicyclic intermediate (**6a**) with a nitrogenous sidechain which could undergo a 1,5-benzyl shift and produce the red product (**5a**) by elimination of the same species as in route (i). However, only the latter route (ii) explains the formation of the yellow 7-alkoxyimidazo-tetrazine (**8b**) along with the triazole (**9a**). It is possible that the two routes (i) and (ii) are competitive, with route (i) playing a greater role when benzyl alcohol replaces methanol as solvent. However as the eliminated species are the same for each reaction pathway, their identification does not distinguish between the mechanisms proposed.

Alkylation Reactions.—Following the failure to alkylate 3,6-dibenzyl-*s*-tetrazine in alkoxide–alcohol solutions, attention was turned to the use of LDA in dry tetrahydrofuran (despite the fact that it had already been noted that 3,6-diaryl-*s*-tetrazines rearranged under such conditions[4]). The alkylation, with methyl iodide, proceeded successfully but always gave a mixture of products *viz.* a preponderance of 3,6-bis(α-methylbenzyl)-*s*-tetrazine (**18**) over 3-benzyl-6-(α-methylbenzyl)-*s*-tetrazine (**1c**) when a 2:1 molar ratio of LDA to parent tetrazine (**1a**) was used. When the LDA:tetrazine (**1a**) molar ratio was reduced to 1.5:1, the mono-alkylated product (**1c**) predominated but quantities of unchanged starting material were now recovered and this recovery increases at lower LDA ratios. There appeared to be no evidence of any α,α-dimethylbenzyltetrazine (**10**). 3,6-Bis(α-methylbenzyl)-*s*-tetrazine (**18**) synthesized *via* methyl hydratropimidate hydrochloride† was identical with that obtained by alkylation. Both tetrazines (**18**) and (**1c**) were liquids which decomposed on attempted distillation and were purified by chromatography—this is in keeping with the fact that many of the lower 3,6-dialkyl-*s*-tetrazines are liquids although their 3,6-diaryl counterparts are well defined solids.[5] Tetrazine (**18**) can exist as diastereoisomers but it is not known with certainty whether our derived product is one form or a mixture of forms although t.l.c. examination revealed a single spot and no possible differences due to diastereoisomerism were observed in the n.m.r. spectra of the different samples.

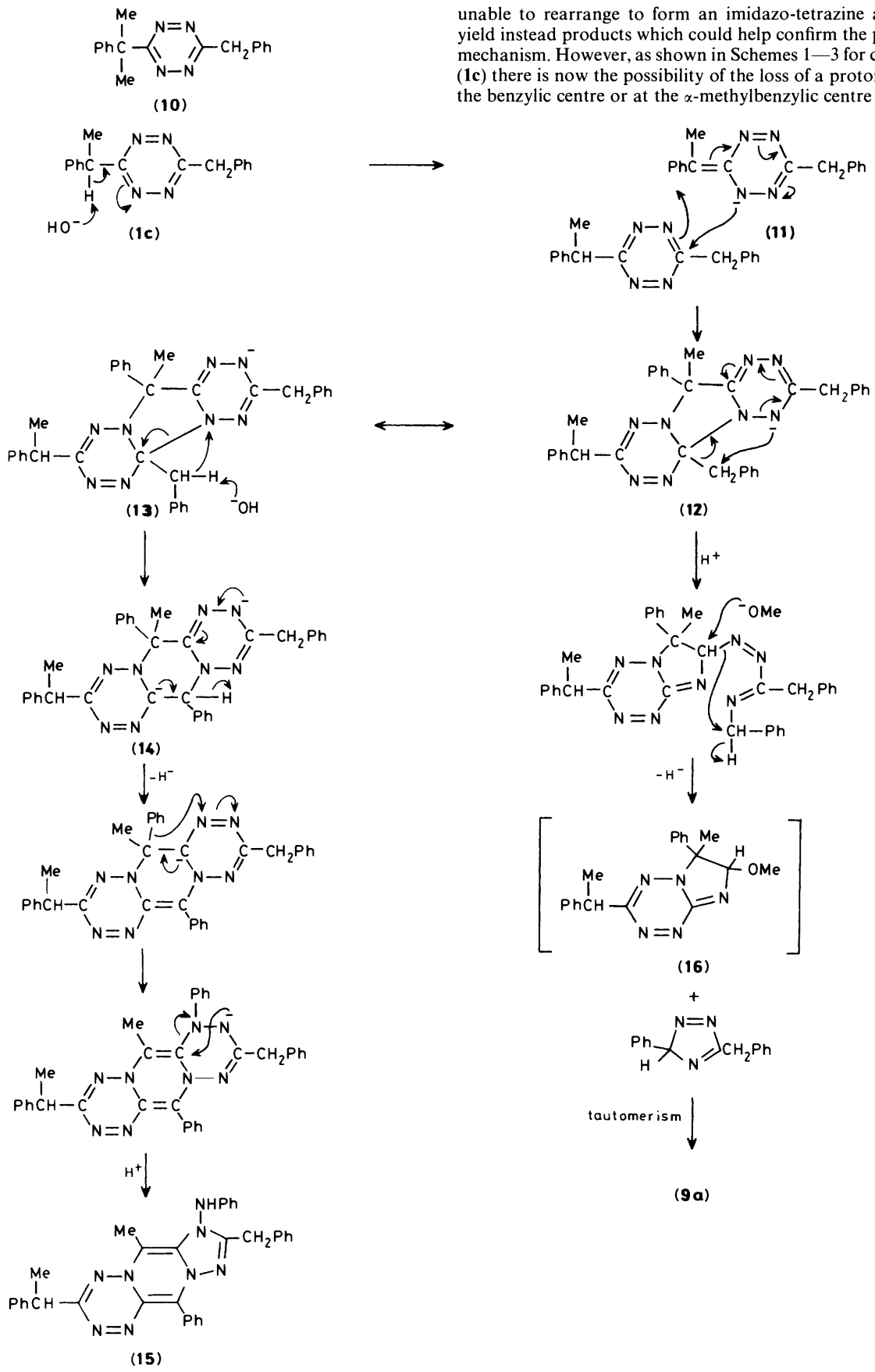
† Hydratropimidate ≡ 2-phenylpropanimidate.



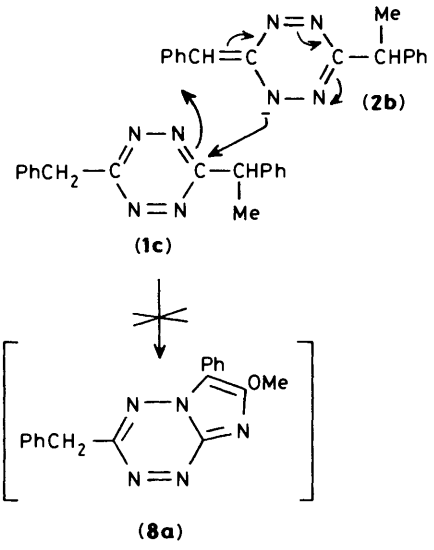
Scheme 1.

Base Induced Rearrangements.—(a) 3-*Benzyl*-6-(α-*methylbenzyl*)-s-*tetrazine* (**1c**). As the mechanism proposed for the base induced rearrangement of 3,6-dibenzyl-*s*-tetrazine involves hydride ion transfer *e.g.*, structure (**6a**) ⟶ (**7a**), it was felt that 3-benzyl-6-(α-methylbenzyl)-*s*-tetrazine (**1c**) might react under similar conditions but, because of the tertiary benzylic centre, be

unable to rearrange to form an imidazo-tetrazine and hence yield instead products which could help confirm the postulated mechanism. However, as shown in Schemes 1—3 for compound (**1c**) there is now the possibility of the loss of a proton at either the benzylic centre or at the α-methylbenzylic centre (although

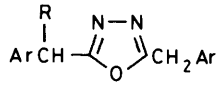


Scheme 2.



Scheme 3.

the former is the more likely on electronic grounds) and, in addition, attack by each of these anions (**2b**) and (**11**) on a tetrazine ring carbon adjacent to either a benzylic or α-methylbenzylic group. Examination of the products of the reaction of tetrazine (**1c**) with potassium hydroxide in methanol appeared to rule out attack of either of these anions on the second tetrazine molecule at the carbon adjacent to the α-methylbenzyl group (Scheme 3)—probably because of steric hindrance. Attack of the benzylic anion (**2b**) at the unsubstituted benzylic end of the tetrazine (**1c**) would be expected to lead to a reaction similar to that discussed for 3,6-dibenzyl-*s*-tetrazine[1,2] (**1a**) (Scheme 1) but resulting in the formation of 7-methoxy-3-(α-methylbenzyl)-6-phenylimidazo[1,2-*b*]-*s*-tetrazine (**8c**) and 3-(α-methylbenzyl)-5-phenyl-1,2,4-triazole (**9b**) and indeed these two products were characterised. 2-Benzyl-5-(α-methylbenzyl)-1,3,4-oxadiazole (**17b**) was also isolated and this arises by a mechanism discussed in earlier papers.[2,3]



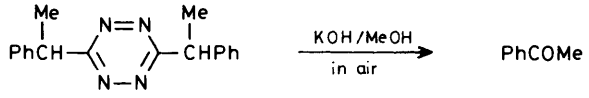
(**17**)

a; R = H, Ar = Ph

b; R = Me, Ar = Ph

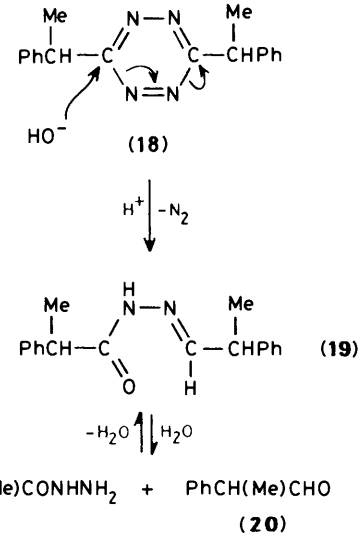
Attack on tetrazine (**1c**) by the other anion (**11**) formed at the α-methylbenzyl centre results in the formation of an intermediate (**12**) ⟷ (**13**) which, unlike intermediate (**3a**) ⟷ (**4a**), does not have the ability to lose a hydride ion as is required for the formation of an imidazo-tetrazine (**8a**). It is feasible that intermediate (**12**) could rearrange to give a 6-methyl-6,7-dihydroimidazo-tetrazine (**16**) along with 3-benzyl-5-phenyl-1,2,4-triazole (**9a**). However, no trace of this dihydroimidazo-tetrazine (**16**) was found, although the triazole (**9a**) was isolated in yields which suggest this pathway was operative. Consideration of the other canonical form (**13**) of anion (**12**) ⟷ (**13**) suggests that a ring expansion reaction can take place by loss of a proton and incorporation of the benzylic entity into the central imidazo ring. By loss of a hydride ion the newly formed intermediate (**14**) would then give a novel *s*-tetrazino[1′,6′:4,5]pyrazino[1,2-*b*]-*s*-tetrazine structure (such hydride transfers being known to take place in the presence of tetrazines[2,3,4]) which would rearrange to the proposed compound, 7-anilino-8-benzyl-6-methyl-3-(α-methylbenzyl)-11-phenyl-1,2,4-triazolo[1′,5′:4,5]pyrazino [1,2-*b*]-*s*-tetrazine (**15**). Structure (**15**) is assigned on the basis of chemical analysis and mass spectra data which gave a satisfactory molecular weight, cyanotropylium as the base peak and a peak at (*M* − 28) due to loss of nitrogen. The n.m.r. chemical shift of the proton on nitrogen and the shifts and pattern of aromatic protons on one of the phenyl groups related more closely to a heterocyclic *N*-anilino substituent rather than to a dihydrotetrazine structure when compared with model compounds (Table), hence the structure assignments (**15**).

(b) 3,6-*Bis*(α-*methylbenzyl*)-*s*-*tetrazine* (**18**). This tetrazine (**18**) failed to react with potassium hydroxide in methanol under the normal conditions used for the parent tetrazine (**1a**). [This is in keeping with the failure to see any products derived by attack by anion at the ring carbon attached to the α-methylbenzyl centre of 3-benzyl-6-(α-methylbenzyl)-*s*-tetrazine (**1c**), *cf.* (a) above]. When the reaction mixture was warmed complete decomposition took place. However when the reaction time was extended to one week at room temperature, acetophenone was identified as the principal product. If the reaction was carried



(**18**)

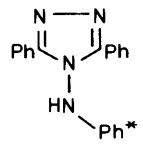
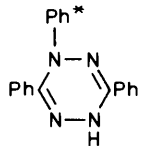
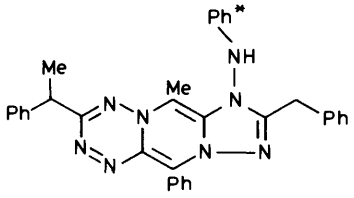
out under nitrogen no acetophenone was identified although decomposition of the tetrazine (**18**) again took place. This suggests that the hydratrophic centre is undergoing air oxidation—a well known property of benzylic centres.[6] The tetrazine (**18**) in alkali could yield either hydratroponitrile or the alkylidene hydrazide (**19**)—such hydrazides having been characterised in earlier work studying the action of alkali on *s*-tetrazines and especially in the case of 3,6-diaryl-*s*-tetrazines.[1,7] Earlier work[3] has also shown that an alkylidene hydrazide (**19**) is in equilibrium with its constituent aldehyde (Scheme 4)—in



Scheme 4.

this case hydratropaldehyde. Hydratroponitrile was shown to be stable in air under the conditions of our experiment whereas hydratropaldehyde was converted into acetophenone by oxygen in alkaline conditions although stable under nitrogen.

Table.

Compound	δ (p.p.m.) ($CDCl_3$) NH	Ph*	Other aromatic signals
	9.6 (1 H, s)[a]	6.4—7.1 (5 H, m)[a]	7.4—7.9 (10 H, m)[a]
	7.8 (1 H, s)[a]	7.1 (5 H, s)[a]	7.2—7.7 (10 H, m)[a]
	9.3 (1 H, s)	6.4—6.9 (5 H, m)	7.1—7.5 (15 H, m)

[a] Ref. 16.

In a separate experiment the hydrazide (**19**), prepared by an independent route, was shown to generate acetophenone under the reaction conditions employed with the tetrazine (**18**). Hence the tetrazine (**18**) possessing only a methine hydrogen at the benzylic centres reacts in a manner more akin to the 3,6-diaryl-*s*-tetrazines[1,7] generating the hydrazide (**19**) which, because of the equilibrium existing between it and its constituent aldehyde (**19**) $\rightleftharpoons$ (**20**) allows air to oxidize the resultant aldehyde to acetophenone, the isolated product.

Experimental

M.p.s were determined on an Electrothermal Melting Point Apparatus and are uncorrected. ^{1}H N.m.r. spectra were run on a Varian EM 360 (60 MHz) instrument, using TMS as an internal standard. Coupling constants for CH_3CH of α-methylbenzyl groups were 8 Hz in all cases.

Preparation of Imidate Salts.—Standard Pinner syntheses[8,9] were used to prepare ethyl phenylacetimidate hydrochloride, m.p. 100—102 °C (decomp.) [lit.,[10] 99—100 °C (decomp.)] and ethyl 4-chlorophenylacetimidate hydrochloride, m.p. 180—183 °C (lit.,[1] 180—183 °C). Methyl hydratropimidate hydrochloride was prepared by a similar method[11] and had m.p. 97—98 °C (decomp.).

Preparation of s-*Tetrazines.*—(a) 3,6-*Dibenzyl*-s-*tetrazine* (**1a**), m.p. 74—75 °C (lit.,[12] 74 °C) and 3,6-bis(4-chlorobenzyl)-*s*-tetrazine (**1b**), m.p. 135—136 °C (lit.,[1] 135—137 °C), were prepared according to literature methods.[1]

(b) 3,6-*Bis*(α-*methylbenzyl*)-s-*tetrazine* (**18**) was prepared as follows. Methyl hydratropimidate hydrochloride (50 g) was added in portions, with stirring, to a mixture of hydrazine hydrate (99%; 80 ml) and ethanol (130 ml) at 0 °C. The mixture was stirred for a further 2 h at 0 °C and finally for 2 h at room temperature. Water (500 ml) was then added and the mixture extracted with dichloromethane. Drying ($MgSO_4$) and evaporation of the solvent left a red oil, to which sodium nitrite (8 g) and water (50 ml) were added. This mixture was stirred vigorously at 0 °C while glacial acetic acid (50 ml) was added dropwise. Stirring was continued for 2 h at 0 °C, and then sodium nitrite (2 g) and glacial acetic acid (10 ml) were added and the mixture stirred for a further 2 h at room temperature. Finally, water (500 ml) was added and the mixture was extracted with dichloromethane. After being dried ($MgSO_4$), the solvent was evaporated and the crude product was purified first by chromatography [silica; eluted with diethyl ether–light petroleum (b.p. 40—60 °C), (1:9)] and then by distilling off a colourless impurity (b.p. 55 °C/0.1 Torr) (bath temperature 130 °C) under reduced pressure. The *tetrazine* (**18**) (9.8 g, 12.6%) thus obtained was a red oil which decomposed on attempted distillation; $\delta_H(CDCl_3)$ 1.9 (6 H, d, 2 Me), 4.75 (2 H, q, 2 × CH), and 7.2—7.5 (10 H, m, ArH); $\lambda_{max.}$ 316 (log ε 3.91) and 545 nm (log ε 3.77); $\nu_{max.}$ (liquid film) 1 490 cm^{-1} (C=N) (Found: M^+, 290.153147. $C_{18}H_{18}N_4$ requires M, 290.15313). Tetrazine (**18**) gave a one spot t.l.c. [diethyl ether–light petroleum (b.p. 40—60 °C) (1:10) or toluene–ethanol (100:1)].

(c) *Methylation of* 3,6-*Dibenzyl*-s-*tetrazine* (**1a**). Lithium di-isopropylamide (LDA) was prepared by slowly adding butyl lithium (1.6M; 2.6 ml) to a solution of di-isopropylamine (0.56 ml) in dry THF (10 ml) with stirring at −10 °C under dry nitrogen.

(I) A solution of the tetrazine (**1a**) (0.525 g; 0.002 mol) in dry THF (5 ml) was added dropwise with stirring to the solution of LDA (0.004 mol) prepared as above, at −70 °C and the mixture stirred for 10 min at this temperature. A solution of methyl iodide (0.5 ml) in dry THF (3 ml) was added dropwise with stirring, and stirring was continued for 10 min. The reaction mixture was then poured into dilute hydrochloric acid (1M; 100 ml) and extracted with ethyl acetate. After being dried ($MgSO_4$), the solvent was evaporated, and the products were separated by chromatography [silica; eluted with diethyl ether–light petroleum (b.p. 40—60 °C), (1:9)] yielding: (i) 3,6-*bis*(α-*methylbenzyl*)-s-*tetrazine* (**18**) (88 mg, 15.2%), a red oil; identical with

that obtained from methyl hydratropimidate hydrochloride, see (*b*) above.

(ii) 3-*Benzyl*-6-(α-*methylbenzyl*)-s-*tetrazine* (**1c**) (37 mg, 6.7%) a red oil which decomposed on attempted distillation; $\delta_H(CDCl_3)$ 1.9 (3 H, d, Me), 4.5 (2 H, s, CH_2), 4.7 (1 H, q, CH), and 7.2—7.5 (10 H, m, ArH); $\lambda_{max.}$ 316 (log ε 4.03), and 545 nm (log ε 3.83); $\nu_{max.}$ (liquid film) 1 490 cm^{-1}, (C=N) (Found: M^+, 276.137 497. $C_{17}H_{16}N_4$ requires *M*, 276.137 48). Compound (**1c**) gave a single spot t.l.c. [diethyl ether–light petroleum (b.p. 40—60 °C), (1:10) or toluene–ethanol (100:1)].

(II) When experiment (I) was repeated using less LDA (0.003 mol), but otherwise unaltered, the products obtained were: (i) tetrazine (**18**) (27 mg, 4.6%); (ii) tetrazine (**1c**) (106 mg, 19.2%); and (iii) recovered 3,6-dibenzyl-*s*-tetrazine (**1a**) (66 mg, 12.6%).

Action of Potassium Hydroxide in Benzyl Alcohol on 3,6-*Dibenzyl*-s-*tetrazine* (**1a**).—A solution of potassium hydroxide (0.15 g) in benzyl alcohol (5 ml) was added dropwise with stirring at room temperature to a mixture of the tetrazine (**1a**) (0.5 g) and benzyl alcohol (10 ml). Stirring was continued for 1 h and the mixture left sealed overnight before being poured into water (400 ml) and extracted with chloroform. The solution was dried ($MgSO_4$), the chloroform was removed under reduced pressure at 40 °C, and most of the benzyl alcohol was removed by distillation at 65 °C/0.4 Torr. The residue was then separated by chromatography [ether–light petroleum (b.p. 40—60 °C), (1:1)] and yielded: (i) 3,7-*dibenzyl*-6-*phenylimidazo*[1,2-b]-s-*tetrazine* (**5a**) (54 mg, 15.0%) which had m.p. 130—131 °C (from ethanol) (Found: M^+, 377.155 709. $C_{24}H_{19}N_5$ requires *M*, 377.164 02); δ_H ([$^2H_6$]acetone) 4.35 (2 H, s, CH_2), 4.4 (2 H, s, CH_2), and 7.25—8.4 (15 H, m, Ar); $\nu_{max.}$(Nujol) 1 510 cm^{-1}, (C=N). Compound (**5a**) exhibited a single spot t.l.c. [diethyl ether–light petroleum (1:10) or toluene–ethanol (100:1)].

(ii) 3-*Benzyl*-7-*benzyloxy*-6-*phenylimidazo*[1,2-b]-s-*tetrazine* (**8b**) (17 mg, 4.5%) which had m.p. 149—151 °C [from light petroleum (b.p. 80—100 °C)] (Found: M^+, 393.160 010. $C_{24}N_{19}N_5O$ requires *M*, 393.158 93); $\delta_H(CDCl_3)$ 4.4 (2 H, s, CH_2), 5.75 (2 H, s, OCH_2), 7.2—8.4 (15 H, m, ArH); $\nu_{max.}$(Nujol) 1 570 cm^{-1} (C=N). Compound (**8b**) exhibited a single spot t.l.c. [diethyl ether–light petroleum (b.p. 40—60 °C) (1:5) or toluene–ethanol (100:1)];

(iii) 3-Benzyl-5-phenyl-1,2,4-triazole (**9a**) (50 mg, 11.2%), identical with an authentic sample.[2]

Action of Potassium Hydroxide in Benzyl Alcohol on 3,6-*Bis*-(4-*chlorobenzyl*)-s-*tetrazine* (**1b**).—Following the method described in the preceding experiment, the tetrazine (**1b**) (0.5 g) yielded: (i) 3,7-*bis*(4-*chlorobenzyl*)-6-(4-*chlorophenyl*)*imidazo*-[1,2-b]-s-*tetrazine* (**5b**) (0.130 g, 38.5%) which had m.p. 194—195 °C (from ethanol) (Found: C, 58.8; H, 3.6; N, 14.0. $C_{24}H_{16}Cl_3N_5 \cdot \frac{1}{2} H_2O$ requires C, 58.8; H, 3.6; N, 14.3%); δ_H([$^2H_6$]acetone) 4.35 (2 H, s, CH_2), 4.45 (2 H, s, CH_2), and 7.3—8.5 (12 H, m, ArH); $\nu_{max.}$(Nujol) 1 530 cm^{-1} (C=N).

(ii) 7-*Benzyloxy*-3-(4-*chlorobenzyl*)-6-(4-*chlorophenyl*)*imidazo*-[1,2-b]-s-*tetrazine* (**8d**) (75 mg, 10.7%) which had m.p. 178—179 °C (from ethanol–acetone) (Found: C, 62.0; H, 3.8; N, 15.0. $C_{24}H_{17}Cl_2N_5O$ requires C, 62.3; H, 3.7; N, 15.2%), $\delta_H(CDCl_3)$ 4.35 (2 H, s, CH_2), 5.75 (2 H, s, OCH_2), and 7.3—8.4 (12 H, m, ArH); $\nu_{max.}$(Nujol) 1 570 cm^{-1} (C=N).

(iii) 3-(4-*Chlorobenzyl*)-5-(4-*chlorophenyl*)-1,2,4-*triazole* (**9c**) (90 mg, 19.7%), identical with an authentic sample.[2]

Action of Potassium Hydroxide in Methanol on 3-*Benzyl*-6-(α-*methylbenzyl*)-s-*tetrazine* (**1c**).—A solution of potassium hydroxide (0.3 g) in methanol (5 ml) was added dropwise with stirring at room temperature to a solution of the tetrazine (**1c**) (1.0 g) in methanol (10 ml). Stirring was continued for 1 h and the mixture left sealed overnight before being poured into water (100 ml) and extracted with ethyl acetate. After being dried ($MgSO_4$) and evaporated, the products were separated by chromatography [silica; eluted with diethyl ether–light petroleum (b.p. 40—60 °C), (1:2)] yielding: (i) 7-*Methoxy*-3-(α-*methylbenzyl*)-6-*phenylimidazo*[1,2-b]-s-*tetrazine* (**8c**) (22 mg, 3.7%) as yellow crystals which had m.p. 172—173 °C (from ethanol); $\delta_H(CDCl_3)$ 1.9 (3 H, d, $CHCH_3$), 4.3 (3 H, s, OMe), 4.6 (1 H, q, $CHCH_3$), and 7.2—8.3 (10 H, m, ArH); $\nu_{max.}$(Nujol) 1 570 and 1 530 cm^{-1} (C=N) (Found: C, 69.3; H, 5.2; N, 21.1. $C_{19}H_{17}N_5O$ requires C, 68.9; H, 5.1; N, 21.1%).

(ii) 2-*Benzyl*-5-(α-*methylbenzyl*)-1,3,4-*oxadiazole* (**17b**) (64 mg, 6.6%), identical with oxadiazole (**17b**) prepared by an independent route (see below).

(iii) 7-*Anilino*-8-*benzyl*-6-*methyl*-3-(α-*methylbenzyl*)-11-*phenyl*-1,2,4-*triazolo*[1′,5′:4,5]*pyrazino*[1,2-b]-s-*tetrazine* (**15**) (63 mg, 6.3%) as a red solid which had m.p. 156—157 °C [from toluene–light petroleum (b.p. 80—100 °C)]; $\delta_H(CDCl_3)$ 1.8 (3 H, d, $CHCH_3$), 2.0 (3 H, s, Me), 4.1 (2 H, s, CH_2), 4.8 (1 H, q, $CHCH_3$), 6.4—7.4 (20 H, m, ArH), and 9.3 (1 H, s, NH); $\nu_{max.}$(Nujol) 3 150 cm^{-1} (NH) and 1 540 cm^{-1} (C=N) (Found: C, 73.7; H, 5.5; N, 19.9. $C_{34}H_{30}N_8$ requires C, 74.2; H, 5.5; N, 20.4%); *m/z*: M^+, 550.258 49. $C_{34}H_{30}N_8$ requires *M*, 550.259 31: other peaks at *m/z* 522, 131, 117, and 116.

(iv) 3-(α-*Methylbenzyl*)-5-*phenyl*-1,2,4-*triazole* (**9b**) (37 mg, 4.1%) identical with triazole (**9b**) prepared by an independent route (see below).

(v) 3-Benzyl-5-phenyl-1,2,4-triazole (**9a**) (107 mg, 12.6%) identical with triazole (**9a**) prepared by an independent route.[2]

Action of Potassium Hydroxide in Methanol on 3,6-*Bis*(α-*methylbenzyl*)-s-*tetrazine* (**18**). (a) *In Air*. (i) A solution of potassium hydroxide (0.4 g) in methanol (5 ml) was added dropwise with stirring at room temperature to a solution of the tetrazine (**18**) (1.1 g) in methanol (11 ml) in air. Stirring was continued for 1 h and the mixture left sealed overnight before being poured into water (200 ml) and extracted with diethyl ether. After being dried ($MgSO_4$), the solvent was evaporated, and the unchanged tetrazine (**18**) (1.03 g, 93.6%) was recovered.

(ii) The experiment described in (i) above was repeated, allowing the reaction mixture to stand sealed for 7 days before being poured into water and extracted as before. This treatment resulted in degradation of the tetrazine (**18**) into many products, of which only acetophenone (68 mg, 3.3%) could be identified.

(b) *Under Nitrogen*. The experiment described in (*a*) (ii) above was carried out under an atmosphere of nitrogen, and yielded several products which could not be identified. The ^1H n.m.r. spectra and t.l.c. results on all of these products showed the absence of acetophenone at a measurable level.

Preparation of 3-(α-*Methylbenzyl*)-5-*phenyl*-1,2,4-*triazole* (**9b**).—The *triazole* (**9b**) was prepared from methyl hydratropimidate and benzohydrazide by a published procedure,[13] and had m.p. 125—126 °C [from toluene–light petroleum (b.p. 80—100 °C)]; $\delta_H(CDCl_3)$ 1.6 (3 H, d, Me), 4.1 (1 H, q, $CHMe$), and 7.1—7.9 (11 H, m, ArH and NH); $\nu_{max.}$(Nujol) 3 130 (NH) and 1 550 cm^{-1} (C=N) (Found: C, 76.8; H, 6.1; N, 16.7. $C_{16}H_{15}N_3$ requires C, 77.1; H, 6.0; N, 16.9%).

Preparation of 2-*Benzyl*-5-(α-*methylbenzyl*)-1,3,4-*oxadiazole* (**17b**).—*N*′-(2-phenylpropylidene)phenylacetohydrazide (0.53 g) prepared by reacting phenylacetohydrazide with hydratropaldehyde in refluxing ethanol, was oxidized[14] in dichloromethane (5 ml) by the addition of a solution of lead tetra-acetate (0.88 g) in dichloromethane (5 ml) under a drying tube ($CaCl_2$) at room temperature with stirring. Stirring was continued for 4 h before water (50 ml) was added. The mixture was filtered and the organic layer of the filtrate washed with saturated aqueous sodium hydrogen carbonate and then with water. After being

dried ($MgSO_4$), the solvent was evaporated and the product was purified by chromatography [silica; eluted with diethyl ether–light petroleum (b.p. 40—60 °C) (1:1)], and yielded the *oxadiazole* (**17b**) (0.24 g, 45.6%) which had m.p. 73—74 °C [from light petroleum (b.p. 80—100 °C]; $\delta_H(CDCl_3)$ 1.7 (3 H, d, Me), 4.0 (2 H, s, CH_2), 4.2 (1 H, q, C*H*Me), and 7.3 (10 H, m, ArH); $\nu_{max.}$(Nujol) 1 580 and 1 550 cm^{-1} (C=N) (Found: C, 77.7; H, 6.2; N, 10.6. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6%).

Preparation of N'-(2-*phenylpropylidene*)*hydratropohydrazide* (**19**).—Following a published method[15] the *hydrazide* (**19**) was prepared as a mixture of stereoisomers from hydratropohydrazide and hydratropaldehyde, and had m.p. 113—116 °C (from aqueous ethanol); $\delta_H(CDCl_3)$ 1.4 (6 H, d, 2 Me), 3.4 and 4.4 (2 H, m, 2 C*H*Me), 7.1 (11 H, m, CH=N and ArH), and 9.8 (1 H, s, NH) (Found: C, 77.0; H, 7.2; N, 9.9. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.1; N, 10.0%).

Action of Potassium Hydroxide in Methanol on Hydratropaldehyde.—(a) *Under Oxygen.* Hydratropaldehyde (0.66 g) was added to a solution of potassium hydroxide (0.75 g) in methanol (37 ml) at room temperature under an atmosphere of oxygen, and the solution shaken for 24 h, during which 111 ml of oxygen (at atmospheric pressure) were absorbed. The reaction mixture was then poured into dilute hydrochloric acid (1M; 200 ml) and extracted with diethyl ether. After being dried ($MgSO_4$), the solvent was evaporated to yield a mixture of acetophenone (0.49 g, 82.9%) and unchanged hydratropaldehyde (0.06 g, 9.1%) which were identified by ^1H n.m.r. and i.r. spectroscopy.

(b) *Under Nitrogen.* When the experiment described in (*a*) above was repeated under an atmosphere of nitrogen, no acetophenone was formed, and the hydratropaldehyde (0.64 g, 97.0%) was recovered.

Action of Potassium Hydroxide in Methanol.—(a) *On hydratroponitrile.* Hydratroponitrile (0.137 g) was added to a solution of potassium hydroxide (0.15 g) in methanol (7.5 ml) at room temperature in air. After 7 days the reaction mixture was poured into dilute hydrochloric acid (1M; 100 ml) and extracted with diethyl ether. After being dried ($MgSO_4$) evaporation of the solvent gave the unchanged hydratroponitrile (0.132 g, 96.4%).

(b) *On the hydrazide* (**19**). Following the method described in (*a*) above, the hydrazide (**19**) (0.23 g) yielded acetophenone (44 mg, 44.6%) which was purified by preparative t.l.c. and identified by its ^1H n.m.r. and i.r. spectra.

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