SYNTHESIS AND PROPERTIES OF PHENYLENEBIS-1H-TETRAZOLES

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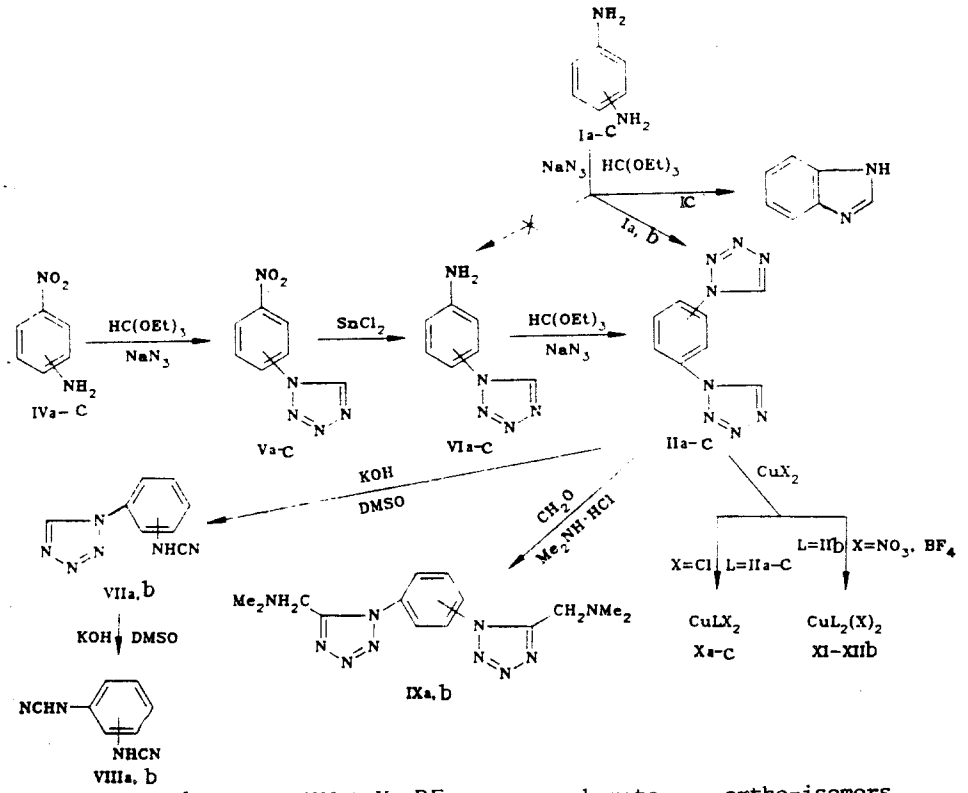
Heterocyclization of m- and p-phenylenediamines with orthoformic ester and sodium azide has given phenylenebis-1H-tetrazoles. Under these conditions, o-phenylenediamine gives benzimidazole. o-, m-, and p-Phenylenebis-1H-tetrazoles were also obtained from the nitroanilines via the intermediate nitro- and aminophenyltetrazoles. The reactions of the bistetrazoles examined were basic hydrolysis, aminomethylation, and complex formation with copper salts.

It has recently been shown, using a wide variety of primary monofunctional amines, that heterocyclization with orthoformic ester and sodium azide provides a convenient method for the preparation of many 1-substituted tetrazoles [1]. The behavior of polyamines (other than ethylenediamine) in this reaction has not been studied. It was of interest to assess the potential of this method for the synthesis of bistetrazoles, especially in the aromatic series, and to examine the properties of compounds containing two tetrazole rings. With this aim in view, the isomeric phenylenediamines (Ia-c) were heterocyclized as described above.



XI b X=NO_3, XII b X=BF_4; a para-, b meta-, c ortho-isomers

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TABLE 1. Characteristics of Compounds Obtained

Compound	Empirical formula	mp, °C*1	IR spectrum, cm^{-1}	PMR spectrum, ppm	Yield, %
IIa	$C_8H_6N_8$	245*2	3131 (ν_{C_5-H}); 1084, 1043, 1008, 991 (ν, δ_{Tr})*3; 846 ($\omega_{C-H_{arom}}$)	10,21 (1H, s, 5-H); 8,21 (4H, s, C_6H_4)	94
IIb	$C_8H_6N_8$	210...211	3128 (ν_{C_5-H}); 1093, 1062, 1040, 1008 (ν, δ_{Tr}); 789, 757 ($\omega_{C-H_{arom}}$)	10,22 (1H, s, 5-H); 8,54 (1H, s, 2-H); 8,10 (2H, d, 4, 6-H); 7,93 (1H,t, 5-H)	91
IIc	$C_8H_6N_8$	170...171	3221 (ν_{C_5-H}); 1070, 1044, 1017, 983 (ν, δ_{Tr}); 748 ($\omega_{C-H_{arom}}$)	10,03 (1H, s, 5-H); 8,16 (2H, d, 3, 6-H); 8,08 (2H,d, 4, 5-H)	83
VIIa	$C_8H_6N_6$	176...178	3110 (ν_{C_5-H}); 2221 ($\nu_{C\equiv N}$); 1600 (δ_{N-H}); 1076, 1031, 1001 (ν, δ_{Tr}); 829 ($\omega_{C-H_{arom}}$)	10,04 (1H, s, 5-H); 7,86 (2H, d, 2, 6-H); 7,17 (2H,d, 3, 5-H)	93
VIIb	$C_8H_6N_6$	173...175	3111 (ν_{C_5-H}); 2225 ($\nu_{C\equiv N}$); 1604 (δ_{N-H}); 1081, 1060, 1048, 1008 (ν, δ_{Tr}); 780 ($\omega_{C-H_{arom}}$)	10,12 (1H, s, 5-H); 7,58 (2H, m, 2, 6-H); 7,45 (1H, d, 4-H); 7,09 (1H, dd, , 5-H)	94
VIIIa	$C_8H_6N_4$	206...208*4	2220 ($\nu_{C\equiv N}$); 1608 (δ_{N-H}); 824 ($\omega_{C-H_{arom}}$)	10,08 (1H, br.s, H); 6,96 (4H, s, C_6H_4)	86
VIIIb	$C_8H_6N_4$	188...190*4	2225 ($\nu_{C\equiv N}$); 1610 (δ_{N-H}); 767, 677 ($\omega_{C-H_{arom}}$)	10,35 (1H,br.s, H); 7,25 (1H, t, 5-H); 6,60 (3H, m, 2, 4, 6-H)	82
IXa	$C_{14}H_{20}N_{10}$	187...188	3053 (ν_{C-H}); 2962...2787 (ν_{CH_2,CH_3}); 1078, 1039, 1005 (ν, δ_{Tr}); 834 ($\omega_{C-H_{arom}}$)	7,97 (4H, s, C_6H_4); 3,63 (4H, s, CH_2); 2,27 (12H, s, CH_3)	69
IXb	$C_{14}H_{20}N_{10}$	137...138	3048 (ν_{C-H}); 2974...2785 (ν_{CH_2,CH_3}); 1087, 1051, 1046 (ν, δ_{Tr}); 783 ($\omega_{C-H_{arom}}$)	8,49 (1H, s, 2-H); 8,08 (2H, d, 4, 6-H); 7,95 (1H, t, 5-H); 3,63 (4H, s, CH_2); 2,24 (12H,s, CH_3)	96
Xa	$C_8H_6Cl_2CuN_8$	220*2	3102 ($\nu_{C-H_{Tr}}$); 1520 (δ_{benz}) 1082, 1060, 996 (ν, δ_{Tr}) 843 ($\omega_{C-H_{arom}}$)		94
Xb	$C_8H_6Cl_2CuN_8$	200*2	3090 ($\nu_{C-H_{Tr}}$); 1603, 1518 (δ_{benz}); 1082, 1046, 1006 (ν, δ_{Tr}); 823, 753 ($\omega_{C-H_{arom}}$)		88
Xc	$C_8H_6Cl_2CuN_8$	170*2	3097 ($\nu_{C-H_{Tr}}$); 1526 (δ_{benz}); 1073, 1021, 987 (ν, δ_{Tr}); 826, 753 ($\omega_{C-H_{arom}}$)		85
XIb	$C_{16}H_{12}CuN_{18}O_6$	180*2	3090 ($\nu_{C-H_{Tr}}$); 1600, 1507 (δ_{benz}); 1350...1375 (ν_{NO_3}); 1078, 1034, 1000 (ν, δ_{Tr}); 783, 747 ($\omega_{C-H_{arom}}$)		87
XIIb	$C_{16}H_{12}B_2CuF_8N_{16}$	182*2	3089 ($\nu_{C-H_{Tr}}$); 1607, 1510 (δ_{benz}); 1097...1031 (ν_{BF_4}); 1004 (ν, δ_{Tr}); 789, 758 ($\omega_{C-H_{arom}}$)		94

*1(IIa, c) were crystallized from DMSO–water (10:1), (IIb) from CH_3COOH, (VIIa) and (VIIIa) from water, (VIIb) and (IXa, b) from i-propanol, and (VIIIb) from methanol–water (1:1).

*2Temperature at which decomposition starts.

*3Tr indicates tetrazole.

*4The compounds changed color to yellowish-green without visible fusion, and thereafter did not melt or decompose up to 300°C, but when placed on a heated surface (~250°C), rapid decomposition took place.

It was found that p- and m-phenylenediamines (Ia, b) reacted readily with triethyl orthoformate and sodium azide in acetic acid, to give the phenylenebis-1H-tetrazoles (IIa, b) in high yield (90-95%). The reaction of o-phenylenediamine (Ic) under the same conditions gave benzimidazole (III) as the main product which is, in principle, in accordance with our earlier observation that amidines are formed as intermediates in reactions of this type [1, 2]. Conversion of the benzimidazole, a cyclic amidine, to the tetrazole does not occur, apparently as a result of stabilization of the molecule by the formation of a conjugated aromatic system.

Attempts to carry out the reaction of (Ia-c) at a single amino group to obtain the monosubstituted compounds (VI), by varying the reaction conditions and the proportions of the reactants, were unsuccessful, heterocyclization taking place in all instances at both amino groups.

It was found that the o-phenylenebis-1H-tetrazole (IIc), as well as the isomeric (IIa, b), can be obtained in high yields from the nitroanilines (IV) (Scheme 1). The heterocyclization step proceeds smoothly with all the isomers (IV) and (VI) to give (IIa, b) and (Va, b) in yields of 90-95%, the yield of the o-isomer being somewhat lower (85%); the overall lower yields of (IIa-c) obtained by this route arise at the reduction stage (V → VI, yields 50-70%).

The phenylenebistetrazoles (IIa-c) were obtained as crystalline solids with fairly high melting points and low solubility in the usual organic solvents (they were soluble in DMSO and DMF, and sparingly so in acetic acid).

With compounds (IIa) and (IIb), cleavage of one of the tetrazole rings occurred with ease, with the elimination of nitrogen, when treated with caustic alkali in DMSO. The reaction occurs even at ~0°C, and proceeds vigorously over a few minutes at room temperature, to give the 1-cyanoaminophenyltetrazoles (VIIa, b) in near-quantitative yields. Under more severe conditions (heating, excess alkali), cleavage of the second tetrazole ring occurs to give the phenylenebiscyanamides (VIIIa, b). Bearing in mind the relatively high lability of the hydrogen of the CH group in the tetrazole ring [3, 4], and the strongly ionizing properties of the base-DMSO mixture, the reaction may be assumed to proceed via the intermediate carbanion, which is then stabilized by cleavage of the tetrazole ring and ejection of a molecule of nitrogen. In view of the ease of synthesis of the bistetrazoles (II), this reaction provides a convenient preparative route to both the tetrazoles (VII) and the phenylenebiscyanamides (VIII).

We have recently reported [5] that 1-substituted tetrazoles are highly reactive in the Mannich reaction as the CH-acidic component. The compounds (II) also undergo this reaction, but it only takes place in acid solution, and the yields of tetrazoles (IXa, b) are substantially increased if water is removed by azeotropic distillation. Unlike the ring cleavage reaction, aminomethylation of the bistetrazoles (IIa, b) takes place at both heterocycles, to give the disubstituted Mannich bases (IXa, b) irrespective of the reaction conditions and the reactant ratios.

Like N-alkyltetrazoles [5], (IIa-c) react with copper salts in organic solvents to give the complexes (Xa-c), (XIb), and (XIIb). The o- and m-isomers (IIb) react with copper(II) chloride rapidly at room temperature, but the p-isomer, in consequence of its very low solubility, requires heating of the reaction mixture. 1-Alkyltetrazoles are known to react with CuX_2 as monodentate ligands, giving complexes with a ligand:salt ratio of 2:1 (X = Cl) [6], 3:1 (X = NO_3), 4:1 and 6:1 (X - BF_4) [7]. Compounds (IIa-c) react with these copper salts in ratios of 1:1 (X = Cl) and 2:1 (X = NO_3 and BF_4), suggesting the bidentate nature of the phenylenebistetrazoles. The changes seen in the IR spectra when tetrazoles (IIa-c) react with copper(II) salts in the stretching (1500-1100 cm^{-1}) and stretching-deformational (1000-950 cm^{-1}) vibration regions, together with the absorption for the CH bond (3100-3090 cm^{-1}) in the tetrazole rings, indicate that complex formation, as in the case of 1-alkyltetrazoles [8], involves the most basic nitrogen atoms (N^4) of the heterocycle. According to thermogravimetry, the decomposition of complexes (X-XII) proceeds exothermically in 2-3 basic steps, the maximum weight loss corresponding to total decomposition of the ligand [63-65% for (Xa-c)] and formation of metallic copper [90% for (XIIb)] or copper(II) oxide [83% for (XIb)].

The compositions and structures of all the compounds obtained were confirmed by their elemental analyses, IR and PMR spectra.

EXPERIMENTAL

The IR spectra (4000-400 cm^{-1}) were obtained on a Specord IR-75 in KBr disks or as suspensions in Vaseline grease. The PMR spectra were obtained on a JEOL-NMR PS-100 spectrometer in DMSO-D_6 [for (II), (III), and (V-VIII)] or $CDCl_3$ (IX), internal standard HMDS. Derivatograms were obtained on an OD-102 apparatus in a stationary air atmosphere. A weighed sample (0.05 g) was diluted with SiO_2,. and heating carried out at 5°C/min over the range 20-600°C.

The properties of the compounds obtained are shown in Table 1. The elemental analyses for C, H, and N were in agreement with the calculated values.

Phenylenebis-1H-tetrazoles (IIa-c). **A.** To a stirred mixture of 10.8 g (100 mmoles) of the phenylenediamine (Ia, b) and 15.6 g (240 mmoles) of sodium azide in 50 ml of triethyl orthoformate was added 100 ml of acetic acid, and the mixture heated on a boiling water bath for 3 h. The mixture was then cooled, and poured with stirring into 1 liter of water. The solid which separated was filtered off, washed with water, and dried.

B. To a mixture of 3.22 g (20 mmoles) of the 1-(aminophenyl)tetrazole (VIa-c) and 1.56 g (24 mmoles) of sodium azide in 10 ml of triethyl orthoformate was added 10 ml of acetic acid, and the mixture stirred for 3.5 h at 95-100°C. After cooling, the reaction mixture was poured with stirring into 200 ml of water, and the product which separated was filtered off, washed with water, and dried. The spectra of the bistetrazoles (IIa, b) were identical with those of samples obtained by method **A**.

1-(Nitrophenyl)tetrazoles (Va-c). To a suspension of 9.55 g (50 mmoles) of the nitroaniline (IVa-c) and 3.9 g (60 mmoles) of sodium azide in 25 ml of triethyl orthoformate was added with stirring 40 ml of acetic acid, and the mixture heated for 4 h at 95-100°C. After cooling, the mixture was treated with 7 ml of concentrated HCl, filtered, the filtrate evaporated under reduced pressure, and the residue crystallized from a mixture of acetone and water (2:1) (Va, b) or 2-propanol (Vc). The yields of tetrazoles (Va-c) were 85-90%: (Va), mp 183-185°C ([9] 182-184°C); (Vb), mp 110-111°C ([9] 109-110°C); (Vc), mp 85-86°C ([9] 85-86°C).

1-(Aminophenyl)tetrazoles (VIa-c) were obtained by reducing the nitro compounds (Va, b) with $SnCl_2$ in hydrochloric acid as described in [10], or by catalytic hydrogenation of (Vc) in ethanol over PtO_2 as described in [9]. Compounds (VIa, b) were crystallized from water, and (VIc) from hexane; yields 55-70%. The constants of the compounds obtained were as reported in [9].

1-(Cyanoaminophenyl)tetrazoles (VIIa, b). To a solution of 2.14 g (10 mmoles) of the bistetrazole (IIa, b) in 10 ml of DMSO was added a solution of 0.67 g (12 mmoles) of KOH in 2 ml of ethanol, whereupon vigorous evolution of nitrogen occurred. The mixture was stirred at room temperature for ~30 min, diluted to ~50 ml with water, and acidified with hydrochloric acid. The crystalline product which separated was filtered off, washed with a small amount of water, and dried.

Phenylenebiscyanamides (VIIIa, b). To 2.14 g (10 mmoles) of the bistetrazole (IIa, b) in 10 ml of DMSO was added a solution of 1.68 g (30 mmoles) of KOH in 5 ml of 2-propanol, and the mixture stirred at 75-80°C for 2.5 h. The solution was cooled, diluted with twice its volume of water, and acidified with hydrochloric acid. The crystalline solid which separated was filtered off, washed with water, and dried.

Phenylenebis-1H-(5-dimethylaminomethyl)tetrazoles (IXa, b). To a mixture of 1.71 g (8 mmoles) of the tetrazole (IIa, b), 1.3 g (16 mmoles) of dimethylamine hydrochloride, and 1.5 g (50 mmoles) of paraformaldehyde in 20 ml of acetic acid was added 25 ml of benzene. The mixture was boiled for 1.5-2 h with an attachment for the removal of water. After cooling, the solvent was decanted from the viscous residue, 25 ml of water added to dissolve the product, and the solution poured into 50 ml of 20% NaOH. The amine which separated was filtered off, washed with water, and dried.

Phenylenebis-1H-tetrazolecopper(II) Chlorides (Xa-c). To a solution of 0.25 g (1.5 mmoles) of copper(II) chloride dihydrate in 15 ml of alcohol (methanol or ethanol) was added with stirring 0.32 g (1.5 mmoles) of the phenylenebistetrazole (IIa-c). The mixture was stirred for 15-20 min, and the solid then isolated by filtration, washed with alcohol and ether, and dried in air to give the complexes as bright green powders.

m-Phenylenebis-1H-tetrazolecopper(II) Nitrate (XIb) and Tetrafluoroborate (XIIb). To 0.32 g (1.5 mmoles) of the ligand, dissolved in 50 ml of boiling acetonitrile, was added with stirring a hot solution of the appropriate salt in 10 ml of the same solvent. The mixture was stirred for 15-20 min, filtered, washed with acetonitrile and alcohol, and dried in air at 60°C. The complexes were obtained as light blue powders.

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5,7-DIARYL-5,6-DIHYDRO-4H-TETRAZOLO[1,5-b]-1,2,4-TRIAZEPINES

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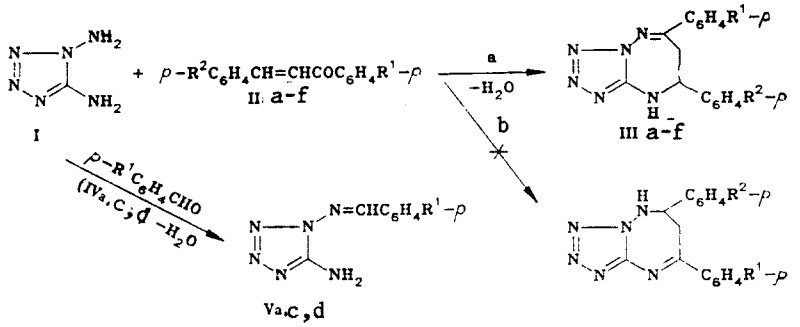
Cyclocondensation of 1,5-diaminotetrazole with chalcones has given aryl-5,6-dihydro-4H-tetrazolo[1,5-b]-1,2,4-triazepines.

The purpose of this investigation was to examine the cyclocondensation of 1,5-diaminotetrazole (I) with aromatic α,β-unsaturated ketones (chalcones). The reduced nucleophilicity of (I) resulted in the failure of attempts to carry out the condensation, either under mild conditions [1-3], or by boiling in triethylamine or acetic acid. 1,5-Diaminotetrazole reacted with the chalcones (IIa-f) on boiling in DMF for ~3 h. The sole cyclocondensation products were the compounds (IIIa-f), which according to their elemental analyses and spectral properties (Tables 1 and 2) were dihydrotetrazolotriazepines, no cleavage of the "hydrazine" amino group, such as occurs with 1,2-diaminobenzimidazole [4], being observed.



II—V a, e, f R^1=H, b R^1=CH_3, c R^1=OCH_3, d R^1=NO_2; a—d R^2=H, e R^2=CH_3, f R^2=Cl

In the IR spectra of (IIIa-f), $\nu_{C=N}$ and ν_{NH} absorptions were reliably identified at 1620-1632 and 3405-3483 cm^{-1}, respectively (Table 1). The PMR spectra of these compounds showed (Table 2), in addition to multiplets for the aromatic protons and a singlet for the methyl groups [in the case of (IIIb, c, e)], signals for the NH group and three quartets attributed to the protons of the CH–CH_2 fragment. The mass spectrum of (IIIa) showed a strong (13%) molecular ion peak, m/z 290, further fragmentation involving cleavage in one sequence or another of a molecule of nitrogen or HN_3, HCN, benzonitrile, stilbene, or phenylacetylene (see Experimental).

The nonequivalence of the amino groups in 1,5-diaminotetrazole makes it possible for dihydrotriazepine ring formation to occur by either of two routes (a and b). 1-Aminotetrazole is known [5] to readily afford a Schiff base, whereas 5-aminotetra-

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