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Tetrazole Analogues of Benzilic Acid Esters and Substituted Glycolic Acid Esters

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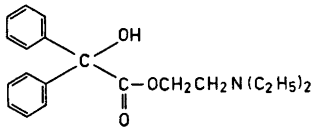
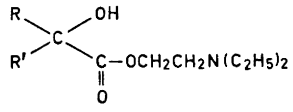
A series of new 5-tetrazolylmethanols has been prepared and these in turn have been alkylated in the tetrazole nucleus, thus giving rise to a mixture of 1,5- and 2,5-disubstituted tetrazolylmethanols. The isomers were separated by means of fractional crystallization or chromatography. ^{1}H NMR-spectroscopy was used for the structural assignment, and this was confirmed in one case by an unambiguous synthesis.

Several benzilic acid esters, *e.g.* benactyzine (I) and their substitution products, as well as many substituted glycolic acid esters of type II are known to possess anticholinergic activity in the same order of magnitude as atropine.[1] Combined with a cholinesterase reactivator, *e.g.* TMB-4, [1,1′-trimethylenebis(4-formylpyridiniumbromide)dioxime] these substances I or II afford a notable increase in the LD_{50} of many organophosphates. The clinical use of these benactyzine analogues is limited by a pronounced effect on the central nervous system, very often causing hallucinations.[1a] The most potent of these compounds are even considered to belong to the hallucinogenes.[1a] By introducing the tetrazole nucleus in I and II instead of the oxycarbonyl moiety, we hope to retain the anticholinergic potency and to reduce or eliminate the hallucinogenic properties. The compounds selected for synthesis (Xa–e, XIa–e), are listed in Scheme 1 and they are all analogues of compounds with an anticholinergic activity exceeding that of atropine.



I



II

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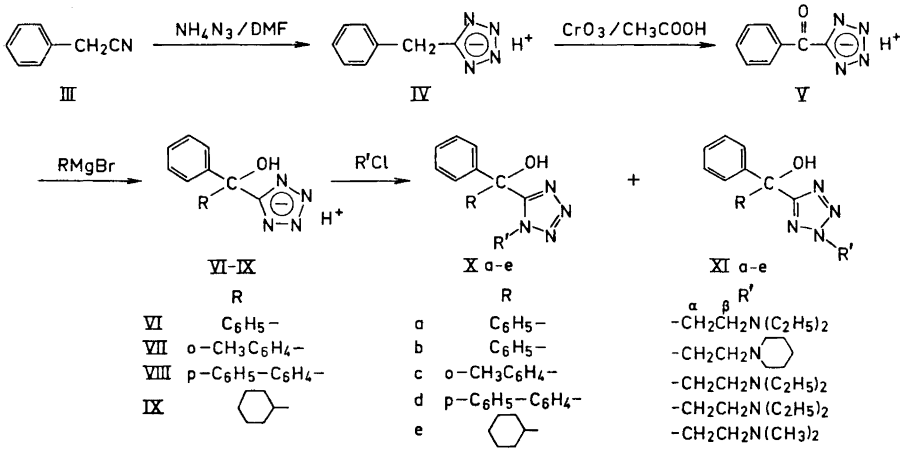
Synthesis. The synthesis proceeded through 4 steps as outlined in Scheme 1. The starting material, benzyl cyanide (III), was reacted to give 5-benzyltetrazole (IV) [2] which upon oxidation gave 5-benzoyltetrazole (V).[3]

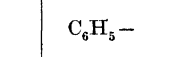
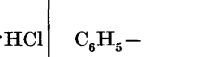


Reaction of V with the appropriate Grignard reagent led to the tetrazolylmethanols VI – IX and these in turn were alkylated with suitable aminoalkyl chlorides, giving rise to isomer mixtures of the new 1,5- and 2,5-disubstituted tetrazoles Xa – e and XIa – e. The first steps of the synthesis generally proceeded in good yields whereas the final alkylations only yielded 10 – 40 % of the isomer mixtures.

The compounds with a free amino group as well as their corresponding hydrochlorides or methiodides were prepared and the isomers were separated by fractional crystallization or by chromatographic methods. The identity of X and XI was established by elemental analysis, IR and ^{1}H NMR-spectroscopy.

Assignment of structure. The structural assignment of X and XI was based on ^{1}H NMR-spectroscopy. In a previous paper [4] it has been demonstrated that the signals from the protons of the methyl and methylene groups directly attached to a nitrogen atom in the tetrazole nucleus (α-protons) appear at the higher field for the 1-isomer compared to the signals of the corresponding 2-isomer. In our case (Scheme 1), the signals of the α-protons (triplet) could easily be identified in the hydrochlorides of X and XI as the methylene protons attached to the amino group (β-protons, Scheme 1) gave rise to a perturbed signal. Consequently we used the hydrochlorides for the isomer assignment. Considering the free amines, both signals move upfield compared to those of the hydrochlorides due to the reduced electronegativity of the nitrogen atom, but the difference between the chemical shifts of the α- and β-protons in the salts is smaller as to be expected from the greater deshielding effect of the neighbouring quaternized nitrogen atom on the β-protons.

Further support to the isomer assignment was lent by the ^{1}H NMR-spectroscopical observations (Table 3) that in the 1,5-disubstituted tetrazoles

Compound	R	R′	Yield %	Melting point °C	Method of separation	Crystallized from	Formula	Analyses (C,H,N,Halogen)
Xa	C_6H_5-	$-CH_2CH_2N(C_2H_5)_2$	18	117–119	2	Acetone–petrol ether	$C_{20}H_{25}N_5O$	Found: 68.20 7.19 19.90 Calc.: 68.35 7.17 19.93
Xa.HCl	C_6H_5-	$-CH_2CH_2N(C_2H_5)_2.HCl$	13	213–217	1	Abs. ethanol	$C_{20}H_{26}N_5ClO$	Found: 61.51 6.80 18.32 9.06 Calc.: 61.93 6.75 18.06 9.14
Xb	C_6H_5-		12	164–166	6	Acetone	$C_{21}H_{25}N_5O$	Found: 69.45 7.07 19.37 Calc.: 69.39 6.93 19.27
Xb·HCl	C_6H_5-		–	231–233	Prepared from Xb	Abs. ethanol	$C_{21}H_{26}N_5ClO$	Found: 63.05 6.61 17.67 8.78 Calc.: 63.06 6.55 17.52 8.87
Xc	*o*-$CH_3C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2$	10	84–87	2	Cyclo-hexane	$C_{21}H_{26}N_5O$	Found: 69.10 7.57 19.26 Calc.: 69.01 7.45 19.16
Xc.HCl	*o*-$CH_3C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2.HCl$	–	134–137	Prepared from Xc	Abs. ethanol–petrol ether	$C_{21}H_{27}N_5ClO$	Found: 61.95 7.08 16.90 8.46 Calc.: 62.76 7.02 17.43 8.82
Xd	*p*-$C_6H_5-C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2$	23	148–150	4	Benzene	$C_{26}H_{29}N_5O$	Found: 73.50 6.59 16.82 Calc.: 73.01 6.83 16.44
Xd.HCl	*p*-$C_6H_5-C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2.HCl$	14	198–201	1	Abs. ethanol	$C_{26}H_{30}N_5ClO$	Found: 66.98 6.59 15.20 7.79 Calc.: 67.32 6.52 15.10 7.61
Xe		$-CH_2CH_2N(CH_3)_2$	5	oil	3	–	–	
Xe.CH_3I		$-CH_2CH_2\overset{\oplus}{N}(CH_3)_3.\overset{\ominus}{I}$	5	242–244	5 or prepared from Xe	Acetone	$C_{19}H_{30}N_5IO$	Found: 48.05 6.45 14.90 27.38 Calc.: 48.40 6.42 14.86 26.92
Xf	H–	$-CH_2CH_2N(C_2H_5)_2$	23	oil	3	–	$C_{14}H_{21}N_5O$	Found: 60.52 7.76 25.33 Calc.: 61.07 7.69 25.43

Compound	R	R′	Yield %	Melting point °C	Method of separation	Crystallized from	Formula	Analyses (C,H,N,Halogen)
XIa	C_6H_5-	$-CH_2CH_2N(C_2H_5)_2$	17	71–74	2	Acetone–petrol ether	$C_{20}H_{25}N_5O$	Found: 68.40 7.27 19.99 Calc.: 68.35 7.17 19.93
XIa.HCl	C_6H_5-	$-CH_2CH_2N(C_2H_5)_2.HCl$	13	135–138	1	Abs. ethanol–petrol ether	$C_{20}H_{26}N_5ClO$	Found: 61.50 6.82 18.11 9.03 Calc.: 61.93 6.75 18.07 9.14
XIb	C_6H_5-		11	111–114	6	Acetone–petrol ether	$C_{21}H_{25}N_5O$	Found: 69.50 7.13 19.19 Calc.: 69.39 6.93 19.27
XIb.HCl	C_6H_5-		–	169–172	Prepared from XIb	Abs. ethanol–petrol ether	$C_{21}H_{26}N_5ClO$	Found: 62.90 6.58 17.50 8.79 Calc.: 63.06 6.55 17.52 8.87
XIc	$o\text{-}CH_3-C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2$	15	59–62	2	Chloroform–petrol ether	$C_{21}H_{26}N_5O$	Found: 68.49 7.57 19.08 Calc.: 69.01 7.45 19.16
XIc.HCl	$o\text{-}CH_3-C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2.HCl$	–	161–163	Prepared from XIc	Abs. ethanol–petrol ether	$C_{21}H_{27}N_5ClO$	Found: 62.15 7.03 17.37 8.80 Calc.: 62.76 7.02 17.43 8.82
XId	$p\text{-}C_6H_5-C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2$	17	116–118	4	Ether–petrol ether	$C_{26}H_{29}N_5O$	Found: 73.60 6.96 16.46 Calc.: 73.01 6.83 16.44
XId.HCl	$p\text{-}C_6H_5-C_6H_4-$	$-CH_2CH_2N(C_2H_5)_2.HCl$	12	166–169	1	Abs. ethanol–petrol ether	$C_{26}H_{30}N_5ClO$	Found: 67.20 6.59 14.95 7.67 Calc.: 67.32 6.52 15.10 7.61
XIe		$-CH_2CH_2N(CH_3)_2$	7	123–125	3	Acetone–petrol ether	$C_{18}H_{27}N_5O$	Found: 65.65 8.32 21.20 Calc.: 65.61 8.26 21.26
XIe.CH_3I		$-CH_2CH_2\overset{\oplus}{N}(CH_3)_3.\overset{\ominus}{I}$	10	170–172	5 or prepared from XIe*	Acetone–petrol ether	$C_{19}H_{30}N_5IO$	Found: 47.68 6.28 14.62 26.66 Calc.: 48.40 6.42 14.86 26.92
XIf	H–	$-CH_2CH_2N(C_2H_5)_2$	15	oil	3	–	–	

* Followed by purification by PLC as described in method 5.

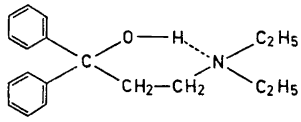
Table 3. Chemical shifts (δ-values in ppm) of α- and β-protons in disubstituted tetrazoles.

Compound	1,5-Isomers α-H	1,5-Isomers β-H	Solvent	Compound	2,5-Isomers α-H	2,5-Isomers β-H	Solvent
Xa	4.21 (m)	2.78 (m)	$CDCl_3$	XIa	4.67 (t) [a]	3.03 (t)	$CDCl_3$
Xa.HCl	4.79 (t) [a]	3.40 (b)	DMSO-d_6	XIa.HCl	5.21 (t) [a]	3.70 (b)	DMSO-d_6
Xb	4.27 (m)	2.64 (m)	$CDCl_3$	XIb	4.69 (t) [a]	2.89 (t)	$CDCl_3$
Xb.HCl	4.81 (t) [a]	3.37 (b)	DMSO-d_6	XIb.HCl	5.33 (t) [a]	3.72 (b)	DMSO-d_6
Xc	4.25 (m)	2.85 (m)	$CDCl_3$	XIc	4.63 (t) [a]	3.00 (t)	$CDCl_3$
Xc.HCl	4.88 (t) [a]	3.50 (b)	DMSO-d_6	XIc.HCl	5.18 (t) [a]	3.66 (b)	DMSO-d_6
Xd	4.23 (m)	2.79 (m)	$CDCl_3$	XId	4.66 (t) [a]	3.02 (t)	$CDCl_3$
Xd.HCl	4.87 (t) [a]	3.50 (b)	DMSO-d_6	XId.HCl	5.27 (t) [a]	3.71 (b)	DMSO-d_6
Xe	4.33 (m)	2.60 (m)	$CDCl_3$	XIe	4.65 (t) [a]	2.89 (t)	$CDCl_3$
Xe.CH_3I	4.84 (t) [a]	3.76 (t)	DMSO-d_6	XIe.CH_3I	5.30 (t) [a]	4.06 (t)	DMSO-d_6
Xf	4.33 (m)	2.82 (m)	$CDCl_3$	XIf	4.61 (t) [a]	2.98 (t)	$CDCl_3$
Xa	4.32 (t) [a]	2.67 (t)	DMSO-d_6/$CDCl_3$ 3:2	XIa	4.67 (t) [a]	2.96 (t)	DMSO-d_6/$CDCl_3$ 3:2
Xa.HCl	4.84 (t) [a]	3.50 (b)	DMSO-d_6/$CDCl_3$ 3:2	XIa.HCl	5.31 (t) [a]	3.78 (b)	DMSO-d_6/$CDCl_3$ 3:2

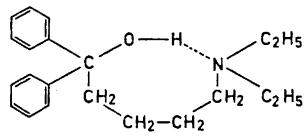
[a] $J_{\alpha\beta}=7$ Hz. m=multiplet; b=broad; t=triplet.

with a free amino group in the side chain (Xa–e) the signals of the α- and β-protons appeared as symmetric multiplets when deuteriochloroform was used as a solvent but as normal triplets when a mixture of deuteriochloroform and dimethyl sulfoxide-d_6 was used. In the corresponding 2,5-disubstituted tetrazoles XI a–e, the α- and β-protons gave rise to triplet signals in both solvents. The ^{1}H NMR data are summarized in Table 3.

The multiplet signals in the compounds Xa–e can be explained by the assumption that an intramolecular hydrogen bond has been formed between the tertiary alcohol group and the basic nitrogen atom in the side chain, giving rise to an eight-membered ring in which the geminal protons in the α- and β-position respectively would be non-equivalent. This hydrogen bond is broken in dimethyl sulfoxide-d_6 probably due to interaction of the solvent with the alcohol group. The ^{1}H NMR-spectra as well as the IR-spectra of the compounds Xa–e will be subjected to further investigations. Our observations may be in accordance with those (from IR-spectroscopy) of Kuznetsov [5] who reported intramolecular hydrogen bonds in the compounds XII and XIII



XII

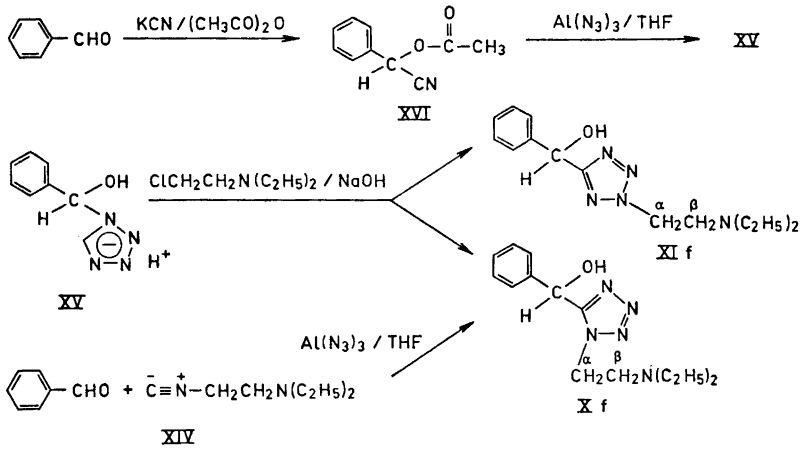


XIII

giving rise to a six- and eight-membered ring, respectively. Further evidence of an eight-membered ring in X is provided by studies on molecular models.

From these it is obvious that hydrogen bond formation is only possible in the 1,5-disubstituted tetrazoles.

In order to provide chemical evidence of the above structural assignment we tried to prepare compound Xa by an unambiguous synthesis using 2-diethylaminoethyl isocyanide (XIV), benzophenone, and aluminium azide according to the analogous method of Ugi and Meyr.[6] This procedure is known to give only the 1,5-disubstituted tetrazole. The benzophenone, however, was too unreactive. Instead we prepared compound Xf by this method,[6] starting with 2-diethylaminoethyl isocyanide (XIV), benzaldehyde, and aluminium azide. Furthermore both Xf and XIf were synthesized by alkylation of XV, which was prepared by known procedures.[7,8]



The ^{1}H NMR-spectrum of Xf, prepared by the latter method, showed the same splitting pattern of the α- and β-protons as was seen in the spectra of Xa – e, and XIf showed triplet signals from the α- and β-protons as was seen for XIa – e.

Compound Xf as obtained by the unambiguous synthesis was identical to Xf obtained by alkylation of XV as shown by IR- and ^{1}H NMR-spectroscopy.

EXPERIMENTAL

Microanalyses were carried out by Preben Hansen, Microanalytical Department of Chemical Laboratory II, University of Copenhagen. Melting points were determined with a hot stage microscope (Mikroskop-Heiztisch 350, Ernst Leitz G.m.b.H., Wetzlar). The ^{1}H NMR-spectra were recorded on a Varian A 60 NMR-spectrophotometer operating at 60 Mc. All values of δ (ppm) are relative to TMS = 0. The IR-spectra were recorded on a Perkin-Elmer 337 spectrophotometer.

5-Benzyltetrazole (IV) was prepared from benzyl cyanide (III) and ammonium azide in DMF according to Finnegan *et al.*[2] Yield 79 %. M.p. 128°C. (Lit.[2] 84 %; m.p. 123 – 125°C.)

5-Benzoyltetrazole (V) was obtained by oxidation of IV with chromium trioxide following the procedure of Yates and Farnum.[3] Yield 71 %. M.p. 135–137°C. (Lit.[3] 66 %; m.p. 136–137°C.)

Diphenyl-5-tetrazolylmethanol (VI) was synthesized from V and phenylmagnesium bromide according to Fisher *et al.*[7] Yield 70 %. M.p. 174–176°C. (Lit.[7] 64 %; m.p. 172–174°C).

Phenyl-5-tetrazolyl-2-tolylmethanol (VII) was synthesized analogously to VI from V and 2-tolylmagnesium bromide. Yield 72 %. M.p. 177–180°C. (Found: C 67.80; H 5.42; N 21.13. Calc. for $C_{15}H_{14}N_4O$: C 67.62; H 5.30; N 21.03.)

4-Biphenylyl-phenyl-5-tetrazolylmethanol (VIII). Magnesium turnings (0.1 mol) were covered with tetrahydrofuran (THF) and 5 ml of a solution of 0.1 mol of *p*-bromobiphenyl in 40 ml of THF was added. As an entrainment procedure a crystal of iodine and 0.5 ml of ethyl bromide [9] was added and the reaction mixture was heated. After the reaction had started the remainder of the solution of *p*-bromobiphenyl in THF was added during 20 min, followed by refluxing for 15 min. Under continued reflux a solution of 0.02 mol of benzoyltetrazole in 50 ml of THF was added during 1 h and refluxing was continued for another hour. After cooling to room temperature the reaction mixture was acidified with ice-cold 4 N sulfuric acid and the organic layer was separated. The aqueous phase was extracted with three 50 ml portions of ether and the combined organic fractions were extracted with 50 ml of 2 N sodium hydroxide. The alkaline solution was adjusted to pH = 1 with 4 N sulfuric acid and extracted with three 50 ml portions of ether. The pooled ether fractions were dried over anhydrous magnesium sulphate and concentrated to 20 ml. Petroleum ether was added until slight turbidity and crystallization was induced by cooling and scratching. After one hour, the colourless crystals were collected. Yield 53 %. M.p. 145–148°C. (Found: C 72.90; H 5.05; N 16.93. Calc. for $C_{20}H_{16}N_4O$: C 73.15; H 4.91; N 17.06.)

Cyclohexyl-phenyl-5-tetrazolylmethanol (IX). IX was prepared in the same way as VI and VII using 5-benzoyltetrazole and cyclohexylmagnesium bromide. A semi-crystalline, yellow product, contaminated with 5-benzoyltetrazole as shown by TLC was isolated. The product could not be obtained in an analytically pure form and was used without further purification as the identity was established by means of the ^{1}H NMR-spectrum.

1,5- and 2,5-Disubstituted tetrazoles (Xa–f, XIa–f). General procedure. 0.02 Mol of the aminoalkyl chloride hydrochloride, 0.02 mol of the tetrazolylmethanol, (VI–IX) and 0.04 mol of sodium hydroxide (pellets) was suspended in a mixture of 4 ml of water and 40 ml of acetone and refluxed with stirring for 1 h. Then the reaction mixture was poured into 50 ml of water and extracted with five 50 ml portions of benzene. The combined benzene fractions were dried over anhydrous magnesium sulphate and evaporated to give a yellow oil consisting of the 1,5- and 2,5-disubstituted tetrazoles and unreacted aminoalkyl chloride. Melting points and analytical data of the tetrazoles are given in Tables 1 and 2.

Separation of the isomeric tetrazoles. Separation of the isomers was performed by one of the following methods, and after separation, the isomers were recrystallized from a suitable solvent as indicated in Tables 1 and 2.

1. The oily mixture of the isomers was dissolved in anhydrous ether and precipitated with dry hydrogen chloride as either colourless crystals or a gum. Upon recrystallization from the minimum amount of absolute ethanol, the hydrochloride of the 1,5-disubstituted tetrazole was isolated. Addition of petroleum ether to the filtrate caused precipitation of the hydrochloride of the 2,5-disubstituted tetrazole.

2. Alternatively the oily mixture of isomers was separated on a silica gel column (0.05–0.2 mm Merck) using benzene–acetone 9:1 as an eluent. After separation, the isomers were crystallized from a suitable solvent.

3. The isomers were chromatographed on 20 × 40 cm plates with a 1 mm layer of silica gel (Merck PF_{254}) using benzene–abs. ethanol 8:2 as an eluent.

4. The oily mixture of isomers was dissolved in anhydrous ether and cooled at 4°C for 24 h, to precipitate the 1,5-disubstituted tetrazole. Addition of petroleum ether to the filtrate yielded the 2,5-disubstituted tetrazole.

5. 10 g of the isomer mixture was dissolved in 200 ml of acetone and 6 ml of methyl iodide was added. The solution was boiled for 15 min and kept overnight at 4°C, after which the methiodide of the 1,5-disubstituted tetrazole was filtered off. Addition of

petroleum ether to the filtrate gave the methiodide of the 2,5-isomer which was further purified by chromatography on 20 × 40 cm plates using benzene – abs. ethanol 1:3 as an eluent.

6. Recrystallization from acetone gave the 1,5-isomer and upon addition of petroleum ether to the filtrate the 2,5-isomer precipitated.

Mandelonitrile acetate (XVI) was synthesized from benzaldehyde, sodium cyanide, and acetic anhydride in glacial acetic acid according to the analogous method of Fisher *et al.*[7] Yield 46 %. B.p. 134 – 137°C/10 mm. (Lit.[10] B.p. 134.5 – 135°C/10 mm.)

Phenyl-5-tetrazolylmethanol (XV). Mandelonitrile acetate was reacted with aluminium azide in THF following the procedure of Behringer and Kohl.[8] Yield 46 %. M.p. 159 – 160°C. (Lit.[8] 80 %, m.p. 159°C.)

2-Diethylaminoethyl isocyanide (XIV) was prepared from diethylaminoethylamine, chloroform, and sodium hydroxide in benzene as described by Smith and Kalenda.[11] Distillation of the resulting product through a 40 cm column packed with Raschig rings yielded 8.5 % of the isocyanide. B.p. 64 – 65°C/10 mm. (Lit.[11] 14.8 %. B.p. 94 – 95°C/45 mm.) IR-spectrum (neat): 2150 cm^{-1} (isocyanide).

Phenyl-5-[1-(2-diethylaminoethyl)tetrazolyl]methanol (Xf). A mixture of 0.019 mol of the isocyanide XIV, 0.023 mol of freshly distilled benzaldehyde, 0.012 mol of aluminium azide in 64 ml of THF,[12] and 3 drops of boron trifluoride etherate was placed in an Erlenmeyer flask, fitted with a calcium chloride drying tube. The reaction mixture was left at room temperature for 80 h, and then poured into 2 N sodium hydroxide. After 1 h, the solution was acidified with 4 N hydrochloric acid, and the organic layer was separated and discarded. The aqueous phase was made alkaline with 2 N sodium hydroxide and extracted with four 100 ml portions of ether. The combined ether fractions were dried over anhydrous magnesium sulphate and evaporated to a yellow oil, which was chromatographed on 20 × 40 cm plates with a 1 mm layer of silica gel (Merck PF_{254}) using benzene – abs. ethanol 8:2 as an eluent. 1.45 mmol (8 %) of a colourless oil was isolated. The product was identical to the compound Xf obtained by alkylation of XV, as shown by the ^1H NMR and IR-spectra.

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