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Tetrazole Analogues of Benzilic Acid Esters and Substituted Glycolic Acid Esters. II

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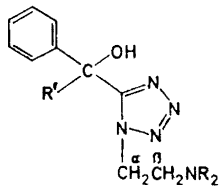
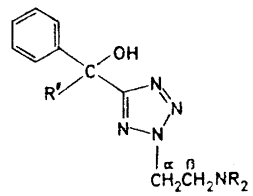
A number of 1,5- and 2,5-disubstituted tetrazolylmethanols have been synthesized as potential anticholinergic compounds. The presence of an intramolecular hydrogen bond in the 1,5-isomers is shown by IR-spectroscopy, and the ^{1}H NMR-spectra are discussed.

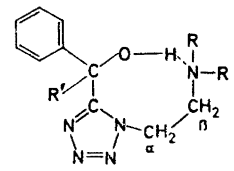
In a previous paper [1] the syntheses of a number of new 1,5- and 2,5-disubstituted tetrazoles (I–II) were given. The assignment of structure to the isomers was based on their ^{1}H NMR-spectra, and confirmed by synthesis.



I



II



I'

An unexpected splitting pattern in the ^{1}H NMR-spectra of the 1,5-disubstituted tetrazoles led us to assume the presence of an intramolecular hydrogen bond in these isomers (I'). In the present paper this assumption is confirmed by IR-spectroscopy. The syntheses of an additional number of tetrazoles (Scheme 1; I a–e, II a–e) of the corresponding structure are given.

These tetrazoles have been selected for synthesis after a preliminary test [2] for anticholinergic activity was carried out on the earlier prepared compounds.[1] The presence of a cycloalkane ring is a common feature of the tetrazolyl-

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Table 1. 1,5-Disubstituted tetrazoles (I a – e).

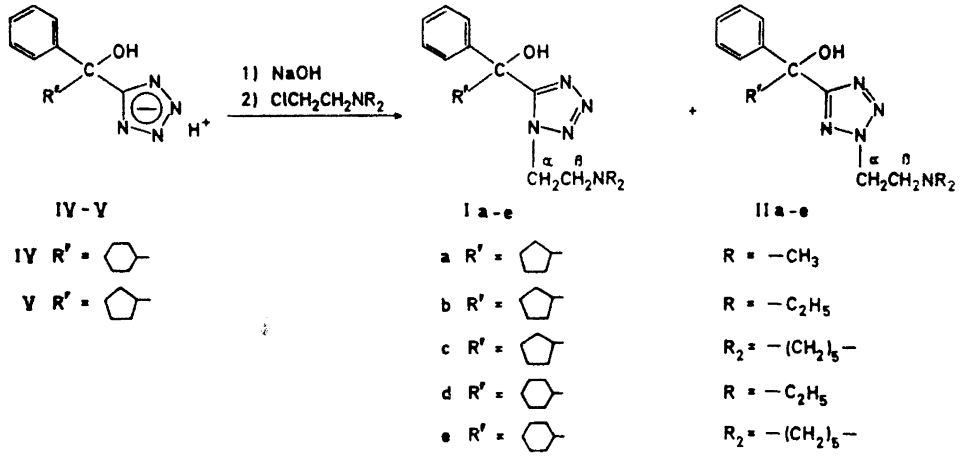
Compound	Yield, %	Melting point °C	Eluent for PLC	Crystallized from	Formula	Analyses (C, H, N, Cl)	Chemical shifts (ppm)[a] δH_α	δH_β
Ia	11	Oil	Benzene-abs. ethanol 8:2	–	$C_{17}H_{25}N_5O$		4.35 (m)	2.73 (m)
Ia, HCl	–	119–124	–	Abs. ethanol	$C_{17}H_{26}N_5ClO$	Found: 57.35 7.40 19.58 10.32 Calc.: 58.04 7.45 19.91 10.08	–	–
Ib	7	77– 79	Benzene-acetone 8:2	Ethanol-water	$C_{19}H_{29}N_5O$	Found: 66.60 8.79 20.48 Calc.: 66.43 8.51 20.39	4.21 (m)	2.77 (m)
Ic	2	116–118	Benzene-acetone 8:2	Ether	$C_{20}H_{29}N_5O$	Found: 67.50 8.29 19.57 Calc.: 67.57 8.22 19.71	4.26 (m)	2.68 (m)
Id	9	126–128	Benzene-acetone 9:1	Abs. ethanol	$C_{20}H_{31}N_5O$	Found: 67.30 8.75 19.61 Calc.: 67.19 8.74 19.59	4.34 (m)	2.83 (m)
Ie	8	119–121	Benzene-acetone 9:1	Cyclohexane	$C_{21}H_{31}N_5O$	Found: 68.10 8.52 18.73 Calc.: 68.27 8.46 18.95	4.36 (m)	2.68 (m)

[a] (m) = multiplet.

Table 2. 2,5-Disubstituted tetrazoles (II a – e).

Compound	Yield, %	Melting point, °C	Eluent for PLC	Crystallized from	Formula	Analyses (C, H, N)	Chemical shifts (ppm)[a] δH_α	δH_β
IIa	3	103 – 104	Benzene-abs. ethanol 8:2	Abs. ethanol	$C_{17}H_{25}N_5O$	Found: 64.55 8.11 22.26 Calc.: 64.76 7.99 22.21	4.69 (t)	2.90 (t)
IIb	4	67 – 69	Benzene-acetone 8:2	Ether	$C_{19}H_{29}N_5O$	Found: 66.25 8.60 20.23 Calc.: 66.43 8.51 20.39	4.63 (t)	3.01 (t)
IIc	8	77 – 80	Benzene-acetone 8:2	Ether-petroleum ether	$C_{20}H_{29}N_5O$	Found: 67.35 8.24 19.78 Calc.: 67.57 8.22 19.71	4.70 (t)	2.92 (t)
IId	12	78 – 80	Benzene-acetone 9:1	Ethanol-water	$C_{10}H_{31}N_5O$	Found: 66.90 8.92 19.08 Calc.: 67.19 8.74 19.59	4.66 (t)	3.05 (t)
IIe	9	82 – 84	Benzene-acetone 9:1	Cyclohexane	$C_{21}H_{31}N_5O$	Found: 68.40 8.52 18.98 Calc.: 68.27 8.46 18.95	4.70 (t)	2.93 (t)

[a] $J_{\alpha\beta}$ = 7 Hz; (t) = triplet.



Scheme 1.

methanols I a–e and II a–e. Some special features of the ^{1}H NMR-spectra of this type of compounds are discussed.

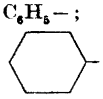
Synthesis. The procedure for synthesizing I a–e and II a–e was identical to that presented earlier [1,3,4a] (Scheme 1).

^{1}H NMR-spectra. The chemical shifts of the α- and β-protons (I – II) of the new 1,5- and 2,5-disubstituted tetrazoles are given in Tables 1 and 2. Of each isomer pair, the compound in which the α-protons appeared at a lower δ-value was assigned the 1,5-isomeric structure according to previous findings.[1] The ^{1}H NMR-spectra of all the 1,5-tetrazoles showed multiplet signals from the α- and β-protons whereas the corresponding signals from the 2,5-isomers were triplets.

Table 3. Chemical shifts of phenyl protons of tetrazoles with structures I and II (δ-values in ppm; solvent: deuteriochloroform). I and II f, g and h were published in Ref. 1.

Compound	δH_o, $\delta H_{m,p}$	Compound	δH_o	$\delta H_{m,p}$	$\Delta = \delta H_o - \delta H_{m,p}$
Ia	7.40	IIa	7.69	7.29	0.40
Ib	7.33	IIb	7.71	7.30	0.41
Ic	7.39	IIc	7.68	7.29	0.39
Id	7.43	IId	7.69	7.31	0.38
Ie	7.41	IIe	7.71	7.33	0.38
If[a]	7.37	IIf[a]	7.33		–
Ig[b]	7.33	IIg[b]	7.63	7.26	0.37
Ih[c]	7.39	IIh[c]	7.41		–

[a] R′ = C_6H_5–; R = C_2H_5–

[b] R′ =  ; R = CH_3–

[c] R′ = H–; R = C_2H_5–

The chemical shifts of the benzene protons of I a–e and II a–e are given in Table 3. In the tetrazoles I a–e all the benzene protons give rise to one multiplet, whereas in II a–e there is a marked difference between the chemical shifts of the *ortho*-protons and those of the *meta*- and *para*-protons. We have only observed this effect in compounds of type II in which R′ is a cycloalkyl group. If, *e.g.*, R′ = C_6H_5-(II f) or R′ = H-(II h), the benzene protons only give rise to one multiplet signal. The difference ($\Delta = \delta H_o - \delta H_{m,p}$) between the chemical shifts of the *ortho*-protons and the *meta*- and *para*-protons is rather constant, about 0.4 ppm.

Tentative calculations of the benzene part of the spectrum of II c gave good agreement with the observed spectrum when the chemical shifts relative to benzene of the *ortho*-, *meta*-, and *para*-protons were 0.39, 0.00, and −0.083 ppm, respectively. The calculations were performed for an AA′BB′C system using the coupling constants of trichloromethylbenzene given by Hayamizu and Yamamoto.[4b]

Similar observations have been reported for 2-methyl-5-phenyltetrazole when compared to 1-methyl-5-phenyltetrazole [5] and in 2-(5-phenyltetrazolyl)-acetic- or propionic acids when compared to the 1-substituted compounds.[6]

In these compounds a substituent in the tetrazole ring affects the chemical shifts of the protons of a benzene ring attached directly to the tetrazole nucleus.[5] In our case, however, a carbon atom is inserted between the benzene- and tetrazole rings.

IR-spectra. The intramolecular hydrogen bond in the 1,5-isomers. In order to show the presence of the intramolecular hydrogen bond in compounds of type I, the infrared spectra of diphenyl-5-[1-(diethylaminoethyl)tetrazolyl]methanol (I f) (R′ = C_6H_5−, R = C_2H_5−) and diphenyl-5-[2-(diethylaminoethyl)tetrazolyl]methanol (II f) (R′ = C_6H_5−, R = C_2H_5−) in tetrachloromethane were recorded (Fig. 1).

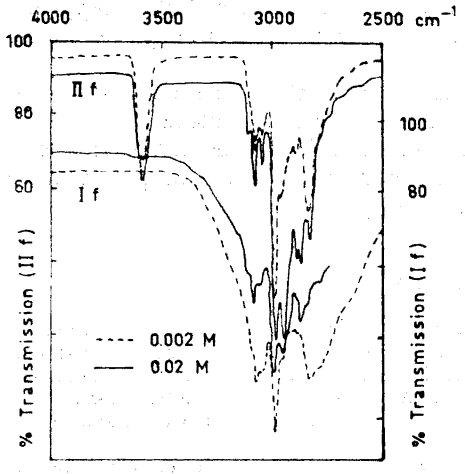


Fig. 1. IR-spectra of I f and II f. Cell path: 1 mm for 0.02 M solutions and 10 mm for 0.002 M solutions. Solvent: CCl_4.

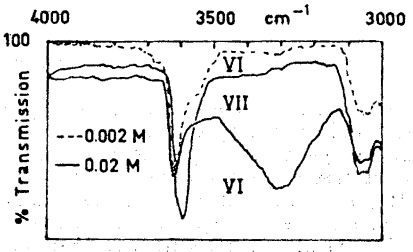
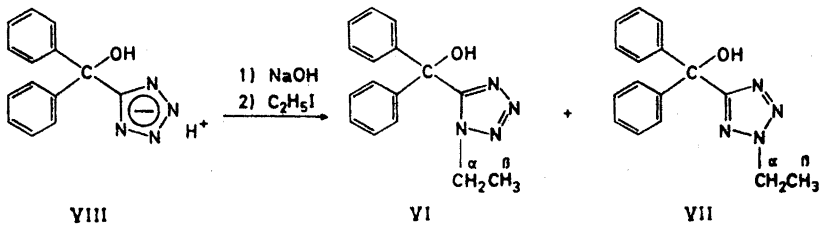


Fig. 2. IR-spectra of VI and VII. Cell path: 1 mm for 0.02 M solutions and 10 mm for 0.002 M solutions. Solvent: CCl_4.

The spectrum of II f in 0.02 M solution showed absorption at 3590 cm^{-1} arising from non-bonded OH and weak broad absorption at 3450 cm^{-1} arising from bonded OH, while the spectrum of I f (0.02 M solution) showed a broad absorption in the region 2500 – 3300 cm^{-1} indicating a strongly bonded OH group. At tenfold dilution combined with a corresponding increase in cell path the spectrum of I f showed no changes while the broad band from bonded OH in the spectrum of II f had disappeared (Fig. 1).

These spectra fully support the assumption that in the compound I f the hydrogen atom of the alcohol group is internally bound to the amino group (I') whereas this is not the case for the compound II f in which the two interacting groups are too far from each other.[1]

The tetrazole ring has been reported to possess base properties.[7] In order to show that the above-mentioned intramolecular hydrogen bond is not established between the alcohol group and the tetrazole ring itself, the IR-spectra of the model compounds VI and VII (Scheme 2) were recorded (Fig. 2).



Scheme 2.

The spectra of VI show the presence of bonded and non-bonded OH in 0.02 M solution; on tenfold dilution the absorption from bonded OH disappears. In the spectra of I f no absorption from non-bonded OH was present even in 0.002 M solution. (Fig 1).

The ^1H NMR-spectra of VI and VII in deuteriochloroform showed triplet signals from the β-protons and quartet signals from the α-protons.

From the similar multiplet pattern of the α- and β-protons in the ^1H NMR-spectra of all the tetrazoles I a–e it is concluded that the amino group in all cases is internally bound to the tertiary alcohol group.

EXPERIMENTAL

Microanalysis 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 ^1H NMR-spectra were recorded on a Varian A 60 NMR-spectrometer 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.

Cyclopentyl-phenyl-5-tetrazolylmethanol (V) was prepared from cyclopentylmagnesium bromide and 5-benzoyltetrazole [3] (III) as described for IV.[1] It could not be obtained in a crystalline, analytically pure form and was used without further purification as its structure was proved by its ^1H NMR-spectrum.

1,5- and 2,5-Disubstituted tetrazoles (I a–e, II a–e). The procedure outlined in Ref. 1 was used except that the reagents were stirred for 2 h. After isolation of the isomer mixtures (as oils) separation of the 1,5- and 2,5-disubstituted tetrazoles was performed by PLC on 20 × 100 cm plates with a 2 mm layer of silica gel (Merck PF_{254}), with a suitable eluent. After separation the compounds were crystallized. In one case (II a) the hydrochloride was prepared, as the free amine could not be obtained in a crystalline state.

Eluents, solvents of crystallization, yields and analytical data are given in Tables 1 and 2.

Diphenyl-5-[(1- or 2-ethyl)tetrazolyl]methanol (VI, VII). 0.01 mol of VIII,[4] 0.01 mol of sodium hydroxide, and 0.01 mol of ethyl bromide were dissolved in 0.5 ml of water and 5 ml of acetone. The mixture was kept at 40°C for 3 h, and then extracted with two 25 ml portions of ether. The etheral solution was dried with anhydrous magnesium sulphate, filtered and evaporated to an oily mixture of the isomers.

This residue was chromatographed on silica gel (Merck PF_{254}) using benzene-acetone 9:1 as an eluent. The isomers were identified by means of ^1H NMR-spectroscopy. Yields: VI 2 %; VII 9 %. Melting points: VI oil; VII 115.5–117.0°C. (Analysis, VII. Found: C 68.50; H 5.81; N 19.92. Calc. for $C_{16}H_{16}N_4O$: C 68.58; H 5.76; N 19.99.)

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