ACTA CHEMICA SCANDINAVICA 26 (1972) 541–548

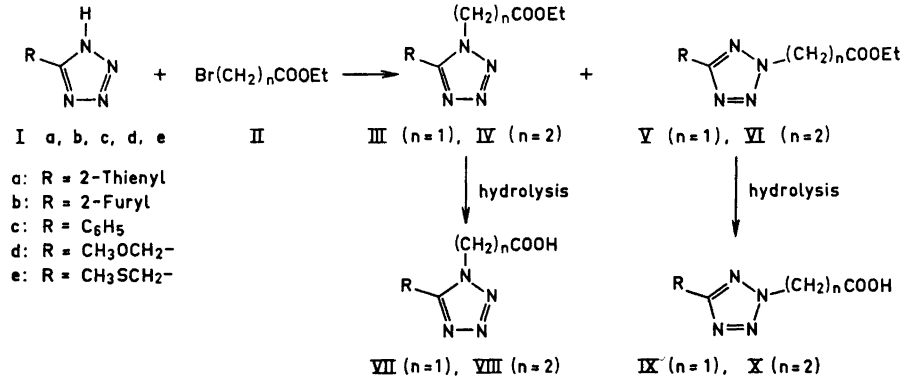
Syntheses of Some New Tetrazolylacetic Acids and the Corresponding 3-Substituted Propionic Acids

A. K. SØRENSEN and N. A. KLITGAARD

Danish Civil Defence Analytical-Chemical Laboratory, Universitetsparken 2, DK-2100 Copenhagen, Denmark

A series of new 5-substituted tetrazolylacetic acids and the corresponding 3-substituted propionic acids has been prepared. In all cases a mixture of the 1- and 2-tetrazolyl derivatives was obtained. Separation of the isomers was achieved by column chromatography or by fractional distillation. Discussions of the constitution of the isomers were based on ^{1}H NMR spectroscopy and on chemical evidence.

In a search of new anticholinergic compounds a series of 5-substituted 1- and 2-tetrazolylacetic acids and the corresponding 3-substituted propionic acids was synthesized as intermediates.



Scheme 1.

The synthetic route leading to the title compounds is shown in Scheme 1. The esters III – VI were prepared by alkylating the sodium salts of I using ethyl bromoacetate and ethyl 3-bromopropionate, respectively. In all cases mixtures of the isomeric ethyl 1- and 2-tetrazolylalkanoates were obtained. The yields of the isomers are given in Table 1 and 3.

Table 1. 5-Substituted ethyl tetrazolylacetates (III and V).

R	Yield %	B.p. °C (mmHg)	M.p. °C	Formula	Analysis					
					% C		% H		% N	
					Found	Calc.	Found	Calc.	Found	Calc.
2-Thienyl (1-isomer)	18		68–69	$C_9H_{10}N_4O_2S$	45.70	45.36	4.43	4.23	23.60	23.52
2-Thienyl (2-isomer)	61		71–72		45.27		4.30		23.60	
2-Furyl (1-isomer)	31		54–56	$C_9H_{10}N_4O_3$	48.75	48.65	4.63	4.55	25.10	25.22
2-Furyl (2-isomer)	45		63–65		48.45		4.54		25.38	
C_6H_5- (2-isomer)	80[a]		84–86							
CH_3OCH_2- (1-isomer)	47	146–148 (0.8)		$C_7H_{12}N_4O_3$	41.87	41.99	6.12	6.04	27.80	27.98
CH_3OCH_2- (2-isomer)	38	130–134 (0.8)			42.10		6.03		27.85	
CH_3SCH_2- (1-isomer)	43	165–169 (0.9)	64–67	$C_7H_{12}N_4O_2S$	38.71	38.87	5.64	5.59	26.13	26.03
CH_3SCH_2- (2-isomer)	28	149–151 (0.9)			38.78		5.51		26.12	

[a] The ^1H NMR spectrum indicates a ratio of 1:16 of the 1- and the 2-isomer.

The acids VII a,b,c and IX a,b,c (Table 2) were obtained in almost quantitative yields by alkaline hydrolysis of the corresponding esters. Attempts to prepare the acids VII d,e and IX d,e by a similar procedure were unsuccessful. Upon acid hydrolysis of VII d,e and IX d,e only VII e was formed. The 3-(1- and 2-tetrazolyl)propionic acids VIII a–c and X a–c (Table 4) were obtained in almost quantitative yields by acid hydrolysis of the corresponding esters IV a–c and VI a–c. Upon alkaline hydrolysis of VIII and X the only isolable products were the tetrazoles I a–e which is in accordance with the results of Buckler *et al.*[1] We did not succeed in isolating the acids VIII d,e and X d,e.

The isomer mixtures were separated by column chromatography. The relative yields of the isomers so obtained are given in Tables 1 and 3. In addition separation of the isomer pairs III d, V d and III e, V e were effected by fractional distillation, and from the isomer mixtures IIIa, V a; III b, V b, and III c and V c, the 2-isomers were isolated upon extraction with petroleum ether.

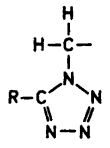
Table 2. 5-Substituted tetrazolylacetic acids (VII and IX).

R	M.p. °C	Formula	Analysis					
			% C		% H		% N	
			Found	Calc.	Found	Calc.	Found	Calc.
2-Thienyl (1-isomer)	131–132	$C_7H_6N_4O_2S.H_2O$ [a]	36.61	36.85	3.58	3.53	24.42	24.56
2-Thienyl (2-isomer)	174–177	$C_7H_6N_4O_2S$	40.00	40.00	2.96	2.88	26.62	26.64
2-Furyl (1-isomer)	150–151	$C_7H_6N_4O_3$	43.38	43.30	3.19	3.12	28.68	28.85
2-Furyl (2-isomer)	158–162		43.18		3.22		29.05	
C_6H_5- (1-isomer)	147–150							
C_6H_5- (2-isomer)	184–186							
CH_3SCH_2- (1-isomer)	135–136	$C_5H_8N_4O_2S$	31.94	31.91	4.36	4.29	29.88	29.77

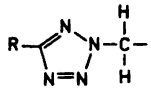
[a] Crystallized with 1 mol of water of crystallization.

The relative yield of the isomers showed that changing the substitution in the 5-position of the tetrazole ring from being aromatic to aliphatic a markable change toward higher yields of the 2-isomer was achieved. This is in accordance with the findings that the proportional yield of the 2-isomer increases with increasing electron attracting ability of the substituent at the 5-position.[2–5]

Structural assignment. It has previously been demonstrated [5–10] that in ^1H NMR spectra the protons attached to the α-carbon atom of XI give rise to signals at a higher field than the corresponding protons at the α-carbon atom of XII. As seen from Table 5 we have made the same observations. This assignment was confirmed by the unequivocal synthesis of III a, III b, III d, IV a, IV b and IV d from the ethyl ester of appropriately acylated amino



XI



XII

Fig. 1.

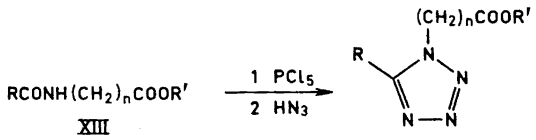
Table 3. 5-Substituted ethyl 3-(tetrazolyl)propionates (IV and VI).

R	Yield %	B.p. °C (mmHg)	Formula	Analysis					
				% C		% H		% N	
				Found	Calc.	Found	Calc.	Found	Calc.
2-Thienyl (1-isomer)	8	169–170 (0.5)	$C_{10}H_{12}N_4O_2S$	47.58	47.61	4.80	4.80	22.38	22.20
2-Thienyl (2-isomer)	40	161–162 (0.5)		47.45		4.91		21.99	
2-Furyl (1-isomer)	16	158–160 (0.5)[a]	$C_{10}H_{12}N_4O_3$	50.80	50.85	5.10	5.12	23.71	23.72
2-Furyl (2-isomer)	30	152 (0.6)		50.61		5.09		23.61	
C_6H_5- (1-isomer)[b]	5–6								
C_6H_5- (2-isomer)[b]	35								
CH_3OCH_2- (1-isomer)	21	139–142 (0.4)	$C_8H_{14}N_4O_3$	44.80	44.86	6.52	6.59	26.12	21.16
CH_3OCH_2- (2-isomer)	19	125–127 (0.4)		44.65		6.57		26.11	
CH_3SCH_2- (1-isomer)[b]	19								
CH_3SCH_2- (2-isomer)	17	149 (0.9)	$C_8H_{14}N_4O_2S$	41.62	41.71	6.23	6.13	24.44	24.24

[a] M.p. 40–41°C from ethyl acetate–petroleum ether.
[b] The compounds decomposed during attempted distillation.

alkanoic acids (XIII, Scheme 2) according to the method of Jacobsen and Amstutz.[11] The IR and ^1H NMR spectra of these 1-isomeric tetrazoles were identical to those obtained by the alkylation method.

The following intermediate compounds XIII were prepared but not isolated in analytically pure form: (R, R′, n, m.p./b.p, recrystallizing solvent in parenthesis) 2-thienyl, C_2H_5, 1, 88–89° (water); 2-thienyl, H, 2, 137–139°(water);



Scheme 2.

Table 4. 5-Substituted 3-(tetrazolyl)propionic acids (VIII and X).

R	M.p. °C	Formula	Analysis					
			% C		% H		% N	
			Found	Calc.	Found	Calc.	Found	Calc.
2-Thienyl (1-isomer)	114–115	$C_8H_8N_4O_2S$	42.74	42.86	3.68	3.60	25.04	25.00
2-Thienyl (2-isomer)	131–132		42.72		3.59		25.00	
2-Furyl (1-isomer)	106–107	$C_8H_8N_4O_3$	46.00	46.15	3.91	3.87	26.83	26.94
2-Furyl (2-isomer)	93–96		46.35		3.96		26.97	
C_6H_5- (1-isomer)	147–149	$C_{10}H_{10}N_4O_2$	54.85	55.02	4.74	4.62	25.67	25.68
C_6H_5- (2-isomer)	128–129		55.02		4.67		25.82	

Table 5. ^{1}H NMR data of 5-substituted ethyl tetrazolylacetates (III a–e and V a–e) and of the corresponding ethyl 3-(tetrazolyl)propionates (IV a–e and VI a–e).

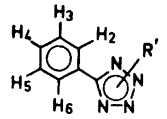
Compound	Chemical shifts (τ-values) of the 1-isomers		Compound	Chemical shifts (τ-values) of the 2-isomers	
	$\overset{a}{-CH_2-}COO$	$=N-\overset{b}{CH_2}$		$-\overset{b}{CH_2}-COO-$	$=N-\overset{a}{CH_2}-$
III a	4.22 (s)		V a	4.15 (s)	
III b	4.25 (s)		V b	4.09 (s)	
III c	4.30 (s)		V c	4.07 (s)	
III d	4.50 (s)		V d	4.25 (s)	
III e	4.51 (s)		V e	4.23 (s)	
IV a	6.92 (t)	5.12 (t, $J_{a,b}$ = 6.5 Hz)	VI a	6.85 (t)	5.03 (t, $J_{a,b}$ = 6.5 Hz)
IV b	6.88 (t)	5.08 (t, $J_{a,b}$ = 6.5 Hz)	VI b	6.83 (t)	5.00 (t, $J_{a,b}$ = 6.5 Hz)
IV c	7.03 (t)	5.38 (t, $J_{a,b}$ = 6.5 Hz)	VI c	6.89 (t)	5.05 (t, $J_{a,b}$ = 6.0 Hz)
IV d	7.12 (t)	5.23 (t, $J_{a,b}$ = 6.5 Hz)	VI d	6.90 (t)	5.08 (t, $J_{a,b}$ = 6.5 Hz)
IV e			VI e	6.92 (t)	5.12 (t, $J_{a,b}$ = 6.5 Hz)

2-thienyl, C_2H_5, 2, 75–76° (water + ethanol); 2-furyl, C_2H_5, 1, 76° (water); 2-furyl, H, 2, 140–142° (water); 2-furyl, C_2H_5, 2, 56–57° (water + ethanol); CH_3OCH_2, C_2H_5, 1, 46–47° (water + ethanol); CH_3OCH_2, H, 2, 67–69° (water); CH_3OCH_2, C_2H_5, 2, 156–158°/12 mmHg. Among these only XIII with R = 2-furyl, (n = 1) and 2-thienyl, (n = 1) and R′ = ethyl have been described previously.

The melting points of the 2-isomer compounds V a and V b are higher than those of the corresponding 1-isomers (III a and III b). This does not agree with the general conclusion made by Norris [3] and Raap.[12]

The boiling points of the compounds III and V (Table 1) and IV and VI (Table 3) are in accordance with previous observations [2,3,13] that the boiling points of the 1-isomers are higher than those of the corresponding 2-isomers.

An interesting observation concerns the phenyl protons H_2 and H_6 of III c–VI c (Fig. 2). The signals of these protons appear at a higher field in



R' = CH_2COOEt (IIIc; Vc)

R' = CH_2CH_2COOEt (IVc; VIc)

Fig. 2. Isomers obtained from 5-phenyltetrazole upon alkylation with ethyl bromoacetate and ethyl β-bromopropionate respectively.

the ^1H NMR-spectra for the 1-isomers (III c and IV c) compared to those of the 2-isomers (V c and VI c) the assignment of the resonance lines being based on a theoretical calculation of the spin-spin coupling pattern. This downfield movement of the *ortho* protons seems to be a common feature of *N*-substituted 5-phenyltetrazoles since we have made the same observations for 5-phenyltetrazoles containing $R' = CH_3-$ or $R' = -CH_2CH_2OH$. This shift of the signals of H_2 and H_6 might be valuable for the assignment of constitution of *N*-substituted 5-phenyltetrazoles.

EXPERIMENTAL

The ^1H NMR spectra were recorded in hexadeuterodimethyl sulfoxide on a Varian A 60 NMR-spectrophotometer operating at a fixed frequency of 60 MHz using tetramethylsilane as an internal standard.

The melting points were all uncorrected and determined with a hot stage microscope (Mikroskop–Heiztisch 350, Ernst Leitz, Wetzlar, West Germany). The microanalyses were made by Preben Hansen, Microanalytical Department of Chemical Laboratory II, University of Copenhagen.

Starting materials. The tetrazoles I a–d were prepared by the methods of Finnegan *et al.*[14] and Raap.[12] The *N*-substituted amides (XIII) were prepared by treating the amino acid esters with the appropriate acid chlorides according to literature methods.[11,15,16]

5-[(Methylthio)methyl]tetrazole (I e). To a stirred solution of 8.7 g (0.1 mol) of (methylthio)acetonitrile in 40 ml of DMF was added 6.7 g (0.11 mol) of sodium azide and 5.6 g (0.11 mol) of ammonium chloride and stirring was continued for 18 h at 110°C. After cooling to room temperature DMF was removed under reduced pressure and the residue was dissolved in 40 ml of water. The aqueous solution was made alkaline by 2 N sodium hydroxide, extracted with 20 ml of ether and acidified to pH 2 with concentrated hydrochloric acid. The aqueous solution was concentrated to dryness and the residue was extracted with ethanol. Upon evaporation the ethanolic solution left a white solid which on recrystallization from benzene yielded 41 % of product. M.p. 122–123°C. (Found: C 27.85; H 4.73; N 43.26; S 24.37. Calc. for $C_3H_6N_4S$: C 27.86; H 4.65; N 43.03; S 24.62.)

5-Substituted 1-tetrazolylacetic esters and the corresponding 3-(1-tetrazolyl)propionic esters. General procedure. Phosphorus pentachloride (0.05 mol) was added in portions to a stirred solution of the appropriate amide (XIII) (0.05 mol) dissolved in 80 ml of dry benzene. The solution was refluxed until consumption of phosphorus pentachloride and after cooling a benzene solution of hydrazoic acid (0.05 mol) was added. The mixture was stirred for 1 h at 0°C and for 16 h at reflux, cooled, and evaporated under reduced pressure. The residue was refluxed for 5 min with 30 ml of water, cooled and extracted with three 30 ml portions of ether. The combined ether layers were dried and evaporated, and the residue was either distilled under reduced pressure or crystallized from ethyl acetate – petroleum ether.

5-Substituted tetrazolylacetic esters (III a–e and V a–e). General procedure. The 5-substituted tetrazole (I; 0.02 mol) was dissolved in 6 ml of water containing 0.02 mol of sodium hydroxide. To the cooled solution 0.02 mol of ethyl bromoacetate dissolved in 30 ml of acetone was added and the mixture was refluxed for 5 h. After cooling the reaction mixture was extracted with two 25 ml portions of benzene, the combined benzene layers were washed with water, dried over calcium chloride and evaporated. The residue was chromatographed on a silica gel (0.05 – 0.20 mm, Merck) column using benzene – acetone 9:1 as an eluent. The fractions containing the two separated isomers were evaporated and the residues were either crystallized from ethyl acetate – petroleum ether or distilled under reduced pressure. Yields together with physical and analytical data are summarized in Table 1.

The solid 2-isomers of (V) were also isolated from the crude reaction product by extraction with petroleum ether (b.p. < 50°) in a Soxhlet extraction apparatus for 24 h. The yields obtained by this procedure ranged from 20 % to 30 % of the crude isomer mixture.

5-Substituted tetrazolylacetic acids. General procedure. Methanolic sodium hydroxide (3 N; 4 ml) was added to 5 ml of a methanolic solution of the tetrazolylacetic ester (0.01 mol). The sodium salt immediately started to precipitate and upon standing for 1 h at room temperature the reaction mixture was evaporated and the residue was dissolved in a minimum of water. The aqueous solution was acidified with 2 N hydrochloric acid. The solid formed was filtered off and recrystallized from ethyl acetate – petroleum ether. Yields were almost quantitative. Physical and analytical data are summarized in Table 2.

1-[5-(2-Thienyl)tetrazolyl]acetic acid (VII a), crystallized with 1 mol of water of crystallization as shown by the elementary analysis and the ^{1}H NMR spectrum.

1-{5-[(Methylthio)methyl]tetrazolyl}acetic acid (VII e) was prepared by acid hydrolysis according to the general procedure for the preparation of 3-(tetrazolyl)propionic acids.

5-Substituted 3-(tetrazolyl)propionic esters (IV a–e and VI a–e). General procedure. A solution of 0.05 mol of ethyl 3-bromopropionate in 70 ml of acetone was added to a solution of 0.05 mol of the tetrazole (I) in 15 ml of water containing 0.05 mol of sodium hydroxide. After refluxing for 8 h the reaction mixture was extracted with three 50 ml portions of benzene, the combined benzene layers were washed, dried over magnesium sulfate and evaporated. The residues were chromatographed as described for the tetrazolylacetic esters and the separated isomers were distilled under reduced pressure. However, IV c, e and VI c decomposed during attempted distillation. Yields of products together with physical and analytical data are summarized in Table 3.

5-Substituted 3-(tetrazolyl)propionic acids. General procedure. The tetrazolylpropionic ester (0.01 mol) was dissolved in a mixture of 10 ml of glacial acetic acid, 2 ml of concentrated hydrochloric acid and 4 ml of water. After refluxing for 3 h the solution was evaporated to dryness and the residue was recrystallized from water. Yields were almost quantitative. Physical and analytical data are summarized in Table 4.

REFERENCES

1. Buckler, R. T., Hayao, S., Lorenzetti, O. J., Sancilio, L. F., Hartzler, H. E. and Strycker, W. G. *J. Med. Chem.* **13** (1970) 725.
2. Raap, R. and Howard, J. *Can. J. Chem.* **47** (1969) 813.
3. Norris, W. P. *J. Org. Chem.* **27** (1962) 3248.
4. Henry, R. A. and Finnegan, W. G. *J. Am. Chem. Soc.* **76** (1954) 923.
5. Butler, R. N. and Scott, F. L. *J. Org. Chem.* **31** (1966) 3182.

6. Markgraf, J. H., Bachmann, W. T. and Hollis, D. P. *J. Org. Chem.* **30** (1965) 3472.
7. Barlin, G. B. and Batterham, T. J. *J. Chem. Soc.* **B 1967** 516.
8. Butler, R. N. and Scott, F. L. *J. Org. Chem.* **32** (1967) 1224.
9. Scott, F. L. and Butler, R. N. *J. Chem. Soc.* **B 1967** 919.
10. Moore, D. W. and Whittaker, A. G. *J. Am. Chem. Soc.* **82** (1960) 5007.
11. Jacobsen, C. R. and Amstutz, E. D. *J. Org. Chem.* **21** (1956) 311.
12. Raap, R. *Can. J. Chem.* **47** (1969) 3677.
13. Finnegan, W. G. and Henry, R. A. *J. Org. Chem.* **24** (1959) 1565.
14. Finnegan, W. G., Henry, R. A. and Lofquist, R. *J. Am. Chem. Soc.* **80** (1958) 3908.
15. Karrer, P. and Miyamichi, E. *Helv. Chim. Acta* **9** (1926) 336.
16. Hanson, H. T. and Smith, E. L. *J. Biol. Chem.* **175** (1948) 833.

Received May 20, 1971.