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Thermolysis of Derivatives of β-Substituted α-(1-Tetrazolyl)acrylic Acids. I. Formation of Some Imidazolones and a Thiazolone

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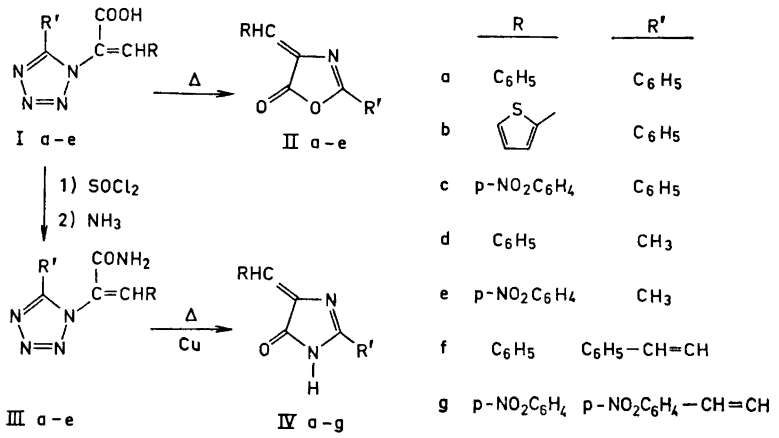
A new method of preparing unsaturated 5-imidazolones (2-substituted 4-arylmethylene-5-imidazolones) involving copper catalyzed thermolysis of β-substituted α-(1-tetrazolyl)acrylamides has been developed. Some of the imidazolones are new. Transformation of a β-substituted α-(1-tetrazolyl)thioacrylic S-acid to the unsaturated 5-thiazolone was accomplished by heating alone but the product was contaminated with the corresponding oxazolone. Attempts to prepare an *as*-triazine by heating of a β-substituted α-(1-tetrazolyl)-acrylohydrazide only led to the corresponding 1-vinyltetrazole.

In a previous paper[1] we described how attempted decarboxylation of the β-substituted α-(1-tetrazolyl)acrylic acids I gave rise to the unsaturated 5-oxazolones II. This observation prompted us to investigate whether the β-substituted α-(1-tetrazolyl)acrylamides III, the thiocarboxylic acid VIa and the hydrazide VIIIa could be converted into the unsaturated 5-imidazolones IV, the unsaturated 5-thiazolone VIIa and the *as*-triazine IXa, respectively.

Thermolysis of β-substituted α-(1-tetrazolyl)acrylamides. Attempts to prepare 2-phenyl-4-benzylidene-5-imidazolone (IVa) from α-(5-phenyl-1-tetrazolyl)-cinnamamide (IIIa) under conditions which transformed the acid Ia to the unsaturated 5-oxazolone IIa were unsuccessful. Thus heating of the amide IIIa to about the melting point as well at atmospheric pressure as *in vacuo*, in a high boiling solvent such as sulfolane or in organic bases only resulted in unchanged amide or in complete decomposition.

The deep-seated decompositions of the amide IIIa emphasized the necessity for a catalyst allowing the reaction to proceed at a lower temperature. Copper powder is known to form a complex with the tetrazole ring.[2] The copper complex of 5-aminotetrazole is reported to decompose with rupture of the tetrazole ring in the presence of dilute acids, although 5-aminotetrazole is



Scheme 1.

relatively stable in the presence of acid.[3] Likewise copper powder is found to lower the decomposition temperature of 1,5-diphenyltetrazole by about 60°C, although the product formed was a black mass from which no pure substance could be isolated.[4]

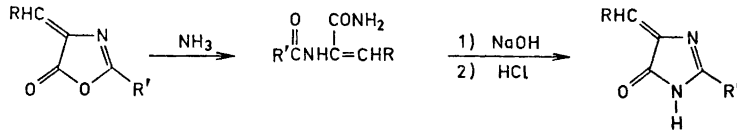
Addition of copper powder to the amide IIIa lowered the decomposition temperature by about 50°C. The principal product of this reaction, which proceeded optimally *in vacuo* at temperatures about the melting point, was identified as the imidazolone IVa. The method was successfully used for the cyclization of the amides IIIb – d. The vigorous evolution of gas during the process in the case of IIIb and IIIe could be subdued by carrying out the reaction in quinoline. The imidazolone IV was formed in yields ranging from 10 – 60 % (see Table 1).

The principal product from thermolysis of IIId was shown by an elemental analysis to contain two nitrogen atoms less than the starting material. Thin layer chromatography rendered probable that analogous compounds were formed by thermolysis of IIIa, IIIb and IIIe. The elucidation of the structure of the unknown compounds is going on in these laboratories. The observation of nitrogen loss together with the fact that no hydrazoic acid was detected [6] in the gaseous product from thermolysis of III made us suggest that the thermal breakdown of III proceeded through nitrogen liberation as the initial step. This is supported by the finding of Smith and Leon,[7] who reported that the thermal decomposition of 1,5-diaryltetrazoles only gave rise to products formed by loss of one molecule of nitrogen. Contrary to this the thermal breakdown of the acid I proceeded through hydrazoic acid liberation in agreement with the thermolytic studies of Huisgen *et al.* on 5-phenyltetrazole.[5]

It is noteworthy that the carboxylic acids I and thiocarboxylic acid VIa (see p. 2690) were converted into the oxazolones II and the thiazolone VIIa, respectively, without using copper powder. Strong acid has been shown to catalyze the release of nitrogen from 1,5-substituted tetrazoles, but it also

alters the course of reaction by forming amines and carbon dioxide as the final products.[8] The catalytic effect of the acid is supposed to be due to a protonation of the tetrazole ring.[8] In the α-(1-tetrazolyl)acrylic acids the tetrazole ring is partly protonated,[1] which may possibly explain why the thermolysis of carboxylic and thiocarboxylic acids need no copper powder as a catalyst.

The imidazolones IV were identified by comparing the melting points and the IR-spectra with compounds prepared by independent syntheses involving ammonolysis of the corresponding oxazolones II and subsequent cyclization of the intermediate amides V by treatment with hot aqueous alkali.



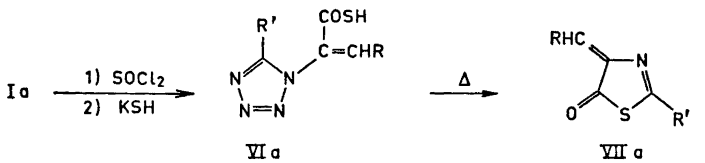
II a-f V a-f IV a-f

Scheme 2.

The imidazolones IVb, c, e and the amide intermediates Vb, c, e have not previously been described. 2-Methyl-4-*p*-nitrobenzylidene-5-imidazolone (IVe) crystallized as a monohydrate. Removal of water of crystallization upon heating was accompanied by simultaneous destruction of the compound, but the imidazolone structure could be definitely established on IR- and ^{1}H NMR-spectroscopical evidence.

Heating of α-(5-methyl-1-tetrazolyl)cinnamamide (IIId) yielded as by-product 13 % of 2-styryl-4-benzylidene-5-imidazolone (IVf) as identified by comparison with an authentic sample of IVf prepared by a known procedure.[9] Considering α-(5-methyl-1-tetrazolyl)-*p*-nitrocinnamamide (IIIe) this compound in analogy to IIId afforded as by-product the new 2-(*p*-nitrostyryl)-4-(*p*-nitrobenzylidene)-5-imidazolone (IVg) but only in a few per cent yield. IVg was further synthesized by the procedure described for IVf [9] but attempts to obtain an analytically pure product failed.

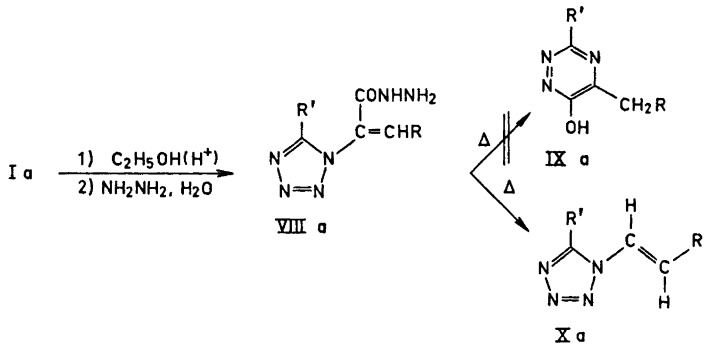
The β-substituted α-(1-tetrazolyl)acrylamides III, which are all new, were prepared from the corresponding acids I by treatment with thionyl chloride and subsequent reaction with ammonia.



VI a VII a

Scheme 3.

Thermolysis of α-(5-phenyl-1-tetrazolyl)thiocinnamic S-acid. The α-(5-phenyl-1-tetrazolyl)thiocinnamic S-acid (VIa) yielded almost quantitatively the 2-phenyl-4-benzylidene-5-thiazolone (VIIa) on heating to 150°C *in vacuo*, but the thiocarboxylic acid VIa could not be obtained in a pure state. All attempts to prepare the thiocarboxylic acid VIa by treating the corresponding acid chloride with alkali hydrosulfide in ethanol [12] under continued hydrogen sulfide supply were accompanied by the formation of the corresponding carboxylic acid, ester, and disulfide due to the easy hydrolysis, ethanolysis, and oxidation, respectively, of the thiocarboxylic acid.[12] Compound VIa could not be separated from the carboxylic acid by the usual methods, *i.e.* distillation or recrystallization and so upon heating a mixture of the thiazolone VIIa and the corresponding oxazolone IIa, was formed. The optimal thiocarboxylic acid synthesis led to thiazolone and oxazolone in a ratio of three to one. Several attempts to separate these compounds failed and hence the reaction following the pathway of Scheme 3 is unsuitable for preparative purpose.



Scheme 4.

Thermolysis of α-(5-phenyl-1-tetrazolyl)cinnamohydrazide. The thermal decomposition of α-(5-phenyl-1-tetrazolyl)cinnamohydrazide (VIIIa) did not afford cyclization to the *as*-triazine IXa. The only product isolated was the *trans*-1-vinyltetrazole Xa as indicated by the ^{1}H NMR-spectrum. An earlier paper [1] describes the synthesis of the *cis*-1-vinyltetrazole by decarboxylation of α-(5-phenyl-1-tetrazolyl)cinnamic acid (Ia).

The hydrazide VIIIa was synthesized from the carboxylic acid Ia which was esterified [13] and subsequently treated with hydrazine hydrate according to Scheme 4.

EXPERIMENTAL

The IR-spectra were recorded on a Perkin-Elmer 337 spectrophotometer (KBr discs) and the ^{1}H NMR-spectra were recorded at 60 MHz on a Varian A 60 spectrometer using tetramethylsilane as an internal standard.

Table 1. New β-substituted α-(1-tetrazolyl)acrylamides III and their thermal transformation into the imidazolones IV.

Compound, *cf.* Scheme 1	Recryst. from	Yield %	M.p. °C	Formula	Analysis (C,H,N,S)	Thermal transformation of the amides III into the imidazolones IV: Method	Reaction time, min.	Reaction temp. °C	Yield of IV [a] %
IIIa	aqueous ethanol	75	180–82	$C_{16}H_{13}N_5O$	Found: 66.00; 4.51; 24.20 Calc.: 65.97; 4.50; 24.04	A	50	180	40
IIIb	ethyl acetate/ petroleum ether	60	207–08	$C_{14}H_{11}N_5OS$	Found: 56.42; 3.83; 24.09; 10.98 Calc.: 56.53; 3.73; 23.56; 10.79	A B	10 60	207 195	30 60
IIIc	aqueous ethanol/DMF	70	230–32	$C_{16}H_{12}N_6O_3$	Found: 57.30; 3.78; 25.25 Calc.: 57.14; 3.60; 24.99	A	10	207	55
IIId	ethanol/DMF	65	204–12	$C_{11}H_{11}N_5O$	Found: 57.60; 4.92; 30.70 Calc.: 57.63; 4.84; 30.55	A	15	207	10
IIIe	aqueous ethanol/DMF	65	250–53	$C_{11}H_{10}N_6O_3$	Found: 48.01; 3.84; 31.14 Calc.: 48.17; 3.68; 30.65	B A	20 2	210 230	30 13

[a] Yields calculated after separation by preparative layer chromatography.

The melting points were determined with a hot stage microscope (Mikroskop-Heiztisch 350 Ernst Leitz G.m.b.H., Wetzlar). The microanalyses were made by Preben Hansen, Microanalytical Department of Chemical Laboratory II, University of Copenhagen.

The preparative layer chromatography was made on 1 mm silica gel PF_{254} (Merck) plates.

The α-(1-tetrazolyl)acrylic acids I,[1] the reference imidazolones IVa [14] and IVd,[15] the reference thiazolone VIIa [16] and the reference *as*-triazine IXa [17] were prepared by literature methods.

β-Substituted α-(5-methyl- or 5-phenyl-1-tetrazolyl)acrylamide (III). General procedure. The α-(1-tetrazolyl)acrylic acid I (0.025 mol) and 0.4 mol (in the case of IIIa, IIIb, and IIId) or 0.8 mol (in the case of IIIc and IIIe) of thionyl chloride were refluxed until the solution became clear and the evolution of hydrogen chloride had ceased (1 – 5 h). Excess of thionyl chloride was evaporated *in vacuo* (12 mmHg) and traces of thionyl chloride were removed by evaporation with dry benzene. The crude acid chloride was dissolved in 30 ml of dry benzene or in the case of IIIe in 30 ml of dry chloroform and added dropwise with stirring to 100 ml of cold concentrated aqueous ammonia, at such a rate that the temperature did not exceed 5°C. Stirring and cooling were continued for another hour and the precipitate was collected, dried and recrystallized from a suitable solvent (see Table 1). IR-spectra (cm^{-1}): 3300 – 3420s (N – H), 3120 – 3170s (N – H) and 1690 – 1710s (C = O). Indication of intensity: s = strong, m = medium.

Thermolysis of β-substituted α-(1-tetrazolyl)acrylamides (III). (Scheme 1). General procedures. Method A. A mixture of III (4 mmol) and 10 % by weight of copper powder (reduced by hydrogen) was heated *in vacuo* (12 mmHg) for 2 – 50 min at 180 – 230°C. The imidazolone formed was isolated by preparative layer chromatography using benzene-ethyl acetate 1 : 1 as an eluent. Experimental data are summarized in Table 1.

Method B. A mixture of III (4 mmol) and 10 % by weight of copper powder (reduced by hydrogen) in 2 ml of quinoline was heated during 20 – 60 min at 195 – 210°C. The mixture was cooled and poured into 7 ml of 4 N hydrochloric acid and the suspension was adjusted to pH 4 – 5 with 2 N sodium hydroxide. The precipitate was collected and the imidazolone was isolated as described under method A.

Unsaturated 5-imidazolones (IV) prepared by independent synthesis. General procedure. II (10 mmol) was stirred in 50 ml of saturated ethanolic ammonia for 20 min. The reaction mixture was cooled to 0°C and the substituted acrylamide V was collected and recrystallized from a suitable solvent. Experimental and analytical data are summarized in Table 2.

Table 2. New β-substituted α-acetamido or α-benzamidoacrylamides V.

Compound	Recryst. from	Yield %	M.p. °C	Formula	Analysis (C,H,N,S)
Vb	aqueous methanol	75	218 – 19	$C_{14}H_{12}N_2O_2S$	Found: 61.62; 4.51; 10.24; 11.70. Calc.: 61.76; 4.44; 10.29; 11.76.
Vc[a]	methanol	63	204 – 7	$C_{16}H_{13}N_3O_4$	Found: 61.80; 4.30; 13.37. Calc.: 61.73; 4.21; 13.50.
Ve	aqueous methanol	69	232 – 34	$C_{11}H_{11}N_3O_4$	Found: 52.90; 4.50; 16.90. Calc.: 53.01; 4.45; 16.86.

[a] Crystallized with ½ mol of water found by a Karl Fischer titration and an elemental analysis. (Found: C 59.95; H 4.32; N 13.17. Calc. for $C_{16}H_{13}N_3O_4 \cdot \frac{1}{2}H_2O$: C 60.01; H 4.41; N 13.12). The water could be removed upon heating at 100°C.

The amide V (7 mmol) was treated with 7 ml of 2 N sodium hydroxide and heated on a steam bath for 5 min (Vb – c) or 2 min (Ve), and the solution was adjusted to pH

4 – 5 with 4 N hydrochloric acid. The precipitate formed IV was collected and recrystallized from a suitable solvent. Experimental and analytical data are summarized in Table 3.

Table 3. New 4-unsaturated 2-methyl or 2-phenyl-5-imidazolones IV prepared by the independent synthesis outlined in Scheme 2.

Compound	Recryst. from	Yield %	M.p. °C	Formula	Analysis (C,H,N,S)
IVb	aqueous methanol	60	316 – 19	$C_{14}H_{10}N_2OS$	Found: 65.65; 4.15; 10.96; 12.30. Calc.: 66.10; 3.96; 11.02; 12.61.
IVc	methanol	70	315 – 19	$C_{16}H_{11}N_3O_3$	Found: 65.50; 3.99; 14.20. Calc.: 65.52; 3.78; 14.33
IVe, H_2O	aqueous methanol	45	225 – 27	$C_{11}H_9N_3O_3.H_2O$	Found: 53.29; 4.63; 16.82. Calc.: 53.10; 4.45; 16.86.

The IR-spectra of V (cm^{-1}): Two bands in the range 3170 – 3500m (N – H) and a triplet at 1640 – 1670s (C = O). The IR-spectra of IV (cm^{-1}): 3050 – 3130m (broad band) (N – H), 1700 – 1720s (C = O) and 1630 – 1660s (C = C).[18]

The ^1H NMR-spectrum of (IVe, H_2O), (DMSO): $\tau = 7.69$ ppm (singlet, 3 H, CH_3); $\tau = 6.63$ ppm (singlet, 2 H, H_2O); $\tau = 3.07$ ppm (singlet, 1 H, CH = C); $\tau = 1.64$ ppm (quartet, 4 H, $C_6H_4NO_2$); $\tau = -1.49$ ppm (singlet, 1 H, NH).

2-Phenyl-4-benzylidene-5-thiazolone (VIIa). A solution of 0.054 mol of KOH in 30 ml of 90 % ethanol was saturated with hydrogen sulfide at 10 – 15°C under stirring. During continued hydrogen sulfide supply 0.0097 mol of α-(5-phenyl-1-tetrazolyl)cinnamoyl chloride (m.p. 91 – 92°C as freshly recrystallized from cyclohexane) was added in small portions over a period of 30 min. The stirring and cooling was continued for 1 h and the reaction mixture poured into 150 ml of cold water. The solution was made alkaline and extracted with ether. The aqueous layer was then acidified with ice cold 4 N hydrochloric acid and extracted with peroxide-free ether. The ether layer was washed with cold water and dried with anhydrous sodium sulphate. The ether was evaporated under reduced pressure to give a viscous oil. The oil was taken up in dry benzene leaving a small amount of a compound identified as 5-phenyltetrazole. Upon evaporation of the benzene solution the crude thiocarboxylic acid was obtained.

The crude thiocarboxylic acid VIa was then heated *in vacuo* (12 mmHg) for 40 min at 170°C. The reaction mixture was extracted with benzene and the insoluble residue (10 %) was identified as 5-phenyltetrazole. The benzene solution was concentrated and hot ethanol was added to the boiling solution to incipient turbidity. Upon cooling a mixture of the thiazolone VIIa and the corresponding oxazolone IIa separated (70 %). In our hands neither fractional crystallization in ethanol nor chromatography afforded any separation of the two compounds.

An IR-analysis of the mixture was carried out on basis of the absorption bands of the carbonyl group at 1700 cm^{-1} and 1805 cm^{-1} belonging to the thiazolone and oxazolone, respectively. This analysis showed the relative amounts of the thiazolone and the oxazolone to be as three to one.

Ethyl α-(5-phenyl-1-tetrazolyl)cinnamate. A solution of Ia (10 mmol) in 100 ml of ethanol was treated with dry hydrogen chloride during 20 min at such a rate as to keep the ethanol refluxing. The reflux was continued for another 3 h and the mixture was evaporated under reduced pressure. The residue was recrystallized from cyclohexane. Yield 80 %; m.p. 87.0 – 89.0°C. (Found: C 67.20; H 5.06; N 17.75. Calc. for $C_{18}H_{16}N_4O_2$: C 67.48; H 5.03; N 17.49). The IR-spectrum (cm^{-1}): A triplet at 2980m (C_2H_5) and a singlet 1720s (C = O).

α-(5-Phenyl-1-tetrazolyl)cinnamohydrazide (VIIIa). A mixture of 3.0 mmol of ethyl α-(5-phenyl-1-tetrazolyl)cinnamate in 5 ml of ethanol and 4.5 mmol of 100 % hydrazine hydrate was stirred at room temperature for 10 min. After cooling the precipitate formed was collected and recrystallized from ethanol. Yield 85 %; m.p. 220–21°C. (Found: C 62.75; H 4.68; N 27.90. Calc. for $C_{16}H_{14}N_6O$: C 62.73; H 4.61; N 27.44). The IR-spectrum (cm^{-1}): 3090s, 3150s and 3210s (N–H) and 1730s (C=O).

trans-*1-Styryl-5-phenyltetrazole (Xa).* The hydrazide VIIIa (20 mmol) and 10 % by weight of copper powder (reduced by hydrogen) were heated *in vacuo* (12 mmHg) during 50 min at 220°C. The 1-styryltetrazole formed was isolated by preparative layer chromatography using benzene-ethyl acetate 6 : 4 as an eluent. Recrystallization from cyclohexane-petroleum ether yielded 65 % of product; m.p. 146–147°C. (Found: C 72.50; H 5.02; 22.48. Calc. for $C_{15}H_{12}N_4$: C 72.56; H 4.89; N 22.57). The IR-spectrum (cm^{-1}): 950s (*trans* CH=CH). ^1H NMR-spectrum (DMSO): $\tau = 2.14$ ppm and $\tau = 2.45$ ppm (AB-quartet, ($J = 14.4$ Hz), 2 H, CH=CH); $\tau = 2.00 - 2.70$ ppm (multiplet, 10 H, 2 C_6H_5).

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