Preparation of Some 2,4-Disubstituted Imidazole-5-carboxamides by Thermolysis of β-Substituted α-(1-Tetrazolyl)acrylamides

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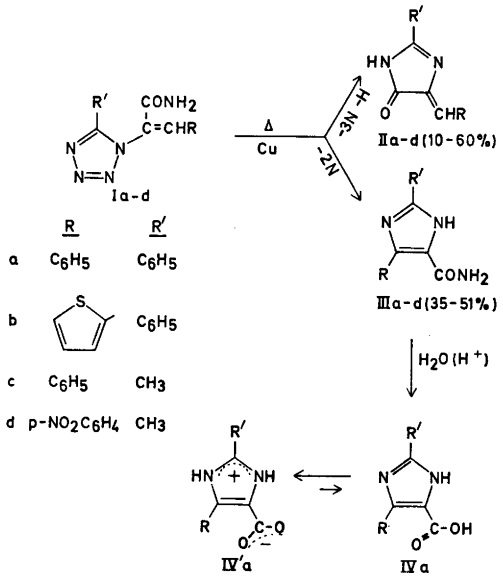
In a previous paper [1] it was described that the β-substituted α-(1-tetrazolyl)acrylamides I by copper catalyzed thermolysis were transformed into the unsaturated 5-imidazolones II by an overall loss of three nitrogen atoms and one hydrogen atom. Further it was mentioned that another, unidentified, type of compound was simultaneously formed by an overall loss of two nitrogen atoms. In the present paper it is shown that the latter compounds are 2,4-disubstituted imidazole-5-carboxamides III, and a modification of the thermolytic procedure is given which forms a convenient synthetic route to these compounds. No 4-alkylated, 4-arylated or 4-heteroarylated imidazole-5-carboxamide has to our knowledge been reported in the literature.

4-Aminoimidazole-5-carboxamide (AICA), which is a purine precursor, and some analogous compounds, *e.g.* 4-chloroimidazole-5-carboxamide, enhance the carcinostatic activity of 8-azaguanine, presumably because these compounds are inhibitors of guanine deaminase.[2-4] Furthermore antitumor activity of some 4-(3-dialkylated-triazeno)imidazole-5-carboxamides has been detected.[5-7] These findings suggest that the 2,4-disubstituted imidazole-5-carboxamides III might be taken into consideration as potential anticancer agents.



The imidazole-5-carboxamides III were formed in optimum yields (35–51 %) by heating the compounds I with copper powder *in vacuo* under the conditions summarized in Table 1. The intermediately formed imidazole-copper-complexes [8] were decomposed with ethanol, and the amides III were isolated from the ethanolic extract by preparative layer chromatography.

The amide IIIa was hydrolyzed by refluxing with 6 N hydrochloric acid. The acid IVa thus obtained was identical (melting point and IR spectrum) with 2,4-diphenylimidazole-5-carboxylic acid prepared by alkaline hydrolysis of the corresponding ethyl ester, which had been formed by action of ammonium acetate on ethyl α-benzoyloxybenzoylacetate according to Strzybny *et al.*[9] The IR, ^{1}H NMR and mass spectrum of IIIa were recorded. Using these data the structures of the analogous compounds IIIb–d could be established by spectroscopy supported by elemental analyses.

The acid IVa exists predominantly as the zwitterion IV'a as indicated by the IR spectrum.[10] This is in accordance with the structure found for imidazole-5-carboxylic acid.[11]

Unsuccessful attempts were made to prepare IIIa from the corresponding ethyl ester by treatment with 30 % aqueous ammonia.

Experimental. Recording of IR spectra and ^{1}H NMR spectra, determination of melting points and microanalyses were performed as previously described.[1] The mass spectra were obtained with an AEI MS 902 mass spectrometer operating at 70 eV.

2,4-Disubstituted imidazole-5-carboxamides III. General procedure. A mixture of the tetrazolylacrylamide I [1] (4 mmol) and 10 % by weight of copper powder (BDH Ltd., Laboratory reagent, reduced by hydrogen) was heated under reduced pressure (12 mmHg) for 2–15 min at 197–230 °C. The mixture was extracted with several portions of boiling ethanol, and the ethanol was evaporated under reduced pressure. From the residue the imidazole-5-carboxamide III was isolated by preparative layer chromatography on 1 mm silica gel PF_{254} (Merck) plates using benzene–ethyl acetate 1:1 (in the case of IIIa and b) or benzene–ethanol 8:2 (in the case of IIIc and d) as eluent. Experimental and analytical data are given in Table 1.

IR spectra of IIIa–d were recorded and found in accordance with data published for other primary amides:[10] 2900–3600 cm^{-1} (m) (broad band with one submaximum about 3450 cm^{-1} (N–H, free) and another, very broad submaximum about 3150 cm^{-1} (N–H, bonded)), 1670 cm^{-1} (s) (amide I, C=O) and 1590–1610 cm^{-1} (s) (amide II, mostly NH_2). Intensities are indicated as s (strong), m (medium), or w (weak).

Table 1. Preparation of 2,4-disubstituted-5-imidazolecarboxamides IIIa – d by copper catalyzed thermolysis of the β-substituted α-(1-tetrazolyl)acrylamides Ia – d.

Starting material M.p. °C	Reaction conditions Temp. °C	Time min	Product	Yield[a] %	Recryst. from[b]	M.p. °C	Formula	Analyses C, H, N, S
Ia 180–182	197–203	15	IIIa[c]	51	A	217–219	$C_{16}H_{13}N_3O$	Found: 72.65; 5.10; 16.07 Calc.: 72.98; 4.98; 15.96
Ib 207–208	207	2	IIIb	38	B	82–85	$C_{14}H_{11}N_3SO$	Found: 62.50; 4.60; 15.76; 11.51 Calc.: 62.45; 4.12; 15.61; 11.88
Ic 204–212	207	10	IIIc	37	C	194–197	$C_{11}H_{11}N_3O$	Found: 65.57; 5.66; 20.85 Calc.: 65.57; 5.51; 20.88
Id 250–253	230	2	IIId[d]	35	B	207–210	$C_{11}H_{10}N_4O_3 \cdot \frac{1}{2}H_2O$	Found: 52.05; 4.19; 21.80 Calc.: 51.76; 4.35; 21.95

[a] Yields calculated after isolation by preparative layer chromatography. [b] A, dry toluene; B, dry xylene-light petroleum; C, dry toluene-light petroleum. [c] Crystallizes from benzene-ethyl acetate with ½ mol of water. M.p. 197–210 °C. (Found: C 70.55; H 5.00. N 15.20. Calc. for $C_{16}H_{13}N_3O.\frac{1}{2}H_2O$: C 70.60; H 5.18; N 15.44). [d] Dried *in vacuo* at 180 °C over P_2O_5 for 3 h. Decomposes slowly above 180 °C without releasing water.

^{1}H NMR spectra (DMSO-d_6) were recorded for IIIa, c and d. IIIa: δ 8.3–7.9 (m, 4 aromatic *o*-protons), 7.7–7.0 (m, 6 aromatic *m*- and *p*-protons and 3 NH protons). IIIc: δ 8.0–7.7 (m, 2 aromatic *o*-protons), 7.5–6.9 (m, 3 aromatic *m*- and *p*-protons and 3 NH protons), 2.33 (s, 3 methyl protons). IIId: δ 8.26 (s, 4 aromatic protons), 8.2–7.0 (broadened signal, 3 NH protons), 2.38 (s, 3 methyl protons). By deuteration of IIIa, c, and d with D_2O approximately two NH protons were exchanged.

Mass spectra were recorded for IIIa and c. The spectra display fragmentation patterns which are in accordance with data published for primary amides [12] and for imidazoles.[12,13] Prominent peaks in the mass spectra of IIIa and IIIc, respectively: Molecular ion (M) (*m/e* 263 (100 %) and *m/e* 201 (100 %); M–H (42 resp. 46 %), M–NH_2 (23 resp. 38 %), M–NH_3 (40 resp. 41 %), M–$CONH_2$ (8 resp. 3 %), M–$CONH_3$ (23 resp. 4 %), R'CNCCO (14 resp. 43 %), R'CNC (36 resp. 5 %), R'CNH (26 resp. 19 %). Ions common for IIIa and IIIc: C_6H_5CCN (36 resp. 9 %), C_6H_5CNH (26 resp. 15 %), C_6H_5C (42 resp. 23 %), $CONH_2$ (8 resp. 6 %).

2,4-Diphenylimidazole-5-carboxylic acid (IVa). A solution of IIIa (0.3 mmol) in 10 ml of 6 N hydrochloric acid was refluxed for 2 h. After cooling to room temperature a reddish precipitate was removed, and the pH of the solution was adjusted to about 3 by means of sodium hydroxide (30 %). The carboxylic acid IVa precipitated was filtered and washed with several portions of water. Yield 75 %. M.p. (decomp.) 204–206 °C (3 °C/min), 210–213 °C (5 °C/min). (Lit.[9] m.p. (decomp.) 209–210 °C). (Found: N 10.43. Calc. for $C_{16}H_{12}N_2O_2$: N 10.61). IR spectrum: 1600 (s) and 1380 cm^{-1} (s) (COO^-); 3200–1800 cm^{-1} (m) (broad band with submaxima at 1950, 2600, 2800 and 2900 cm^{-1}) (NH^+); 3600 cm^{-1} (m) (OH, free), 3400 cm^{-1} (m) (NH, free), 1720 cm^{-1} (w-m) (C=O in COOH).

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Shaking with Aqueous Sodium Hydrogen Sulfite; a Simple Procedure for Removing Some Norbornene Impurities

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When preparing nortricyclyl compounds *via* homoallylic rearrangement of norbornenyl starting materials [1–3] or by addition of appropriate reagents to norbornadiene,[4–6] undesired norbornenyl compounds often remain or form. Also hydrogenation of norbornenyl compounds to norbornyl analogs may be imperfect. Procedures for removing these norbornene impurities have been presented, *e.g.* shaking with aqueous potassium permanganate [5] or with aqueous silver nitrate,[6] and precipitation with nitrosyl chloride in chloroform.[4] A cheap, gentle and as yet new procedure is now being reported: shaing with aqueous sodium hydrogen sulfite, which seems best suitable for removing norbornenones and norbornenols.

It is generally known that sodium hydrogen sulfite easily forms addition compounds with aldehydes and ketones if they are not sterically hindered (reversible reactions) and it adds fairly easily at the carbon-carbon double bond conjugated with the carbon-oxygen double bond or with the carbon-nitrogen triple bond (irreversible reactions).[7,8] Simple olefinic double bonds generally react with hydrogen sulfite poorly.[7] However, the reaction between the hydrogen sulfite ion and 2-norbornenols seems to be fairly rapid, but 2-norborneols and 3-nortricyclanols do not react under the same conditions.

Disappearance rates of some substituted norbornenes were studied by shaking *ca.* 2 mmol of the substrate and an equal amount of an internal standard (2-norborneols and 3-nortricyclanols or corresponding acetates) in 20 ml ether with 50 ml of 1 M aqueous sodium hydrogen sulfite at room temperature. If the reaction was not complete in half an hour, shaking by hand was replaced by magnetic stirring. The ether phase was analyzed by GLC (an FFAP column). The following rough disappearance times (at least 99 % of the substrate had reacted) were measured: 2-norbornenone 10 min, *endo*-2-norbornenol 5 min, *exo*-2-norbornenol 30 min, 2-methyl-*endo*-2-norbornenol 5 min, 2-methyl-*exo*-2-norbornenol 40 min, *endo*- and *exo*-2-norbornenylmethanols 10 – 15 min, 2-methyl-*endo*- and 2-methyl-*exo*-2-norbornenylmethanols a few hours. The corresponding acetates also reacted, but much more slowly (10 – 100 h), and the disappearance times of norbornene and norbornadiene were very long (100 – 1000 h). The sequence of disappearance times does not evidently follow the sequence of rates of the homogeneous reactions in the aqueous solutions owing to differences in partitions of the substrates between the ether and aqueous phases. Measurements of rates of the homogeneous reactions for some compounds are under way.

Addition of a free-radical inhibitor, *e.g.* hydroquinone (4 mmol),[8] totally prevents the reaction of the alcohols studied or at least retards it very markedly. Addition of sulfuric acid (final pH ≈ 0) or sodium hydroxide (final pH ≈ 14) into the aqueous phase after the reaction has proceeded to completion does not liberate the alcohols. Thus, the sulfuric atom of the hydrogen sulfite anion (or sulfite anion) [8] attacks the double bond of the substrate *via* a free-radical mechanism producing substituted norbornanesulfonate anions, which dissolve easily in the aqueous phase.

Addition of hydroquinone retarded the reaction of 2-norbornenone, but did not stop it. About 10 % of the substrate remained unreacted (measured 18 h after the reaction had started). About two thirds of the initial ketone was regenerated by addition of sodium hydroxide. In the absence of hydroquinone, addition of alkali did not liberate any of the completely reacted 2-norbornenone. Thus, in the case of the unsaturated ketone the irreversible, mostly free-radical, attack at the carbon-carbon double bond and the reversible ionic attack at the carbon-oxygen double bond compete. The latter reaction also occurred in the case of 2-norbornanone (hydroquinone had no effect on its disappearance rate) leading to equilibrium (*ca.* 30 % of the substrate was left after 19 h). The release of 2-norbornanone occurred quantitatively by addition of alkali. Thus, shaking with sodium hydrogen sulfite also removes irre-