Reactions of Diazo Derivatives of 5-Membered Heterocycles with Hydrazines (1)

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Interaction of hydrazine or dimethylhydrazine with 5-diazoimidazole-4-carboxamide produced, presumably *via* tetrazenes, high yields of 5-azidoimidazole-4-carboxamide. In contrast, when semicarbazide reacted with either the diazoimidazole or the analogous diazo-1,2,3-triazole, the yield of the azidoheterocycle was low, and the yield of biurea, and presumably the aminoheterocycle, was high. 3-Azidopyrazole-4-carboxamide was obtained from a reaction of hydrazine with the diazopyrazole. Both azido and amino derivatives were formed from reactions of diazoimidazole esters with hydrazine or thiosemicarbazide.

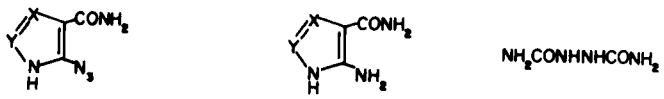
During studies of the preparation of triazeno derivatives of 5-membered heterocycles (2-5), reactions of the isolated, precursor diazoheterocycles (I) with hydrazine and with substituted hydrazines were investigated. It has been shown previously that triazenes formed from primary alkyl amines and these diazoheterocycles revert in aqueous or methanol solutions to the corresponding aminoheterocycles (2,3,5). However, arylazides are formed, sometimes in high yields, from the reaction of aryldiazonium salts and hydrazine (6). The tetrazene intermediates (II), therefore, may dissociate in one, or both, of these two ways: either aminoheterocycles (mode *a*) or azidoheterocycles (mode *b*) may be formed.

After a reaction of 5-diazoimidazole-4-carboxamide (Ia) with hydrazine in ethanol at room temperature in the dark, 5-azidoimidazole-4-carboxamide (IIIa) was isolated in 80% yield. 3-Azidopyrazole-4-carboxamide (IIIb) and ethyl 5-azidoimidazole-4-carboxylate (VIIa) were isolated in yields of 60 and 46%, respectively, following similar reactions of hydrazine with the diazoheterocycles (Ib and VIa). Ethyl 5-aminoimidazole-4-carboxylate (VIIIa) was detected as a product of the reaction of VIa with hydrazine. A reaction of dimethylhydrazine with Ia also afforded a high yield of the azidoimidazole (IIIa).

Treatment of the diazoimidazoleamide (Ia) or 5-diazo-1,2,3-triazole-4-carboxamide (Ic) with semicarbazide in methanol-ethyl acetate solution in the dark gave contrastingly different results. Although the azido derivatives (IIIa and IIIc) were isolated in low yields, the major product isolated after both reactions was biurea (V). The aminoheterocycles (IVa and IVc) were identified as products by thin-layer chromatography or mass spectroscopy, but the quantities formed were not determined. If, as seems likely, they were formed by the same mode of dissociation that led ultimately to biurea, they were the major heterocycles formed. Little, or no, biurea was formed from semicarbazide alone under the conditions employed in these reactions.

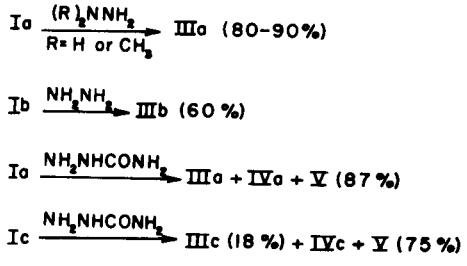
Reactions of the 5-diazoimidazole esters (VIa and VIb) with thiosemicarbazide resulted in the formation of both the azido and the amino derivatives. The yields of

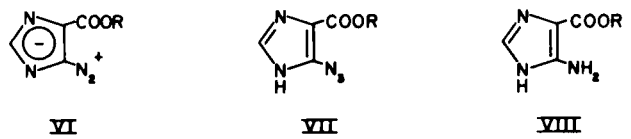
I II



III IV V

a: X = N, Y = CH
b: X = CH, Y = N
c: X = Y = N





VI VII VIII

a: R = C_2H_5, b: R = CH_3

VIa $\xrightarrow{NH_2NH_2}$ VIIa (46%) + VIIIa

VIa $\xrightarrow{NH_2NHCSNH_2}$ VIIa (40%) + VIIIa

VIb $\xrightarrow{NH_2NHCSNH_2}$ VIIb (33%) + VIIIb

NH_2CON_3

IX

isolated azido esters VIIa and VIIb were 40 and 33%, respectively. Ethyl 3-azidopyrazole-4-carboxylate has been obtained similarly by diazotizing VIIIa and adding an *N*-aminopyridinium salt (7). The aminoimidazole esters (VIIIa and VIIIb) were not isolated, but formation of these derivatives was demonstrated. Identification of other products was not attempted.

The heterocyclic azides must have arisen by cleavage of the intermediate tetrazenes by mode *b* (II). Cleavage of an intermediate formed from semicarbazide according to mode *a* should yield carbamoyl azide (IX) in addition to the aminoheterocycle. Biurea (V) has been obtained as one of the products of photochemical decomposition of carbamoyl azide (8). The formation of V was attributed to generation of carbamoylazene from IX, reaction of the azene with another molecule of IX, and reduction of the resulting azo compound by the alcohol used as solvent. Two other potential routes to biurea from Ia or Ic appear to be more likely since the reaction mixtures were shielded from light and were kept at room temperature. Since carbamoyl azides may undergo direct displacement of the azido group by amines or hydrazine (9,10), biurea may have been formed by reaction of carbamoyl azide with the excess of semicarbazide present in the reaction mixtures. Alternatively, decomposition of IX to hydrazoic and isocyanic acids (9), and reaction of the latter with excess semicarbazide might also account for the production of biurea. Thiocarbamoyl azide, presumably formed from the reactions of thiosemicarbazide with VIa and with VIb, should cyclize to 5-amino-1,2,3,4-thiatriazole (11-14).

EXPERIMENTAL

Unless otherwise stated, decomposition and melting temperatures were determined in capillary tubes heated in a Mel-Temp apparatus; those labelled "KH" were determined on a Kofler Heizbank apparatus (gradiently heated bar). Ultraviolet spectra were recorded with a Cary Model 14 spectrophotometer, and maxima are reported in nm. Solutions for ultraviolet determinations were prepared by diluting a 5-ml. aliquot of a methanol or ethanol solution to 50 ml. with 0.1 *N* hydrochloric acid, phosphate buffer (*p*H 7), or 0.1 *N* sodium hydroxide; absorption maxima are reported as being at *p*H 1, 7, or 13, respectively. Infrared spectra were recorded with Perkin-Elmer Model 521 or 221 spectrometers from samples in KBr disks; s = strong, m = medium. Mass spectral data were taken from low resolution spectra determined with a Hitachi-Perkin-Elmer RMU-7 double focusing instrument. Unless otherwise indicated, thin-layer chromatography (tlc) was performed on plates of silica gel, and spots were detected by ultraviolet light (254 nm) before and after spraying the chromatogram with an optical whitening agent, Ultraphor WT (BASF Colors and Chemicals, Inc., Charlotte, N. C.). The developing solvents are shown parenthetically at the appropriate places in the procedures.

5-Azidoimidazole-4-carboxamide (IIIa).

To a solution of 0.1 ml. of hydrazine ($\geq$ 95%) and 15 ml. of absolute ethanol was added 143 mg. of 5-diazoimidazole-4-carboxamide (Ia) (15) during 40 minutes. The mixture (protected from light) was stirred for 20 hours at room temperature. The mixture became homogeneous soon after the diazo compound had been added, and the product began to precipitate after 2-3 hours. The precipitate was collected on a filter, washed with ethanol, and dried *in vacuo* at room temperature: yield, 128 mg. (80%); explosive decomposition at 145-147°, darkened at 130-140° (inserted at 100°). A specimen for analysis was dried at 50° for 30 minutes; ir (2200-1200 cm^{-1} region) 2145s and 2125 (N_3), 1665s (amide CO), 1605s (amide II), 1565, 1490, 1420ms, 1330ms, 1300, 1215ms; uv max 265 at *p*H 1, 269 at *p*H 7, 285 at *p*H 13.

Anal. Calcd. for $C_4H_4N_6O$: C, 31.58; H, 2.65; N, 55.25. Found: C, 31.58; H, 2.50; N, 55.35.

The azido derivative (328 mg.) precipitated from a reaction mixture consisting of 500 mg. of Ia, 2.8 ml. of 1,1-dimethylhydrazine, and 20 ml. of ethyl acetate (16). A second portion (170 mg.) was obtained by diluting the filtrate with hexane: total yield, 89.7%. The infrared spectra of the two portions were identical with the spectrum of pure IIIa obtained as described above.

3-Azidopyrazole-4-carboxamide (IIIb).

The same procedure and quantities employed in the preparation of IIIa were used in treating 3-diazopyrazole-4-carboxamide (Ib) (5,17) with hydrazine; but precipitation did not occur, and the reaction solution was stirred for 48 hours. The mixture was diluted with ether (100 ml.), filtered to separate a yellow precipitate (6 mg.), and concentrated with a current of nitrogen to about 10 ml. The addition of cyclohexane (200 ml.) precipitated a white crystalline solid: yield, 95 mg. (59.9%); m.p. 168-170° dec., darkened at 150° (inserted at 80°, 3°/minutes). The ir spectrum was identical with that of the analytical sample which was prepared by recrystallizing this material from acetonitrile: m.p. 173-175° dec., darkened at 160° (inserted at 85°, 3°/minute); ir (2200-1200 cm^{-1} region) 2145s (N_3), 1675s (amide CO), 1595s (amide II), 1565ms, 1510, 1470ms, 1435, 1380, 1290, 1240ms; uv max (ϵ x 10^{-3}) 243 (9.1) at *p*H 1 and 7, 227 (12.2) and 264 (9.9) at *p*H 13.

Anal. Calcd. for $C_4H_4N_6O$: C, 31.58; H, 2.65; N, 55.25. Found: C, 31.43; H, 2.52; N, 55.00.

Ethyl 5-Azidoimidazole-4-carboxylate (VIIa).

A. From VIa and Thiosemicarbazide.

To a solution of 2.80 g. (30.6 mmoles) of thiosemicarbazide in 220 ml. of water was added, in one portion, 1.70 g. (10.2 mmoles) of VIa (18). Evolution of a gas began immediately, and the solution progressively darkened to a deep red color. The solution, protected from light during all operations, was stirred at room temperature for 2 hours, and then extracted with chloroform (4 x 150 ml.). The chloroform solution was washed with saturated aqueous sodium chloride solution, dried with magnesium sulfate, and concentrated *in vacuo* at room temperature to a pink solid: yield, 736 mg. (40%). Pale yellow platelets were obtained by treating an ethyl acetate solution (10 ml.) of the crude product with activated carbon, diluting the filtrate with cyclohexane (100 ml.), and chilling: weight, 343 mg.; m.p. 141-142° dec. (KH): ir (2200-1200 cm^{-1} region) 2140s and 2090 sh. (N_3), 1700s (ester CO), 1565ms, 1495, 1478, 1412, 1380, 1355, 1315, 1275, 1215, 1190ms, 1160; uv max (ϵ x 10^{-3}) 266 (10.9) at *p*H 1, 272 (17.4) at *p*H 7, 287 (15.4) at *p*H 13.

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.78; H, 3.90; N, 38.67. Found: C, 39.63; H, 3.61; N, 38.46.

The water layer remaining after chloroform extraction of the reaction mixture was shown by tlc in several solvent systems to contain ethyl 5-aminoimidazole-4-carboxylate (VIIIa), as well as other ultraviolet-absorbing components. Comparison of the mass spectrum of a specimen of VIIIa with a mass spectrum of the residue obtained from an aliquot of the water layer confirmed that VIIIa was a prominent component of the mixture: m/e 155 (M^+ of VIIIa), 127 (M^+ -C_2H_5 + H), 109 (M^+ -OC_2H_5 + H), 104.06 (metastable, 155 → 127). Included among other peaks in the spectrum were peaks of m/e 91 and m/e 76 corresponding to the molecular ions of thiosemicarbazide and thiourea, respectively.

B. From VIa and Hydrazine.

Ethyl 5-diazoimidazole-4-carboxylate (VIa, 166 mg.) was treated with hydrazine by the procedure used to prepare IIIa. As each portion of the diazo compound dissolved, some evolution of gas was observed. Aliquots removed from the reaction solution after 2 hours and 18 hours were shown by tlc (95:5 chloroform-methanol) to contain (a) the azide (VIIa), apparently the major component; (b) ethyl 5-aminoimidazole-4-carboxylate (VIIIa), identified by spotting an authentic specimen alongside the aliquot; and (c) minor uv-absorbing or fluorescing components. The solvent was evaporated *in vacuo*, an ethyl acetate solution of the residue was treated with activated carbon, and the solvent was evaporated in a current of nitrogen. A water (20 ml.) solution of the residue was extracted with chloroform (4 x 15 ml.). The chloroform solution was washed with water (25 ml.), dried with magnesium sulfate, treated with activated carbon, and concentrated *in vacuo* to a white solid: yield, 84 mg. (46%); m.p. 138-139° dec. (KH). The infrared spectrum was identical with that of VIIa obtained by Method A.

Methyl 5-Azidoimidazole-4-carboxylate (VIIb).

A reaction of methyl 5-diazoimidazole-4-carboxylate (VIb) (4) and thiosemicarbazide afforded VIIb: yield, 33%; m.p. 157-158° dec. The procedure was the same as that described for the preparation of VIIa; evolution of nitrogen was also observed during the reaction, and the presence of considerable methyl 5-aminoimidazole-4-carboxylate (VIIIb) in the aqueous layer was detected by tlc (butanol-water). Recrystallization of the product from chloroform-hexane as described for VIIa gave a white solid: m.p. 160-161° dec. (KH); ir (2200-1200 cm^{-1} region) 2140 sh. (N_3), 2115s (N_3), 2080 (N_3), 1700s (ester CO), 1565ms, 1495, 1475, 1440, 1380ms, 1320, 1270, 1210, 1200ms, 1160; uv max (ϵ x 10^{-3}) 266 (11.1) at *p*H 1, 271 (17.0) at *p*H 7, 227 (8.8) and 287 (15.2) at *p*H 13.

Anal. Calcd. for $C_5H_5N_5O_2$: C, 35.93; H, 3.02; N, 41.91. Found: C, 36.26; H, 3.36; N, 41.96.

Reaction of 5-Diazo-1,2,3-triazole-4-carboxamide with Semicarbazide.

To a solution (shielded from light) of 2.42 g. (21.7 mmoles) of semicarbazide hydrochloride, 2.2 g. (21.7 mmoles) of triethylamine, 10 ml. of methanol, and 40 ml. of ethyl acetate was added 500 mg. (3.62 mmoles) of 5-diazo-1,2,3-triazole-4-carboxamide (Ic) (3,15) in portions during 1 hour. Precipitation was observed before the addition had been completed. The mixture was stirred in the dark for 24 hours, and a white precipitate was separated by filtration, washed with 4:1 ethyl acetate-methanol and dried *in vacuo:* yield of biurea, 320 mg. (75%, based on Ic); m.p. 252-255° dec. [lit., *e.g.*, 250-252° (8), 245-246° (19)]. (Calcd. for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.45. Found: C, 20.50; H, 5.10; N, 47.33). The ir spectrum included prominent bands at 3400s, 3300, 3210s, 3050, 1690s, 1660, 1620, 1600, 1500, 1460, 1420, 1110, 995, 760, 660, 610, 595, and 560s cm^{-1} (*cf.* 20) and was identical with that of a commercial sample of biurea.

The filtrate was concentrated to dryness *in vacuo*, and the residue was subjected to tlc (8:2 chloroform-methanol) with 5-amino-1,2,3-triazole-4-carboxamide (IVc) and 5-azido-1,2,3-triazole-4-carboxamide (IIIc, from a previous experiment) as reference compounds. Spots that moved with both reference compounds were detected; the amino derivative appeared to be the major component. A water (25 ml.) solution of the filtrate residue was filtered, acidified to *p*H 3.6 with 1 *N* hydrochloric acid, and chilled in an ice bath. A white solid was collected by filtration, washed with water, and dried *in vacuo*: yield of IIIc, 100 mg. (18%); explosive decomposition at 175° (inserted at 150°, 3°/minute); ir (2200-1200 cm^{-1} region) 2150 and 2135 (strong doublet, N_3), 1675s (amide CO), 1590 (amide II), 1530, 1450, 1360, 1330, 1230, 1200.

Anal. Calcd. for $C_3H_3N_7O$: C, 23.53; H, 1.98; N, 64.04. Found (21): C, 23.72; H, 2.35; N, 63.30.

Reaction of 5-Diazoimidazole-4-carboxamide with Semicarbazide.

The procedure for the treatment of 5-diazoimidazole-4-carboxamide (496 mg., 3.62 mmoles) with semicarbazide was identical with that described for the triazole except that 3 equivalents of semicarbazide hydrochloride (10.9 mmoles) and of triethylamine (10.9 mmoles) were used (instead of 6). The reaction mixture was stirred in the dark for 46 hours, and filtered to remove biurea: yield, 374 mg. (87%); ir spectrum identical with that of an authentic sample. The filtrate was treated with activated carbon and concentrated to dryness *in vacuo*. The residue was stirred with water (15 ml.), and an undissolved solid was separated by filtration; weight, 27 mg. The filtrate was acidified to *p*H 3.5, chilled in an ice bath, and filtered to remove a white precipitate; weight, 41 mg. The ir spectra of the second and third isolated fractions showed that they were predominantly the azido derivative (IIIa); bands at 3400 and 560 cm^{-1} and other weak bands or inflections indicated that biurea was the principal (or only) contaminant. The filtrate from the third fraction was concentrated to dryness *in vacuo*, and the gummy residue was subjected to tlc on silica gel in 4 solvent systems (5:1 chloroform-methanol, 86:14 butanol-water, 4:1 ethanol-15 *N* ammonia,

5:3:2 butanol-water-acetic acid, detection by uv light before and after spraying with Ultraphor WT and by iodine vapor). Several spots were detected on each of the 4 chromatograms, and a major spot on each chromatogram moved with 5-aminoimidazole-4-carboxamide (IVa) free base, which was spotted as a reference compound. The mass spectrum confirmed the presence of IVa; the molecular ion peak (m/e 126) of IVa and a fragment peak of m/e 109 (126 − 17) were the most intense peaks in the spectrum at a direct-probe inlet temperature at 270°. Other peaks observed at 270° or at lower temperatures were m/e 152 (weak, M^+ of IIIa), 101 (strong, M^+ of triethylamine), 94.3 (metastable, 126 → 109), 86 (strong, triethylamine -CH_3), 75 (weak), 60 (weak). The latter two peaks may be due to the molecular ions of semicarbazide and urea, respectively.

Semicarbazide in the Absence of a Diazo Compound.

A solution of 2.42 g. of semicarbazide hydrochloride, 2.2 g. of triethylamine, 25 ml. of anhydrous methanol, and 40 ml. of anhydrous ethyl acetate was filtered to remove a small amount (12 mg.) of biurea, identified by its infrared spectrum, that was apparently present in the semicarbazide. The filtrate was stirred in the dark at room temperature for 5 days. Precipitation did not occur. In contrast, an identical solution to which 500 mg. of Ic was added had deposited 301 mg. of biurea (70% yield based on Ic) after 24 hours of stirring. These experiments showed that direct conversion of semicarbazide to biurea did not contribute significantly to the yield of biurea obtained from reactions of semicarbazide with Ia and with Ic.

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