Pyridazines. LI. Synthetic Approaches to Pyridazino[2,3-*a*]-1,3,5-triazines, a Novel Heterocyclic System[1]

M. ZUPAN, B. STANOVNIK, AND M. TIŠLER*

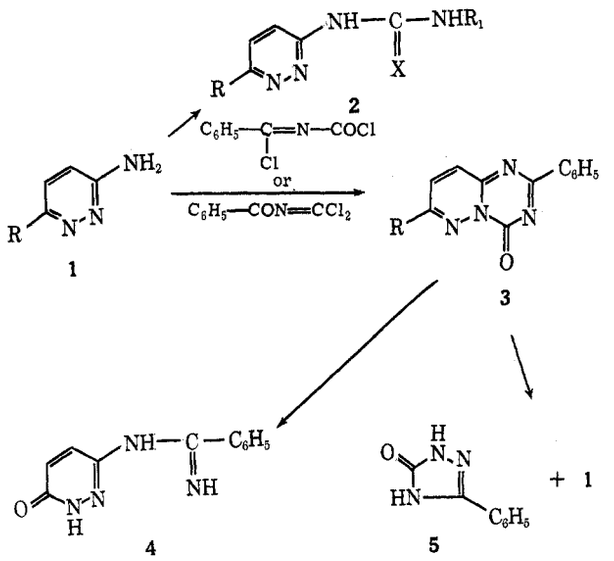
Department of Chemistry, University of Ljubljana, 61001 Ljubljana, Yugoslavia

Received March 10, 1972

Three synthetic pathways leading to a novel heterocyclic system, pyridazino[2,3-*a*]-1,3,5-triazine, and some of its transformations are described.

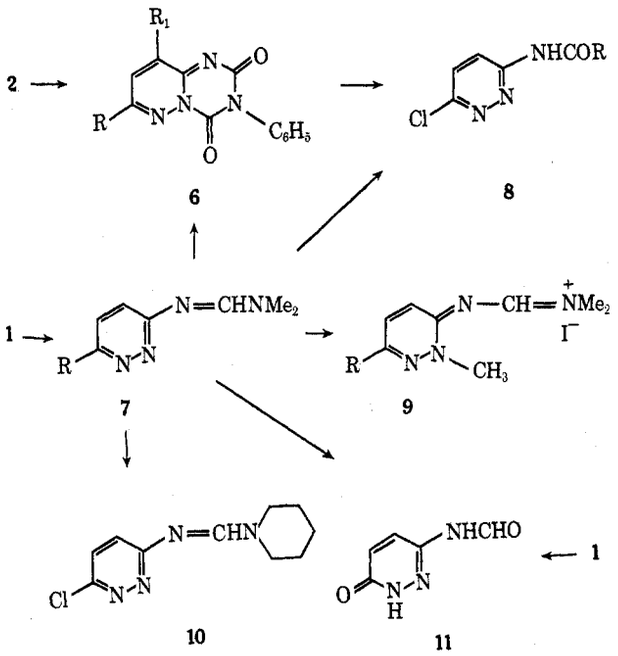
Neither the parent heteroaromatic pyridazino[2,3-*a*]-1,3,5-triazinium system nor its derivatives have so far been synthesized. Earlier work in this laboratory directed towards azolo- and azinoazines with bridgehead nitrogen[2,3] stimulated the investigation on pyridazino-[2,3-*a*]-1,3,5-triazines. We would like to report on several synthetic approaches toward this bicyclic system, as well as on some investigations concerning its reactivity.

All syntheses which we have developed use 3-amino-pyridazines as starting material. In this manner, 3-amino-6-chloropyridazine with either *N*-(phenyl-chloromethylene)carbamic acid chloride or benzoyl isocyanide dichloride formed the bicyclic compound (**3**, R = Cl) in moderate yield. The system is stable in the presence of bases and the halogen atom at position 7 could be replaced by nucleophiles. A similar reaction took place with hydrazine at low temperature, but at room temperature and in particular when heat was applied, the bicyclic system was degraded to 3-phenyl-1,2,4-triazol-5(4*H*)-one (**5**) and 3-amino-6-chloropyrid-



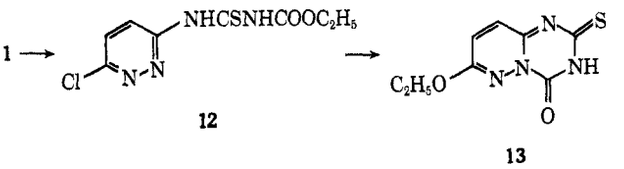
azine. Similar ring cleavage could be observed also when **3** was treated with boiling diluted hydrochloric acid and the substituted formamidine (**4**) could be isolated and characterized.

A second approach to this bicyclic system consisted of condensing either the corresponding *N*-(pyridazinyl-2′)-*N*′-phenylurea (**2**, X = O; R_1 = Ph) or *N*,*N*-dimethyl-*N*′-(pyridazinyl-3′)formamidine (**7**) with phenyl isocyanate. In both cases the corresponding 3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-diones (**6**) were formed, and they undergo electrophilic substitution (bromination) at position 9. This may be anticipated if we take into account that this position is most susceptible for electrophilic attack also with related pyrimido[1,2-*b*]pyridinazines, as shown from the calculated electron densities.[2] On the other hand, the stability of this system toward bases is greatly diminished by the introduction of the 3-phenyl group, and attempted nucleophilic displacement of the 7-chlorine atom with sodium ethoxide proceeded by ring opening to give the pyridazine (**8**, R = OEt).



N,*N*-Dimethyl-*N*′-(pyridazinyl-3′)formamidine or its 6′-chloro analog (**7**) formed a quaternary salt with methyl iodide, and nmr spectroscopic investigation revealed that the methyl group entered in the pyridazine ring to give the conjugated formamidinium salt (**9**). On the other hand, the formamidine **7** can undergo a displacement of the dimethylamino group with piperidine to give **10**.

Finally, another convenient preparative route to the bicyclic system was developed by preparing *N*-carbethoxy-*N*′-(6′-chloropyridazinyl-3′)thiourea (**12**) which, upon heating in the presence of sodium ethoxide, afforded the compound **13**. Other less basic promotors,



(1) Heterocycles. Part XCVII.

(2) A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **36**, 2457 (1971).

(3) B. Stanovnik, M. Tišler, and B. Stefanov, *ibid.*, **36**, 3812 (1971), and other references cited therein.

such as pyridine or triethylamine, proved to be ineffective as cyclizing agents. We have observed the same situation recently when synthesizing the related pyrido[1,2-*a*]-1,3,5-triazines.[4]

Experimental Section

Melting points were taken on a Kofler micro hot stage. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (TMS as internal standard), and mass spectra were recorded on a CEC 21-110C instrument using direct sample insertion into the ion source.

***N*-(6′-Chloropyridazinyl-3′)-*N*′-benzoylurea (2, R = Cl; X = O; R_1 = PhCO).**—A filtered solution of 3-amino-6-chloropyridazine (2.0 g) in dioxane (80 ml) was treated with benzoyl isocyanate (2.4 g), and the reaction mixture was heated under reflux for 15 min. The separated product was filtered and crystallized from dioxane (3.3 g, 78%): mp 245°; ir (KBr) 1709 and 1689 (CO), 3300 and 3165 cm^{-1} (NH); mass spectrum M^+ = 276.

Anal. Calcd for $C_{12}H_9ClN_4O_2$: C, 52.24; H, 3.28; N, 20.30. Found: C, 52.24; H, 3.72; N, 20.40.

If the compound was heated with polyphosphoric acid at 120° for 3 hr, a sublimate was identified as benzoic acid and the mixture, after being diluted with water, afforded 3-amino-6-chloropyridazine.

2-Phenyl-7-chloropyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = Cl). A.—A suspension of 1 (R = Cl) (1.0 g) in a mixture of chloroform (30 ml) and toluene (30 ml) was vigorously stirred under nitrogen. An ethereal solution of *N*-(phenylchloromethylene)carbamic acid chloride[5] (1.0 g) was added portionwise and, after being stirred for 4 hr at room temperature, the mixture was then heated under reflux for 30 min. The solvent was evaporated *in vacuo* and the product was crystallized from dimethyl sulfoxide (0.2 g, 25%): mp 310–312°; ir (KBr) 1740 cm^{-1} (CO); mass spectrum M^+ = 258; nmr (DMSO-d_6, 130°) τ 2.33 (s, H_8, H_9), 2.33, and 1.45 (m, Ph).

Anal. Calcd for $C_{12}H_7ClN_4O$: C, 55.71; H, 2.73; N, 21.65. Found: C, 55.99 H, 3.06; N, 21.65.

B.—A suspension of 1 (R = Cl) (1.0 g) in dry ethyl acetate (10 ml) was stirred and benzoyl isocyanide dichloride[5] (1.0 g) was added. Stirring under nitrogen was continued for 3 hr and, upon filtration, the residue was suspended in ethyl acetate (30 ml) and filtered again. This procedure was repeated twice. The filtrates were combined and dried, and the solvent was evaporated *in vacuo*. The residue was treated with cyclohexane and, after 1 hr, the product was filtered off (0.3 g, 15%). It is essentially pure, mp 310–312°, and identical with the product obtained as described under A.

7-Methoxy-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = OCH_3).—To a cooled (0°) solution of sodium methylate (prepared from 0.1 g of sodium and 8 ml of methanol) the chloro compound (3, R = Cl) (1.0 g) was added portionwise under stirring. The suspension was stirred at 0° for 2 hr and the product was filtered off (0.8 g, 81%). It was crystallized from *N*,*N*-dimethylformamide and ethanol: mp 274–276°; ir (KBr) 1718 cm^{-1} (CO); nmr (DMSO-d_6, 139°) τ 2.13 (d, H_8), 2.42 (d, H_9), 5.92 (s, CH_3O), 2.50 and 1.65 (m, C_6H_5), $J_{8,9}$ = 9.0 Hz.

Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.67; H, 4.34; N, 21.66.

The same product was obtained if the chloro compound was stirred at room temperature in a methanolic solution of potassium hydroxide.

7-Phenylthio-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = C_6H_5–S–) was prepared in a likewise manner with sodium thiophenolate: mp 275° (from *N*,*N*-dimethylformamide and ethanol); ir (KBr) 1736 cm^{-1} (CO); nmr (DMSO-d_6, 154°) τ 2.22 (d, H_8), 2.48 (d, H_9), 2.5 (m, C_6H_5S–), 2.5 and 1.65 (m, 2-C_6H_5), $J_{8,9}$ = 9.0 Hz.

Anal. Calcd for $C_{18}H_{12}N_4OS$: C, 65.05; H, 3.64; N, 16.86. Found: C, 64.62; H, 3.68; N, 16.83.

7-Hydrazino-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one (3, R = $NHNH_2$).—A suspension of the chloro compound (3, R = Cl) (1.0 g) in methanol (10 ml) was cooled to 0°, hydrazine hydrate (3 ml of 100%) was added, and the mixture was stirred at 0° for 3 hr. The product (0.7 g, 71%) had mp 250–252°; ir (KBr) 3322 (NH_2) and 1700 cm^{-1} (CO); nmr (DMSO-d_6, 130°) τ 2.50 (s, H_8, H_9), 2.60 and 2.25 (m, C_6H_5), 6.8 (broad, NH).

Anal. Calcd for $C_{12}H_{10}N_6O$: C, 56.68; H, 3.96; N, 33.06. Found: C, 56.50; H, 4.10; N, 32.83.

The compound formed a **benzylidene derivative (3, R = $NHN{=}CHC_6H_5$)** which was prepared in the usual way: mp 320° (from *N*,*N*-dimethylformamide and toluene); nmr (DMSO-d_6, 107°) τ 2.10 (s, H_8, H_9), 2.5 and 1.8 (m, C_6H_5CH).

Anal. Calcd for $C_{19}H_{14}N_6O$: C, 66.65; H, 4.12; N, 24.55. Found: C, 66.39; H, 4.36; N, 24.10.

If the reaction between the chloro compound and hydrazine was conducted at room temperature, a mixture of the 7-hydrazino compound (0.58 g) and the triazolone (5) (0.3 g) was obtained.

Degradation of 7-Chloro-2-phenylpyridazino[2,3-*a*]-1,3,5-triazin-4-one with Hydrazine Hydrate.—A suspension of compound 3 (R = Cl) (1.0 g) in methanol (30 ml) and hydrazine hydrate (2 ml of 100%) was heated under reflux for 1 hr. The solvent was evaporated *in vacuo* to half of its original volume; the product was filtered off and crystallized from ethanol (0.5 g). The compound was identified as 3-phenyl-1,2,4-triazol-5(4*H*)-one, mp 315–320° (dec), when compared with an authentic specimen prepared according to literature[6] (lit.[6] mp 321–322°): ir (KBr) 1730 cm^{-1} (CO); mass spectrum M^+ = 161; nmr (DMSO-d_6) τ 2.70 and 2.35 (m, C_6H_5), −2.0 (broad, NH).

Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.04; H, 4.26; N, 26.19.

When the filtrate from the above experiment was evaporated to dryness, the remaining product (0.3 g) was identified as 3-amino-6-chloropyridazine.

3-(Phenylformamidino)pyridazin-6(1*H*)-one (4).—A mixture of compound 3 (R = Cl) (0.5 g) and hydrochloric acid (7 ml of 1:4) was heated under reflux for 2 hr. The cooled solution was then neutralized with solid sodium bicarbonate. The separated product was filtered off and sublimed at 270° (1 mm) (0.3 g, 72%): mp 273–274°; ir (KBr) 3311 (NH), 1679 cm^{-1} (CO); mass spectrum M^+ = 214.

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 62.09; H, 4.83; N, 26.13.

***N*-(Pyridazinyl-3′)-*N*′-phenylthiourea (2, R = H; X = S; R_1 = C_6H_5).**—3-Aminopyridazine (1.0 g), methanol (15 ml), and phenyl isothiocyanate (1.0 g) were mixed together and the mixture was heated under reflux for 2 hr. The solvent was evaporated *in vacuo* and the residue crystallized from 25% ethanol (1.2 g, 45%), mp 180°.

Anal. Calcd for $C_{11}H_{10}N_4S$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.80; H, 4.42; N, 23.74.

***N*-(6′-Chloropyridazinyl-3′)-*N*′-phenylurea (2, R = Cl; X = O; R_1 = C_6H_5).** A.—A solution of 3-amino-6-chloropyridazine (1.0 g) in dioxane (60 ml) and phenyl isocyanate (1.0 g) was heated under reflux for 2 hr. The separated product (1.4 g, 72%) was crystallized from *N*,*N*-dimethylformamide and water (1:5): mp 280°; ir (KBr) 1712 cm^{-1} (CO); nmr (DMSO-d_6, 108°) τ 1.95 (d, $H_{4'}$), 2.42 (d, $H_{5'}$), 2.7 (m, C_6H_5), $J_{4',5'}$ = 9.5 Hz.

Anal. Calcd for $C_{11}H_9ClN_4O$: C, 53.21; H, 3.64; N, 22.60. Found: C, 53.19; H, 4.04; N, 22.68.

B.—The same compound was obtained when 7-chloro-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (0.5 g) was heated with water (10 ml) and ethanol (1 ml) for 10 min.

If the product was heated with acetic anhydride under reflux for 3 hr, the separated product was identified as 3-acetylamino-6-chloropyridazine, mp 252–254°.

***N*-(Pyridazinyl-3′)-*N*′-phenylurea (2, R = H; X = O; R_1 = C_6H_5).** A.—The same procedure as above under A was applied: mp 290° (dec) (from dioxane, 57% yield); ir (KBr) 1718 cm^{-1} (CO); nmr (DMSO-d_6) τ 2.12 (dd, $H_{4'}$), 2.55 (dd, $H_{5'}$), 1.28 (dd, $H_{6'}$), 2.75 (m, C_6H_5), 0.2 (broad, NH), $J_{4',5'}$ = 9.0, $J_{4',6'}$ = 1.5, $J_{5',6'}$ = 4.5 Hz.

B. The compound was obtained in a similar experiment as described above under B from 3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione.

C.—A mixture of the thiourea (2, R = H; X = S; R_1 = C_6H_5) (1.0 g), ethanol (10 ml), hydrogen peroxide (6 g of 3%), and some diluted hydrochloric acid was heated for 2 min. Upon cooling, water (5 ml) was added and neutralized with ammonia. The product (0.6 g) was identical in all respects with the compound prepared as described under A or B.

(4) B. Stanovnik and M. Tišler, *Synthesis*, 308 (1972).

(5) R. Neidlein and W. Haussmann, *Chem. Ber.*, **99**, 239 (1966).

(6) D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 4067 (1952).

N,N-**Dimethyl-*N'*-(pyridazinyl-3)formamidine** (**7**, **R = H**).—A mixture of 3-aminopyridazine (1.0 g) and *N,N*-dimethylformamide dimethyl acetal (1.2 g) was heated under reflux for 1 hr. After excess of the reagent was removed *in vacuo*, the residue was treated with ethyl acetate (1 ml) and the separated product was filtered off and purified by distillation at 120° (1 mm) (1.2 g, 76%): mp 42–46°; ir (KBr) 1631 cm^{-1} (C=N); nmr (DMSO-d_6) τ 3.12 (dd, H_4), 2.78 (dd, H_5), 1.40 (dd, H_6), 1.59 (s, CH), $J_{4,5} = 9.0$, $J_{5,6} = 4.5$, $J_{4,6} = 2.0$ Hz.

Anal. Calcd for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 55.68; H, 7.03; N, 36.94.

N,N-**Dimethyl-*N'*-(6-chloropyridazinyl-3)formamidine** (**7**, **R = Cl**).—The compound was prepared in the same manner as described above for the unsubstituted analog: mp 115° (from ethyl acetate); ir (KBr) 1626 cm^{-1} (C=N); nmr (DMSO-d_6) τ 2.96 (d, H_4), 2.55 (d, H_5), 1.62 (s, CH), $J_{4,5} = 9.4$ Hz.

Anal. Calcd for $C_7H_9ClN_4$: C, 45.55; H, 4.91 N, 30.34. Found: C, 46.00; H, 5.17; N, 30.34.

7-Chloro-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R = Cl**; **R_1 = H**). **A.**—A suspension of **2** (R = Cl; X = O; $R_1 = C_6H_5$) (1.0 g) in dioxane (35 ml) and pyridine (5 ml) was treated with phenyl isocyanate (0.8 g) and the mixture was then heated under reflux for 48 hr. Upon filtration, the filtrate was evaporated to dryness and the crude product was sublimed at 150° (1 mm) to separate the unchanged urea. The residue was thereafter sublimed at 210° (1 mm) (0.05 g, 4.5%): mp 280°; ir (KBr) 1757, 1683 cm^{-1} (CO); nmr (TFAA) τ 1.70 (d, H_8), 1.82 (d, H_9), 2.40 (m, C_6H_5), $J_{8,9} = 9.5$ Hz.

Anal. Calcd for $C_{12}H_7ClN_4O_2$: C, 52.47; H, 2.57; N, 20.40. Found: C, 52.23; H, 2.94; N, 20.20.

B.—The method, as described for the following example, was applied and the compound was obtained from the formamidine **7** (R = Cl) in 81% yield, mp 280° (from toluene). It was identical with the product obtained as described under A.

3-Phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R = R_1 = H**).—A solution of the formamidine **7** (R = H) (1.0 g) in dry toluene (20 ml) was treated with phenyl isocyanate (2.0 g) and the mixture was heated under reflux for 3 hr. The product (1.4 g, 87%) was for analysis sublimed at 230° (1 mm): mp 252–253°; ir (KBr) 1757 and 1683 cm^{-1} (CO); nmr (TFFA) degenerated ABX τ 0.92 (t, H_7), 1.70 (d, H_8, H_9), $J_{7,8} = 4.0$, $J_{8,9} = 9.2$, $J_{7,9} = 1.0$ Hz.

Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.33. Found: C, 60.23; H, 3.63; N, 23.16.

9-Bromo-7-chloro-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R = Cl**; **R_1 = Br**).—A solution of **6** (R = Cl; R_1 = H) (0.5 g) in glacial acetic acid (10 ml) was treated with bromine (0.3 g) and the mixture was left at room temperature for 2 hr. The separated bromo complex was filtered off, suspended in acetic acid, and then heated under reflux for 2 hr. The obtained product was crystallized from acetic acid (0.35 g, 55%): mp 255° dec; ir (KBr) 1757 and 1689 cm^{-1} (CO); nmr (TFFA) τ 1.83 (s, H_8), 2.40 (m, C_6H_5).

Anal. Calcd for $C_{12}H_6BrClN_4O_2$: C, 40.76; H, 1.71; N, 15.85. Found: C, 40.33; H, 2.01; N, 15.62.

9-Bromo-3-phenylpyridazino[2,3-*a*]-1,3,5-triazine-2,4-dione (**6**, **R = H**; **R_1 = Br**) was prepared similarly in 44% yield: mp 240° dec (from acetic acid); ir (KBr) 1757 and 1681 cm^{-1} (CO); nmr (DMSO-d_6) τ 1.72 (d, H_7), 1.85 (d, H_8), 2.60 (m, C_6H_5), $J_{7,8} = 4.5$ Hz.

Anal. Calcd for $C_{12}H_7BrN_4O_2$: C, 45.16; H, 2.21; N, 17.55. Found: C, 45.02; H, 2.28; N, 17.50.

3-Carbethoxyamino-6-chloropyridazine (**8**, **R = OEt**).—A mixture of **6** (R = Cl; R_1 = H) (1.0 g) and ethanolic sodium ethylate (prepared from 0.3 g of sodium and 7 ml of ethanol) was heated under reflux for 15 min, cooled, acidified to pH 5, and the product was filtered off (0.5 g, 67%). For analysis it was sublimed at 120° (1 mm): mp 192–193°; ir (KBr) 3279 (NH) and 1718 cm^{-1} (COOEt); nmr (DMSO-d_6, 79°) τ 1.90 (d, H_4), 2.30 (d, H_5), 5.80 (q, CH_2CH_3), 8.68 (t, CH_2CH_3), −0.5 (broad, NH), $J_{4,5} = 9.5$, $J_{Et} = 7.5$ Hz.

Anal. Calcd for $C_7H_8ClN_3O_2$: C, 41.71; H, 4.00; N, 20.84. Found: C, 42.21; H, 4.03; N, 20.90.

N-(**2-Methyl-6-chloropyridazinylene-3**)-*N',N'*-**dimethylformamidinium Iodide** (**9**, **R = Cl**).—A mixture of the formamidine **7** (R = Cl) (1.0 g), methanol (10 ml), and methyl iodide (1.0 g) was heated under reflux for 3 hr. The solvent was evaporated *in vacuo*, ethyl acetate (2 ml) was added, the product was filtered off and dissolved in hot glacial acetic acid, the acid was evaporated *in vacuo*, and the residue was treated with ethyl acetate (1 ml). The product was crystallized from ethyl acetate and ethanol (1:3) (0.8 g, 45%): mp 178–179°; nmr (DMSO-d_6) τ 1.70 (d, H_5), 1.80 (d, H_4), 1.13 (s, CH), 5.96 (s, 2-NCH_3), 6.63 (s) and 6.76 (s) for $N(CH_3)_2$, $J_{4,5} = 9.4$ Hz.

Anal. Calcd for $C_8H_{12}ClIN_4$: C, 29.52; H, 3.71; N, 17.21. Found: C, 29.43; H, 3.65; N, 17.26.

N-(**2-Methylpyridazinylene-3**)-*N',N'*-**dimethylformamidinium Iodide** (**9**, **R = H**).—The compound was prepared in a similar manner as above in 66% yield: mp 192–193° (from ethyl acetate and ethanol, 1:3); nmr (DMSO-d_6) τ 2.26 (d, H_4), 1.85 (dd, H_5), 0.75 (d, H_6), 1.55 (s, CH), 5.67 (s, 2-NCH_3), 6.80 (s) and 6.94 (s) for $N(CH_3)_2$, $J_{4,5} = 9.2$, $J_{5,6} = 6.0$ Hz.

Anal. Calcd for $C_8H_{13}IN_4$: C, 32.89; H, 4.48; N, 19.18. Found: C, 33.21; H, 4.85; N, 18.90.

6-Chloro-3-[(*N'*-piperidinomethylene)amino]pyridazine (**10**).—The formamidine **7** (R = Cl) (1.0 g) and piperidine (1.3 g) were heated at 120° for 1 hr, with dimethylamine being evolved. The cooled reaction mixture was treated with ethyl acetate (3 ml) and the product was filtered off and crystallized from ethyl acetate (0.9 g, 74%): mp 104–105°; nmr (DMSO-d_6) τ 2.63 (d, H_4), 3.03 (d, H_5), 1.66 (s, CH), 6.50 and 8.40 (m, piperidine CH_2), $J_{4,5} = 9.0$ Hz.

Anal. Calcd for $C_{10}H_{13}ClN_4$: C, 53.45; H, 5.83; N, 24.94. Found: C, 53.05; H, 6.06; N, 25.52.

3-Formylamino-6-chloropyridazine (**8**, **R = H**).—A mixture of **7** (R = Cl) (1.0 g) and glacial acetic acid (5 ml) was heated just to boiling, the solvent was evaporated *in vacuo*, and the residue, when treated with ethyl acetate (3 ml), afforded the formyl derivative (0.6 g, 70%). For analysis it was sublimed at 130° (1 mm): mp 208–210°; ir (KBr) 3247 (NH) and 1692 cm^{-1} (CO); nmr (DMSO-d_6, 95°) τ 2.12 (d, H_4), 2.35 (d, H_5), 1.22 (s, CHO), −1.0 (broad, NH), $J_{4,5} = 9.4$ Hz.

Anal. Calcd for $C_5H_4ClN_3O$: C, 38.36; H, 2.58; N, 26.83. Found: C, 38.57; H, 3.10; N, 26.55.

3-Formylaminopyridazin-6(1*H*)-one (**11**).—If the same procedure as above was applied, but with heating for 2 hr, the compound was obtained in 34% yield: mp 285–286° (sublimed at 200° (1 mm); nmr (DMSO-d_6, 83°) τ 2.56 (d, H_4), 3.30 (d, H_5), 1.70 (s, HCO), 7.10 (broad, NH, OH), $J_{4,5} = 9.0$ Hz.

Anal. Calcd for $C_5H_5N_3O_2$: C, 43.17; H, 3.62. Found: C, 42.80; H, 3.72.

The same compound could be prepared if 3-amino-6-chloropyridazine was heated with formic acid under reflux for 18 hr (74% yield).

N-**Carbethoxy-*N'*-(6-chloropyridazinyl-3)thiourea** (**12**).—3-Amino-6-chloropyridazine (1.29 g) was dissolved in *N,N*-dimethylformamide (15 ml) with gentle warming and a solution of carbethoxy isothiocyanate (1.31 g) in the same solvent (3 ml) was added. The mixture was warmed to 80° for 5 min, and cooled, water (50 ml) was added, and the product filtered off (0.82 g). It was crystallized from 70% ethanol, mp 168–170°.

Anal. Calcd for $C_8H_9ClN_4O_2S$: C, 36.86; H, 3.48; N, 21.49. Found: C, 36.96; H, 3.34; N, 21.12.

7-Ethoxy-2-thioxopyridazino[2,3-*a*]-1,3,5-triazin-4(3*H*)-one (**13**).—The above thiourea (**12**) (1.16 g) and a solution of sodium ethylate (prepared from 0.12 g of sodium and 15 ml of ethanol) was heated under reflux for 1 hr. The obtained product was treated with diluted hydrochloric acid to pH 4 and then crystallized from ethanol (1.0 g): mp 223–226°; mass spectrum M^+ 224; nmr (TFAA) τ 2.06 (d, H_8), 2.24 (d, H_9), 5.40 (q, CH_2CH_3), 8.49 (t, CH_2CH_3), $J_{8,9} = 9.4$, $J_{Et} = 6.7$ Hz.

Anal. Calcd for $C_8H_8N_4O_2S$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.96; H, 3.79; N, 25.01.

Registry No.—**2** (R = Cl; X = O; R_1 = PhCO), 35053-39-5; **2** (R = H; X = S; R_1 = Ph), 35053-40-8; **2** (R = Cl; X = O; R_1 = Ph), 35053-41-9; **2** (R = H; X = O; R_1 = Ph), 35053-42-0; **3** (R = Cl), 35053-43-1; **3** (R = OCH_3), 35053-44-2; **3** (R = PhS), 35053-45-3; **3** (R = $NHNH_2$), 35053-46-4; **3** (R = NH–N=CHPh), 35053-47-5; **4**, 35053-48-6; **5**, 939-07-1; **6** (R = Cl; R_1 = H), 35053-50-0; **6** (R = R_1 = H), 35053-51-1; **6** (R = Cl; R_1 = Br), 35053-52-2; **6** (R = H; R_1 = Br), 35053-53-3; **7** (R = H), 35053-54-4; **7** (R = Cl), 35053-55-5; **8** (R = CH_3), 14959-31-0; **8** (R = OEt), 35053-57-7; **8** (R = H), 35053-

58-8; **9** (R = Cl), 35053-59-9; **9** (R = H), 35053-60-2; **10**, 35053-61-3; **11**, 35053-62-4; **12**, 35053-63-5; **13**, 35053-64-6.

Acknowledgment.—We take pleasure in thanking Drs. V. Kramer and J. Marsel, Institute J. Stefan, for recording the mass spectra.

Alkaline Sodium Dithionite and Catalytic Reduction of Di-, Tri-, and Tetraalkoxycarbonylpyrazines. The Synthesis of 1,2-Dihydropyrazines

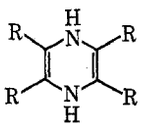
JOHN R. WILLIAMS,* JAMES J. COSSEY, AND MARGARET ADLER

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

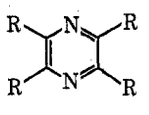
Received March 13, 1972

Catalytic reduction of di-, tri- and tetraalkoxycarbonylpyrazines afford 1,2-, not 1,4-dihydropyrazines, as the major products. 2,3,5,6-Tetraethoxycarbonylpyrazine (**2b**) and 3,5-dimethoxycarbonylpyrazine (**9**) yield only the 1,2-dihydropyrazines **3b** and **10**, respectively. 2,3,5,6-Tetramethoxycarbonylpyrazine (**2a**) gave tetramethoxycarbonyl-1,2-dihydropyrazine (**3a**) together with the tetra- and hexahydro products **4** and **5**, respectively. 2,3,5-Trimethoxycarbonylpyrazine (**6**) afforded the 1,2-dihydropyrazine **7** and the tetrahydropyrazine **8**. The 3,5-dimethoxycarbonylpyrazine **9** afforded the 1,2-dihydropyrazine **10**, whereas the 2,5-dimethoxycarbonylpyrazine **11** gave the tetrahydropyrazine **12**. The unstable tetrahydropyrazines **8** and **12** were identified by spectral data. Alkaline sodium dithionite reduction of tetra- and trialkoxycarbonylpyrazines **3a**, **3b**, and **6** yielded their 1,2-dihydropyrazines as the only product. Attempted reduction of disubstituted pyrazines led to hydrolysis of the esters.

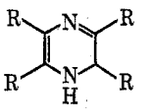
According to quantum mechanical calculations, systems with $4n$ π electrons ought to have antiaromatic character, *i.e.*, be destabilized by resonance.[1] This prediction has been extensively examined for the simplest system having $4n$ π electrons where $n = 1$.[1b] The 1,4-dihydropyrazine ring system **1a**, a cyclic conjugated system with $4n$ π electrons ($n = 2$), is generally thought to be a known structure.[2] However, recent results have cast doubt on the structures of many previously reported 1,4-dihydropyrazines.[3] We have reexamined the reduction of alkoxycarbonylpyrazines reported to yield 1,4-dihydropyrazines and find the original structural assignments to be in error. We now wish to report a convenient method for the synthesis of 1,2-dihydropyrazines.



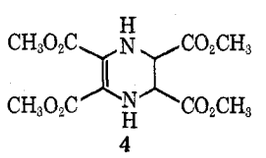
1a, R = H
b, R = $CO_2C_2H_5$



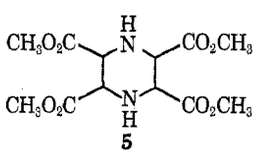
2a, R = CO_2CH_3
b, R = $CO_2C_2H_5$



3a, R = CO_2CH_3
b, R = $CO_2C_2H_5$



4



5

Mager and Berends[4,5] reported that alkaline sodium dithionite and catalytic reduction under vigorous conditions of 2,3,5,6-tetraethoxycarbonylpyrazine (**2b**) yielded the 1,4-dihydropyrazine **1b**. In contrast, we find that catalytic reduction occurs readily at room temperature to yield the same yellow product as was isolated previously.[4,5] The nmr spectrum of this product showed two doublets, δ 5.50 (1 H, J = 5.0 Hz) and 6.85 (1 H, J = 5.0 Hz), together with two very complex multiplets due to the different environments of the four ethyl ester groups. This spectrum is clearly inconsistent with **1b**. Deuteration caused the peak at δ 6.85 to disappear and that at δ 5.50 to collapse to a singlet. The ir spectrum confirmed the presence of a secondary amine. Therefore, the yellow product is assigned the 1,2-dihydropyrazine structure **3b**.

To simplify the nmr spectrum, the tetramethoxycarbonylpyrazine **2a** was reduced under identical conditions. In contrast to the single product formed in the ethyl case, the tetramethyl ester was reduced further to yield a mixture of the di-, tetra-, and hexahydro derivatives. In the nmr spectrum of the 1,2-dihydropyrazine **3a** the C-2 hydrogen, initially a singlet at δ 5.55, changed to a multiplet upon hydration.

The nmr spectrum of the second product showed two absorption peaks at δ 3.74 and 3.78 for the four methyl esters. Peaks at δ 4.28 were assigned to the hydrogens on the carbon next to nitrogen and the ester, and a broad absorption at 4.30 was due to the NH proton, which disappeared upon deuteration. This data is consistent with the 1,2,3,4-tetrahydropyrazine structure **4**, for the second product.

The third product showed a singlet at δ 3.69 for the four methyl esters, a singlet at δ 3.87 (4 H) for the hydrogens on the carbon next to nitrogen and the ester, and a broad 2 H multiplet at δ 2.82 due to the NH. There was no absorption maximum in the uv above 210 nm, confirming the structure of the compound as 2,3,5,6-tetramethoxycarbonylpiperazine (**5**).

Disproportionation, previously observed for 1,2-dihydropyridine,[6] did not occur in the case of the 1,2-dihydropyrazine **3a**.

To test the generality of this reaction, catalytic reduction of tri- and dimethoxycarbonyl-substituted pyrazines was investigated.

Catalytic reduction of 2,3,5-trimethoxycarbonylpy-

(1) For leading references see (a) J. F. Labarre and F. Crasnier, *Fortschr. Chem. Forsch.*, **24**, 33 (1971); (b) R. Breslow, *Angew. Chem.*, **7**, 565 (1968).
(2) Y. T. Pratt and R. C. Elderfield, *Heterocycl. Compounds*, **6**, 414 (1957).
(3) S. J. Chen and F. W. Fowler, *J. Org. Chem.*, **35**, 3987 (1970).
(4) H. I. X. Mager and W. Berends, *Recl. Trav. Chim., Pays-Bas*, **79**, 282 (1960).
(5) H. I. X. Mager and W. Berends, *ibid.*, **76**, 28 (1957).
(6) U. Eisner, *Chem. Commun.*, 1348 (1969).