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Pyridazines. LXXVIII. Use of *N,N*-Dimethylaminomethylene Derivatives of Some Amino and Hydrazino Heterocycles in Organic Synthesis

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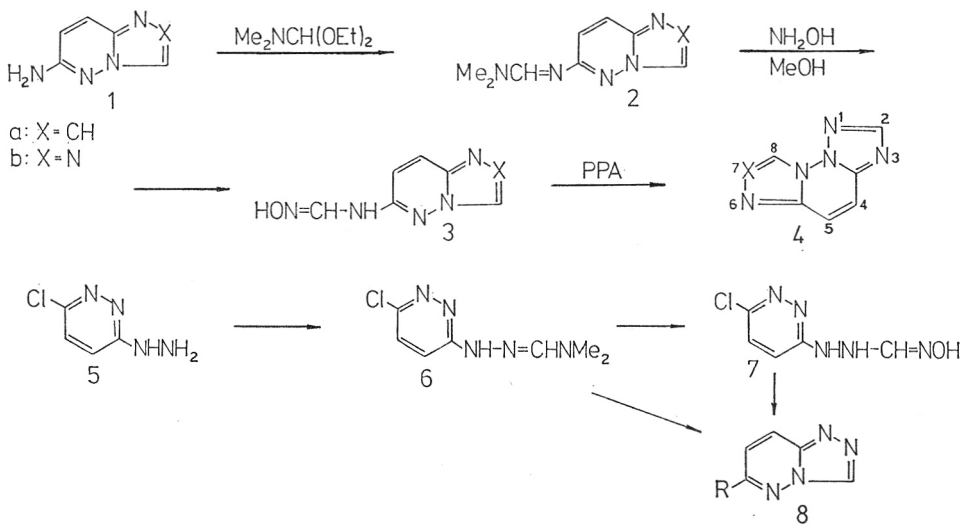
The formation of *N,N*-dimethylaminomethylenehydrazino derivatives of pyridazine and azolopyridazines is described and the synthetic utility of these compounds is explored. An unusual transformation could be observed with a aminomethylenehydrazino derivative where upon nitrosation the side chain is transformed into an azido group. From the corresponding *N,N*-dimethylaminomethyleneamino derivatives two new tricyclic azolotriazolopyridazines could be prepared.

Recently we described a novel method of annelation of the 1,2,4-triazolo ring of the N_2—C_3 bond to azines[1]. As starting material *N,N*-dimethylaminomethyleneamino heterocycles were used, the side chain serving to preform the triazole part. As an extension of these reactions we now describe some further applications as well as experiments with the related *N,N*-dimethylaminomethylenehydrazino derivatives.

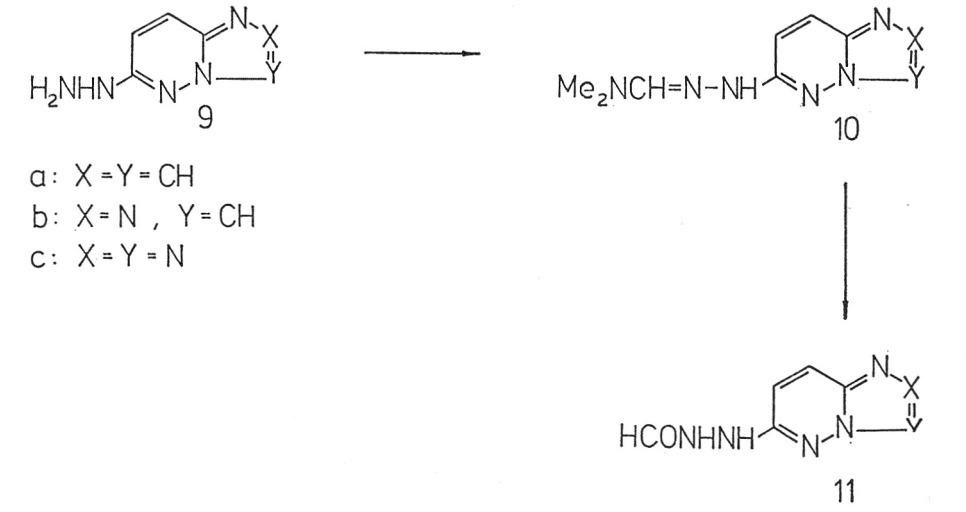
6-Aminoimidazo(1,2-*b*)- (*1a*) or 6-amino-*s*-triazolo(4,3-*b*)pyridazine (*1b*) when treated with *N,N*-dimethylformamide diethyl acetal afforded the corresponding 6-*N,N*-dimethylaminomethyleneamino derivatives (*2a* or *2b*). These reacted with methanolic hydroxylamine to give the corresponding 6-hydroxyiminomethyleneamino derivatives (*3a* or *3b*) which upon treatment with polyphosphoric acid at 70—80 °C for 10 h afforded the tricyclic compounds *4a* or *4b* in reasonable yields. However, in the cyclization step *3a* to *4a* compound *3a* was partially transformed into 6-aminoimidazo(1,2-*b*)pyridazine.

In contrast to *N,N*-dimethylaminomethyleneamino heterocycles, the corresponding derivative of hydrazinopyridazine (*6*) proved to be thermally less stable. Over 105 °C it was converted to the *s*-triazolo(4,3-*b*)pyridazine (*8*, R = = Cl) with a simultaneous dimethylamine elimination. This transformation appears to be easier in solution and when in contact with silica, as exemplified by an attempted chromatographic purification. Similar transformation could be observed when compound *6* was treated with hot hydrazine hydrate and here, besides the formation of the fused triazolo ring, a nucleophilic substitution of the chlorine took place also to give compound *8* (R = $NHNH_2$). The transformation of *6* with hydroxylamine into the corresponding hydroxyiminomethylenehydrazino derivative (*7*) was easily accomplished. By using $^{15}NH_2OH$

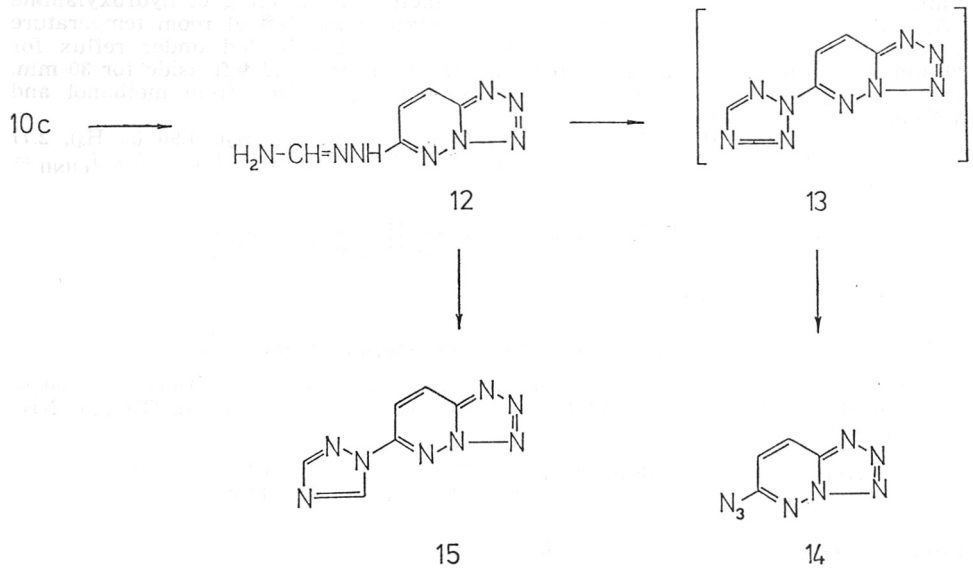


the labeled compound 7 was prepared, the side chain at position *3* being --NHNHCH = ^{15}NOH. From its NMR spectrum it could be established that the compound exists in the hydroxyimino form, similarly as we have established in the case of related hydroxyiminomethyleneamino derivatives[9]. The $J_{^{15}N=CH}$ (16.0 Hz) is of the same order of magnitude as, for example, in the case of 3-pyridazinyl-NH—CH = ^{15}NOH.

6-Hydrazinoazolopyridazines (*9a*, *9b* and *9c*) reacted also with *N,N*-dimethylformamide diethyl acetal to give the corresponding 6-*N,N*-dimethylaminomethylenehydrazino derivatives (*10a*, *10b* or *10c*). Acid or basic catalyzed



hydrolysis of these derivatives led to the corresponding formylhydrazino derivatives *11*. However in liquid ammonia compound *10c* was transformed into the aminomethylenehydrazino derivative *12* which was stable when acid catalyzed hydrolysis was attempted. When treated with nitrous acid, compound *12* was transformed into 6-azidotetrazolo(1,5-*b*)pyridazine (*14*). This unusual transformation can be explained in terms of an intermediate tetrazole derivative *13* giving upon elimination of HCN the azido compound.



The substituted triazole *15* was prepared from *12* after treatment with triethyl orthoformate and the product was stable in comparison with the analogous intermediate tetrazole (*13*). Finally, it should be mentioned that compound *6* when heated in an alcoholic solution of a primary amine (*n*-propylamine, benzylamine or aniline) was transformed into the corresponding 3-aminopyridazine with dimethylaminomethylene group elimination. This contrasts the decomposition path as discussed above for *6* where the dimethylamine elimination was followed by cyclization to give compound *8*.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR measurements were made on a JEOL JNM-C-60-HL spectrometer (TMS as internal standard) and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L mass spectrometer.

6-N,N-Dimethylaminomethyleneaminoimidazo(1,2-b)pyridazine (2a)

A mixture of 6-aminoimidazo(1,2-*b*)pyridazine[3] *(1a)* (1.2 g) and *N,N*-dimethylformamide diethyl acetal (3.5 g) was heated under reflux for 2 h. The reaction mixture was evaporated to dryness and the residue was dissolved in chloroform. The solution was charcoaled, filtered and the filtrate evaporated to dryness. The crude product was crystallized from chloroform and petrolether, m. p. 77—78 °C (yield 1.60 g, 95%).

Mass spectrum: $M^+ = 189$. NMR (DMSO-d_6): $\tau = 2.45$ (d, H_2), 2.06 (m, H_3), 3.14 (d, H_7), 2.15 (dd, H_8), 1.73 (s, —CH=), 6.86 and 6.96 (s, NMe_2), $J_{2,3} = 1.1$, $J_{7,8} = 9.5$, $J_{3,8} = 0.8$ Hz.

Anal. $C_9H_{11}N_5$ (189.22) calc'd: C 57.12; H 5.86; N 37.02%
found: C 56.97 H 6.29 N 36.92%.

*6-Hydroxyiminomethyleneaminoimidazo(1,2-*b*)pyridazine* (3a)

Compound *(2a)* (0.98 g) was treated with a methanolic solution of hydroxylamine (prepared from 0.2 g sodium in 15 ml methanol and 0.7 g of hydroxylamine hydrochloride in 15 ml of methanol) and the mixture was left at room temperature in a sealed vessel for 12 h. The reaction mixture was heated under reflux for 30 min, evaporated to dryness, treated with water (15 ml) and left aside for 30 min. The crude product was filtered off (0.87 g) and crystallized from methanol and *N,N*-dimethylformamide, m. p. 188—190 °C (dec.).

Mass spectrum: $M^+ = 177$. NMR (DMSO-d_6): $\tau = 2.31$ (s, H_2), 1.90 (s, H_3), 2.71 (d, H_7), 1.93 (d, H_8), 2.17 (d, —CH=), —0.67 (s, OH), 0.16 (d, NH), $J_{7,8} = 10.0$, $J_{CHNH} = 10.0$ Hz.

Anal. $C_7H_7N_5O$ (177.17) calc'd: C 47.45; H 3.98; N 39.53%
found: C 47.26; H 3.88; N 39.59%.

In the same manner was prepared:

*6-Hydroxyiminomethyleneamino-*s*-triazolo(4,3-*b*)pyridazine* (3b)

m. p. 219—223 °C (dec.). Mass spectrum: $M^+ = 178$. NMR (DMSO-d_6): $\tau = 0.80$ (s, H_3), 2.76 (d, H_7), 1.85 (d, H_8), 2.39 (s, —CH=), 0.05 and —0.56 (broad, OH and NH), $J_{7,8} = 10.0$ Hz.

Anal. $C_6H_6N_6O$ (178.16) calc'd: C 40.45; H 3.39; N 47.18%
found: C 40.66; H 3.33; N 46.85%.

*Imidazo(2,1-*f*)-*s*-triazolo(2,3-*b*)pyridazine* (4a)

Finely powdered *3a* (1.0 g) was thoroughly mixed with polyphosphoric acid (56 g) and the reaction mixture was heated at 70—80 °C for 10 h. The cooled mixture was diluted with water (300 ml), neutralized with sodium bicarbonate and extracted seven times with chloroform (each time using 50 ml). After drying and evaporation of the solvent the residue (0.55 g) consisted of *4a* and 6-aminoimidazo-(1,2-*b*)-pyridazine *(1a)* in a ratio of 3 : 2. For purification the reaction mixture was sublimed at 115—120 °C/5 mm and the sublimate was crystallized from chloroform and *n*-hexane, m. p. 151—156 °C.

Mass spectrum: $M^+ = 159$. NMR ($CDCl_3$): $\tau = 1.71$ (s, H_2), 2.42 (d, H_4), 2.17 (dd, H_5), 2.30 (d, H_7), 1.77 (dd, H_8), $J_{4,5} = 10.4$, $J_{7,8} = 1.3$, $J_{5,8} = 0.7$ Hz.

Anal. $C_7H_5N_5$ (159.15) calc'd: C 52.82; H 3.17; N 44.01%
found: C 52.81 H 3.39; N 43.85%.

s-*Triazolo(4,3-*b*)-*s*-triazolo(5,1-*f*)pyridazine* (4b)

The compound was prepared similarly as the above desaza analog from *3b* in 21% yield. It was purified by crystallization from methanol, m. p. 220—222 °C.

Mass spectrum: $M^+ = 160$. NMR (DMSO-d_6): $\tau = 1.45$ (s, H_2), 2.17 (d, H_4), 1.85 (dd, H_5), 0.08 (d, H_8), $J_{4,5} = 10.2$, $J_{5,8} = 0.7$ Hz.

Anal. $C_6H_4N_6$ (160.14) calc'd: C 45.00; H 2.52; N 52.48%
found: C 45.05; H 2.47; N 52.66%.

6-Chloro-3-dimethylaminomethylenehydrazinopyridazine (6)

A solution of 6-chloro-3-hydrazinopyridazine *(5)* (1 g) in chloroform (15 ml) was cooled to 0 °C and under stirring *N,N*-dimethylformamide dimethyl acetal (2.2 ml)

was added dropwise. After 5 min. petrolether (20 ml) was added, the product was filtered off and washed with petrolether (10 ml). The crude product (0.93 g) was purified by dissolving in chloroform (40 ml) and adding charcoal. After 10 min the mixture was filtered into petrolether (100 ml). The procedure was repeated once more and the pure compound was dried *in vacuo* at room temperature. When heated over 105 °C crystals are transformed gradually into another type of crystals which had m. p. 200—202 °C, transformation into 6-chloro-*s*-triazolo(4,3-*b*)pyridazine (*8*, R = Cl) taking place.

Mass spectrum: $M^+ = 199$. NMR (DMFA-d_7): $\tau = 2.60$ and 2.84 (d, $H_{4,5}$), 2.15 (s, —CH=), 7.14 (s, NMe_2), 2.0 (s, NH).

Anal. $C_7H_{10}ClN_5$ (199.97) calc'd: C 42.11; H 5.05; N 35.08%
found: C 42.24; H 5.31; N 34.97%.

The compound when heated 130—135 °C for 15 min is cyclized into 6-chloro-*s*-triazolo(4,3-*b*)pyridazine (*8*, R = Cl)[4]. The same conversion could be observed when a solution of the compound *6* was chromatographed on silica (DC-Fertigplatten Kieselgel F 254) and eluted with chloroform and methanol (4 : 1).

If the compound *6* was heated with an ethanolic solution of hydrazine hydrate (80%) for 1.5 hr, the solution evaporated and after addition of diethyl ether 6-hydrazino-*s*-triazolo(4,3-*b*)pyridazine[5] (*8*, R = $NHNH_2$) was obtained.

In a similar manner as for *6*, except that the reaction mixture wah heated under reflux 30—60 min. the following compounds were prepared:

6-Dimethylaminomethylenehydrazinoimidazo(1,2-b)pyridazine (10a)

m. p. 154—156 °C (from chloroform and petrolether) in 98% yield from *9a*. Mass spectrum: $M^+ = 204$. NMR (DMSO-d_6): $\tau = 2.62$ (d, H_2), 2.25 (d, H_3), 3.12 (d, H_7), 2.28 (d, H_8), 2.32 (s, —CH=), 0.46 (s, NH), 7.18 (s, NMe_2), $J_{2,3} = 1.3$, $J_{7,8} = 9.4$ Hz.

Anal. $C_9H_{12}N_6$ (204.23) calc'd: C 52.92; H 5.92; N 41.15%
found: C 52.92; H 6.14; N 41.34%

6-Dimethylaminomethylenehydrazino-s-triazolo(4,3-b)pyridazine (10b)

m. p. 192—194 °C (from chloroform and petrolether, 1 : 3) in 97% yield from *9b*. Mass spectrum: $M^+ = 205$. NMR (DMSO-d_6): $\tau = 0.94$ (d, H_3), 3.09 (d, H_7), 2.1 dd, H_8), 2.28 (s, —CH=), 7.15 (s, NMe_2), 0.11 (s, NH), $J_{7,8} = 10.0$, $J_{3,8} = 0.7$ Hz.

Anal. $C_8H_{11}N_7$ (205.22) calc'd: C 46.82; H 5.40; N 47.78%
found: C 46.43; H 5.40; N 47.60%

6-Dimethylaminomethylenehydrazinotetrazolo(1,5-b)pyridazine (10c)

m. p. 203—206 °C (from methanol and petrolether, 2 : 1) in 97% yield from *9c*. Mass spectrum: $M^+ = 206$. NMR (DMSO-d_6): $\tau = 2.85$ (d, H_7), 1.93 (d, H_8), 2.35 (s, —CH=), 7.17 (s, NMe_2), —0.28 (broad, NH), $J_{7,8} = 9.7$ Hz.

Anal. $C_7H_{10}N_8$ (206.21) calc'd: C 40.77; H 4.89; N 54.34%
found: C 40.74; H 5.13; N 54.45%.

6-Chloro-3-hydroxyiminomethylenehydrazinopyridazine (7)

A mixture of compound *6* (1.0 g), methanol (25 ml) and hydroxylamine hydrochloride (0.4 g) was stirred at room temperature for 10 min. After standing for further 30 min the product was filtered off and washed with ether. For purification it was dissolved in methanol to which some *N,N*-dimethylformamide was added and the solution was poured into diethyl ether (yield 47%). When heated for m. p. determination, the compound is over 120 °C slowly transformed by cyclization into 6-chloro-*s*-triazolo(4,3-*b*)pyridazine (*8*, R = Cl), m. p. 202—204 °C. Mass spectrum: *m/e* 154 ($M^+ - NH_2OH$). NMR (DMFA-d_7): $\tau = 2.82$ (d, H_4), 2.38 (d, H_5), 3.19 (s, —CH=), 1.96 (s, OH), 0.36 and 1.0 (broad, NHNH), $J_{4,5} = 9.5$ Hz.

Anal. $C_5H_6ClN_5O$ (187.59) calc'd: C 32.02; H 3.22; N 37.33%
found: C 32.11; H 3.23; N 37.18%.

In an analogous way the labeled compound, R—NHNH—CH = ^{15}NOH, was prepared from $^{15}NH_2OH$ hydrochloride. The NMR spectrum (in DMFA-d_7) revealed among others the following $J : J^{15}_{N=CH} = 16.0$ Hz.

Hydrolysis of N,N-*dimethylaminomethylenehydrazino Heterocycles*

A. — A mixture of 10 (3 mmoles) and acetic acid (15 ml of 1 : 4) was heated under reflux for 1 h, cooled and neutralized with sodium bicarbonate. The obtained formylhydrazino compound *11* was filtered off and crystallized from an appropriate solvent.

B. — A mixture of *10* (3 mmoles), ethanol (9 ml) and potassium hydroxide (0.6 g) was heated under reflux for 2 h. The cold solution was neutralized with 1 M hydrochloric acid and the product was filtered off.

By these two procedures the following compounds were obtained in 54% yield: Compound *11a*[3], m. p. 217—219 °C (from water), compound *11b*[6], m. p. 252—253 °C (from methanol) and compound *11d*[6], m. p. 216—219 °C (from ethanol).

*6-Aminomethylenehydrazinotetrazolo(1,5-*b*)pyridazine* (12)

Compound *10c* (3.7 g) and liquid ammonia (80 ml) were placed in an autoclave and the mixture was left in the sealed vessel 3 days at room temperature. The obtained suspension was carefully diluted with ethanol and filtered. The crude product (3.1 g) was crystallized from methanol and *N,N*-dimethylformamide, m. p. 167—169 °C. Mass spectrum: $M^+ = 178$. NMR (DMSO-d_6) $\tau = 2.96$ (d, H_7), 1.79 (d, H_8), 2.75 (broad, —CH=), $J_{7,8} = 10.0$ Hz.

Anal. $C_5H_6N_8$ (178.16) calc'd: C 33.71; H 3.39; N 62.90%
found: C 33.73; H 3.24; N 62.64%.

The compound was stable when hydrolysis was attempted with 1 M hydrochloric acid at room temperature for 3 days.

However, when an ice cold solution of compound *12* in 1 M hydrochloric acid was treated with aqueous sodium nitrite at 0 °C and the mixture extracted with chloroform, after evaporation of the solvent 6-azidotetrazolo(1,5-*b*)pyridazine (*14*)[7] was obtained in 22% yield and identified.

*6-(Triazolyl-1′)tetrazolo(1,5-*b*)pyridazine* (15)

Compound *12* (0.15 g) and triethyl orthoformate (5.5 ml) were heated under reflux for 7 h. The reaction mixture was evaporated to dryness, diethyl ether (5 ml) was added, the product filtered off and washed with diethyl ether. The crude product was crystallized from methanol, m. p. 210—213 °C (yield 0.118 g, 74%). Mass spectrum: $M^+ = 188$. NMR (DMSO-d_6): $\tau = 1.75$ (d, H_7), 1.09 (d, H_8), 1.66 (s, $H_{3'}$), 0.53 (s, $H_{5'}$), $J_{7,8} = 10.0$ Hz.

Anal. $C_6H_4N_8$ (188.16) calc'd: C 38.30; H 2.14; N 59.56%
found: C 38.76 H 2.14; N 59.87%.

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IZVLEČEK

Piridazini. LXXVIII. Uporaba *N,N*-dimetilaminometilenskih derivatov nekaterih amino in hidrazino heterociklov v organski sintezi

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Opisana je sinteza *N,N*-dimetilaminometilenhidrazinovih derivatov piridazina in azolopiridazinov ter raziskana sintetska uporabljivost teh spojin. Pri aminometilenhidrazino derivatu smo ugotovili nenavadno pretvorbo, ko se pri nitroziranju stranska veriga pretvori v azidno skupino. Iz ustreznih *N,N*-dimetilaminometilenaminskih derivatov smo sintetizirali dva nova triciklična azolotriazolopiridazina.

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