Pyridazines. LXXXIV. Studies on Borohydride Reduction of Pyridazine Compounds (1a)

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Imidazo[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]pyridazine and tetrazolo[1,5-*b*]pyridazine and some derivatives thereof were reduced with sodium borohydride to give the corresponding 5,6,7,8-tetrahydro derivatives. A mechanism for these reductions is proposed and reduction at the C_7-C_8 bond occurs before the reduction of the C_6-N_5 bond. Substituents at position 7 and/or 8 cause a significant decrease in the extent of reduction or lead to a 5,6-dihydro derivative by competitive attack at the 6 position.

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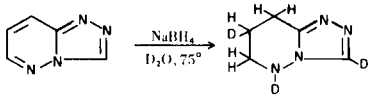
Although much attention has been devoted to the investigation of the different phases of the chemistry of pyridazine compounds in the past two decades (2,3), hardly any studies have been conducted with respect to the reduction of these compounds. Most of the reduced pyridazines known presently (di-, tetra-, and hexahydro-), have been derived indirectly through cyclization reactions (2); only some hexahydropyridazines have been obtained through reduction of the readily accessible tetrahydro compounds, using catalytic hydrogenation, lithium aluminum hydride, or sodium and ethanol (2). Very few pyridazines have been reduced to dihydro compounds by direct reduction procedures (2).

There are no reports in the literature on the reduction of bicyclic pyridazines. The use of complex metal hydrides in the reduction of heterocyclic compounds is a recent advance in heterocyclic chemistry (4) and we undertook an investigation of the reduction of azolopyridazines with sodium borohydride. Since these are the first examples of the borohydride reduction of azolopyridazines, the mechanism of their reduction has also been elucidated.

Discussion of Results.

Azolopyridazines with a bridgehead nitrogen (Ia-c) undergo smooth reduction with sodium borohydride to give the 5,6,7,8-tetrahydro derivatives (IIa-c) in high yields. Although mechanistic studies indicate reduction to proceed through an intermediate dihydro compound, the latter could not be isolated; neither was it possible to detect any dihydro intermediate in an nmr probe. On the other hand, it has been possible to isolate a 7,8-dihydro compound in the catalytic reduction of Ib over palladized carbon (5). In both cases of reduction, the reactivity decreases in the order Ic → Ia. The borohydride reduction of Ia required 4.5 hours of reflux to yield 72% pure IIa as compared against Ic which gave 92% IIc after only 1 hour of reflux. Under the conditions of catalytic reduction, Ia is reduced only over platinum oxide (5).

Scheme I



The mechanism of the borohydride reduction of azolopyridazines has been derived mainly from spectroscopic studies. In order to understand the reduction mechanism, it is important to determine whether the C=C or the C=N bond of the pyridazine nucleus is reduced first. Although the sodium borohydride reduction of pyridinium salts has been found to proceed *via* a dihydro intermediate (6), there was no spectral evidence for the formation of a dihydroazolopyridazine compound. However, we found that 7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazine (III), obtained by catalytic reduction, could be reduced with sodium borohydride in ethanol with extreme ease even at room temperature to give the tetrahydro compound (IIb).

Mechanistic studies of the reduction of pyridinium (6), thiazolium (7) and azolium (8) salts have firmly established the importance of an immonium moiety in borohydride reductions. By analogy, the azolopyridazines should first form an immonium ion by protonation of the 5-nitrogen, followed by an attack at the 8-position by a hydride ion derived from sodium borohydride. The resulting enamine moiety could then reform an immonium ion which could then undergo protonation at the electron rich C-7 position with subsequent reduction to the tetrahydro compound. Thus, reduction involving an immonium ion system requires that the C=C bond be reduced first. Although, based on electron density calculations (9), one would expect initial protonation to occur at N-1, protonation at N-5 is not precluded. The reaction may be conceived as proceeding through minute amounts of immonium ion present, continually formed as that present is removed by reaction with hydride ion. Furthermore, *N*-oxidation of azolopyridazines is known to occur exclusively at the 5-position (10).

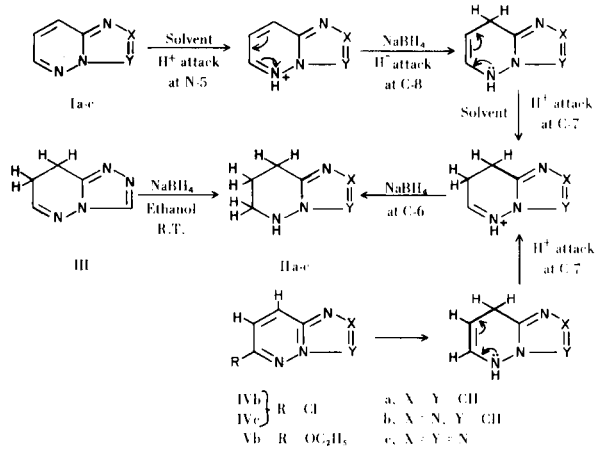
It has been possible to follow the various steps involved in the reduction by studying the sodium borohydride reduction of *s*-triazolo[4,3-*b*]pyridazine (Ib) in deuterium oxide. A deuterated tetrahydropyridazine was obtained, the mass spectrum of which gave a parent peak at m/e, 127, that corresponded to the presence of three deuterium atoms. It was also found that, when Ib was dissolved in deuterium oxide, it completely and rapidly exchanged the hydrogen atom at C-3 for deuterium; this was evidenced by the almost instantaneous disappearance of the sharp singlet at 0.85 τ in the nmr spectrum (11). The tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (IIb), on the other hand, rapidly exchanged both N-5 and C-3 hydrogens at room temperature. However, there was no evidence to indicate any exchange between deuterium and the hydrogen atoms of the 6-, 7-, or 8-methylene groups even after 2 hours at 80°. Apparently then, the third deuterium atom in the deuterated tetrahydropyridazine compound arose from the protonation of the enamine moiety involving the lone pair of electrons at N-5; there was no indication of a previous reduction of the enamine intermediate by the hydride ion, followed by a deuterium exchange (Scheme 1).

A comparison of the nmr spectra of the deuterated and undeuterated tetrahydro-*s*-triazolo[4,3-*b*]pyridazine revealed the exact location of the third deuterium atom. Both spectra were very similar except for the C-3 proton singlet at 2.09 τ and the NH triplet at 4.06 τ, which were absent in that of the deuterated compound. The triplet at 7.07 τ arising from the C-8 methylene protons was reduced to a doublet at 7.03 τ in the deuterated compound; also the C-6 protons in the deuterated compound were changed from a doublet of a triplet at 6.74 τ to a simple doublet at 6.77 τ, all of which indicated absence of the N-5 proton and presence of only one proton at C-7. Finally, the multiplet for the C-7 methylene protons at 8.01 τ had given way to a broad peak (12) at 8.03 τ, due to geminal H-D coupling. The relative area of the peak was also in agreement with the presence of only one proton at the C-7 position.

Likewise, mass spectral and nmr analyses of the deuterated tetrahydrotetrazolo[1,5-*b*]pyridazine indicated the presence of two deuterium atoms in the molecule, one at the N-5 and the other at the C-7 position.

On the basis of isotope labelling and spectral studies, the gross mechanism of the sodium borohydride reduction of bicyclic azolopyridazines with a bridgehead nitrogen may be represented as shown in Scheme 2.

Scheme 2

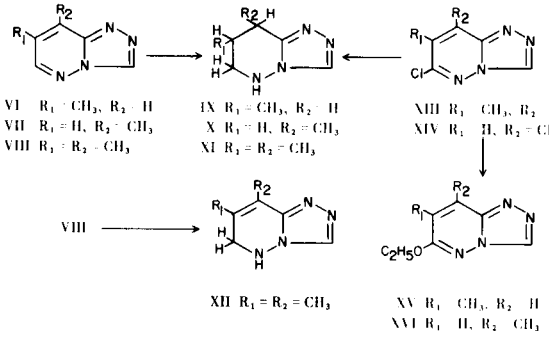


The mechanism proposed here is also supported by several other pieces of experimental evidence gathered in these and other laboratories. The formation of piperidines, from the borohydride reduction of pyridine and picoline methiodides, has been explained by a reduction path similar to the one envisaged here, through the initial formation of a 1,4-dihydropyridine intermediate (13).

Chemical data on the reduction of several substituted azolopyridazines are also in agreement with the reaction path proposed here. 6-Chlorosubstituted azolopyridazines (IVb-c) underwent borohydride reduction to give the reduced compounds (IIb-c), at greatly enhanced rates at room temperature. This is consistent with the mechanism of hydride attack at C-8 and formation of the highly reactive 5,8-dihydro intermediate. It is most likely that an azocarbonium ion is formed by solvolysis of the imidoyl chloride (14), and this would then facilitate hydride attack at C-8 and help form the enamine moiety with ease (see Scheme 2). Likewise, the 6-ethoxy compound (Vb) underwent reduction to give IIb, although, the less reactive imidoyl ester does not produce an enhancement in the reduction.

Finally, reduction studies of 7- and 8-substituted azolopyridazines lend support to the proposed mechanism. If the C_7=C_8 bond was indeed undergoing reduction before the C_6=N_5 bond, then one should expect that substituents in the 7- and/or 8-position would cause a significant decrease in the extent of reduction or lead to a 5,6-dihydro derivative by competitive attack at the 6-position. And this is indeed the case. Unlike the 6-chloroazolopyridazines (IVb-c), compounds XIII and XIV bearing 7- or 8-methyl group, do not undergo facile reduction. There was no reduction at room temperature; while some dechlorination occurred with XIII, XIV was almost completely converted to the 6-ethoxy compound. Even after 2.5 hours under reflux, the extent of reduction, as indicated by nmr spectral analysis, was only 82% in the case of XIII and 70% in the case of XIV. Similarly, yields of the tetrahydro products IX and X from VI and VII, respectively, were of the order of 60% or less, as compared with 85% from the unsubstituted pyridazine Ib. Likewise, compound VIII after 5 hours of reflux, indicated only 25% reduction to the tetrahydro compound (XI); almost 70% of the reduction product consisted of the 5,6-dihydro derivative (XII).

The present studies on borohydride reductions, along with catalytic hydrogenation, provide a useful and convenient synthetic route for the preparation of a number of reduced azolopyridazines.



EXPERIMENTAL (15)

Preparation of Azolopyridazines (Ia-c).

Azolopyridazines (Ia-c) were prepared by dechlorination of the corresponding 6-chloro derivatives using controlled catalytic hydrogenation, according to published procedures (16,17). *s*-Triazolo[4,3-*b*]pyridazine (Ib), obtained in this manner, after crystallization from benzene-methanol, had m.p. 156-158°. The low m.p. 134°, reported in the literature (17), is probably that of the 7,8-dihydro-*s*-triazolo[4,3-*b*]pyridazine (III), now known to be a by-product in the dechlorination procedure.

Sodium Borohydride Reduction of Ia-c).

A solution of the appropriate azolopyridazine (3 mmoles) in ethanol (95%, 15 ml. or more, depending on the solubility of the compound) was added at room temperature from a dropping (30 mmoles in 20 ml. of ethanol) in a two-necked flask, over a period of 30-40 minutes. The reaction mixture was then heated under reflux (for a period of time depending on the ease with which the compound was reduced), cooled and the unreacted sodium borohydride decomposed with dilute hydrochloric acid (1:1). It was then made basic with 10% aqueous sodium hydroxide, evaporated to dryness under reduced pressure and the residue extracted several times with hot chloroform. The combined extracts were dried and evaporated to give the 5,6,7,8-tetrahydro derivatives (IIa-c).

In all cases, a white crystalline precipitate appeared during the addition of sodium borohydride and increased greatly in bulk during reflux. It appeared to be sodium borate and offered a good estimate of the extent of reduction. There was no precipitation when reactions were performed in an aqueous medium, as the inorganic matter was water-soluble.

5,6,7,8-Tetrahydroimidazo[1,2-*b*]pyridazine (IIa).

This compound was obtained in 72% yield after 4.5 hours of reflux, m.p. 115-116° (from a mixture of chloroform-petroleum ether); nmr: τ = 3.30 (H_2 and H_3), 4.92 (broad, 5-NH), 6.80 (t, 6-CH_2), 7.17 (t, 8-CH_2), 8.05 (m, 7-CH_2); mass spectrum: M^+ 123.

Anal. Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.57; H, 7.42; N, 34.10.

When the reflux time was reduced to 1 hour, the yield of IIa was reduced to 20%.

5,6,7,8-Tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (IIb).

This compound was obtained in 92% yield after 2 hours of reflux, m.p. 127-128° (from chloroform-petroleum ether); nmr: τ = 2.09 (s, H_3), 4.06 (t, 5-NH), 6.74 (dt, 6-CH_2), 7.07 (t, 8-CH_2), 8.01 (m, 7-CH_2); mass spectrum: M^+ 124.

Anal. Calcd. for $C_5H_8N_4$: C, 48.37; H, 6.50; N, 45.13. Found: C, 48.52; H, 6.29; N, 45.30.

When the reaction mixture was heated under reflux for 1 hour, the yield of IIb was reduced to 72%; and reduction with 3 mmoles of sodium borohydride at room temperature yielded mostly unreacted Ib. Analysis of the crude reaction product by nmr and mass spectra gave no evidence of the presence of a dihydro compound.

5,6,7,8-Tetrahydrotetrazolo[1,5-*b*]pyridazine (IIc).

This compound, m.p. 158-159° (from chloroform), was obtained in 91% yield after 1 hour of reflux with 3 mmoles of sodium borohydride; nmr (DMSO-d_6): τ = 2.61 (t, 5-NH), 6.74 (dt, 6-CH_2), 7.0 (t, 8-CH_2), 8.11 (m, 7-CH_2).

Anal. Calcd. for $C_4H_7N_5$: C, 38.39; H, 5.64; N, 55.97. Found: C, 38.31; H, 5.71; N, 55.73.

Reduction of 7,8-Dihydro-*s*-triazolo[4,3-*b*]pyridazine (III).

A solution of III (244 mg., 2 mmoles) in ethanol (10 ml.) was added dropwise to a stirred solution of sodium borohydride (760 mg., 20 mmoles) in ethanol (15 ml.), over a period of 30 minutes. Stirring was continued for an additional 1.5 hours at room temperature. The reaction mixture was worked up as described under the reduction of Ia-c and a brownish yellow residue was obtained (170 mg., 69%), m.p. 115-120°. It crystallized from chloroform-petroleum ether, m.p. 122-126°; the mixture m.p. with an authentic sample was undepressed and nmr and mass spectrum were identical with those of IIb.

Reduction of Compounds Ib-c using Deuterium Oxide as Solvent.

A solution of Ib (360 mg., 3 mmoles) in deuterium oxide (10

(114 mg., 3 mmoles) in deuterium oxide (5 ml.), maintained at 75°. The reaction mixture was stirred and heated at 75° for 2 hours. It was then evaporated to dryness and the residue analyzed by nmr and mass spectrometry. The nmr spectrum indicated 40% reduction to a deuterated tetrahydro compound as computed from the relative intensities of the integrated H_7 peaks for the reduced and unreduced compound; τ = 6.77 (d, 6-CH_2), 7.03 (d, 8-CH_2), 8.03 (broad, 7-CH). The peak at 8.03 τ integrated to give only one proton. There were no peaks corresponding to H_3 and 5-NH. The mass spectrum of the residue gave an intense peak at M^+ 127 along with peaks at m/e, 121 (3-deuterio-*s*-triazolopyridazine) and 127 (a weak signal indicating traces of a 5,7-deuteriotetrahydro-*s*-triazolopyridazine).

The reaction was repeated in the same manner, using water in place of deuterium oxide. The nmr spectrum of the residue showed 38% reduction according to the relative intensities of the integrated H_3 peaks for the reduced and unreduced compounds. Similarly, the mass spectrum showed M^+ 124 and 120.

Reduction of 6-Chloro-*s*-triazolo[4,3-*b*]pyridazine (IVb) to IIb.

A solution of the pyridazine compound (464 mg., 3 mmoles) (18) in ethanol (40 ml.) was added dropwise over a period of 1 hour to a stirred solution of sodium borohydride (114 mg., 3 mmoles) in ethanol (5 ml.) at room temperature. The reaction mixture was worked up as described earlier and the residue (250 mg., m.p. 115-155°) was found to contain a mixture of tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (IIb) and 6-ethoxy-*s*-triazolo[4,3-*b*]-pyridazine (Vb). The nmr spectrum showed, in addition to the chemical shifts arising from IIb, those of Vb: τ = 1.25 (s, H_3), 2.18 (s, H_8), 3.25 (d, H_7), 5.60 (q, CH_2 of 6-OC_2H_5), 8.55 (t, CH_3 of 6-OC_2H_5). The integrated ratio of the H_3 peaks of the two compounds indicated 70% of IIb and 30% of Vb; mass spectrum: M^+ 124 (IIb) and 164 (Vb); there was no unchanged chloro compound. Recrystallization of the residue from chloroform-diethyl ether yielded pure IIb in 55% yield.

In order to avoid chlorine displacement by ethanol, the experiment was repeated using reverse addition. A solution of sodium borohydride (114 mg., 3 mmoles) in ethanol (20 ml.) was added to the compound (464 mg., 3 mmoles) partly suspended in ethanol (40 ml.) and maintained at a temperature of 25°. At the end of 1 hour, when addition had been completed, the reaction mixture was worked up as usual to yield a colorless residue (250 mg., 68%), m.p. 123-127°. Analysis by nmr and mass spectrum indicated only tetrahydropyridazine IIb; there was no evidence of any ethoxy compound Vb. However, in a second run carried out in a similar manner using reverse addition, nmr spectrum of the residue, m.p. 105-120°, indicated about 10% of the 6-ethoxy compound Vb and the mass spectrum showed traces of unchanged chloro compound, M^+ 154 and 156.

Reduction of 6-Chlorotetrazolo[1,5-*b*]pyridazine (V) to IIc.

A solution of IVc (466 mg., 3 mmoles) (18), reduced in the same manner as IVb using reverse addition, yielded IIc (260 mg., 69%), m.p. 155-158°. The nmr and mass spectrum also characterized the product as IIc.

Reduction of 6-Ethoxy-*s*-triazolo[4,3-*b*]pyridazine (Vb) to IIb.

Compound Vb (492 mg., 3 mmoles) (19) was reacted with sodium borohydride (1.14 g., 30 mmoles) at reflux temperature for 2 hours as described under Ia-c. It was worked up as usual and the brownish yellow residue (170 mg., 46%) was triturated with chloroform-petroleum ether mixture to give the pure compound, m.p. 124-126°. The mixture m.p. of the compound with IIb was M^+ 124 and traces of 164 (unchanged Vb). When Vb (492 mg., 3 mmoles) was reacted with sodium borohydride (114 mg., 3 mmoles) in the same manner as IVb for 1.5 hours at room temperature, there was no reduction and it was recovered unchanged. The residue had m.p. 174-175° and was undepressed with Vb. The nmr and mass spectrum were the same of that of Vb.

Reduction of 8-Methyl-*s*-triazolo[4,3-*b*]pyridazine (VII) to 8-Methyl-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (X).

To a solution of the compound VII (134 mg., 1 mmole in 10 ml. of ethanol) (9,20) was added a solution of sodium borohydride (380 mg., 10 mmoles in 7 ml. of ethanol). The mixture was heated under reflux for 2 hours and treated in the usual manner to isolate the product. The oily residue consisted of the 8-methyl-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (X), as shown by nmr analysis. Distillation under reduced pressure yielded the pure compound (79 mg., 57%), b.p. 120°/1 mm; nmr: τ = 2.08 (s, H_3), 4.4 (broad, NH), 6.75 (m, 6-CH_2, partially overlapped by the 8-CH multiplet), 6.95 (m, 8-CH partially overlapped by the 6-CH_2 multiplet), 8.05 (m, 7-CH_2), 8.62 (d, 8-CH_3); $J_{8CH_3,8CH}$ = 7.2 Hz; mass spectrum: M^+138.

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.15; H, 7.30; N, 40.55. Found: C, 52.36; H, 7.53; N, 40.19.

Reaction of 6-Chloro-8-methyl-*s*-triazolo[4,3-*b*]pyridazine (XIV).

The compound (170 mg., 1 mmole) (21,22) dissolved in ethanol (15 ml.) was added to a solution of sodium borohydride (40 mg., 1 mmole) in ethanol (5 ml.) over a period of 1 hour with stirring at room temperature. The reaction mixture, worked up in the usual manner, yielded a residue (155 mg.) which consisted 80% of compound XVI and 20% of compound X as shown by the integrated ratio of the H_3 peaks of the two compounds; nmr spectrum of XVI: τ = 1.27 (s, H_3), 3.52 (q, H_7), 5.69 (q, CH_2 of OC_2H_5), 7.42 (d, 8-CH_3), 8.59 (t, CH_3 of OC_2H_5).

The reaction was repeated by heating under reflux for 2.5 hours. It was worked up as usual and nmr analysis of the semi-oily residue indicated 70% of reduction.

Reduction of 7-Methyl-*s*-triazolo[4,3-*b*]pyridazine (VI) to 7-Methyl-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (IX).

The compound (268 mg., 2 mmoles) (9,20), reduced in the same manner as the isomeric 8-methyl pyridazine VII, yielded colorless crystals (185 mg., 65%), m.p. 110-115°; nmr: τ = 2.07 (s, H_3), 3.67 (broad, NH), 6.8 (m, 6CH_2), 7.05 (m, 8CH_2), 7.75 (m, 7CH), 8.89 (d, 7CH_3); mass spectrum: M^+ 138.

Reaction of 6-Chloro-7-methyl-*s*-triazolo[4,3-*b*]pyridazine (XIII).

The compound (21,22), treated at room temperature exactly as described under XIV, gave a residue having m.p. 120-150°. No reduction was detected from the nmr spectrum and mass spectrum gave M^+ 168 and 170, along with a trace of m/e, 134, indicating some dechlorination of XIII.

The reaction was repeated at reflux temperature for 2.5 hours. The nmr spectrum of the residue, m.p. 60-90°, indicated that it consisted mainly of the tetrahydro product (82%) and minor amounts of XV (18%). The mass spectrum gave M^+ 138 (IX), 134 (VI), and 178 (XV).

Reduction of 7,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazine (VIII) to 7,8-Dimethyl-5,6-dihydro-*s*-triazolo[4,3-*b*]pyridazine (XII).

A mixture of VIII (740 mg., 5 mmoles) (20) and sodium borohydride (1.9 g., 50 mmoles) in ethanol (50 ml.) was heated under reflux for 2 hours. The reaction mixture, worked up in the usual

by repeated trituration with hot chloroform-petroleum ether mixture to give the pure 5,6-dihydro-derivative (XII) (300 mg., 40%), m.p. 155-165°; nmr: τ = 1.8 (s, H_3), 4.36 (t, NH), 6.18 (d, 6-CH_2), 7.84 (s, 8-CH_3), 8.04 (s, 7-CH_3); mass spectrum: M^+ 150.

Anal. Calcd. for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 55.89; H, 6.65; N, 37.58.

The crude reaction product, m.p. 125-150°, consisted of a mixture of the dihydro compound (XII) (62.5%), the tetrahydro XI (25%) and unchanged VIII (12.5%), according to nmr analysis. The mass spectrum also gave M^+ 148 (VIII), 150 (XII) and 152 (XI). Increasing the reaction time did not significantly change the ratio of products. After 5 hours of reflux, the nmr spectrum of the residue indicated 66% of XII, 28% of XI and 6% of VIII. The mass spectrum also gave peaks corresponding to M^+ 148, 150 and 152.

Reduction of 7,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazine (VIII) to 7,8-Dimethyl-5,6,7,8-tetrahydro-*s*-triazolo[4,3-*b*]pyridazine (XI).

Reduction of 7,8-dimethyl-5,6-dihydro-*s*-triazolo[4,3-*b*]pyridazine (XII), according to the procedure used for the reduction of 8-methyl-*s*-triazolo[4,3-*b*]pyridazine (VII), gave after 5 hours of reflux only traces of the tetrahydro product (XI), as indicated by nmr analysis. In order to improve the yield of the tetrahydro compound (XI), a slightly modified procedure was used.

To a solution of VIII (148 mg., 1 mmole in 10 ml. of ethanol) was added a solution of sodium borohydride (380 mg., 10 mmoles in 7 ml. of ethanol) and the mixture was heated under reflux for 20 hours. Each hour, an additional amount of sodium borohydride dissolved in ethanol (76 mg., 2 mmoles in 3 ml.) was added to the refluxing mixture. The product, isolated in the usual manner, crystallized from chloroform-*n*-hexane mixture (99 mg., 65%), m.p. 78-80°; nmr: τ = 2.01 (s, H_3), 6.84 (m, 8-CH, partially overlapped), 6.92 (m, 6-CH_2, partially overlapped), 7.90 (m, 7-CH), 8.70 (d, 8-CH_3), 9.05 (d, 7-CH_3), 5.3 (broad, NH); $J_{8CH_3,8CH} = J_{7CH_3,7CH} = 7.0$ Hz; mass spectrum: M^+ 152.10604 (calcd. 152.10619.

Anal. Calcd. for $C_7H_{12}N_4$: C, 55.24; H, 7.95; N, 36.82. Found: C, 55.48; H, 8.31; N, 36.57.

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(15) Melting points were determined using either a Kofler (hot plate) or a Büchi (capillary) melting point apparatus. The nmr spectra were determined on a JEOL JNM C-60 HL spectrometer, using solutions in deuteriochloroform (unless otherwise stated) with TMS as internal standard. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L or a CEC-20-110C high resolution mass spectrometer.

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