Department of Chemistry, Ohio University

Ten π-Electron Nitrogen Heterocyclic Compounds:X The Syntheses and Structure Determinations of Some 1,2,4-Triazolopyrimidines.

William W. Paudler and Larry S. Helmick

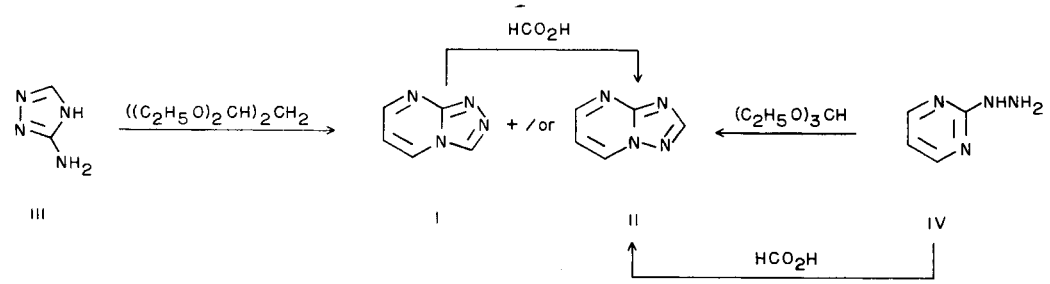
It has been shown that the reaction of 2-hydrazinopyrimidines with ethyl orthoesters yields 1,2,4-triazolo[4,3-a]pyrimidines as well as 1,2,4-triazolo[1,5-a]pyrimidines. The structures of the parent compounds and of some methyl derivatives have been established by NMR spectroscopy.

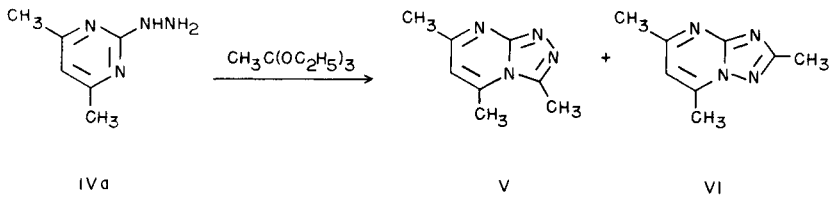
The synthesis of 1,2,4-triazolo[4,3-a]pyrimidine (I) and of 1,2,4-triazolo[1,5-a]pyrimidine (II) can be accomplished by two different routes, either starting with 3-amino-1,2,4-triazole (III) or with 2-hydrazinopyrimidine (IV) (1). The former of these reactions can, in theory, produce either I or II, or both of these compounds, depending upon whether N-2 or N-4 of the 3-amino-1,2,4-triazole is involved in the cyclization reaction (2,3,4). The establishment of the correct structures of these tetraazaindenes is however complicated by the fact that one of these structures, presumably I, can be rearranged under acidic conditions to the 1,2,4-triazolo[1,5-a]pyrimidine (II), which can also be obtained directly from IV and formic acid (3).

The structure determination of these compounds rests largely upon the ultraviolet spectra of some 5-hydroxy (5-oxo) derivatives and upon the demonstration that cyclizations involving either 3-amino-1,2,4-triazoles and 1,3-dicarbonyl compounds or 2-hydrazinopyrimidines and formic acid yields 1,2,4-triazolo[1,5-a]pyrimidines, while the reaction of 2-hydrazinopyrimidines with ethyl orthoformate yields only 1,2,4-triazolo[4,3-a]pyrimidines (2,4).

The major argument in favor of structures of type II appears to be based upon the statement that ethyl orthoformate and 2-hydrazinopyrimidine yield only the non-rearranged compound, 1,2,4-triazolo-[4,3-a]pyrimidine, which can be rearranged under acidic conditions to the 1,2,4-triazolo[1,5-a]pyrimidine.

We have now shown, contrary to reports in the literature (3,4), that the reaction of 4,6-dimethyl-2-hydrazinopyrimidine (IVa) yields two isomeric trimethyl-1,2,4-triazolopyrimidines (V and VI). Thus, the argument that the ethyl orthoformate cyclization with 2-hydrazinopyrimidines yields only compounds of structure I is no longer tenable. It





IVa V VI

is also of some interest that the ultraviolet spectra of the two trimethyl 1,2,4-triazolopyrimidines are essentially superimposable, and consequently, the use of ultraviolet spectra is of no aid in establishing the structures of these trimethyl compounds.

In view of recent observations (6,7) regarding *peri* interactions of the methyl groups in 3,5-dimethyl substituted polyazaindenes (the numbering of the ring positions referred to is the same as that employed for the compounds discussed in this communication) and the effect that these interactions have upon the chemical shifts of the methyl protons in the NMR spectra of these compounds, it appeared reasonable to attempt to establish the structures of these compounds by NMR studies.

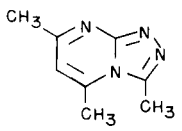
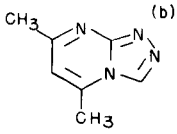
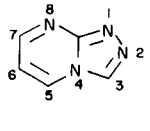
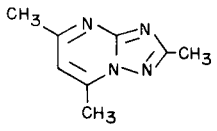
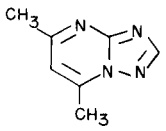
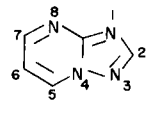
Thus, we would predict that the chemical shifts of the methyl protons of 5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (VIII) will be essentially the same as those of the corresponding methyl group protons in the 2,5,7-trimethyl-1,2,4-triazolo[1,5-a]-pyrimidine (VI). The 5- and 7-methyl group protons in 5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidine (VII) however, would be expected to resonate at positions quite different from those of the corresponding methyl groups in 3,5,7-trimethyl-1,2,4-triazolo[4,3-a]pyrimidine (V). We do indeed observe that the 5- and 7-methyl group protons of the trimethyl compound, m.p. 205-207°, are at considerably more shielded positions than the corresponding methyl group protons in the trimethyl derivative of m.p. 139-141°. Furthermore, these chemical shifts are at positions quite different from the two isomeric 5,7-dimethyl-1,2,4-triazolopyrimidines (VII and VIII). Thus, we can conclude that the compound of m.p. 205-207° is the 3,5,7-trimethyl-1,2,4-triazolo[4,3-a]pyrimidine (V), while the trimethyl compound (m.p. 139-141°) is the 2,5,7-trimethyl-1,2,4-triazolo[1,5-a]pyrimidine (VI).

It now becomes necessary to establish the structures of the dimethyl compounds (VII and VIII) (8). It is clear, from Table I, that H-6 of the trimethyl compound VI appears at the same resonance position as H-6 of the dimethyl compound of m.p. 135.5-137°, while H-6 of the trimethyl compound V has a chemical shift similar to H-6 of the dimethyl compound of m.p. 167-168°. Consequently, the structures of the dimethyl compounds are established as shown in Table I.

We can now correlate the NMR spectra of the parent compounds with those of the dimethyl derivatives. It is anticipated that the protons in the 5-membered ring will be affected only to a small extent by the methyl groups in the 6-membered ring. The structures of the parent compounds can therefore be established by a comparison of the chemical shifts of H-3 of structure I and of H-2 of structure II with the corresponding protons of the dimethyl compounds. The chemical shifts of H-3 of the dimethyl compound VII and of the same proton of the parent compound of m.p. 142-143° are essentially the same. Similarly, the chemical shift of H-2 of the dimethyl compound VIII agrees well with the chemical shift of H-2 of the parent compound of m.p. 208-210°. Thus, the structures of the parent compounds are established as shown in Table I.

TABLE I

NMR Spectral Data of Some Triazolopyrimidines (a)

						
	m.p. 205-207° V	m.p. 167-168° VII	m.p. 142-143° I	m.p. 139-141° VI	m.p. 135.5-137° VIII	m.p. 208-210° II
H_2	----	----	----	----	1.62(1.41)	1.48(1.24)
H_3	----	1.30(0.77)	(0.72)	----	----	----
H_5	----	----	(0.98)	----	----	1.00(0.48)
H_6	3.35(3.20)	3.34(3.07)	(2.85)	3.19(2.88)	3.15(2.78)	2.81(2.54)
H_7	----	----	(1.23)	----	----	1.13(1.02)
$2\text{-}CH_3$	----	----	----	7.40(7.51)	----	----
$3\text{-}CH_3$	7.70(7.72)	----	----	----	----	----
$5\text{-}CH_3$	7.74(7.83)	7.28(7.32)	----	7.23(7.30)	7.18(7.23)	----
$7\text{-}CH_3$	7.70(7.72)	7.38(7.47)	----	7.39(7.44)	7.32(7.39)	----
J_{56}	----	----	6.8	----	----	6.5
J_{67}	----	----	4.0	----	----	4.4
J_{57}	----	----	2.0	----	----	2.0
$J_5\text{-}CH_3, H\text{-}6$	0.4	1.0	----	0.8	0.9	----

(a) Numbers in parentheses refer to 8% solutions in d_6-dimethyl sulfoxide, others refer to 8% solutions in deuteriochloroform. Chemical shifts are reported in τ units and coupling constants in c/s. (b) Prepared from 4,6-dimethyl-2-hydrazinopyrimidine and ethyl orthoformate (3,5).

The condensation of 2-hydrazinopyrimidine with ethyl orthoformate yielded in addition to the reported 1,2,4-triazolo[4,3-a]pyrimidine (I), the isomeric 1,2,4-triazolo[1,5-a]pyrimidine (II). These results again differ from those reported in the literature, in that both isomers are obtained rather than compound I only.

EXPERIMENTAL (9)

1,2,4-Triazolo[4,3-a]pyrimidine (I) and 1,2,4-Triazolo[1,5-a]pyrimidine (II).

A stirred solution of 0.75 g. (6.82 mmoles) of 2-hydrazinopyrimidine and 6 ml. of ethyl orthoformate was warmed in an oil bath at 110° for 45 minutes. The ethanol was allowed to evaporate as it was formed during the reaction. The precipitated solid material was collected and sublimed at 110°/0.10 mm. The sublimed material was extracted with chloroform and the insoluble material was collected and recrystallized from dioxane to afford 1,2,4-triazolo[1,5-a]pyrimidine (II), m.p. 208-210°. The chloroform solution was evaporated to dryness under reduced pressure, and the remaining solid was recrystallized from benzene to yield 1,2,4-triazolo[4,3-a]pyrimidine (I), m.p. 142-143°. The physical properties of this compound (m.p., NMR and uv) are identical to those reported for this substance as prepared from 3-amino-1,2,4-triazole and 1,1,3,3-tetraethoxypropane (2,5), or from 2-hydrazinopyrimidine and formic acid (4).

The sublimation did not cause isomerization, since the crude reaction product does indeed contain both isomers.

2,5,7-Trimethyl-1,2,4-triazolo[1,5-a]pyrimidine (VI) and 3,5,7-Trimethyl-1,2,4-triazolo[4,3-a]pyrimidine (V).

A solution of 4.0 g. (0.023 mole) of 4,6-dimethyl-2-hydrazinopyrimidine hydrochloride, 15 ml. of ethyl orthoacetate and a few drops of a saturated aqueous solution of sodium carbonate was warmed in an oil bath at 90° for 3 hours. The solution was filtered while warm, and the solid material which remained was recrystallized from 95% ethanol, to yield 1.1 g. of a monoacetyl derivative of IVa (m.p. 249-250°). The cooled solution was filtered to remove a precipitate. This solid was chromatographed on neutral Grade III alumina. Elution with ethyl acetate yielded 370 mg. of 2,5,7-trimethyl-1,2,4-triazolo-[1,5-a]pyrimidine (VI), m.p. 139-141°, UV in ethanol: λ max (log ε): 274 mμ (3.76), 213 mμ (4.64). Elution with 10% methanol-90% ethyl acetate afforded 220 mg. of 3,5,7-trimethyl-1,2,4-triazolo[4,3-a]-pyrimidine (V), m.p. 205-207° (from benzene), UV in ethanol: λ max (log ε): 274 mμ (3.50), 223 mμ (3.99).

5,7-Dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (VIII).

A solution of 5.0 g. (0.0362 mole) of 4,6-dimethyl-2-hydrazinopyrimidine and 35 ml. of 88% formic acid was refluxed with stirring for 9 hours. The excess formic acid was removed under reduced pressure. The residue was then neutralized with 20% aqueous sodium hydroxide solution and then extracted with three 100 ml. portions of chloroform. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The solid material was recrystallized from benzene to yield 2.7 g. (50%) of 5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (VIII), m.p. 135.5-137°. The physical properties of this compound (m.p. NMR and uv) are identical to those reported (4,5) for this compound as prepared from 3-amino-1,2,4-triazole and acetyl acetone.

REFERENCES

(1) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms", part 2, Interscience Publishers, Inc., New York, N. Y., pp. 878-889.

(2) C. F. H. Allen, G. A. Reynolds, J. F. Tinker, and L. A. Williams, *J. Org. Chem.*, 25, 361 (1960), and earlier papers in this series.

(3) L. A. Williams, *J. Chem. Soc.*, 1829 (1960).

(4) K. Shirakawa, *Yakugaku Zasshi*, 80, 1542 (1960), and earlier papers in this series.

(5) Y. Makisumi, H. Watanabe, and K. Tori, *Chem. Pharm. Bull. (Japan)*, 12, 204 (1964).

(6) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, 31, 1295 (1966), and earlier papers in this series.

(7) W. L. F. Armarego, *J. Chem. Soc.*, 2778 (1965), and earlier papers by this author describe the ultraviolet spectral changes by these *peri* interactions.

(8) Williams (3) mentions that 4,6-dimethyl-2-hydrazinopyrimidine does not yield the expected dimethyl compound as had been described earlier (1). We have found that this reaction does indeed occur (*cf.* experimental section).

(9) The NMR spectra were recorded with a Varian A-60 instrument. The purity of all compounds was ascertained by silica gel G thin-layer chromatography (50% methanol-50% ethyl acetate). Melting points are corrected.

Received May 22, 1966 Athens, Ohio 45701