Synthesis of Adamantane Derivatives. XV.[1] No Ring-Fission Aptitude of the Homoadamantan-4-one System in the Schmidt and Beckmann Rearrangements

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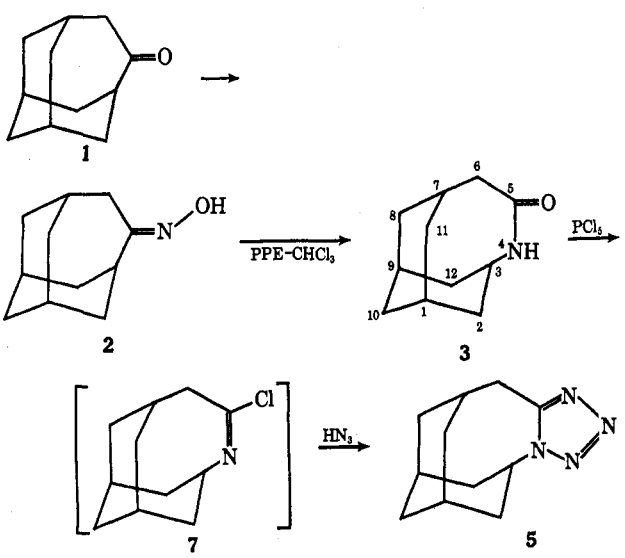
The stereospecific Beckmann rearrangement of *anti*-homoadamantan-4-one oxime (**2**) in PPE yielded 4-azabishomoadamantan-5-one (**3**) in 58% yield. **3** was converted to tetrazolo[4,5-*d*]-4-azabishomoadamantane (**5**) *via* an imino chloride intermediate (**7**). The same rearrangement of **2** in 85% H_2SO_4, however, afforded a 1:4 mixture of **3** and isomeric 5-azabishomoadamantan-4-one (**4**). The Schmidt reaction of homoadamantan-4-one (**1**) with equimolar sodium azide in CH_3SO_3H gave a 1:1 mixture of **3** and **4** (7%) and a 1:1 mixture of **5** and isomeric tetrazolo[4,5-*d*]-5-azabishomoadamantane (**6**) (48%), while that with 2.1 *M* sodium azide gave exclusively the tetrazole mixture (93.5%). The same reaction with equimolar sodium azide in CH_3SO_3H–AcOH (1:1 v/v) gave the lactam mixture (34%) and the tetrazole mixture (24%). These results differ from the adamantanone system and are rationalized by the postulation that the spatial arrangement of the participating bonds is one important factor for determining the Schmidt and Beckmann fission aptitude of these ring systems. A conformational problem of the 4-azabishomoadamantane skeleton is also discussed from nmr data.

Recently, we reported the formation of 4(e)-methylsulfonoxyadamantan-2-one in excellent yield from adamantanone and sodium azide in CH_3SO_3H;[2] this reaction has been demonstrated to proceed *via* a Schmidt fission and recombination path.[2b] A similar type of the reactions has also been reported for adamantanone oxime.[3] Furthermore, the principle of these reactions has been extended to a general preparation of 2-substituted and 2,4-disubstituted adamantane derivatives by the so-called π route.[4] However, the behavior of homoadamantan-4-one (**1**)[5] in the Schmidt reaction and of its oxime **2**[5c] in the Beckmann rearrangement have not been studied. This paper describes the results of these reactions under several conditions. No ring fission was observed, in sharp contrast to the facile fission in the adamantanone system.[2,3]

Schmidt Reaction of 1 and Beckmann Rearrangement of 2.—The oximation of **1** with hydroxylamine in 95% ethanol in the presence of excess potassium hydroxide afforded only anti oxime **2**.[6] Treatment of **2** with PEE (polyphosphate ester) in chloroform at 80° resulted in a stereospecific rearrangement to give 4-azatricyclo[5.3.1.1^{3,9}]dodecan-5-one (**3**) (4-azabishomoadamantan-5-one)[7] in 58% yield and 32% recovery of **2**. **3** had a molecular formula $C_{11}H_{17}NO$ on the basis of analysis and mass spectrum, and characteristic nmr signals at τ 6.48 (q, J = 7.5 Hz, on deuteration changed to t, C_3 methine) and 7.34 (d, J = 3.7 Hz, C_6 methylene) permitted the assignment of formula **3**. **3** was converted to the corresponding tetrazole derivative **5** (tetrazolo[4,5-*d*]-4-azabishomoadamantane)

SCHEME I



via an imino chloride intermediate **7** (Scheme I). The nmr spectrum of **5** had characteristic signals at τ 4.68 (t, C_3 methine) and 6.67 (d, C_6 methylene), supporting structure **5** (Figure 1).

The Beckmann rearrangement of **2** in 85% H_2SO_4 also yielded **3**, accompanied by a large amount of an isomeric lactam **4** (5-azabishomoadamantan-4-one) (1:4 ratio). Considering that sulfuric acid is prone to cause the syn–anti isomerization of oximes, and that PPE in nonpolar solvents is least prone to cause the isomerization,[8] these results can be explained by the isomerization of **2** prior to rearrangement. The fact that no Beckmann fission had occurred even in 85% H_2SO_4 is of much interest compared with the facile ring fission of adamantanone oxime under the similar conditions.[3a]

The absence of ring fission was observed also in the Schmidt reaction of **1**; treatment of **1** with equimolar sodium azide in CH_3SO_3H afforded a lactam mixture of **3** and **4** and a tetrazole mixture of **5** and **6** (Scheme II). The nmr spectrum of the lactam mixture exhibited characteristic signals at τ 6.48 (q), 6.64 (t, partly overlapped with the quartet), 6.92 (t), and 7.34 (d) in a 1:2:1:2 ratio. By nmr spectral comparison with **3**, this mixture was found to be a 1:1 mixture of **3**

(1) Part XIV of this series: T. Sasaki, S. Eguchi, and T. Toru, *Chem. Commun.*, 1239 (1970).

(2) (a) T. Sasaki, S. Eguchi, and T. Toru, *J. Amer. Chem. Soc.*, **91**, 3390 (1969). (b) *J. Org. Chem.*, **35**, 4109 (1970); (c) *Chem. Commun.*, 1285 (1969).

(3) (a) J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 3517 (1969); (b) V. L. Narayanan and L. Setescak, *J. Med. Chem.*, **6**, 445 (1969).

(4) (a) D. J. Raber, G. J. Kane, and P. v. R. Schleyer, *Tetrahedron Lett.*, 4117 (1970); (b) M. A. McKervey, D. Faulkner, and H. Hamill, *ibid.*, 1971 (1970); (c) R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970).

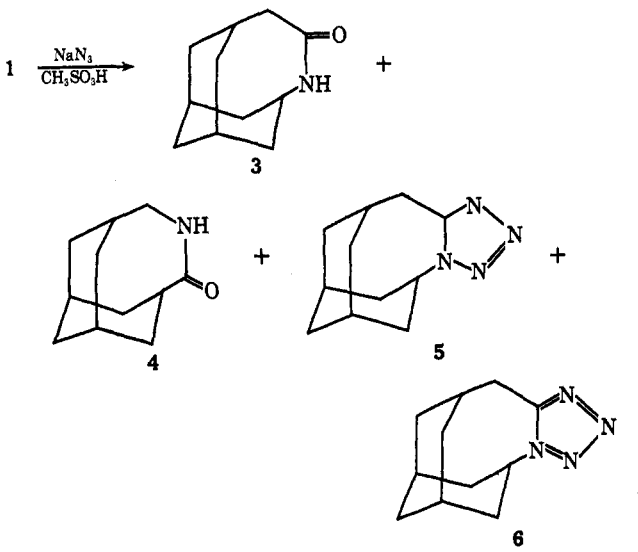
(5) (a) J. E. Nordlander, F. Y.-H. Wu, S. P. Jindal, and J. B. Hamilton, *J. Amer. Chem. Soc.*, **91**, 3962 (1969); (b) P. v. R. Schleyer, E. Funke, and S. H. Liggero, *ibid.*, **91**, 3965 (1969); (c) J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970); (d) I. Tabushi, Z. Yoshida, and N. Takahashi, *J. Amer. Chem. Soc.*, **92**, 6670 (1970).

(6) The prefix "anti" refers to the direction of the oxime hydroxyl group with respect the methine group. The anti stereochemistry of **2** was based on nmr data. *Cf.* P. A. Smith, "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 485, and also see ref 5c.

(7) This trivial name was used in this paper.

(8) See ref 6, pp 483–527.

SCHEME II



and **4**. The tetrazole mixture was similarly characterized as a 1:1 mixture of **5** and tetrazolo[4,5-*d*]-5-azabishomoadamantane (**6**) by its nmr signals at τ 4.68 (t), 5.45 (d), 6.00 (t), and 6.67 (d) in a 1:2:1:2 ratio. The reaction of **1** with 2.1 *M* sodium azide in CH_3SO_3H afforded exclusively the tetrazole mixture, while that with equimolar sodium azide in CH_3SO_3H–AcOH gave a somewhat higher yield of the lactam mixture than that of the tetrazole mixture (Table I).

TABLE I
PRODUCT DISTRIBUTION OF THE SCHMIDT REACTION OF HOMOADAMANTAN-4-ONE (1)

Catalyst-solvent	NaN_3 (molar ratio to 1)	Products (yield, %) 3 + 4	5 + 6	Recovered 1, %
CH_3SO_3H	2.1	0	93.5	0
CH_3SO_3H	1.0	7	48	29
CH_3SO_3H–AcOH (1:1 v/v)	1.0	34	24	17

Since tetrazole formation is indicative of the presence of an iminium cation,[9] the exclusive formation of **5** and **6** in the presence of excess hydrogen azide indicates that the Schmidt reaction of **1** proceeds *via* path B[10] and not *via* path A[11] (Scheme III) in contrast to the adamantanone system,[2b] where both reaction paths A and B are involved. Surprisingly, neither fission products nor their derivatives were found in the Schmidt reaction of **1** contrary to the reported facile ring fission of adamantanone *via* path B.[2b]

From these striking differences between **1** and adamantanone in the Schmidt and Beckmann rearrangements, it is concluded that the spatial arrangement of the participating bonds in these reactions is a prominent factor for determining the ring-fission aptitude. Although electronic factors such as the charge delocalization on the participating bonds, *e.g.*, a–e in **11** and **12**, are assumed to be more or less similar, the spatial arrangement of $H-C_\beta-C_\alpha-C{=}N{\sim}N_2^+$ is obviously different from **1** and adamantanone because

(9) For example, see P. A. S. Smith and W. L. Berzy, *J. Org. Chem.*, **26**, 27 (1961).
(10) P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 320 (1948).
(11) M. S. Newman and H. Gildenhon, *ibid.*, **70**, 317 (1948).

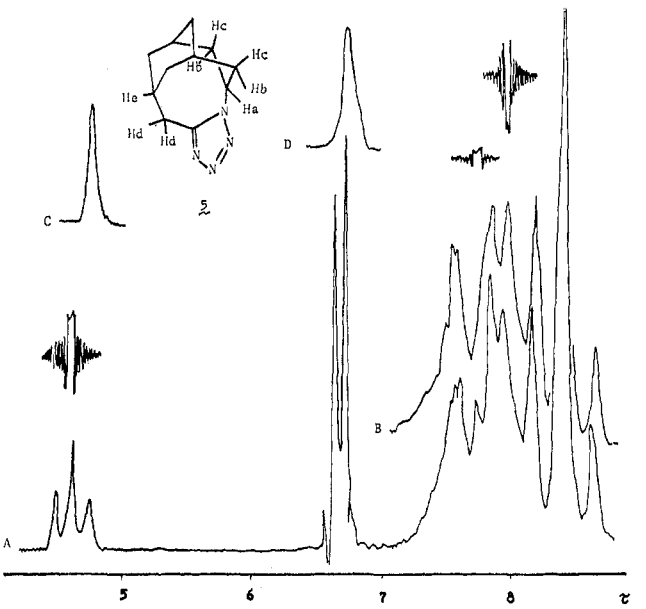


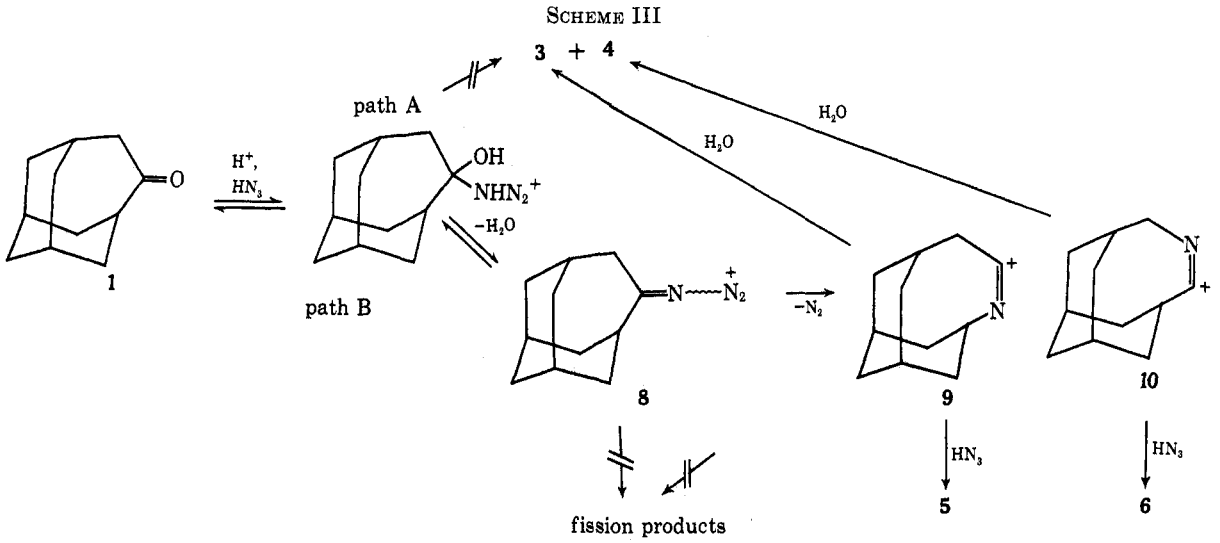
Figure 1.—Nmr spectrum of **5** ($CDCl_3$, 60 MHz): (A) standard spectrum; (B) spectrum decoupled from H_a; (C) H_a band decoupled from H_c; (D) H_d band decoupled from H_e.

of the presence of seven-membered rings in **1**. An inspection on the Dreiding stereomodel suggested that the spatial arrangement of $H-C_4-C_3-C_2{=}N{\sim}N_2^+$ for adamantanone is almost ideally antiparallel for C_2-C_8 bond fission,[2b] but that of $H-C_2-C_3-C_4{=}NN{\sim}N_2^+$ and/or $H-C_6-C_5-C_4{=}N{\sim}N_2^+$ for **1** is deviated from the ideally antiparallel one for C_3-C_4 and/or C_4-C_5 bond fission assuming an untwisted conformation of **1**.[5,12] In addition, consideration of the energy balance due to the ring strain in the fission of the rearrangement (*i.e.*, the ring expansion) suggests that ring fission of **1** might be more favorable than rearrangement compared with adamantanone.[13]

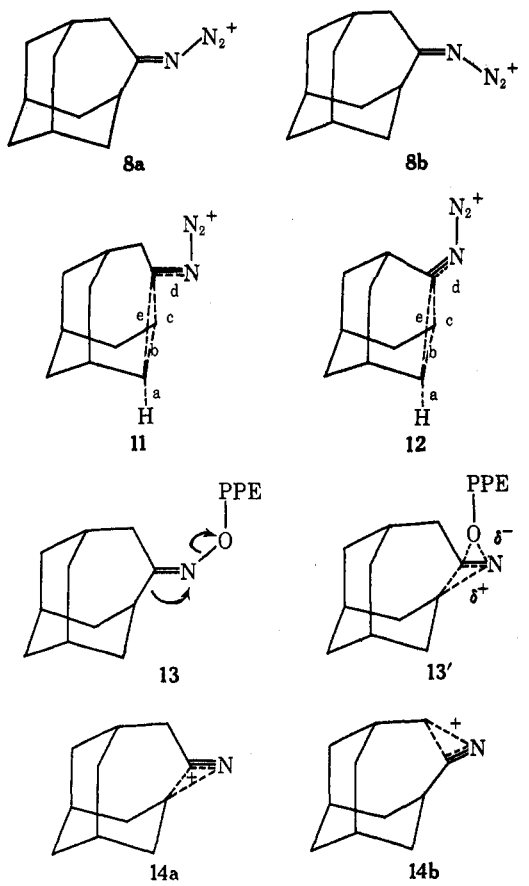
Evidently, the Schmidt reaction of **1** proceeds *via* a different transition state from that of the Beckmann rearrangement of **2** with PPE, which seems to take place concertedly *via* **13** or **13′** from the observed stereospecificity. On the other hand, the nonstereospecific rearrangement of **1** in the Schmidt reaction could be explained reasonably by assuming the intervention of a highly energetic cationic species which is generated by the loss of nitrogen from **8**, and rearranges nonstereospecifically to **9** and **10** *via* **14a** and **14b**. The possibility that the relative population of isomeric diazonium cations **8a** and **8b** could determine the product ratio *via* their stereospecific rearrangement seems implausible because the Beckmann rearrangement of **2** under equilibrating conditions (85% H_2SO_4) affords the lactams in a different ratio from that in the Schmidt

(12) The deviation of $H-C_6-C_5-C_4{=}N{\sim}N_2^+$ is less extent than that of $H-C_2-C_3-C_4{=}N{\sim}N_2^+$; however, the C_4-C_5 bond fission is disfavored by the fact that a primary carbonium ion adjacent to the carbonyl is possible; see ref 2b and references cited there.
(13) The calculated total strain energies for bicyclo[3.3.1]nonane, homoadamantane, and bishomoadamantane rings relative to adamantane ring are reported as *ca.* 12, 14, and 18–20 kcal/mol, respectively. Hence, a considerable strain increase could be expected for **1** → **9** + **10** conversion but no appreciable strain change for fission of **1**, while a large strain increase is accompanied for both rearrangement and fission of adamantanone. *Cf.* G. J. Gleicher and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967); P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *ibid.*, **92**, 2377 (1970); R. C. Fort, Jr., Ph.D. Thesis, Princeton University, Princeton, N. J., 1964.

SCHEME III



reaction, and also because of the possible steric preference of one isomer of **8** (*e.g.*, **8a**) to the other.



Conformational Study of the 4-Azabishomoadamantane Skeleton.—A conformational problem exists in the 4-azabishomoadamantane skeleton as in the homoadamantane ring.[5] Is the C_3–N_4–C_5–C_6–C_7 bond twisted or not?

The nmr spectrum of **5** is shown in Figure 1, in which the signals at τ 4.68, 7.75, 6.67, and 7.97 are assigned to H_a, H_c, H_d, and H_e, respectively, with the aid of spin-decoupling experiments. The appearance of C_6-methylene protons (H_d) in a doublet with J = 4.5 Hz indicates that the two protons are equivalent and that the dihedral angle for H_d and H_e is approximately 50° according to the Karplus relation. Similarly, a triplet with J = 6.4 Hz due to C_3-methine proton (H_a) indicates that $J_{a,c}$ = 6.4 and $J_{a,b}$ = 0 Hz, and hence the dihedral angle for H_a and H_e is *ca.* 30°, and that for H_a and H_b, is *ca.* 90°. These coupling patterns of H_a and H_d signals, therefore, suggest an untwisted bridged conformation of the eight-membered rings in **5**.[14] The preference of an untwisted conformation is also postulated in homoadamantane ring.[5]

The nmr spectrum of the lactam **3** had similar coupling patterns of C_3-methine and C_6-methylene protons as described above, suggesting also an untwisted conformation of **3**. A recent report[15] that 4,6-diazabishomoadamantan-5-one takes a partially flattened chair conformation of the two six-membered rings is compatible with the above conclusion for **3** and **5**.

Experimental Section[16]

Preparation of *anti*-Homoadamantan-4-one Oxime (2).—A mixture of homoadamantan-4-one (1) (1.0 g, 6.1 mmol), hydroxylamine hydrochloride (1.0 g, 14.4 mmol), and potassium hydroxide (4.0 g, 71.3 mmol) in 95% ethanol (20 ml) was refluxed overnight. The cooled mixture was evaporated under reduced pressure, diluted with water (30 ml), and extracted with ether (five 30-ml portions). The washed (water) and dried (Na_2SO_4) extract was evaporated to give a solid residue which was recrystallized from ethanol to afford anti oxime **2** (0.94 g, 76%) as colorless crystals: mp 158–159° (lit.[5c] 147–149°); ir (KBr) 3180, 3040, and 1635 cm^{-1}; nmr ($CDCl_3$) τ 1.35 (br s, 1, OH), 7.19 (m, 1, C_3 methine), 7.32 (d, 2, J = 3.5 Hz, C_5 methylene), and 7.60–8.85 (m, 13, other ring protons).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.77; H, 9.43; N, 7.71.

Beckmann Rearrangement of 2. A. With PPE.—A mixture of **2** (1.0 g, 5.6 mmol) and PPE (6.0 g) in chloroform (5 ml) was heated at 85° for 10 min. The mixture was diluted with water (100 ml), stirred for 1 day at room temperature, and then heated at 80° for 10 min. The cooled mixture was basified with 10% aqueous potassium hydroxide and extracted with chloroform (five 50-ml portions). The dried (Na_2SO_4) extract was evaporated to afford a brownish oil which was purified on a silica gel

(14) However, the possibility of a rapid equilibrium of more than two conformers on the nmr time scale could not be ruled out.

(15) V. G. Keizer, J. G. Korsloot, F. W. v. Deursen, and M. E. v. d. Heeden, *Tetrahedron Lett.*, 2059 (1970).

(16) All melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Nmr spectra were determined with a JEOL JNM-C-60HL spectrometer at 60 MHz and mass spectra with a JEOL JMS-01SG spectrometer at 70 eV. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer.

column eluting with chloroform to give recovered **2** (0.32 g, 32% recovery) and 4-azabishomoadamantan-5-one (**3**) (0.58 g, 58%) as colorless crystals from acetone: mp 184–185°; ir (KBr) 3440, 3240, 3140, 3000, and 1635 cm^{-1}; nmr ($CDCl_3$) τ 2.95 (br s, 1, NH), 3.52 (q, 1, J = 7.5 Hz, C_3 methine, t in $CDCl_3$–D_2O), 7.34 (d, 2, J = 3.7 Hz, C_6 methylene), and 7.48–8.85 (m, 13, other ring protons); mass spectrum m/e (rel intensity) 179 (M^+, 100), 164 (20), and 151 (50).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.36; H, 9.47; N, 7.89.

B. With Sulfuric Acid.—A solution of **2** (0.20 g, 1.3 mmol) in 85% (v/v) sulfuric acid (6.5 ml) was heated at 110° for 12 min. The cooled solution was poured onto ice–water (20 ml), neutralized with solid sodium bicarbonate, and extracted with chloroform (five 20-ml portions). The washed and dried (Na_2SO_4) extract was evaporated to give a solid residue which was purified on a silica gel column, eluting with chloroform to afford a 1:4 mixture of the lactams **3** and **4** (0.12 g, 60%).

Tetrazolo[4,5-*d*]-4-azabishomoadamantane (5).—To a solution of phosphorus pentachloride (0.20 g, 0.96 mmol) in chloroform (2 ml) was added a solution of **3** (0.20 g, 1.1 mmol) in chloroform (2 ml) with stirring at room temperature. After stirring was continued for 1 day, a mixture of sodium azide (0.20 g, 3.1 mmol) and sulfuric acid (0.1 ml) in benzene (10 ml) was added to the mixture. The resulting mixture was stirred for 10 hr at room temperature, basified with 10% aqueous potassium hydroxide, and extracted with chloroform (five 30-ml portions). The washed and dried (Na_2SO_4) extract was evaporated to give a solid residue which was purified on a silica gel column, eluting with chloroform to afford the tetrazole **5** as colorless crystals from acetone: mp 173–174°; ir (KBr) 1530 cm^{-1}; mass spectrum m/e (rel intensity) 204 (M^+, 20), 176 (15), 163 (30), and 149 (100).

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.49; H, 8.01; N, 27.14.

Schmidt Reaction of Homoadamantan-4-one (1). A. In CH_3SO_3H.—To an ice-cooled solution of **1** (0.50 g, 3.0 mmol) in CH_3SO_3H (5 ml) was added portionwise solid sodium azide (0.20 g, 3.1 mmol) during 4 hr with stirring. After stirring was continued for an additional 20 hr, the mixture was poured onto ice–water (30 ml), and the resulting mixture was neutralized with solid sodium bicarbonate and extracted with chloroform (five 30-ml portions). Work-up in the usual way afforded a solid product which was purified on a silica gel column, eluting with chloroform to give recovered **1** (0.145 g, 29% recovery), a 1:1 mixture of the tetrazoles **5** and **6** (0.30 g, 48%), mp 188–189°, and a 1:1 mixture of the lactams **3** and **4** (0.040 g, 7%), mp 153–160°.

Anal. Calcd for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.44; H, 8.00; N, 27.04. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.40; H, 9.57; N, 7.83.

A similar reaction of **1** (0.50 g, 3.0 mmol) with sodium azide (0.41 g, 6.3 mmol) in CH_3SO_3H (8 ml) afforded a 1:1 mixture of the tetrazoles **5** and **6** (0.58 g, 93.5%).

B. In CH_3SO_3H–AcOH.—A similar reaction of **1** (0.50 g, 3.0 mmol) with sodium azide (0.20 g, 3.1 mmol) in CH_3SO_3H (2 ml)–AcOH (2 ml) and work-up as above afforded the tetrazole mixture (0.15 g, 24%), the lactam mixture (0.19 g, 34%), and recovered **1** (0.085 g, 17% recovery).

Registry No.—**2**, 26770-89-8; **3**, 29863-86-3; **4**, 29863-87-4; **5**, 29863-88-5; **6**, 29863-89-6.

Pyridazines. XXXVII. Pyrimido[1,2-*b*]pyridazines

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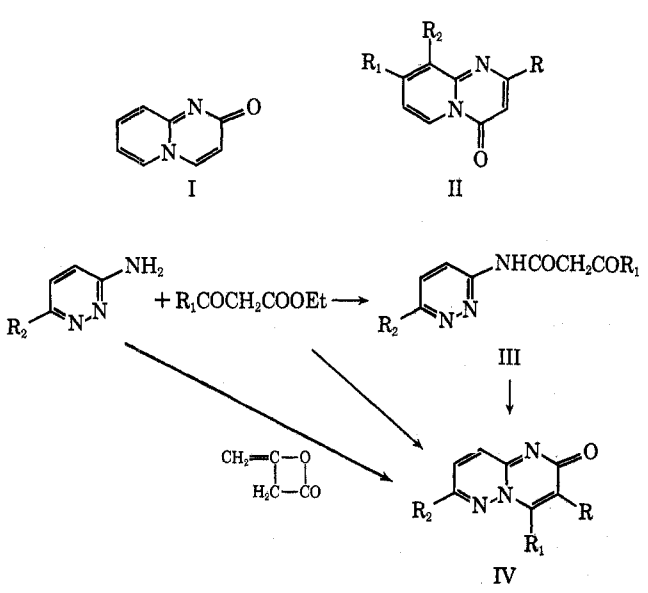
3-Aminopyridazines condense with 1,3-dicarbonyl compounds in polyphosphoric acid to give pyrimido[1,2-*b*]-pyridazines. With β-keto esters pyrimido[1,2-*b*]pyridazin-2-ones are formed, in contrast to 2-aminopyridines which give pyrido[1,2-*a*]pyrimidin-4-ones.

The intriguing structural problem concerning condensation products of amino heterocycles with β-keto esters and related compounds has recently received further interest. In the pyridine series, the controversy regarding the bicyclic products as pyrido[1,2-*a*]-pyrimidin-2-ones (I) or pyrido[1,2-*a*]pyrimidin-4-ones (II) has been solved in favor of the latter ones.[1] The 2-ones were prepared by cyclization of the addition products of the Michael type, formed from aminopyridines and acetylenic compounds.[2] Moreover, mechanism for the formation of 4-ones has been discussed[3] and the reaction was applied to 2-aminothiazoles.[4]



We have extended the reaction to 3-aminopyridazines and with several β-keto esters, derivatives of the recently described pyrimido[1,2-*b*]pyridazine system[5,6] were obtained. 3-Aminopyridazines do not condense with β-keto esters to acylamino derivatives III unless a base, such as triethylamine, is added. On the other hand, the formation of crotonates as intermediates is very unlikely. 3-Acetoacetylaminopyridazine, when heated in polyphosphoric acid (PPA), afforded 4-methylpyrimido[1,2-*b*]pyridazin-2-one (IV, R = R_2 = H; R_1 = Me) which can be obtained also from 3-aminopyridazine and diketene or in a straightforward

(1) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," part II, Interscience, New York, N. Y., 1961, p 1141.
(2) J. G. Wilson and W. Bottomley, *J. Heterocycl. Chem.*, **4**, 360 (1967).
(3) M. Shur and S. S. Israelstam, *J. Org. Chem.*, **33**, 3015 (1968).
(4) G. T. F. Galasko and S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **22**, 121 (1969).
(5) B. Stanovnik and M. Tišler, *Tetrahedron Lett.*, 33 (1968).
(6) S. Ostovernšik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **41**, 135 (1969).