Synthesis of Adamantane Derivatives. XII. The Schmidt Reaction of Adamantan-2-one[1,2]

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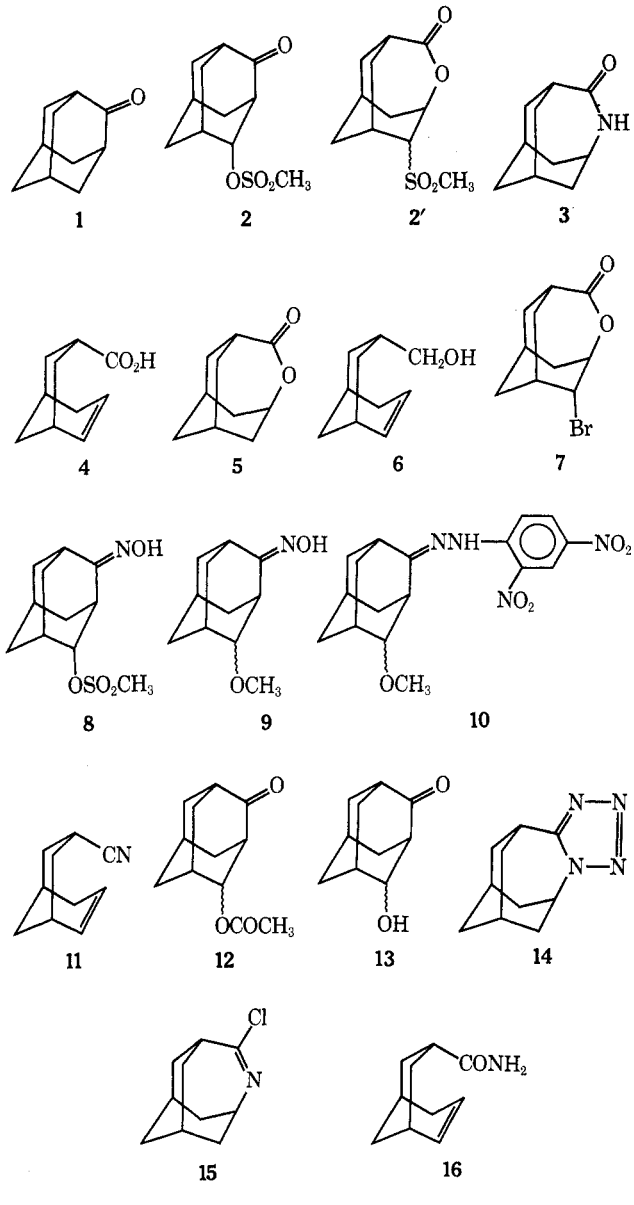
A remarkable catalyst–solvent effect on the product distribution was observed in the Schmidt reaction of adamantan-2-one (1). In methanesulfonic acid, 4(e)-methanesulfonoxyadamantan-2-one (2) was obtained as the major product (88%) and 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (3), the normal Schmidt reaction product, rather as the minor product (11%). In methanesulfonic acid–acetic acid, water, and trichloro- and trifluoroacetic acid, 1 gave bicyclo[3.3.1]non-6-one-3-carbonitrile (11) in 40–61% yields together with lactam 3 in 27–60% yields. In sulfuric acid–acetic acid, 4-acetoxy- (12) and 4-hydroxyadamantan-2-one (13) as well as 3 were obtained. In the presence of excess hydrogen azide, small amounts of a tetrazole derivative 14 were produced in methanesulfonic acid–chloroform and methanesulfonic acid–acetic acid but not in methanesulfonic acid alone. Compound 11 was demonstrated to be a precursor of these 4-substituted adamantan-2-ones (2, 12, and 13), while 3 was produced mainly from an azidohydrin intermediate 17 *via* a hydrated iminocarbonium ion 18. The facile ring fission of 1 to 11 was explained by an ideal geometrical arrangement of the participating bonds in the possible intermediates 19 and 20 and/or 20′. As a conclusion, two reaction paths (a and b) are consistently postulated in the Schmidt reaction of 1 (Scheme III). Several facile ring cleavage reactions of 2 were also described.

In preliminary communications on this subject,[1] we described a novel substitution reaction of adamantan-2-one (1) at its C_4 position under the Schmidt reaction conditions. These results prompted other workers[2c] to publish their findings on the Beckmann rearrangement of 1 oxime.[2] With the aim of obtaining further information on the scope and limitation of such abnormal Schmidt reactions, the Schmidt reaction of 1 was examined under various conditions. This paper deals with an elucidation of the reaction mechanism based on our further findings. The facile availability of 4(e)-methanesulfonoxyadamantan-2-one (2) made it possible to study its reactions in some detail, especially ring fissions as one of the heterolytic fragmentations[3] of adamantane derivatives.

Product Distribution in the Schmidt Reaction of 1 under Various Conditions.—The products of the Schmidt reaction of 1 using *ca.* an equimolar amount of hydrogen azide under various conditions are shown in Table I. In methanesulfonic acid, 4-methanesulfonoxyadamantan-2-one (2) and 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (3) were produced (Scheme I).[1] The structure of 2 was determined by spectral and chemical evidence.[1a] In the nmr spectrum (Figure 1), a triplet signal at δ 4.80 and a singlet at δ 3.05 assignable to C_4 proton adjacent to a methanesulfonoxy group and methyl protons, respectively, were observed besides a complex multiplet due to other adamantane ring protons. Broad signals at δ 2.89, 2.40, and 1.90 were assignable to C_3, C_5, and C_6 and/or C_{10} protons, respectively, on the basis of double and triple resonance experiments; a broad triplet at δ 4.80, soiled by long-range couplings, becomes a clear triplet on irradiation at the δ 1.90 signal and collapses to a doublet (J = 4.0 Hz) when both signals at δ 1.90 and 2.40 were irradiated.



Compound 2 was sensitive to carbonyl reagents and its 2,4-dinitrophenylhydrazone and oxime (8) were obtained. This fact excluded another possible structure

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(1) For preliminary accounts of this work, see (a) T. Sasaki, S. Eguchi, and T. Toru, *J. Amer. Chem. Soc.*, **91**, 3390 (1969); (b) *Chem. Commun.*, 1285 (1969).

(2) During the preparation of this paper, the Beckmann fission of 1 oxime as well as the normal Beckmann rearrangement has been reported in communications: (a) J. G. Korsloot, V. G. Keizer, and J. L. M. A. Schlatmann, *Recl. Trav. Chim. Pays-Bas*, **88**, 447 (1969); (b) V. L. Narayanan and L. Setescak, *J. Heterocycl. Chem.*, **6**, 445 (1969); (c) J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 3517 (1969).

(3) For a recent review, see C. A. Grob, *Angew. Chem. Int. Ed. Engl.*, **8**, 535 (1969).

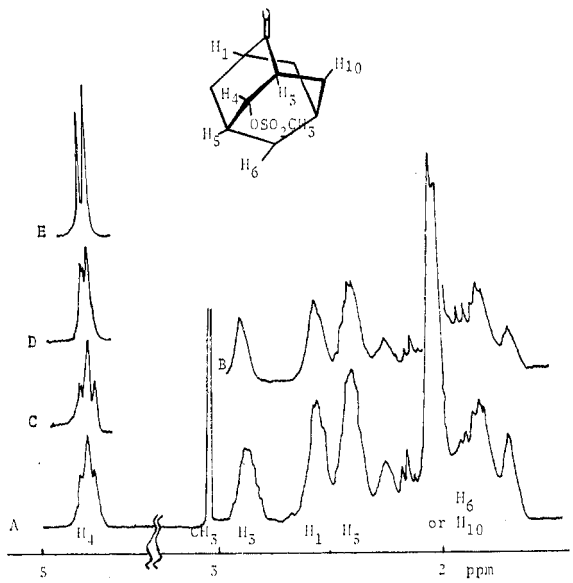
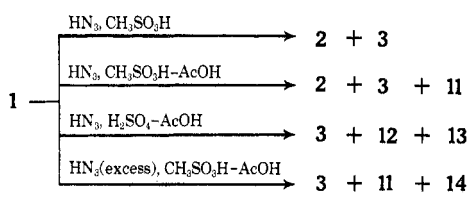


Figure 1.—Nmr spectra of **2**: A, standard spectrum; B, the spectrum decoupled from H_4; C, H_4 band decoupled from H_6 or H_{10}; D, H_4 band decoupled from H_3 and H_8 or H_{10}; E, H_4 band decoupled from H_5 and H_6 or H_{10},

SCHEME I



2′,[4] since 4-oxatricyclo[4.3.1.1^{3,8}]undecan-5-one (**5**) had no reactivity to these carbonyl reagents. Attempted hydrolysis of the mesylate group in **2** with alkali resulted in the formation of bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**4**) in high yields, indicating that the methanesulfonoxy group is attached at the C_4 position from the known quasi-Favorskii reaction[5] of 4(e)-bromoadamantan-2-one.[6] The structure of **4** was confirmed by its superimposable ir spectrum on that of an authentic sample[7] and by its facile conversion to known lactone **5**.[6] Lithium aluminium hydride reduction of **2** afforded bicyclo[3.3.1]non-6-ene-3-carbinol (**6**) in almost quantitative yields, which is also obtainable from the reduction of **4**[6] (Scheme II).

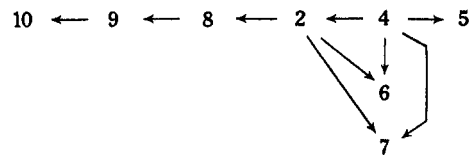
TABLE I

SCHMIDT REACTION PRODUCTS OF 1 UNDER VARIOUS CATALYST-SOLVENT SYSTEMS[a]

Catalyst-solvent (v/v)	Reaction time,[b] hr	Products (yields,[c] %)		
CH_3SO_3H	50	**2** (88)	**3** (11)	
CH_3SO_3H-AcOH (3/4)	1	**2** (3)	**3** (33)	**11** (61)
CH_3SO_3H-AcOH (1/1)	2.5	**2** (5.5)	**3** (27)	**11** (57)
CH_3SO_3H-H_2O (8/3)	25.5	**3** (36)	**11** (54)	
CF_3COOH	3.2	**3** (59.5)	**11** (40.5)[d]	
CCl_3COOH[e]	1.3	**3** (53.5)	**11** (46.5)[d]	
H_2SO_4-AcOH (1/1)	50	**3** (27.4)	**12** (32.2)	**13** (10)
AcOH (glacial)	50[f]			

[a] Reactions were carried out using a small excess of sodium azide at room temperature. [b] Addition times of sodium azide were involved. [c] Based on the isolated amounts of each products. [d] Based on glpc analysis. [e] The reaction was carried out at 50°. [f] Almost completely 1 was recovered.

SCHEME II



A bromolactone **7** was prepared directly from **2** and aqueous bromine at 95°, which is alternatively obtained by bromolactonization of **4** in chloroform.[8] Such facile fragmentation of **2** might suggest 4-equatorial configuration for the methanesulfonoxy group.[3,9]

The structure of **2** was finally verified by the X-ray analysis to have a 4(e)-methanesulfonoxy group.[10]

The sensitive nature of **2** toward both acids and alkalis made it difficult to displace the mesylate group. However, protection of the carbonyl group by oximation, followed by alkaline methanolysis, afforded the corresponding methoxy ketone oxime (**9**) which was converted to the 2,4-dinitrophenylhydrazone (**10**).

The structure of lactam **3** was determined by spectral data and by its reduction to the known 4-azahomoadamantane.[1b]

As is seen from Table I, the main product of the Schmidt reaction of **1** in such catalyst–solvent systems as methanesulfonic acid diluted with water[11] or acetic acid, trifluoro- and trichloroacetic acid was bicyclo[3.3.1]non-6-ene-3-carbonitrile (**11**) which is also prepared by the Beckmann fission of **1** oxime.[2c] 4-Acetoxy- (**12**) and 4-hydroxyadamantan-2-one (**13**) were produced in sulfuric acid–acetic acid. Trifluoroacetic acid seemed the most suitable catalyst–solvent for the preparation of lactam **3**.

Product distributions in the reactions using excess hydrogen azide are summarized in Table II. Tetrazolo[4,5-*d*]4-azohomoadamantane (**14**) was produced in low yields with methanesulfonic acid–acetic acid and methanesulfonic acid–chloroform catalyst–solvent systems but not with methanesulfonic acid only. The structure of **14** was determined by analytical and spectral data, and by an alternative synthesis from **3** *via* an iminochloride **15**.

3 ⟶ **15** ⟶ **14**

(4) Professor P. von R. Schleyer has kindly suggested us to consider **2′** as one of another possible structures for **2**.

(5) (a) A. C. Cope and E. S. J. Graham, *J. Amer. Chem. Soc.*, **73**, 4702 (1951); (b) C. L. Stevens and E. F. Farkas, *ibid.*, **74**, 5352 (1952).

(6) A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 5719 (1968).

(7) Professor H. Wynberg has kindly sent us the ir spectrum of **4**.

(8) *Cf.* iodolactonization; for example, see W. Boehme, E. Schipper, W. G. Scharpf, and J. Nicholls, *J. Chem. Soc.*, 227 (1959).

(9) W. Kraus and W. Rothenwoehrer, *Tetrahedron Lett.*, 1007, 1013 (1968).

(10) The X-ray analysis of **2** was kindly performed by Professor J. Clardy of Iowa State University. C. M. Lee and J. C. Clardy, *Chem. Commun.*, 716 (1970).

(11) Dr. R. N. Schut informed us that **11** was isolated in *ca.* 60% yield by using 2 molar amounts of sodium azide in technical grade methanesulfonic acid (private communication).

TABLE II

SCHMIDT REACTION PRODUCTS OF 1 WITH EXCESS HYDROGEN AZIDE AT ROOM TEMPERATURE

Catalyst–solvent (v/v)	NaN_3 (molar ratio to 1)	Reaction time, hr	Products (Yield %)			
CH_3SO_3H	3.2	48	2 (55)	3 (16)	11 (2)[a]	
CH_3SO_3H–$CHCl_3$ (1/10)	2.3	20	2 (36)	3 (33.5)	11 (10)	14 (7.5)[a]
CH_3SO_3H–AcOH (1/4)	3.7	24	3 (60)	11 (36)	14 (5)[b]	

[a] Based on the isolated amounts. [b] The relative peak area to 3 on glpc analysis.

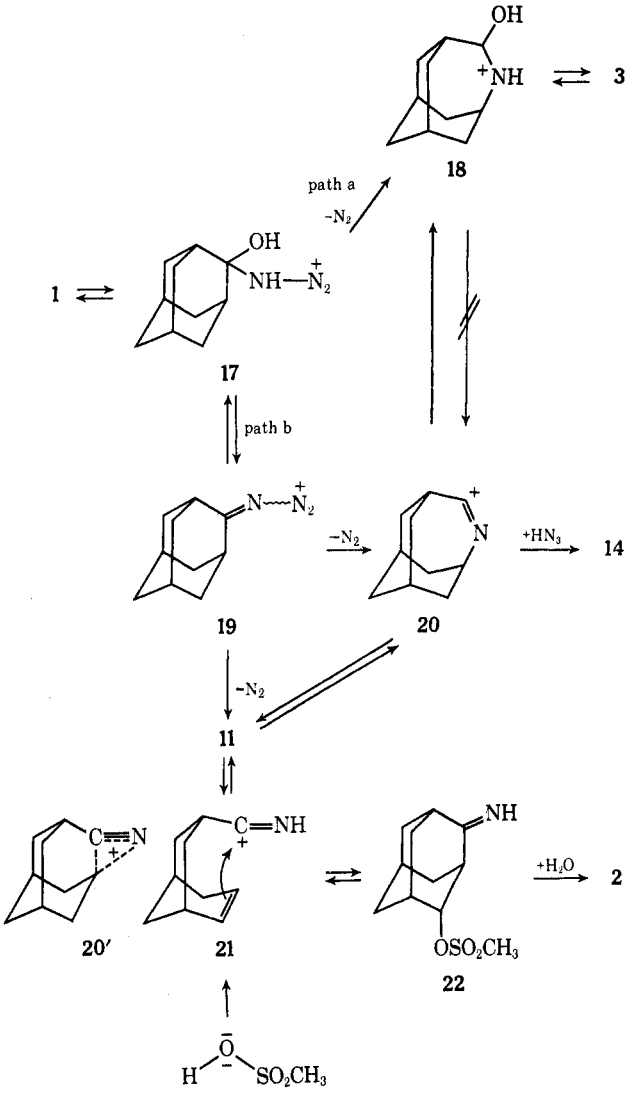
Discussion of the Schmidt Reaction Mechanism of 1.—The Schmidt reaction mechanism has been the subject of considerable attention for over 30 years.[12]

That of ketones is generally postulated to proceed *via* two different mechanistic pathways,[13,14] both of which assume reasonably an azidohydrin intermediate formed by the nucleophilic attack of hydrogen azide on the protonated carbonyl group. Recently, the consistency of both reaction paths has been reported in the Schmidt reactions of *cis*-8-methylhydrindan-1-one[15] and chromanone.[16] Also in the Schmidt reaction of **1**, the consistent two-reaction paths a and b (Scheme III) can be postulated, but with predominant ring fission *via* path b based on the following discussion.

(1) The practical isolation of **11** suggests that the Schmidt reaction of **1** involves the so-called fragmentation–recombination mechanism.[17] In fact, **11** in methanesulfonic acid afforded the cyclic ketone **2** and lactam **3** in over 90 and 1.7% yields, respectively, which indicates clearly that **2** is produced almost exclusively, but **3** partly from **11**. The scant formation of **3** is explainable by the less favorable cyclization aptitude to a strained homoadamantane ring system **20** in the normal Ritter reaction,[18] in which the intermediate **20** was captured by excess hydrogen azide to give **14** on treatment of **11** with the acid. The yield (*ca.* 1%) of **14** corresponds to that (1.7%) of **3** obtained in the absence of hydrogen azide. On the other hand, the Houben–Hoesch type reaction[19] of **11** *via* **21** is facilitated by cyclization to a less strained 2-iminoadamantane ring system **22**, which is hydrolyzed to **2**. The cyclization *via* **21** may proceed by a concerted process rather than by a stepwise one *via* a carbonium ion, since the equatorial configuration for the methanesulfonoxy substituent in **2** has been established.

Any contribution of a path from **11** to **3** *via* an amide **16** was excluded by the fact of complete recovery of **16** on its treatment with methanesulfonic acid.[20] The cyclization of **11** with 96% sulfuric acid has been recently reported to give **13** (77%), **3** (1–2%), and **5** (5.4%).[20]

SCHEME III



Other cyclization products such as **12** and **13** in Table I can be produced similarly *via* **11**.

11 ⇢ 16 ⇢ 3

(2) It is known that tetrazole formation is an indication of the presence of an iminium cation.[12,21] Even in the presence of excess hydrogen azide, no trace of tetrazole **14** was produced in methanesulfonic acid, and only small amounts of **14** were produced in methanesulfonic acid–acetic acid and methanesulfonic acid–chloroform in spite of the larger amounts of the lactam formation (Table II). The lactam **3** did not afford any trace of **14** with excess hydrogen azide in methanesulfonic acid. Aliquots of the reaction mixture of **1** with *ca.* equimolar amount of hydrogen azide in methanesulfonic acid–acetic acid after 1, 2, and 5 hr were treated with excess hydrogen azide in chloroform but no tetrazole formation was confirmed. On the other hand, the product distribution in methanesulfonic acid–acetic acid using an equimolar amount of hydrogen azide was examined at various reaction times, the results of which are summarized in Table III. After 45 sec, *ca.* 20% of **1** reacted to afford lactam **3** and nitrile **11** in *ca.* 1:1 ratio. The

(12) For a recent review, see P. A. S. Smith, "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 507–527.

(13) (a) E. Oliveri-Mandald, *Gazz. Chim. Ital.*, **55** (1), 271 (1925); (b) M. S. Newman and H. Gildenhon, *J. Amer. Chem. Soc.*, **70**, 317 (1948).

(14) P. A. S. Smith, *ibid.*, **70**, 320 (1948).

(15) G. Di Maio and V. Permutti, *Tetrahedron*, **22**, 2059 (1966).

(16) U. T. Bhalerao and G. Thyagarajan, *Can. J. Chem.*, **46**, 3367 (1968).

(17) For example, see (a) R. T. Conley and B. E. Nowak, *J. Org. Chem.*, **26**, 692 (1961); (b) R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Amer. Chem. Soc.*, **87**, 5646 (1965); (c) H. D. Zook and S. C. Paviak, *ibid.*, **77**, 2501 (1955).

(18) For a recent review, see L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).

(19) P. E. Sperri and A. S. DuBois, *ibid.*, **5**, 387 (1949).

(20) For examples of an intramolecular cyclization of unsaturated amides with polyphosphoric acid, see R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957), and ref 17a.

(21) For examples, see P. A. S. Smith and W. L. Berzy, *ibid.*, **26**, 27 (1961).

TABLE III

REACTION TIME DEPENDANCE OF PRODUCT RATIO IN THE SCHMIDT REACTION OF 1 IN METHANESULFONIC ACID–ACETIC ACID[a]

Reaction time	Products,[b] %[c] 1 (unreacted)	3	11
45 sec	79.5	10.0 (49)[d]	10.5 (51)[d]
5 min	50.0	25.5 (51.0)	24.5 (49.0)
30 min	13.0	48.0 (55.0)	39.0 (45.0)
1 hr	5.0	53.5 (56.5)	41.5 (43.5)
5 hr	0	63.0	37.0
24 hr	0	69.5	30.5

[a] To a stirred solution of 0.3 g of 1 in 10 ml of acetic acid and 0.32 ml of methanesulfonic acid was added 0.16 g of sodium azide at *ca.* 20° and each aliquot (1 ml) was analyzed on glpc after dilution with water and making alkaline, followed by extraction with chloroform. [b] Cyclization products of **11** such as **12** were also produced in very small amounts. [c] The relative percentage of **1**, **3**, and **11**. [d] The relative percentage of **3** and **11**.

amounts of both **3** and **11** increase similarly as the reaction proceeds but the relative amounts of **11** to **3** decrease; this is ascribable to the secondary reaction of **11** involving cyclization to **12**. On treatment of **11** with methanesulfonic acid–acetic acid, no lactam **3** but small amounts of **2** and **12** were produced together with the formation of several unidentified products on glpc. All of these facts indicate that lactam **3** might be produced mainly *via* path a involving an intermediate **18**; path b involving **19** and **20** seems not to be important for the lactam formation. The observed solvent effects on the product distribution can be explained by the solvent effect on the equilibrium between **17** and **19**, the latter of which can be a precursory intermediate for nitrile **11**.

(3) There are two types of intermediates postulated for the Beckmann fission of oxime.[22] In our case, **11** could be produced from **19** either *via* **20** or directly by a concerted process. The latter process seems to be more reasonable considering the ideal geometry[3] of H-C_4-C_3-C_2=N⁓N_2^+ bonds in **19** and the facts of non/or scant formation of tetrazole **14**. However, the intervention of a nonclassical ion **20′** in place of **20** may provide another plausible explanation.[23]

Finally it should be mentioned that there are two major aspects in the Schmidt reaction of **1**, which have not been encountered in other cyclic ketones.[24] First, a very high susceptibility of the adamantane ring fission has been observed in spite of a secondary carbonium ion adjacent to the carbonyl group,[17,25] and second, the cyclization products having a nucleophilic group are produced. The latter is ascribable to the unfavorable olefin formation not followed by the Bredt's rule. The former seems very striking since few ring cleavages accompanied with deprotonation are known in the adamantane system[26] except in the case of the recently reported Beckmann fission of **1** oxime.[2c] Certainly, the rigid ring system with the ideal arrangement of the participating bonds is characteristic for adamantane derivatives, and, thus, the Schmidt fission can be facilitated not only by the stability of the ion on the α carbon but also by the geometrical requirement of the bonds in participation.

From the preparative point of view, the above observed catalyst–solvent effects is of particular interest since product formation can be controlled in a sense.

(22) (a) M. Ohno and I. Terasawa, *J. Amer. Chem. Soc.*, **88**, 5683 (1966); (b) G. P. Mose and S. A. Nicolaids, *Chem. Commun.*, 1077 (1969).

(23) R. M. Pinder, *J. Chem. Soc. C*, 1690 (1969).

(24) However, see the Beckmann fission of camphor oxime: B. L. Fox and J. E. Reboulet, *J. Org. Chem.*, **33**, 3639 (1968).

(25) The Beckmann and Schmidt fissions have been known only when the formation of a tertiary carbonium ion adjacent to oxime or ketone is possible.

(26) For ring fissions of 1,3-disubstituted adamantanes, see (a) H. Stetter and P. Tacke, *Angew. Chem.*, **74**, 354 (1962); (b) H. Stetter and P. Tacke, *Chem. Ber.*, **96**, 694 (1963); (c) C. A. Grob and W. W. Schwarz, *Helv. Chim. Acta*, **47**, 1870 (1965); (d) F. M. Stepanov and W. D. Suchowerchow, *Angew. Chem. Int. Ed. Engl.*, **6**, 864 (1967).

Experimental Section[27]

Schmidt Reaction of Adamantan-2-one (1) in Methanesulfonic Acid. 4(e)-Methanesulfonoxyadamantan-2-one (2) and 4-Azatricyclo[4.3.1.1.^{3,8}]undecan-5-one (3).—To a stirred solution of 6.0 g (0.04 mol) of **1** in 50 g of methanesulfonic acid (extra pure reagent grade)[11] was added slowly 2.7 g (0.042 mol) of sodium azide during over 2 hr at room temperature (*ca.* 20°). After 3 days stirring, the reaction mixture was poured onto ice–water, and neutralized with sodium carbonate to afford colorless precipitates (8.0 g) of **2**. Extraction of the mother liquor with chloroform and work-up gave an oily residue which was treated with dry hydrogen chloride in dry ether to afford 0.9 g (11.2%) of **3** hydrochloride. Reprecipitation from chloroform–ether afforded an analytically pure **3** hydrochloride: mp >300°; ν_{max}^{KBr} 2800–2400, 1660, and 1505 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}NOCl$: C, 59.55; H, 7.99; N, 6.94. Found: C, 59.62; H, 7.85; N, 7.23.

Free base **3** was obtained on treatment of an aqueous solution of the hydrochloride with alkali and recrystallization from ether: mp >300°; ν_{max}^{KBr} 3200, 3080, and 1650 cm^{-1}.[1b]

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.49; H, 9.27; N, 8.67.

From the mother liquor, after removal of **3** hydrochloride, a further crop (0.52 g) of **2** was obtained to give a total 88% yield of **2**. An analytical sample was obtained by recrystallization from carbon tetrachloride: mp 73–75°; ν_{max}^{KBr} 3000, 1720, 1340, 1190, and 1180 cm^{-1}.[1a]

Anal. Calcd for $C_{11}H_{18}O_4S$: C, 54.07; H, 6.60. Found: C, 53.82; H, 6.69.

The 2,4-dinitrophenylhydrazone of **2** was obtained as yellow crystals from chloroform, mp 227–229°.

Anal. Calcd for $C_{17}H_{20}N_4O_7S$: C, 48.10; H, 4.75; N, 13.20. Found: C, 48.19; H, 4.78; N, 13.15.

Oxime **8** was obtained on heating **2** with hydroxylamine hydrochloride in ethanol; colorless crystals which were recrystallized from aqueous ethanol, mp 132–133°.

Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.41. Found: C, 50.98; H, 6.53; N, 5.47.

Reduction of 3. 4-Azahomoadamantane.[1b]—A solution of 0.88 g (0.0044 mol) of **3** hydrochloride and 1.0 g of lithium aluminium hydride in 20 ml of dry tetrahydrofuran was refluxed for 36 hr. Work-up in the usual way gave 330 mg (55%) of 4-azahomoademantane which was sublimed to give an analytical sample, mp 198–200° (a sealed tube).[1b]

Anal. Calcd for $C_{10}H_{17}N$: C, 79.40; H, 11.34; N, 9.26. Found: C, 79.14; H, 11.65; N, 9.22.

The picrate of 4-azahomoademantane was obtained as yellow crystals, mp 283–285°.

Anal. Calcd for $C_{16}H_{21}N_3O_5 \cdot H_2O$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.49; H, 5.14; N, 13.80.

Quasi-Favorskii Reaction of 2. Bicyclo[3.3.1]non-6-ene-3-carboxylic Acid (4). A.—A solution of 2.0 g (0.0082 mol) of **2** and 3.0 g of potassium hydroxide in 30 ml of 60% aqueous ethanol was refluxed for 12 hr. The solution was concentrated in order to remove ethanol and acidified with 10% hydrochloric acid. The precipitate was filtered to give 1.15 g (85%) of **4**, recrystallized from aqueous acetone: mp 195–196° (lit.[6] mp 195–198°); ν_{max}^{KBr} 1680 cm^{-1};[7] mass spectrum *m/e* (rel intensity) 166 (12), 148 (33), 120 (7), and 79 (100).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.76.

(27) All melting points were obtained with a Yanagimoto micromelting point apparatus and are uncorrected. Nmr spectra were determined with A-60 and HA-100 Varian spectrometers, and mass spectra with a JEOL JMS-01SG spectrometer at 70 eV. Glpc analyses were performed on a K-23 Hitachi gas chromatograph, and microanalyses with a Perkin–Elmer 240 Elemental Analyzer.

B.—A solution of 0.1 g (0.0004 mol) of **2** and 0.1 g of sodium bicarbonate in 10 ml of 20% aqueous acetone was heated at 60° for 18 hr to give 0.06 g (88%) of **4**.

Reduction of 2 with Lithium Aluminium Hydride. Bicyclo[3.3.1]non-6-ene-3-carbinol (6).—A solution of 0.5 g (0.0021 mol) of **2** and 0.3 g of lithium aluminium hydride in 20 ml of dry ether was refluxed for 6 hr. Work-up as usual gave 0.3 g (97%) of **6** as an oil: ν_{max}^{neat} 3340 and 1030 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.25–5.55 (m, 2 H, vinyl protons), 3.70 (d, J = 6.0 Hz, $-CH_2OH$), 2.60 (s, 1 H, OH), and 2.50–1.10 (m, 11 H, remaining protons).[6]

2(e)-Bromo-4-oxahomoadamantan-5-one (7).—A solution of 0.1 g (0.00041 mol) of **2** in 2 ml of water saturated with bromine was refluxed at 95° for 5 hr. After cooling, the reaction mixture was decolorized by adding solid sodium bisulfite and extracted with chloroform. The combined organic extracts were washed with water, dried over sodium sulfate, and evaporated to afford an oily residue which solidified on standing overnight. Recrystallization from chloroform–carbon tetrachloride gave 0.09 g (90%) of **7**: mp 139–140°; ν_{max}^{KBr} 1720 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.58 (complex m, 1 H, –CHOCO–), 4.43 (m, 1 H, –CHBr), 3.09 (m, 1 H, –CHCOO–), 2.75–1.45 (complex m, 10 H, remaining protons);[28] mass spectrum m/e (rel intensity) 246 (5), 244 (5.5), 165 (1), 149 (6), and 121 (100).

Anal. Calcd for $C_{10}H_{13}O_2Br$: C, 48.68; H, 5.32. Found: C, 48.67; H, 5.09.

Schmidt Reaction of 1 in Methanesulfonic Acid–Acetic Acid. Bicyclo[3.3.1]non-6-ene-3-carbonitrile (11).—To a stirred solution of 1.0 g (0.0067 mol) of **1** in 3 ml of methanesulfonic acid and 4 ml of glacial acetic acid was added portionwise 0.5 g (0.0077 mol) of sodium azide during 45 min. After stirring for a further 20 min, the reaction mixture was poured onto ice–water to precipitate a colorless solid which was filtered to give 0.6 g (61%) of **11**: mp 160–165° (lit.[2c] mp 176.5–181.5°); $\delta_{TMS}^{CCl_4}$ 6.20–5.70 (m, 2 H, vinyl protons), 2.95 (m, 1 H, –CHCN), 2.72–1.20 (m, 10 H, remaining protons); mass spectrum m/e (rel intensity) 147 (100).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.84; H, 8.87; N, 9.29.

The mother liquor was neutralized with sodium bicarbonate to afford 0.05 g (3.0%) of **2**. Extraction of the basified mother liquor with chloroform afforded 0.36 g (33%0 of **3**.

Alkaline Methanolysis of 8. 4-Methoxyadamantan-2-one Oxime (9).—A solution of 0.4 g (0.0015 mol) of **8** and 0.1 g (0.0019 mol) of sodium methoxide in 12 ml of absolute methanol was stirred at room temperature for 2 days. After concentration to *ca.* 1 ml, the reaction mixture was diluted with 20 ml of water and extracted with ether. The combined extracts were dried (Na_2SO_4) and evaporated to give an oily residue which was purified on a silica gel column, eluting with chloroform, affording 0.24 g (79.5%) of **9** as an oil: ν_{max}^{neat} 3220, 3080, 1655, and 1100 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 9.40 (broad s, 1 H, C=NOH), 3.82 (m, 0.5 H, C_4-(e)H), 3.5 (partly overlapped with $-OCH_3$ signal, 0.5 H, C_4-(a)H), 3.38 (s, 1.5 H, C_4-(a)OCH_3), 3.40 (s, 1.5 H, C_4-(e)OCH_3), 2.90–1.25 (m, 12 H, remaining protons); mass spectrum m/e (rel intensity) 195 (3), 180 (20), 148 (68), and 79 (100).

Treatment of **9** with 2,4-dinitrophenylhydrazine afforded the crystalline 2,4-dinitrophenylhydrazone of 4-methoxyadamantan-2-one (**10**) from ethanol–chloroform: mp 200–202°; ν_{max}^{KBr} 3300, 3080, 1615, 1590, 1505, 1100, and 745 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.70 (m, 0.5 H, C_4-(e)H), 3.30 (m, 0.5 H, C_4-(a)H),6. 54 and 6.56 (s, 3 H, OCH_3), and 3.20–1.50 (complex m, 12 H, remaining protons); mass spectrum m/e (rel intensity) 360 (63) and 149 (100).

Anal. Calcd for $C_{17}H_{20}N_4O_5$: C, 56.66; H, 5.59; N, 15.55. Found: C, 56.44; H, 5.74; N, 15.61.

Schmidt Reaction of 1 in Sulfuric Acid–Acetic Acid. 4-Acetoxy- (12) and 4-Hydroxyandamantan-2-one (13).—To a stirred solution of 0.5 g (0.0033 mol) of **1** in 2 ml of concentrated sulfuric acid (*ca.* 98%) and 2 ml of glacial acetic acid was added portionwise 0.26 g (0.004 mol) of solid sodium azide during 2 hr at room temperature. After stirring was continued for 2 days, the reaction mixture was neutralized with sodium bicarbonate and extracted with ether. The ethereal extracts were washed with 10% hydrochloric acid, dried (Na_2SO_4), and evaporated to give an oily residue which was purified on a silica gel column, eluting with chloroform. The first fraction afforded 0.21 g (32%) of **12** as an oil: ν_{max}^{neat} 1730, 1720, and 1230 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.28 (m, 0.2 H, C_4-(e)H), 4.95 (unsymmetrical t, 0.8 H, C_4-(a)H), 2.90–2.45 (m, 3 H, three methine protons), and 2.45–1.50 (m, 12 H, one methine and methylene protons, and OCO-CH_3); mass spectrum m/e (rel intensity) 203 (20), 180 (23), 148 (100), and 120 (75).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.32; H, 7.63.

The second fraction afforded 0.055 g (10%) of **13** as colorless crystals: mp >300° (a sealed tube); ν_{max}^{KBr} 3360 and 1705 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.21 (complex m, 9 H, one methine and methylene protons); mass spectrum m/e (rel intensity) 166 (72), 149 (70), 138 (65), and 79 (100).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.32; H, 8.32.

Schmidt Reaction of 1 in Other Catalyst-Solvents.—The Schmidt reactions of **1** in trifluoro-, trichloroacetic acid, aqueous methanesulfonic acid, and glacial acetic acid were carried out similarly using small excess amounts of sodium azide and the products were analyzed on glpc (Table I).

Tetrazolo[4,5-*d*]-4-azahomoadamantane (14).—To a stirred solution of 0.14 g (0.00085 mol) of **3** in 2 ml of chloroform was added a solution of 0.2 g (0.00096 mol) of phosphorus pentachloride in 2 ml of chloroform under ice cooling. After stirring for 1 day at room temperature, a benzene solution of hydrogen azide prepared from 0.2 g (0.0031 mol) of sodium azide and 20 ml of benzene was added to the reaction mixture with stirring. After stirring was continued for 1 day, the reaction mixture was diluted with 20 ml of water, and the organic layer was separated. The aqueous layer was extracted with chloroform after making it alkaline with 10% aqueous potassium hydroxide, and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated to give a sticky residue which afforded 0.05 g (31%) of **14** as colorless crystals and 0.085 g (61% recovery) of recovered **3** after chromatography on a silica gel column eluting with chloroform: mp 253–255°; ν_{max}^{KBr} 1625 and 1530 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.10 (broad s, 1 H, –CHN–), 3.70 [broad s, 1 H, –CHC(=N–)N–], 2.50–1.50 (m, 12 H, remaining protons); mass spectrum m/e (rel intensity) 190 (100), 162 (90), and 149 (80).

Anal. Calcd for $C_{10}H_{14}N_4$: C, 63.13; H, 7.42; N, 29.45. Found: C, 62.97; H, 7.26; N, 29.77.

Schmidt Reaction of 1 Using Excess Hydrogen Azide.—To a stirred solution of 0.1 g (0.00067 mol) of **1** and 0.16 g (0.0025 mol) of sodium azide in 4 ml of acetic acid was added dropwise 1 ml of methanesulfonic acid during 5 min at room temperature. After stirring was continued for 1 day, work-up as above gave 0.1 g of crude product which was analyzed on glpc. The results are summarized in Table II.

Bicyclo[3.3.1]non-6-ene-3-carboxamide (16).—To a stirred solution of 1.1 g (0.0063 mol) of **4** in 20 ml of *n*-hexane was added 1 ml of oxalyl chloride under ice cooling. After keeping overnight at room temperature, the solvent and excess oxalyl chloride were removed under reduced pressure to give an oily residue which was dissolved in 10 ml of dry tetrahydrofuran. The resulting solution was saturated with dry ammonia under ice cooling. After addition of water, the mixture was extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give a colorless solid which was recrystallized from ether–chloroform to give 0.66 g (54.3%) of **16** as crystals: mp 113–114°; ν_{max}^{KBr} 3320, 3120, and 1630 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.95 (broad s, 2 H, $CONH_2$), 5.80–5.50 (m, 2 H, vinyl protons), 2.70–1.50 (complex m, 11 H, remaining protons).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48 Found: C, 73.13; H, 9.58; N, 8.77.

Treatment of 11 with Methanesulfonic Acid.—A solution of 0.22 g (0.0015 mol) of **11** in 2 ml of methanesulfonic acid was stirred at room temperature for 1 day and work-up as above gave 0.335 g (92%) of **2** and 0.005 g (2%) of **3** hydrochloride.

Registry No.—**1**, 700-58-3; **2**, 26269-28-3; **2** (2,4-dinitrophenylhydrazone), 26269-29-4; **3**, 22607-75-6; **3** (HCl), 24740-32-7; **4**, 21932-98-9; **6**, 21932-99-0; **7**, 26269-32-9; **8**, 26269-33-0; **9**, 26278-40-0; **10** (2,4-dinitrophenylhydrazone), 26278-41-1; **11**, 25219-45-8; **12**, 26278-42-2; **13**, 26278-43-3; **14**, 26278-44-4; **16**, 26269-35-2; 4-azahomoadamantane, 22776-74-5; 4-azahomoadamantane (picrate), 24740-30-5.

(28) A more detailed analysis of the nmr spectrum of **7** with the aid of spin–spin decoupling experiments and the conformational problem will be published elsewhere.

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Phosphorus Derivatives of Nitrogen Heterocycles. 2. Pyridinephosphonic Acid Derivatives[1]

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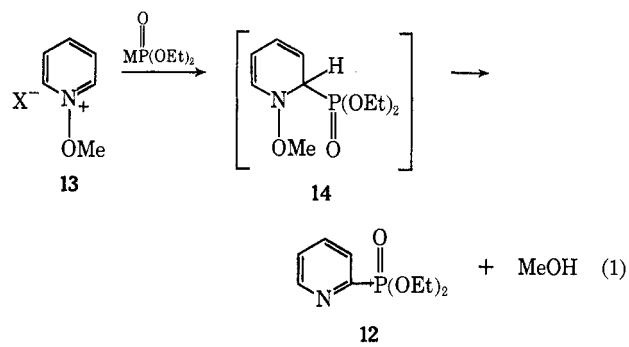
The reaction of *N*-alkoxypyridinium salts with alkali metal derivatives of dialkyl phosphonates provides a general synthesis of dialkyl pyridine-2-phosphonates in yields of 35–65%. 3-Methyl-*N*-methoxypyridinium methosulfate yields a mixture of diethyl 3-methylpyridine-2-phosphonate (**17**) and diethyl 5-methylpyridine-2-phosphonate (**18**) upon reaction with diethyl sodiophosphonate in a ratio of 6:1. The pyridinephosphonate esters are hydrolyzed in 18% HCl to the corresponding pyridinephosphonic acids. 4 substitution was obtained in one case only, the reaction of 2,6-dimethyl-*N*-methoxypyridinium methosulfate with diethyl sodiophosphonate. Nmr and uv spectra of the pyridinephosphonates gave no evidence for d_π–p_π bonding.

The number of examples of nitrogen heterocyclic systems in which phosphorus is attached as a ring substituent has grown recently.[1-7] One of the synthetic methods employed is the 1,3-dipolar addition of diazoalkanes to alkynylphosphonates illustrated in the preparation of the pyrazole (**2**) from diethyl ethynylphosphonate (**1**) and diazomethane.[2] Alternatively, the dipolar addition of α-diazophosphonates to olefins provides a synthesis of dihydropyrazoles exemplified in the addition of diazophosphonate (**3**) to methylvinyl ketone yielding dihydropyrazolephosphonate (**4**).[3] Nucleophilic displacement on diethyl phosphorochloridate by pyrrolyl Grignard reagent (**5**) yields diethyl pyrrole-2-phosphonate (**6**).[4] Other methods include the nucleophilic attack of trialkyl phosphites (Arbusov reaction) or salts of dialkyl phosphonates (Michaelis–Becker–Nylen reaction) on heterocyclic chlorides or bromides.[5] These procedures require reactive halides, so that while 2-chloropyrimidine (**7**) is converted into diisopropyl pyrimidine-2-phosphonate (**8**) by reaction with triisopropyl phosphite[5a] 2-bromopyridine is unreactive to trialkyl phosphites or dialkyl metal phosphonates.[5b] Although no general method for the preparation of pyridine phosphonates has been described, pyridine-3-phosphonic acid (**10**) has been prepared from 3-pyridyl diazonium tetrafluoroborate (**9**) by reaction with phosphorus trichloride followed by hydrolysis,[6] and diethyl pyridine-2-phosphonate (**12**) has been obtained by reaction of triethyl phosphite on 2-nitropyridine *N*-oxide (**11**).[7] The present paper describes a general method for the preparation of dialkyl pyridine-2-phosphonates.

Activation of the pyridine ring to nucleophilic attack by conversion into an *N*-alkoxypyridinium salt (*via* the *N*-oxide) has allowed the preparation of many substituted pyridines.[8] The preparation of cyanopyridines is a particularly elegant illustration of this principle.[9]

It has been found that *N*-methoxypyridinium salts (**13**) react with alkali metal derivatives of diethylphosphonate[10] to form diethyl pyridine-2-phosphonate (**12**) (eq 1). This reaction is a strongly exothermic process



whose efficiency is highly dependent upon the reaction conditions. Although the preparation of diethyl sodiophosphonate has been carried out by reaction of diethyl phosphonate with metallic sodium[13] or sodium hydride[14] in a hydrocarbon or ether solvent, it is more convenient for reaction with *N*-alkoxypyridinium salts to use diethyl phosphonate as solvent for the sodiophosphonate and the quaternary salt. It is important to carry out the addition of the *N*-alkoxypyridinium salt to the dialkyl sodiophosphonate at −15 to 0° in order to obtain good yields of pyridine phosphonate. No direct evidence has been obtained to support the intermediacy of dihydropyridine (**14**), but spectral evidence for dihydropyridines has been obtained in the addition of other nu-

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