water, dried over KOH, and filtered. Solvent removal on the rotary evaporator gave an oily yellow solid. This was sublimed to give 64.8 mg (70%) of **6**.

Registry No.—**1a**, 40386-84-3; **1a** picrate, 40306-86-3; **1b**, 40306-87-4; **1b**-trinitrobenzene, 40306-88-5; **3**, 40306-89-6; **4a**, 40306-90-9; **5a**, 40306-91-0; **5a** picrate, 40531-26-8; **6**, 40306-92-1; **7**, 40306-93-2; **8**, 7342-82-7; **9**, 40306-95-4; **10**, 40306-96-5; benzylamine, 100-46-9; sodium dithionite, 7775-14-6; *n*-butyllithium, 109-72-8; copper(II) chloride, 7447-39-4; *N*,*N*'-dimethylformamide, 68-12-2.

Pteridines. XXXII. 2-Amino-3-cyano-5-chloromethylpyrazine 1-Oxide and Its Conversion to 6-Alkenyl-Substituted Pteridines[1,2]

EDWARD C. TAYLOR* AND T. KOBAYASHI

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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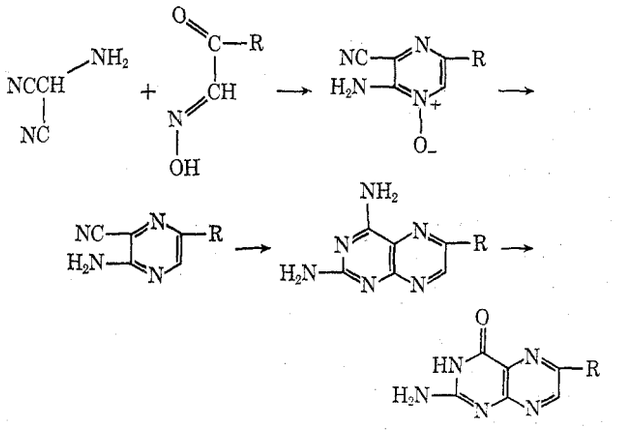
2-Amino-3-cyano-5-chloromethylpyrazine 1-oxide (**2**), prepared by the condensation of β-chloropyruvaldoxime with aminomalononitrile tosylate, was deoxygenated with phosphorus trichloride to 2-amino-3-cyano-5-chloromethylpyrazine (**4**). Both **2** and **4** were converted by conventional procedures to triphenylphosphonium ylides (Wittig reagents) and, hence, by condensation with aldehydes to parallel series of 5-alkenylpyrazines (**9** and **10**). Cyclization of **10a–e** with guanidine gave 2,4-diamino-6-alkenylpteridines (**11a–e**), of interest as intermediates for the synthesis of biopterin and biopterin analogs. Some additional reactions of the above pyrazine intermediates are also described.

We have described in recent articles[1,3] a new, general, and versatile synthetic route to pteridines and pterins which involves, as its initial key step, the condensation of α-aminonitriles with α-oximino carbonyl compounds. For example, aminomalononitrile and α-ketoaldoximes give 2-amino-3-cyano-5-substituted pyrazine 1-oxides; deoxygenation and subsequent condensation with guanidine lead to 2,4-diamino-6-substituted pteridines, which upon acid or base hydrolysis yield pterins. One of the major advantages of this simple procedure over the classical Isay synthesis[4] is the unambiguous positioning of the side chain in the pyrazine ring.



Although this new procedure could, in principle, be adapted to the direct synthesis of pteridine natural products possessing multifunctional C-6 substituents (*i.e.*, biopterin, folic acid, methotrexate), complex, fragile, and difficultly accessible α-ketoaldoxime intermediates would be normally required. We describe in the present and subsequent papers a simple modification of this pteridine synthesis which permits deferral of the elaboration of the requisite C-6 side chains until *after* the initial construction of the pyrazine ring. The key intermediate, from which pteridines of both the biopterin and folic acid classes of natural products can be prepared, is 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**2**). This paper describes the preparation of **2** and its use for the preparation of pyrazines and pteridines suitable for final elaboration into the biopterin series.[5] A following paper will describe the elaboration of **2** to pteridines and pterins related to folic acid.

β-Chloropyruvaldoxime (**1**), readily prepared from diketene,[6] and less conveniently (and unreliably) by chlorination of α-oximinoacetone in chloroform solution,[7] was smoothly converted by reaction with aminomalononitrile tosylate in 2-propanol to **2**. Since **2** could be converted to 2-amino-3-cyano-5-methoxymethylpyrazine 1-oxide (**3**) upon refluxing in methanol solution, it appeared that the chloromethyl group of **2** might well be used for the introduction of diverse side chains at position 5 (pteridine position 6) by nucleophilic displacement reactions with suitable nucleophiles. Vindication of this prediction will be given in future papers in this series.

Treatment of **2** and **3** with phosphorus trichloride at room temperature in tetrahydrofuran solution resulted in smooth deoxygenation to give 2-amino-3-cyano-5-chloromethylpyrazine (**4**) and 2-amino-3-cyano-5-methoxymethylpyrazine (**5**), respectively. The ease with which these deoxygenations proceed contrasts with the vigorous conditions required for deoxygenation of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide[8] and may be a reflection of decreased steric hindrance at the *N*-oxide grouping. Deoxygenation

(1) Part XXXI: E. C. Taylor and R. F. Abdulla, *Tetrahedron Lett.*, 2093 (1973).

(2) This investigation was supported in part by grants to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service (Grants No. CA-2551 and 12876), and the Walter Reed Army Medical Research Institute (Contract No. DA-49-193-2777). This is contribution No. 1190 in the Army Research Program on Malaria.

(3) (a) E. C. Taylor, K. L. Perlman, I. P. Sword, M. Séquin-Frey, and P. A. Jacobi, *J. Amer. Chem. Soc.*, in press; (b) E. C. Taylor, K. L. Perlman, Y.-H. Kim, I. P. Sword, and P. A. Jacobi, *ibid.*, in press.

(4) O. Isay, *Ber.*, **39**, 250 (1906).

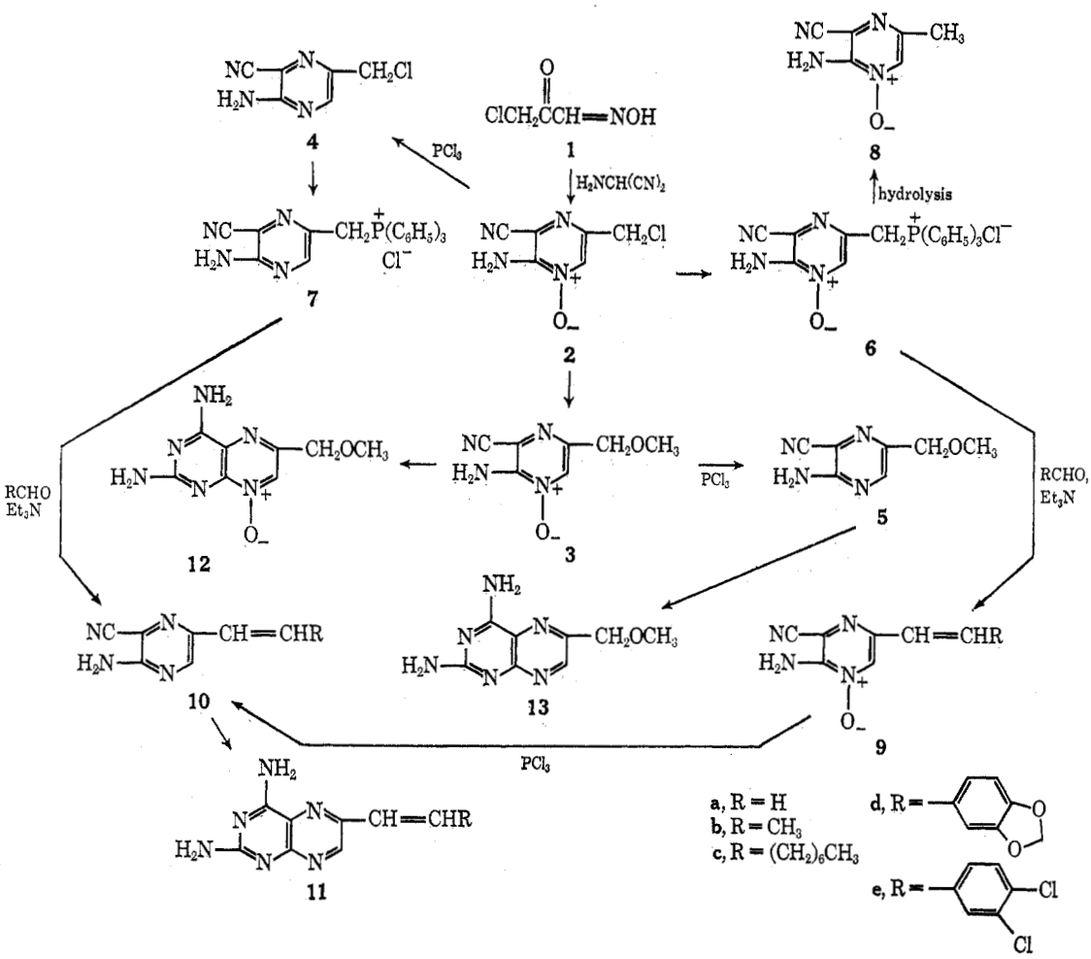
(5) A preliminary report of this work has appeared: E. C. Taylor in "The Chemistry and Biology of Pteridines," Fourth International Symposium, K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Ltd., Tokyo, 1970.

(6) E. C. Taylor and R. C. Portnoy, *J. Org. Chem.*, **38**, 806 (1973).

(7) J. Armand, J.-P. Guette, and F. Valentini, *C. R. Acad. Sci., Ser. C*, 1388 (1966).

(8) E. C. Taylor and T. Kobayashi, manuscript in preparation.

SCHEME I



of **2** could also be effected with sodium hydrosulfite in boiling water, although the yield was poor. Under the same conditions, the isomeric 6-chloromethyl compound underwent both deoxygenation and reductive dehalogenation.

Both **2** and **4** were smoothly converted to the corresponding triphenylphosphonium chlorides (**6** and **7**) by treatment with triphenylphosphine in dimethylformamide. In both cases, the pyrazinylmethyltriphenylphosphonium chloride crystallized directly from the dimethylformamide solution and could be used in subsequent reactions without further purification. The structure of **6** was confirmed by hydrolysis with 30% aqueous ethanol containing a small amount of triethylamine to give 2-amino-3-cyano-5-methylpyrazine 1-oxide (**8**), identical in every respect with an authentic sample prepared as described previously[3b] by condensation of aminomalononitrile tosylate with oximinoacetone.

The phosphonium salts **6** and **7** were converted into trans olefins (the desired isomers since trans hydroxylation *via* epoxide formation and subsequent hydrolysis would yield the erythro glycol configuration found in the biopterin series of pteridine natural products) by reaction with aldehydes in a mixture of chloroform and triethylamine. Attempts to isolate the intermediate phosphoranes (Wittig reagents) were frustrated by the insolubility in water of the phosphonium salts **6** and **7** and by the apparent impurity of the products formed in methanol solution. Since trans olefins were desired, polar solvents such as methanol (in which both **6** and **7** were readily soluble) were avoided; attempts to use nonpolar solvents such as benzene and tetrahydrofuran were unsuccessful owing to insolubility. Mixtures of cis and trans isomers were occasionally obtained in the chloroform–triethylamine system. Thus, reaction of **6** with acetaldehyde gave a mixture of trans and cis isomers of 2-amino-3-cyano-5-(1-propenyl)pyrazine 1-oxide (**9b**) in a ratio of 77:23 (estimated by nmr). Fortuitously, however, the cis isomers in both the *N*-oxide series **9** and the deoxygenated series **10** were more soluble than the isomeric trans olefins, and recrystallization readily gave pure trans isomers. In this manner, the trans olefinic pyrazines **9** and **10** (Scheme I) were prepared from acetaldehyde, octylaldehyde, piperonal, and 3,4-dichlorobenzaldehyde. Treatment of **7** with paraformaldehyde in methanol solution containing triethylamine initially gave 2-methoxymethylamino-3-cyano-5-vinylpyrazine, but this latter intermediate could be hydrolyzed with aqueous acid to the desired 2-amino-3-cyano-5-vinylpyrazine (**10a**). In several cases (see Experimental Section), the olefinic pyrazine 1-oxides **9** were deoxygenated with phosphorus trichloride in tetrahydrofuran at room temperature to **10**.

Finally, annelation of the 2,4-diaminopyrimidine ring to give the pteridines **11**, **12**, and **13** was readily effected in the normal manner by condensation of the *o*-aminonitriles **3**, **5**, and **10** with guanidine in the presence

of sodium methoxide.[9] Since mild acid or base hydrolysis of these 2,4-diaminopteridines should give the corresponding pterins,[10] and trans hydroxylation of the trans olefins **11** must give erythro glycols, the above synthetic pathway should provide unequivocal and flexible procedures for the synthesis of biopterin and biopterin analogs. Furthermore, since annelation of the 2,4-diaminopyrimidine ring from **3** and **5** was effected without loss of the side chain methoxyl group, it would be expected that other side chains, introduced *via* nucleophilic displacement reactions on the chloromethylpyrazines **2** and **4**, would likewise proceed with retention of the side chain, thus offering a simple and unambiguous pathway to pterins related to folic acid. Both of these extensions of the above general pteridine synthesis are described in subsequent publications in this series.

Experimental Section

2-Amino-3-cyano-5-chloromethylpyrazine 1-Oxide (2).—A solution of 10.7 g of aminomalononitrile tosylate and 5.0 g of β-chloropyruvaldoxime[6] in 140 ml of 2-propanol was stirred at room temperature for 24 hr. The resulting dark red solution was evaporated to a small volume under reduced pressure, 100 ml of water added, and the solution extracted continuously overnight with methylene chloride. The extracts were dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure, and the residue was triturated with 50 ml of chloroform and filtered to give 4.7 g (62%) of **2**, mp 140–142° dec, as a bright yellow microcrystalline solid. The analytical sample, mp 143–144° dec, was obtained in the form of yellow prisms by recrystallization from methanol: nmr (DMSO-d_6) δ 4.68 (2, s, CH_2Cl), 8.10 (2, br s, NH_2), 8.71 (1, s, C_6H); ir 3440–3100 (NH_2), 2240 (CN) cm^{-1}.

Anal. Calcd for $C_6H_5ClN_4O$: C, 39.01; H, 2.71; N, 30.38, Cl, 19.25. Found: C, 39.19; H, 2.99; N, 30.37; Cl, 19.08.

2-Amino-3-cyano-5-methoxymethylpyrazine 1-Oxide (3).[11]—A solution of 552 mg of **2** in 10 ml of methanol was heated under reflux for 48 hr, concentrated to a small volume, and chilled. The yellow needles which separated were collected by filtration and washed with cold methanol: yield 412 mg (76%); mp 134–135° (recrystallization from methanol raised the melting point to 137–138°); nmr (DMSO-d_6) δ 3.28 (3, s, OCH_3), 4.32 (2, s, CH_2O–), 7.99 (2, br s, NH_2), 8.45 (1, s, C_6H); ir 3400–3150 (NH_2), 2230 (CN) cm^{-1}.

Anal. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.89; H, 4.56; N, 31.20.

2-Amino-3-cyano-5-chloromethylpyrazine (4).—To a solution of 13.0 g of **2** in 500 ml of tetrahydrofuran was added dropwise and with ice-bath cooling 27.0 g of phosphorus trichloride. The solution was stirred for 45 min at room temperature and then evaporated to a small volume under reduced pressure. Addition of ice water resulted in the separation of a solid which was collected by filtration and washed thoroughly with water to give 9.3 g (79%) of a yellow microcrystalline solid, mp 151–154°. The analytical sample, mp 156–157°, was obtained as pale yellow platelets by recrystallization from methanol: nmr (DMSO-d_6) δ 4.57 (2, s, CH_2Cl), 7.35 (2, br s, NH_2), 8.20 (1, s, C_6H); ir 3420–3220 (NH_2), 2230 (CN) cm^{-1}.

Anal. Calcd for $C_6H_5ClN_4$: C, 42.73; H, 2.97; N, 33.22; Cl, 21.07. Found: C, 42.59; H, 3.25; N, 33.22; Cl, 20.86.

2-Amino-3-cyano-5-methoxymethylpyrazine (5).—In the same manner as described above, 3.0 g of **3** in 180 ml of tetrahydrofuran was deoxygenated with 6.5 g of phosphorus trichloride: yield 1.6 g (59%); mp 137–140°. The analytical sample was prepared in the form of pale yellow platelets, mp 142–143°, by recrystallization from methanol: nmr (DMSO-d_6) δ 3.21 (3, s, OCH_3), 4.26 (2, s, CH_2O–), 7.18 (2, br s, NH_2), 8.20 (1, s, C_6H); ir 3400–3200 (NH_2), 2220 (CN) cm^{-1}.

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.01; H, 4.73; N, 34.37.

(1-Oxy-2-amino-3-cyano-5-pyrazinyl)methyltriphenylphosphonium Chloride (6).—A solution of 5.0 g of **2** and 7.8 g of triphenylphosphine in 55 ml of dimethylformamide was stirred for 3 hr at 80–90°. The precipitate which had formed was collected by filtration and washed thoroughly with ether to give 10.8 g (90%) of pure **6**, mp 300° dec, as a pale yellow microcrystalline solid. The analytical sample was prepared in the form of pale yellow prisms by recrystallization from methanol, but without change in the melting point.

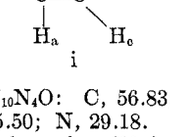
Anal. Calcd for $C_{24}H_{20}ClN_4OP$: Cl, 7.95. Found: Cl, 8.32.

(2-Amino-3-cyano-5-pyrazinyl)methyltriphenylphosphonium Chloride (7).—In the same manner as described above, 13.9 g of **4** and 28.0 g of triphenylphosphine in 80 ml of dimethylformamide gave 32.9 g (quantitative) of **7**, mp 313° dec, as a pale yellow microcrystalline solid. The analytical sample was prepared by recrystallization from methanol without change in the melting point.

Anal. Calcd for $C_{24}H_{20}ClN_4P$: Cl, 8.25. Found: Cl, 8.41.

2-Amino-3-cyano-5-methylpyrazine 1-Oxide (8).—A suspension of 1.0 g of **6** in 70 ml of 30% aqueous ethanol containing 0.25 g of triethylamine was heated under reflux for 3 hr and then evaporated to dryness. The residue was dissolved in chloroform–methanol (95:5) and passed through a short column of silica gel. The eluent was evaporated under reduced pressure to a small volume, benzene added, and the resulting mixture stirred for 30 min. Filtration then gave 0.26 g of **8** as a yellow powder. Recrystallization from methanol gave 0.25 g (75%) of fine yellow platelets, mp 187–188°. This compound was identical with an authentic sample of 2-amino-3-cyano-5-methylpyrazine 1-oxide prepared by the condensation of aminomalononitrile tosylate with oximinoacetone.[3b]

2-Methoxymethylamino-3-cyano-5-vinylpyrazine.—A mixture of 12.0 g of **7** and 8.5 g of paraformaldehyde in 600 ml of methanol containing 7.0 g of triethylamine was stirred at room temperature for 2 days and then heated under reflux for an additional day. The resulting clear solution was evaporated to dryness under reduced pressure and the residue dissolved in 100 ml of ethyl acetate. The resulting solution was washed well with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure to dryness. The residual solid was triturated for 30 min at room temperature with 50 ml of benzene and then filtered to give 3.0 g (57%), mp 159–160°, of a pale yellow microcrystalline solid. The analytical sample, mp 161–162°, was prepared by recrystallization from methanol: nmr ($DCCl_3$) δ 3.39 (3, s, OCH_3), 4.99 (2, d, OCH_2NH), 5.45 (1, q, H_c), 6.07 (1, q, H_b), 6.72 (1, q, H_a), 8.20 (1, s, C_6H) (partial structure **i**) (J_{ab} = 18.0, J_{ac} = 10.5 J_{bc} = 1.5 Hz); ir 3370 (NH), 2230 (CN), 1100 (C—O—C), 990, 900 (C=C) cm^{-1}.



i

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.80; H, 5.50; N, 29.18.

2-Amino-3-cyano-5-vinylpyrazine (10a).—A mixture of 2.0 g of 2-methoxymethylamino-3-cyano-5-vinylpyrazine, 10 ml of 1 *N* hydrochloric acid, and 100 ml of methanol was heated under reflux for 5 hr and then evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of water and the resulting solution neutralized by the addition of solid sodium bicarbonate. Filtration then gave 1.3 g (85%) of **10a**, mp 171–172° dec. For analysis a small sample was recrystallized from methanol: mp 175–176° dec; nmr (DMSO-d_6) δ 5.20 (1, q, H_c) 5.84 (1, q, H_b), 6.58 (1, q, H_a), 7.20 (2, br s, NH_2), 8.30 (1, s, C_6H) (**i**) (J_{ab} = 17.5, J_{ac} = 12.0, J_{bc} = 1.5 Hz); ir 3420–3160 (NH_2), 2230 (CN), 985, 930 (C=C) cm^{-1}.

Anal. Calcd for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.24; H, 4.29; N, 38.48.

2-Amino-3-cyano-5-(1-propenyl)pyrazine 1-Oxide (9b).—A suspension of 15.0 g of **6** in 1 l. of chloroform containing 11.0 g of triethylamine and 15.0 g of acetaldehyde was stirred at room temperature for 24 hr, washed with water, and then evaporated

(9) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Wiley-Interscience, New York, N. Y., 1970.

(10) See, for example, (a) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949); (b) E. C. Taylor and C. K. Cain, *ibid.*, **71**, 2538 (1949); (c) C. M. Baugh and E. Shaw, *J. Org. Chem.*, **29**, 3610 (1964).

(11) This compound was prepared by Robert C. Portnoy.

to dryness under reduced pressure. Trituration of the residual solid with 50 ml of benzene at room temperature for 30 min followed by filtration gave 5.3 g (90%) of crude **9b** as a mixture of trans and cis isomers (ratio of 77:23). Three recrystallizations from methanol gave the pure trans isomer as bright yellow needles: mp 214–215° dec; nmr (DMSO-d_6) δ 1.72 (3, d, CH_3), 6.10 (1, d, H_a), 6.52 (1, m, H_b), 7.64 (2, br s, NH_2), 8.40 (1, s, C_6H) (partial structure ii) (J_{ab} = 16.0 Hz); ir 3400–3100 (NH_2), 2230 (CN), 965 (C=C) cm^{-1}.

$$-CH_a{=}CH_bCH_3$$
ii

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.42; H, 4.64; N, 31.80.

2-Amino-3-cyano-5-(1-propenyl)pyrazine (10b). Method A.—A suspension of 5.0 g of **7** in a mixture of 5.0 g of acetaldehyde, 2.2 g of triethylamine, and 300 ml of chloroform was stirred at room temperature for 24 hr. The resulting homogeneous solution was washed with a small amount of water and then evaporated to dryness. The residue was triturated with 20 ml of benzene for 30 min and then filtered to give 1.25 g (68%) of crude **10b** as a mixture of trans and cis isomers (ratio of 93:7). Recrystallization from methanol gave 0.96 g (52%) of the pure trans isomer of **10b** as bright yellow needles: mp 186–187° dec; nmr (DMSO-d_6) δ 1.69 (3, d, CH_3), 6.11 (1, d, H_a), 6.48 (1, m, H_b), 7.05 (2, br s, NH_2), 8.19 (1, s, C_6H) (ii) (J_{ab} = 16.0 Hz); ir 3420–3180 (NH_2), 2220 (CN), 955 (C=C) cm^{-1}.

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.72; H, 5.12; N, 34.97.

Method B.—To a cooled solution of 5.0 g of crude **9b** (trans–cis 77:23) in 300 ml of tetrahydrofuran was added slowly and with stirring 11.0 g of phosphorus trichloride. After an additional 30 min of stirring at room temperature, the solution was evaporated to a small volume under reduced pressure and poured into ice water. The solid which precipitated was collected by filtration, triturated for 30 min at room temperature with 100 ml of water, and then filtered again to give 3.84 g (85%) of **10b** as a mixture of trans and cis isomers (ratio of 82:18). Recrystallization from methanol then gave 2.95 g of the trans isomer, mp 186–187° dec identical with the compound prepared above by method A.

2-Amino-3-cyano-5-(1-nonenyl)pyrazine (10c).—A suspension of 12.0 g of **7** in 650 ml of chloroform containing 7.5 g of octylaldehyde and 5.7 g of triethylamine was heated under reflux for 2 days. The resulting homogeneous solution was washed with a small amount of water and then evaporated to dryness under reduced pressure. Trituration of the oily residue with 20 ml of methanol resulted in separation of a yellow solid which was collected by filtration and recrystallized from methanol to give 3.6 g (53%) of bright yellow crystals of the pure trans isomer of **10c**: mp 123–124°; nmr (DMSO-d_6) δ 0.82 (3, t, $-CH_3$), ~2.2 (2, m, $=CHCH_2-$), 6.22 (1, d, H_a), 6.58 (1, sextet, H_b), 7.16 (2, br s, NH_2), 8.33 (1, s, C_6H) (partial structure iii) (J_{ab} = 16.0 Hz);

$$-CH_a{=}CH_bCH_2\cdots$$
iii

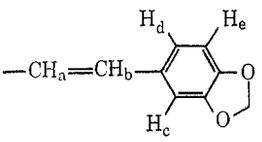
ir 3410–3170 (NH_2), 2940, 2860 (CH_2), 2230 (CN), 965 (C=C) cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.97; H, 8.50; N, 23.12.

2-Amino-3-cyano-5-(3,4-methylenedioxystyryl)pyrazine 1-Oxide (9d).—A suspension of 10.0 g of **6** in 650 ml of chloroform containing 9.0 g of piperonal and 4.4 g of triethylamine was stirred at room temperature for 24 hr and then heated under reflux for an additional 48 hr. The resulting precipitate was collected by filtration and washed with chloroform to give 5.3 g (84%) of **9d** as a deep yellow solid, mp 246° dec. This appeared to be the pure trans isomer by examination of its nmr spectrum (see below). The analytical sample was prepared by recrystallization from methanol without change in the melting point: nmr (DMSO-d_6) δ 5.71 (2, s, OCH_2O), 6.53 (1, d, H_a), 6.53 (1, d, H_e), 6.73 (1, d, H_d), 6.84 (1, s, H_c), 7.05 (1, d, H_b), 7.53 (2, br s, NH_2), 8.23 (1, s, C_6H) (partial structure iv) (J_{ab} = 16.0 Hz); ir 3400–3200 (NH_2), 2220 (CN) cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.81; H, 3.58; N, 19.68.

2-Amino-3-cyano-5-(3,4-methylenedioxystyryl)pyrazine (10d). Method A.—A suspension of 10.0 g of **7** in 650 ml of chloroform containing 7.5 g of piperonal and 5.0 g of triethylamine was stirred



iv

at room temperature for 24 hr and then heated under reflux for an additional 24 hr. The resulting precipitate was collected by filtration and washed with chloroform to give 5.0 g (82%) of the trans isomer of **10d** as a bright yellow solid, mp 225–226° dec. Recrystallization of a small sample from methanol gave the analytical sample: mp 228–229° dec; nmr (DMSO-d_6) δ 5.87 (2, s, $-OCH_2O$), 6.71 (1, d, H_e), 6.84 (1, d, H_a), 6.92 (1, q, H_d), 7.10 (2, s, NH_2), 7.16 (1, d, H_c), 7.24 (1, d, H_b), 8.23 (1, s, C_6H) (iv) (J_{ab} = 16.5 Hz); ir 3440–3100 (NH_2), 2220 (CN), 955 (C=C) cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.88; H, 3.99; N, 20.89.

Method B.—To a cooled solution of 5.0 g of **10d** in 300 ml of tetrahydrofuran was added slowly and with stirring 7.3 g of phosphorus trichloride. After 45 min of stirring at room temperature, the reaction mixture was evaporated to a small volume under reduced pressure and poured into ice water. The solid which was collected by filtration was washed well with water and recrystallized from tetrahydrofuran–methanol to give 3.9 g (83%) of the trans isomer of **10d** as a yellow solid, mp 227–228°. Recrystallization from methanol raised the melting point to 228–229° dec. This compound was identical in all respects with the product obtained as described above by method A.

2-Amino-3-cyano-5-(3,4-dichlorostyryl)pyrazine (10e).—A suspension of 10.0 g of **7** in 650 ml of chloroform containing 8.0 g of 3,4-dichlorobenzaldehyde and 4.7 g of triethylamine was stirred at room temperature for 24 hr. Filtration then gave 5.8 g (86%) of the trans isomer of **10e** as a yellow microcrystalline solid, mp 238–239° dec. The analytical sample, mp 239–240°, was prepared by recrystallization of a small sample from methanol: nmr (DMSO-d_6) δ 7.15 (2, s, CH=CH), 7.29 (2, br s, NH_2), 7.43 (2, s, H_{de}), 7.68 (1, s, H_c), 8.28 (1, s, C_6H); ir 3420–3220 (NH_2), 2220 (CN), 955 (C=C) cm^{-1}.

Anal. Calcd for $C_{12}H_8N_4Cl_2$: C, 53.64; H, 2.75; N, 19.24; Cl, 24.39. Found: C, 53.86; H, 2.94; N, 19.49; Cl, 24.32.

2,4-Diamino-6-methoxymethylpteridine 8-Oxide (12).—Guanidine hydrochloride (2.1 g) was added to a solution of 2.6 g of sodium methoxide in 95 ml of methanol and the precipitated sodium chloride removed by filtration. To the filtrate was added 2.5 g of **3**, the resulting mixture was heated under reflux for 6 hr, cooled, and filtered, and the collected solid was washed well with methanol to give 2.5 g (81%) of crude **12** as a dark green microcrystalline solid. Recrystallization (4×) from DMF (Norit) then gave 1.5 g (49%) of pure **12** as a bright yellow solid: mp 265° dec; nmr (CF_3CO_2H) δ 3.28 (3, s, OCH_3), 4.50 (2, s, $-CH_2O-$), 8.51 (1, s, C_7H).

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.09; H, 4.54; N, 37.82.

The following compounds were prepared in the same manner from guanidine and the corresponding 2-amino-3-cyano-5-substituted pyrazines.

2,4-Diamino-6-vinylpteridine (11a): 63% yield; mp (from methanol) >300° dec; nmr (CF_3CO_2H) δ 5.51 (1, q, H_c), 6.14 (1, q, H_b), 6.65 (1, q, H_a), 8.53 (1, s, C_7H) (i) (J_{ab} = 17.5, J_{ac} = 10.0, J_{bc} = 1.0 Hz).

Anal. Calcd for $C_8H_8N_6$: C, 51.05; H, 4.28; N, 44.66. Found: C, 51.32; H, 4.20; N, 44.37.

2,4-Diamino-6-(1-propenyl)pteridine (11b): 88% yield; mp (from DMF) 312° dec; nmr (CF_3CO_2H) δ 1.62 (3, d, CH_3), 6.24 (1, d, H_a), 6.86 (1, m, H_b), 8.38 (1, s, C_7H) (ii) (J_{ab} = 16.0 Hz).

Anal. Calcd for $C_9H_{10}N_6$: C, 53.45; H, 4.98; N, 41.56. Found: C, 53.47; H, 5.13; N, 41.83.

2,4-Diamino-6-(1-nonenyl)pteridine (11c): 69% yield; mp (from methanol) 275–276° dec; nmr (CF_3CO_2H) δ 0.40 (3, t, CH_3), 1.95 (2, m, $=CHCH_2-$), 6.14 (1, d, H_a), 6.80 (1, sextet, H_b), 8.37 (1, s, C_7H) (iii) (J_{ab} = 16.0 Hz).

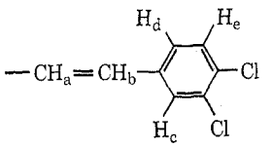
Anal. Calcd for $C_{15}H_{22}N_6$: C, 62.91; H, 7.74; N, 29.35. Found: C, 62.99; H, 7.92; N, 29.55.

2,4-Diamino-6-(3,4-methylenedioxystyryl)pteridine (11d): 93% yield; mp (after extraction with hot methanol) 336–337° dec; nmr (CF_3CO_2H) δ 5.43 (2, s, $-OCH_2O-$), 6.28 (1, d, H_e),

6.55 (1, d, H_a), 6.57 (1, d, H_d), 6.60 (1, s, H_e), 7.30 (1, d, H_b), 8.32 (1, s, C_7 H) (iv) (J_{ab} = 16.0 Hz).

Anal. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92; N, 27.26. Found: C, 58.16; H, 4.04; N, 27.33.

2,4-Diamino-6-(3,4-dichlorostyryl)pteridine (**11e**): 94% yield; mp (after extraction with hot methanol) 358–359° dec; nmr (CF_3CO_2H) δ 6.49 (1, d, H_a), 6.67 (2, s, H_{de}), 6.87 (1, s, H_c), 7.06 (1, d, H_b), 8.12 (1, s, C_7 H) (partial structure v) (J_{ab} = 15.5 Hz).



v

Anal. Calcd for $C_{14}H_{10}N_6Cl_2$: C, 50.45; H, 3.00; N, 25.22; Cl, 21.32. Found: C, 50.28; H, 3.05; N, 25.27; Cl, 21.56.

2,4-Diamino-6-methoxymethylpteridine (**13**): 85% yield: mp (from DMF) 255–256°; nmr (CF_3CO_2H) δ 3.26 (3, s, $-OCH_3$), 4.54 (2, s, $-CH_2O-$), 8.47 (1, s, C_7 H).

Anal. Calcd for $C_8H_{10}N_6O$: C, 46.59; H, 4.89; N, 40.76. Found: C, 46.43; H, 5.16; N, 41.01.

Registry No.—**2**, 40127-89-7; **3**, 40127-90-0; **4**, 40127-91-1; **5**, 40127-92-2; **6**, 40127-93-3; **7**, 40127-94-4; **8**, 19994-56-0; *cis*-**9b**, 40132-91-0; *trans*-**9b**, 40132-92-1; *trans*-**9d**, 40110-58-5; **10a**, 40110-10-9; *cis*-**10b**, 40132-93-2; *trans*-**10b**, 40132-94-3; *trans*-**10c**, 40132-95-4; *trans*-**10d**, 40110-59-6; *trans*-**10e**, 40110-60-9; **11a**, 40110-12-1; *trans*-**11b**, 40110-61-0; *trans*-**11c**, 40110-62-1; *trans*-**11d**, 40110-63-2; *trans*-**11e**, 40110-64-3; **12**, 40110-11-0; **13**, 40110-13-2; 2-methoxymethylamino-3-cyano-5-vinylpyrazine, 40110-14-3; aminomalononitrile tosylate, 5098-14-6; β-chloropyruvaldoxime, 14337-41-8; methanol, 67-56-1; phosphorus trichloride, 7719-12-2; triphenylphosphine, 603-35-0; paraformaldehyde, 30525-89-4; acetaldehyde, 75-07-0; octylaldehyde, 124-13-0; piperonal, 120-57-0; 3,4-dichlorobenzaldehyde, 6287-38-3; guanidine, 113-00-8.

The Cyanogen Azide Ring-Expansion Reaction

JOHN E. MCMURRY* AND ANTHONY P. COPPOLINO

Department of Chemistry, University of California, Santa Cruz, California 95064

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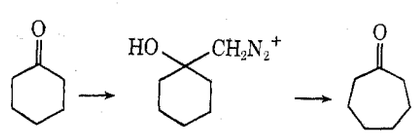
Reaction of alkylidenecycloalkanes with cyanogen azide, followed by hydrolysis, affords ring-expanded cyclic ketones. The reaction is applicable to a wide variety of ring sizes and to both saturated and α,β-unsaturated ketones. Application to several unsymmetrically substituted cyclic ketones indicates low migrational selectivity, paralleling the results of simple diazomethane ring expansion. An important finding is that α-substituted ring-expanded ketones can be obtained readily (ethylidenecyclohexane → 2-methylcycloheptanone, 80%). The method also should prove valuable in many instances since it is operationally simple and yields are good.

Several years ago, we reported briefly[1] on a new method of ring expansion whereby, if one treats a methylenecycloalkane with cyanogen azide, the homologous cycloalkanone is produced rapidly and in high yield. We have now completed an extensive study of the scope of the reaction, and we wish to report our findings.

A great amount of effort has gone into developing methods of ring enlargement, and many ingenious solutions have been put forward.[2] We became interested in the subject in connection with our efforts in natural product synthesis and rapidly found that considerable room for improvements still exists.

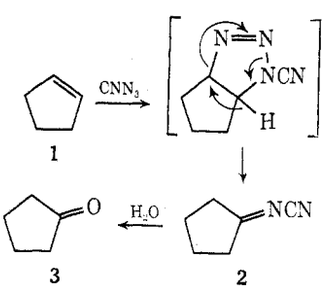
Probably the most generally useful method of one-carbon ring expansion is by a pinacol-like rearrangement of a hydroxy diazonium ion.[2]



The required intermediate can be generated in several ways, but various difficulties usually interfere to some extent. For example, if one generates the intermediate directly from the ketone by reaction with diazomethane, the homologous cycloalkanone is produced and can itself undergo further reaction with diazomethane leading to overhomologated products.[3]

On the other hand, if one attempts to avoid this difficulty by multistep Tiffeneau-type variations, low overall yields often result.

In 1964, Marsh and Hermes reported[4] that, when cyclopentene was treated with cyanogen azide, reaction occurred to yield cyclopentylidenecyanimide (**2**) and then, after hydrolysis, cyclopentanone. Presumably the reaction occurs by 1,3 dipolar addition followed by hydride migration and loss of nitrogen.



Marsh and Hermes also showed that, in unsymmetrical cases, the cyano-bearing nitrogen is always found on the more highly substituted carbon of the olefin, and it therefore occurred to us that, if one were to use an exocyclic olefin such as methylene cyclohexane, cycloaddition followed by alkyl migration might occur. The net effect would be a short and simple ring expansion which, since the required olefins are readily available from the corresponding ketones by Wittig reaction, should have considerable utility.

In fact, when we treated methylenecyclohexane with

(1) J. E. McMurry, *J. Amer. Chem. Soc.*, **91**, 3676 (1969).

(2) For a review of ring enlargements, see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

(3) See, for example, A. P. Giraitis and J. L. Bullock, *J. Amer. Chem. Soc.*, **59**, 951 (1937).

(4) F. D. Marsh and M. E. Hermes, *ibid.*, **86**, 4506 (1964).