**o-Iodoso-N-acetylbenzamide (2-Acetyl-1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodazole, 7-OH).**[11] To 50 mL of concentrated ammonium hydroxide was added with stirring 10 g (38 mmol) of o-iodobenzoyl chloride (Aldrich). The precipitate of crude o-iodobenzamide was filtered, washed with cold water, recrystallized from hot water, and dried to give 8.0 g (32 mmol, 84%) of pure o-iodobenzamide: mp 183–185 °C (lit.[21] mp 183 °C); IR (KBr) 3500, 3400 ($NH_2$), 1680 (C=O) $cm^{-1}$.

To a slurry of 7.0 g (28 mmol) of o-iodobenzamide in 50 mL of glacial acetic acid was added 15 g of Aldrich 34% peracetic acid (67 mmol peracid). The addition was carried out slowly and with stirring at 30 °C. After an additional 30 min, excess water was added, and the precipitate was filtered and dried. It was then extracted with ether to give a residual white powder (7). We obtained 6.3 g (21 mmol, 75%) of 7: $R_f$ 0.35 [on Aldrich precoated silica gel on polyester TLC plates with fluorescent indicator, using MeOH eluent ($R_f$ for o-iodobenzamide is 0.85 under these conditions)]; mp, 143–145 °C dec (lit.[11] mp 140 °C dec); IR (KBr) 1665, 1615 (C=O)[11] $cm^{-1}$. The compound showed 99% of iodoso activity by iodometric titration.[6]

**Kinetic Studies.** Reactions were followed on a Gilford Model 250 spectrophotometer coupled to a Gilford Model 6051 recorder. Constant-temperature circulating baths maintained reaction temperatures at 25 ± 0.5 °C. All buffers were prepared from steam-distilled water (distilled, USP, Electrified Water Co., East Orange, NJ) and were purged with nitrogen. Rate constants were obtained from computer-generated correlations of log ($A_\infty - A_t$) with time for the appearance of p-nitrophenoxide ion at 400 nm (unless otherwise indicated; cf., Table II). Conditions for all of the kinetic runs are described above. Rate constants are depicted graphically in Figures 2 and 3. Micellar reactions were generally followed to >90% completion and showed good first-order kinetics ($r > 0.999$). Values of $k_\psi^{max}$ appear in Table I. Rate constants in the presence of excess PNPDPP are collected in Table II.

**Acknowledgment.** We are grateful to the U.S. Army Research Office for financial support. We thank Dr. Shanti Swarup and Professor Larry Romsted for helpful discussions.

(21) Wachter, B. *Ber.* **1893**, *26*, 1745.

## A Practical Synthesis of Mitomycin A and Its Analogues

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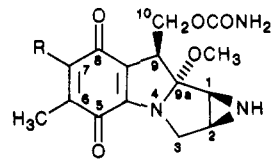
*Received April 17, 1986*

Mitomycin C (1),[1,2] an antineoplastic antibiotic isolated from fermentation broth of *Streptomyces caespetosius*, is currently used clinically in combination cancer chemotherapy against a wide variety solid tumors.[3] Analogue research targeted toward more efficacious and less myelosuppressive derivatives has proceeded at a steady pace. A useful semisynthetic approach has centered on the synthesis of 7-substituted mitosanes, namely, the 7-amino substituted (**2**)[4] and 7-alkoxy (**3**)[5] mitosanes; both of these

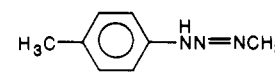


**1**, R = $NH_2$
**2**, R = $R_1NH_2$
**3**, R = $OR_1$
**4**, R = $OCH_3$
**5**, R = OH

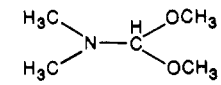
are prepared from mitomycin A (**4**).[4,6] The key source of mitomycin A, besides fermentation[2] (poor yield) is chemical synthesis[6] which involves base hydrolysis of **1** to an unstable intermediate **5** followed by methylation with diazomethane to **4**. Due to the inherent instability of **5** and the hazards involved in working with diazomethane, this process is undesirable for routine and large-scale synthesis. Moreover, with the lack of an efficient in-house fermentation source of mitomycin A (**4**), it was highly desirable for our analogue program to develop a practical and an efficient synthetic route to **4**.

In this paper we report a new synthetic process for mitomycin A (**4**), which is amenable to routine and scale-up preparations. The new methodology described herein is further extended to the preparation of 7-alkoxymitosanes **3**, directly from **5**; hitherto **3** was prepared by a simple alcoholysis process[5] involving reaction of mitomycin A (**4**) with a large excess of alcohol (ROH) in the presence of a catalytic amount of base. The serious limitations of this method are the reactivity (nucleophilicity) and the physical properties of the reacting alcohol; i.e., less nucleophilic alcohols such as 2-fluoroethanol do not react and viscous and solid alcohols are not suitable for the alcoholysis reaction.[7] Moreover, in many instances product isolation and purification is difficult.[7]

At the outset, 7-hydroxy-9a-methoxymitosane (**5**) was considered as a vinylogous acid. Consequently, known reagents which are good esterification agents were regarded as suitable alternatives to diazomethane O-alkylation of **5**. Two such commercial reagents are dimethylformamide dimethylacetal (**6**)[8] and 1-methyl-3-p-tolyltriazene (**7**).[9]



**7**



**6**

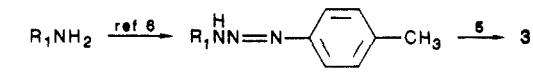
The former, although being a good methylating agent, is also an efficient formylating agent known to react with primary amines, amides, and urethanes to yield the corresponding amidines, whereas triazenes, e.g., **7** are only known to alkylate acids,[9] certain alcohols, phenols, and mercaptans.[10]

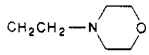
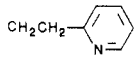
Since all our attempts to methylate 7-hydroxy-9a-methoxymitosane (**5**) with dimethylformamide dimethylacetal failed[11] we focussed our attention on the use of commercially available triazene **7**. Thus, when **5** was treated with approximately 2–3 equiv of triazene **7** in

(1) A trivial system of nomenclature which has found wide use in the mitomycin literature identifies mitomycin C (**1**) as 7-amino-9a-methoxymitosane and mitomycin A (**4**) as 7,9a-dimethoxymitosane.
(2) Remers, W. A. *Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1, pp 221–276 and references cited therein.
(3) Carter, S. K.; Crooke, S. T. *Mitomycin C. Current Status and New Developments*; Academic: New York, 1979; and references cited therein.
(4) Sami, S. M.; Iyengar, B. S.; Tarnow, S. E.; Remers, W. A.; Bradner, W. T.; Schurig, J. E. *J. Med. Chem.* **1984**, *27*, 701 and references cited therein.
(5) Urakawa, C.; Nakano, K. *J. Antibiot.* **1980**, *33*, 804.
(6) Matsui, M.; Yamada, Y.; Uzu, K.; Hirata, T. *J. Antibiot.* **1968**, *21*, 189.
(7) Remers, W. A.; personal communication.
(8) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675 and references cited therein.
(9) White, E. H.; Scherrer, H. *Tetrahedron Lett.* **1961**, *21* 758. Mangia, A.; Scandroglio *Tetrahedron Lett.* **1978**, *52*, 5219.
(10) Pochinok, V. Y. *Ukr. Khim. Zh. (Russ. Ed).* **1955**, *21*, 496, 682; **1952**, *18*, 631.
(11) Treatment of **5** with an excess of acetal in chloroform afforded only the C-10 carbamoyl amidine product of **5**. No indication (TLC) of methylation at the 7-OH functionality was observed.

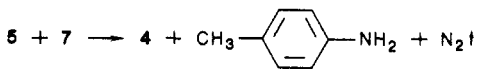
0022-3263/86/1951-4307$01.50/0 

**Table I. Mitomycin A Analogues**




| $R_1$ | amine | triazene | 7-alkoxymitosane (3) (% yield) |
|---|---|---|---|
| $CH_2CH_2CH_2CH_3$ | 8 | 14 | 20 (35) |
| $CH(CH_3)_2$ | 9 | 15 | 21 (31) |
|  | 10 | 16 | 22 (27) |
| $CH_2CH_2OCH_3$ | 11 | 17 | 23 (41) |
| $CH_2CH_2SCH_2Ph$ | 12 | 18 | 24 (32) |
|  | 13 | 19 | 25 (31) |

methylene chloride for ~24 h, mitomycin A (4) was produced as the major product and was isolated by column chromatography on neutral alumina.[12] The spectral ($^1$H




NMR) data of 4 was identical with that of the authentic sample prepared via diazomethane alkylation.[6] It is noteworthy that toluidine, which is produced as a byproduct of the triazene methylation reaction under the above reaction conditions, does not undergo a nucleophilic displacement reaction with the mitomycin A (4) generated in situ to yield 2 ($R_1$ = HNPh-*p*-$CH_3$). This is probably attributable to the nonpolar solvent used in this reaction since in more polar solvents such as methanol, various anilines are known to react with 4 to yield 7-aminomitosanes 2.[4] Using the above described process we have been able to routinely run 2–5-g methylation reactions on 5, which previously was impossible using the diazomethane alkylation process.[13]

The scope and the generality of the triazene alkylation process described above was demonstrated by the synthesis of mitomycin A analogues **20–25** (Table I). Thus, readily available amines **8–13** were converted to the corresponding triazenes **14–19** by reaction with *p*-toluenediazonium chloride according to the published procedure of White et al.[14] The triazenes prepared in this study were partially characterized by $^1$H NMR spectroscopy before reacting with 5. However, the final analogues were fully characterized spectroscopically and by elemental analysis. The process appears to be general; however, the limiting factor will be the stability of the reacting triazene and the availability of the corresponding amine. In the present study no attempts have been made to optimize the yields.

In summary, the triazene-assisted alkylation of 5 to mitomycin A (4) and its analogues **20–25** reported herein, appears to be general and superior to the diazoalkane alkylation[7] in that most triazenes are crystalline, stable materials which are easy to prepare,[14] store and handle. The added advantage of the above technology to that reported by Urakawa et al.[5] for the synthesis of 7-alkoxymitosanes 3 is that it circumvents the use of mitomycin A as a starting material.

## Experimental Section

Melting points are uncorrected. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian XL-100 or on a Jeol FX-90Q (90 MHz) spectrometer in pyridine-$d_5$. Chemical shifts are reported in $\delta$ units. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad signal; dd, doublet of doublets. Infrared spectra were determined on a Beckman Model 4240 spectrophotometer and are reported in reciprocal centimeters. Thin-layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel plates (60F-254). Column chromatography was run either with Woelm silica gel (32–63 $\mu$m) or Alumina Woelm TSC in indicated solvents. Solvents were evaporated under reduced pressure and at temperatures below 40 °C.

**7-Hydroxy-9a-methoxymitosane (5)** was prepared from mitomycin C (1) according to the published procedure of Matsui et al.[6]

**Mitomycin A (4).**[6] To a solution of 5 (1.5 g, 4.5 mM) in methylene chloride (100 mL) was added with stirrig commercial triazene 7 (1.5 g, 10.0 mM). The solution was stirred at room temperature for 24 h; thin-layer chromatography (9:1 $CH_2Cl_2$/MeOH) at this time revealed the appearance of a deep red spot at $R_f$ 0.36 as a major component and a complete disappearance of the starting material ($R_f$ 0.07). The reaction mixture was concentrated to approximately a 30-mL volume, loaded on to a column of Woelm neutral alumina, and subjected to flash chromatography. Elution with methylene chloride (250 mL) and methylene chloride/methanol (30:1, 250 mL) afforded the title compound ($R_f$ 0.36) as an amorphous solid, which precipitated as a dry powder (760 mg, 49%) from methylene chloride and hexane: mp 161 °C; $^1$H NMR (pyridine-$d_5$) $\delta$ 1.82 (s 3 H), 2.74 (dd, 1 H), 3.12 (d, 1 H), 3.24 (s, 3 H), 5.54 (dd, 1 H), 3.96 (dd, 1 H), 4.02 (s, 3 H), 4.22 (d, 1 H), 4.84 (br, 2 H), 5.02 (t, 1 H), 5.38 (dd, 1 H); IR (KBr) 3400, 3300, 2950, 1700, 1630, 1575, 1200, 1060 cm$^{-1}$. Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 54.96; H, 5.44; N, 12.02. Found: C, 54.30; H, 5.59; N, 12.02.

**Triazenes 14–19.** The procedure outlined by White et al.[14] for the synthesis of 1-methyl-3-*p*-tolyltriazene (7) was employed as a general procedure for the preparation of triazenes **14–19** from amines **8–13**, respectively. The triazenes, before use in the alkylation of 5, were purified by column chromatography (neutral Woelm alumina) and partially characterized by $^1$H NMR.

**General Procedure for Preparing Mitomycin A Analogues 20–25.** To a solution of 5 in methylene chloride methanol (4:1) was added with stirring a solution of triazene (~2.4 equiv) in $CH_2Cl_2$/MeOH (4:1). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC (10% MeOH in $CH_2Cl_2$). At the completion of the reaction major product (red) was isolated in a fashion similar to that described for mitomycin A (4).

**7-*n*-Butoxy-9a-methoxymitosane (20):**[5] yield 35%; $^1$H NMR (pyridine-$d_5$) $\delta$ 0.80 (t, 3 H), 1.44 nm, 4 h), 1.84 (s, 3 H), 2.08 (br, 1 H), 2.72 (br, 1 H), 3.08 (br, 1 H), 3.20 (s, 3 H), 3.52 (d, 1 H), 4.00 (dd, 1 H), 4.28 (m, 3 H), 5.04 (t, 1 H), 5.44 (dd, 1 H), 7.64 (br, 2 H). Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30, H, 6.44; N, 10.74. Found: C, 58.34; H, 6.25; N, 10.80.

**7-Isopropoxy-9a-methoxymitosane (21):**[5] yield 31%; $^1$H NMR (pyridine-$d_5$) $\delta$ 1.20 (d, 3 H), 1.28 (d, 3 H), 1.88 ns, 3 H), i.20 (br, 1 H), 2.76 (br, 1 H), 3.16 (br, 1 H), 3.24 (s, 3 H), 3.56 (d, 1 H), 4.00 (dd, 1 H), 4.24 (d, 1 H), 5.00 (m, 2 H), 5.44 (dd, 1 H).

**7-[(2-(4-Morpholinyl)ethyl)oxy]-9a-methoxymitosane (22):** yield 28%; $^1$H NMR (pyridine-$d_5$) $\delta$ 1.96 (s, 3 H), 2.40 (m, j H), 2.56 (t, 2 H), 2.76 (br, 1 H), 3.16 (d, 1 H), 3.24 (s, 3 H), 3.54 (d, 1 H), 3.68 (m, 4 H), 4.00 (dd, 1 H), 4.26 (d, 1 H), 4.60 (m, 2 H), 5.04 (t, 1 H), 5.44 (dd, 1 H); Ir (KBr) 3480, 3260, 2940 1725, 1620, 1210, 1055 cm$^{-1}$. Anal. Calcd. for $C_{21}N_{28}N_4O_7$: C, 52.60; H, 5.95; N, 11.41. Found: C, 52.75; H, 6.00; N, 11.44 (corrected for 0.5 mol % of $CH_2Cl_2$).

**7-[(2-Methoxyethyl)oxy]-9a-methoxymitosane (23):**[5] yield 41%; $^1$H NMR (pyridine-$d_5$ $\delta$ 2.88 (s, 3 H), 2.00 (br, 1 H), 2.72 (br, 1 H), 3.08 (d, 1 h), 3.20 (s, 3 H), 3.24 (s, 3 H), 3.52 (m, 3 H), 3.96 (dd, 1 H), 4.20 (d, 1 H), 4.56 nm, 2 H), 5.04 (t, 1 H), 5.40 (dd, 1 H); IR (KBr) 3440, 3280, 2950, 1700, 1630, 1200, 1065 cm$^{-1}$. Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 54.96; H, 5.89; N, 10.68. Found: C, 54.45; H, 5.85; N, 10.45.

**7-[(2-(Benzylthio)ethyl)oxy]-9a-methoxymitosane (24):** yield 32%; $^1$H NMR (pyridine-$d_5$) $\delta$ 1.92 (s, 3 H), 2.12 (br, 1 H), 2.76 (br, 1 H), 2.84 (t, 2 H), 3.16 (br, 1 H), 3.26 (s, 3 H), 3.56 (d, 1 H), 3.86 (s, 2 H), 4.04 (dd, 1 H), 4.28 (d, 1 H), 4.60 (m, 2 H),

(12) On silica gel the excess of triazene present in the reaction mixture decomposes rapidly, and thus chromatographic separation is seriously hampered.

(13) Poor solubility of 5 in ether (e.g., 500 mg run in 500 mL) also made scale-up methylation difficult.

(14) White, E. H.; Baum, A. A.; Eitel, D. E. *Org. Synth.* **1968**, *48*, 102.

5.12 (t, 1 H), 5.48 (dd, 1 H), 7.46 (m), 7.76 (br); IR (KBr) 3420, 3280, 2930, 1895, 1620, 1210, 1065 $cm^{-1}$. Anal. Calcd for $C_{24}H_{27}N_3O_6S$: C, 59.37; H, 5.60; N, 8.65, S, 6.60. Found: C, 59.26, H, 5.66; N, 8.63; S, 6.66.

**7-[(2-(2-Pyridyl)ethyl)oxy]-9a-methoxymitosane (25)**: yield 31%; $^1H$ NMR (pyridine-$d_5$) $\delta$ 1.68 (s, 3 H), 1.68 (br, 1 H), 2.72 (br, 1 H), 3.08 (br, 1 H), 3.20 (t, 2 H), 3.20 (t, 3 H), 3.50 (d, 1 H), 3.92 (dd, 1 H), 4.16 (d, 1 H), 4.92 (m), 5.38 (dd, 1 H); IR (KBr) 3430, 3300, 2930, 1715, 1625, 1210, 1060 $cm^{-1}$. Anal. Calcd for $C_{22}H_{24}N_4O_6$: C, 59.99, H, 5.49; N, 12.72. Found: C, 59.94; H, 5.66; N, 12.63.

**Registry No.** 4, 4055-39-4; 5, 7041-61-4; 7, 21124-13-0; 8, 109-73-9; 9, 75-31-0; 10, 2038-03-1; 11, 109-85-3; 12, 1007-54-1; 13, 2706-56-1; 14, 53477-45-5; 15, 50707-41-0; 16, 104376-54-7; 17, 104393-20-6; 18, 104376-55-8; 19, 104376-56-9; 20, 56981-64-7; 21, 56981-61-4; 22, 103864-79-5; 23, 76079-90-8; 24, 103840-03-5; 25, 103840-02-4; $p$-$MeC_6H_4N_2^+Cl^-$, 2028-84-4.

## Reduction of Acrylonitrile in the Presence of Viologen Derivatives

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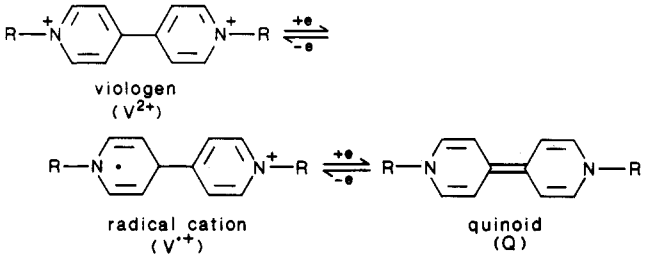
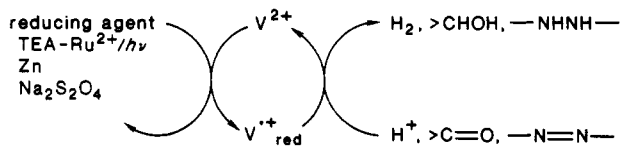
*Received May 20, 1986*

Viologen (*N*,*N*-dialkyl-4,4′-dipyridinium, $V^{2+}$) is well-known to produce the blue radical cation ($V^{\cdot+}$) and quinoid (Q) by one-electron and two-electron reduction, respectively, and show redox behavior as below. The reduction




of some substrates is of great interest using $V^{2+}$ as electron-transfer catalyst (ETC). Methyl viologen ($MV^{2+}$) and viologen polymers (P-$V^{2+}$) have been studied as an effective electron mediator in hydrogen production,[1-4] the reduction of quinones or $\alpha$-keto ester by zinc (Zn).[5,6] Further, we have also reported the reduction of azobenzene[7] by Zn, aromatic aldehydes, and ketones by sodium dithionite ($Na_2S_2O_4$)[8] in the presence of $V^{2+}$ as ETC.

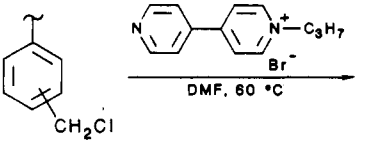


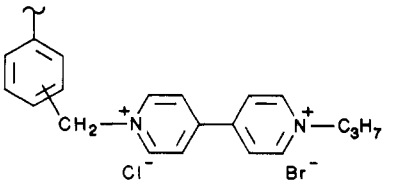

In this article the role of $MV^{2+}$ and P-$V^{2+}$ as ETC is examined in the reduction of acrylonitrile with Zn powder and sodium dithionite.

### Experimental Section

**Materials.** The soluble polymer (P-1) containing viologen moiety was synthesized from poly(chloromethylstyrene–styrene) ($CH_2Cl$; 33 mol %) and 1-propyl(4-pyridyl)pyridinium bromide in dimethylformamide (DMF) at 60 °C for 48 h. After the reaction, P-1 was obtained by reprecipitating with excess acetone (yield 95%, $V^{2+}$ content = 31 mol %). 1-Propyl-4-pyridyl-pyridinium bromide was prepared according to a reported method.[9]

The cross-linked polymer (P-2 $V^{2+}$ content; 12 mol %) carrying $V^{2+}$ moiety was also obtained from cross-linked chloromethylated polystyrene (DVB = 2 mol %, $CH_2Cl$ = 15 mol %, 50 mesh) by the same method described above ($V^{2+}$ content = 12 mol %). The



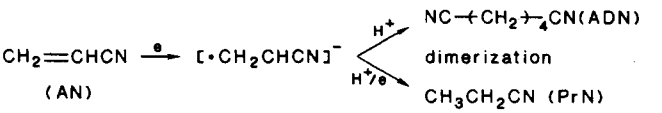

content of $V^{2+}$ in the polymers was estimated by elemental analysis. (P-1; N, 4.36. P-2; N, 2.90.) 1,1′-Dihydrodipyridyl (Q) was prepared according to the reported procedure.[10]

**Reduction of Acrylonitrile by Zinc in the Presence of $V^{2+}$.** A typical procedure for the reduction of acrylonitrile (AN) is as follows: A solution AN (50 mmol) in MeOH–$H_2O$ (5:1 = 5 mL) was added to zinc (Zn, 60 mmol) as a reducing agent and methyl viologen ($MV^{2+}$) or P-1, P-2. ($V^{2+}$/AN = 2–20 mol %). The reaction mixture was stirred at 50 °C for 4 days in sealed tube. After removing Zn with titration, the yield of adiponitrile (ADN) was estimated from the ratio of peak area of AN and ADN by GLC analysis of the solution.

**Reduction of Acrylonitrile by Sodium Dithionite in the Presence of $V^{2+}$.** To an aqueous solution (50 mL) of $Na_2S_2O_4$ (50 mmol), $K_2CO_3$ (100 mmol), and viologens ($V^{2+}$/AN = 2–10 mol %) was added an MeOH solution (50 mL) of AN (50 mmol). The reaction mixture was stirred at room temperature for 4 days under an argon atmosphere. After extracting with either, the solvent was removed in vacuo. The yield of products (ADN and propionitrile) was determined by GLC analysis in same manner as described before. Further, the reduction of fumaronitrile was also carried out by the same method.

### Results and Discussion

**Reduction of Acrylonitrile with Zn/$V^{2+}$ System.** The adiponitrile (ADN) has been industrially produced by the electrochemical reduction of acrylonitrile (AN). As byproducts, propionitrile (PrN) and some oligomers are obtained.[11]




(1) Ageishi, K.; Endo, T.; Okawara, M. *J. Polym. Sci. Polym. Chem. Ed.* **1981**, *19*, 1085.
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