Unsaturated Nitriles from N-Chlorosulfonyl-β-lactams[1]

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N-Chlorosulfonyl-β-lactams are converted into unsaturated nitriles (20–75%) with DMF and heat. Thus, the *N*-chlorosulfonyl derivatives of the following 2-azetidinones, 4,4-dimethyl- (**1**), 4,4-diethyl- (**3**), 3-ethyl-4,4-dimethyl- (**6**), 3-methyl-1-azaspiro[3.5]nonan-2-one (**9**), 3,3,4,4-tetramethyl- (**11**), 4-*tert*-butyl- (**13**), 4-phenyl- (**14**), *cis*- (**16**), and *trans*-3-methyl-4-phenyl- (**17**), 4,4-dimethyl-3-methylene- (**21**), and 4,4-dimethyl-3-isopropylidene (**25**), on treatment with DMF, afforded, respectively, the following products: 3-methyl-2-butenenitrile (**2**), a 9:1 mixture of 3-ethyl-2-pentenenitrile (**4**) and 3-ethyl-3-pentenenitrile (**5**), a 1:1 mixture of 2-ethyl-3-methyl-2-butenenitrile (**7**) and 2-ethyl-3-methylenebutanenitrile (**8**), 2-(1-cyclohexenyl)propanenitrile (**10**), 2,2,3-trimethyl-3-butenenitrile (**12**), *trans*-cinnamonitrile (**15**), α-methyl-*cis*-cinnamonitrile (**18**), 4-chloro-2,3-dimethyl-*trans*-2-butenenitrile (**23**), and 3-cyano-2,4-dimethyl-1,3-pentadiene (**26**). Without DMF, the conversion proceeds thermally in low yields (<5%). Replacement of the nucleophile DMF with DMSO as solvent–reactant afforded no nitriles. Working hypotheses for both the thermal and nucleophilic routes to unsaturated nitrile products are proposed.

The solvolytic conversion of *N*-chlorosulfonyl-β-lactams to α,β-unsaturated nitriles using DMF has been patented,[3,4] while a similar transformation of *N*-chlorosulfonylcarboxamides to nitriles with amides (DMF, formamide, dimethylacetamide, α-pyrrolidone, and *N*-methylpyrrolidone) has been reported.[5] Finally, treatment of *N*-chlorosulfonylcarboxamides with equimolar amounts of tertiary amines (triethylamine, diisopropylethylamine) also affords nitriles in good yields.[6] This latter technique is especially useful on acid-sensitive substrates. Mechanisms have been proposed for the *N*-chlorosulfonylcarboxamide → nitrile transformations,[5,6] but not for the *N*-chlorosulfonyl-β-lactam → α,β-unsaturated nitrile conversions. Further, while the reaction of 1-chlorosulfonyl-4-phenyl-2-azetidinone (**14**) with DMF has been reported, the geometry of the product cinnamonitrile has not been established [it is *trans* (**15**)].

It was the purpose of this research to enlarge the base of information available on the β-lactam–DMF reaction in order to determine its scope and limitations, and therefrom, perhaps to elucidate possible mechanisms for this conversion of β-lactams to unsaturated nitriles. The *N*-chlorosulfonyl derivatives of the following 2-azetidinones were chosen: 4,4-dimethyl- (**1**), 4,4-diethyl- (**3**), 3-ethyl-4,4-dimethyl- (**6**), 3-methyl-1-azaspiro[3.5]nonan-2-one (**9**), 3,3,4,4-tetramethyl- (**11**), 4-*tert*-butyl- (**13**), 4-phenyl- (**14**), *cis*- (**16**) and *trans*-3-methyl-4-phenyl- (**17**), *cis*- (**19**) and *trans*-3,4-diethyl- (**20**), 4,4-dimethyl-3-methylene- (**21**), and 4,4-dimethyl-3-isopropylidene (**25**).

In general, the procedure consisted of dissolution of the *N*-chlorosulfonyl-β-lactam in 3–4 mol equiv of DMF and stirring for 16–64 hr at 70–80°. After conventional work-up, the product nitriles were distilled and identified by comparison with authentic samples, synthesis, and/or degradation and spectral analysis.

Results

Treatment of **1** with DMF afforded solely the α,β-conjugated product 3-methyl-2-butenenitrile (**2**, 30%) (Scheme I). Conversely, **9** led exclusively to the β,γ-unsaturated nitrile, 2-(1-cyclohexenyl)propanenitrile (**10**, 65%). Intermediate between these extremes was the conversion of **3** and **6** to mixtures of both α,β- and β,γ-unsaturated nitriles. Thus **3** led to a separable 9:1 mixture (65–75%) of 3-ethyl-2-pentenenitrile (**4**) and 3-ethyl-3-pentenenitrile (**5**), while the trisubstituted β-lactam **6** was converted to a 1:1 mixture (63%) of 2-ethyl-3-methyl-2-butenenitrile (**7**) and 2-ethyl-3-methylenebutanenitrile (**8**).

In the case of the tetraalkyl-substituted β-lactam **11**, the only olefinic nitrile product possible, 2,2,3-trimethyl-3-butenenitrile (**12**), was isolated in 43% yield. Unexpectedly, this same β,γ-unsaturated nitrile **12** was obtained in 20% yield by treatment of the monosubstituted β-lactam **13** with DMF.

As noted, the reaction between β-lactam **14** and DMF led only to the isolation of *trans*-cinnamonitrile (**15**, 23%); further evidence for the lack of stereoselectivity in this transformation may be adduced by the fact that both *cis*- (**16**) and *trans*-β-lactam (**17**) afforded only α-methyl-*cis*-cinnamonitrile (**18**) in 20 and 25% yields, respectively.

The trans relation of vicinal protons in **15** was indicated by the strong out-of-plane absorption at μ 10.35[7a] in the ir and the magnitude of the coupling constant (J = 17 Hz) in the nmr. The α-styryl proton in **15** (cis to CN) appeared as a doublet at δ 7.20. In **18**, the analogous proton provided a more shielded signal at δ 6.80 indicative of its trans relation to the nitrile group (and/or that it is cis to the methyl group).[7b]

The reaction of *cis*- (**19**) and *trans*-β-lactam (**20**) with DMF led to an oil with no nitrile absorption.

Treatment of **21** with DMF under the usual conditions afforded 4-chloro-2,3-dimethyl-*trans*-2-butenenitrile (**23**, 35%), dehalogenation of which under hydrogen (5% Pd–C) afforded the known[8] and independently prepared 2,3-dimethyl-2-butenenitrile (**24**).

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(2) Graduate Research Assistant (1966–1968) on a grant[1] supported by the NIH; taken entirely from the Ph.D. Thesis of C. Jalandoni, Fordham University, New York, N. Y., 1969.

(3) R. Graf, DBP 1,218,448, Farbwerke Hoechst AG (1963).

(4) K. Matterstock and G. Lohaus, DAS 1,253,704, Farbwerke Hoechst AG (1964).

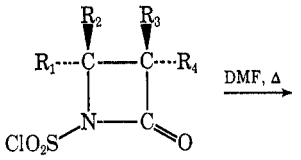
(5) G. Lohaus, *Chem. Ber.*, **100**, 2719 (1967).

(6) H. Vorbruggen, *Tetrahedron Lett.*, 1631 (1968).

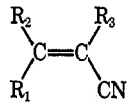
(7) (a) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 45. (b) In methacrylonitrile, *e.g.*, the protons cis and trans to the CN group appear at δ 5.82 and 5.73, respectively: Spectrum No. 97 in "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962; *cf.* also Spectra No. 64 (methyl acrylate) and No. 113 (methyl methacrylate).

(8) Fr. de Laet, *Bull. Soc., Chim. Belges*, **38**, 168 (1929); *Chem. Abstr.*, **23**, 4443 (1929).

SCHEME I



DMF, Δ



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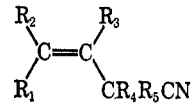


1, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
2, $R_1 = R_2 = CH_3$; $R_3 = H$
3, $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = H$
4, $R_1 = R_2 = C_2H_5$; $R_3 = H$
5, $R_1 = R_4 = R_5 = H$; $R_2 = CH_3$; $R_3 = C_2H_5$
6, $R_1 = R_2 = CH_3$; $R_3 = C_2H_5$; $R_4 = H$
7, $R_1 = R_2 = CH_3$; $R_3 = C_2H_5$
8, $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = C_2H_5$
9, $R_1R_2 = -(CH_2)_5-$; $R_3 = H$; $R_4 = CH_3$
10, $R_1 = R_4 = H$; $R_2R_3 = -(CH_2)_4-$; $R_5 = CH_3$
11, $R_1 = R_2 = R_3 = R_4 = CH_3$
12, $R_1 = R_2 = H$; $R_3 = R_4 = R_5 = CH_3$
13, $R_1 = C(CH_3)_3$; $R_2 = R_3 = R_4 = H$
14, $R_1 = R_3 = R_4 = H$; $R_2 = C_6H_5$
15, $R_1 = R_3 = H$; $R_2 = C_6H_5$
16, $R_1 = R_4 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$
17, $R_1 = R_3 = H$; $R_2 = C_6H_5$; $R_4 = CH_3$
18, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$
19, $R_1 = R_4 = H$; $R_2 = R_3 = C_2H_5$
20, $R_1 = R_3 = H$; $R_2 = R_4 = C_2H_5$
21, $R_1 = R_2 = CH_3$; $R_3R_4 = =CH_2$
22, [$R_1 = R_2 = H$; $R_3 = C(CH_3)=CH_2$]
23, $R_1 = R_3 = CH_3$; $R_2 = CH_2Cl$
24, $R_1 = R_2 = R_3 = CH_3$
25, $R_1 = R_2 = CH_3$; $R_3R_4 = =C(CH_3)_2$
26, $R_1 = R_2 = CH_3$; $R_3 = C(CH_3)=CH_2$

Both **23** and **24** displayed infrared absorptions at 4.50–4.51 (conj C≡N) and 6.08–6.10 μ (C=C). In the nmr, the two *trans*-methyl groups in **23** appeared as singlets at δ 2.11 and 1.99 with an additional two proton singlet at δ 4.23. The methyl protons in **24** appeared as singlets at δ 2.02 and 1.82 with intensity ratio 1:2, respectively. Since protons cis to electronegative substituents are more deshielded than their trans counterparts, the downfield signals at δ 2.11 and 2.02 are attributed to methyl protons cis to the nitrile group in **23** and **24**, respectively. The unusual response of **21** to DMF prompted a similar study of the effect of this nucleophile on similarly structured β-lactam **25**. The only product obtained was the conjugated diene, 3-cyano-2,4-dimethyl-1,3-pentadiene (**26**, 43%).

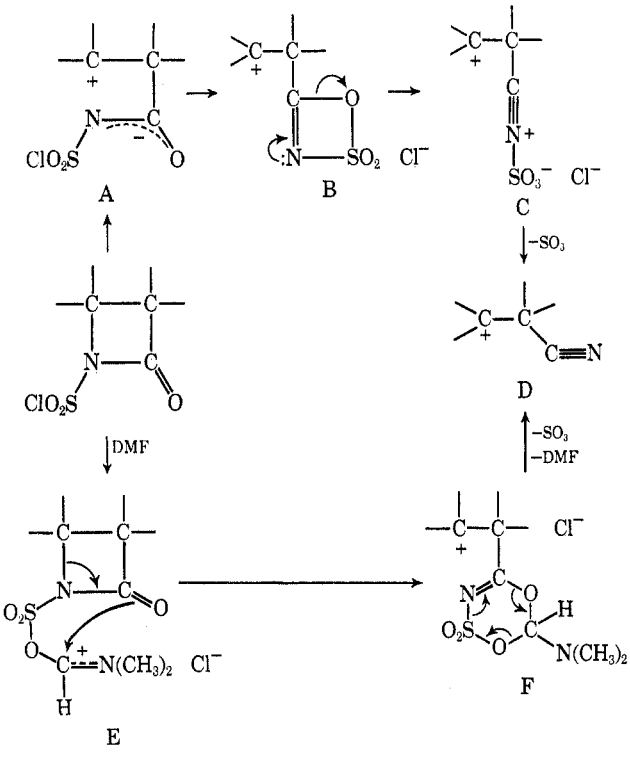
Effect of Nucleophile, Temperature, and Solvent.—Treatment of β-lactam **3** with DMSO, instead of DMF, as solvent–reactant, led to an exothermic reaction with rapid gaseous evolution. After stirring the reactants for several hours at room temperature, extensive polymerization was evident; the mixture darkened and became very viscous. The usual work-up afforded no nitriles.

When **3** and DMF were stirred at room temperature for 18 hr, a 25% yield of nitrile mixture **4** + **5** was obtained. Treatment of **3** (70–80°) for the same period of time in such solvents as hexane, benzene, and acetonitrile, but without DMF, also gave the nitrile mixture but in yields of less than 5%. Thus two mechanisms seem operative, one thermal and the other requiring the nucleophile DMF.

All reactions in this series were accompanied by extensive polymerization, some of which was probably caused by the acidic by-products generated (SO_3, HCl) under the reaction conditions. With DMF, some of this acidity may be neutralized since it forms a stable complex with SO_3.[9] With varying ratios 4–1:1 of β-lactam **3** to DMF, the product mixture yields were in the 10–20% range. When excess DMF was used (3–4 mol equiv), the yield of **4** + **5** rose to 71% which could be increased to 82% by the addition of the base pyridine.[6]

Reaction Mechanism.—Working mechanistic hypotheses for both the thermal and nucleophilic routes to unsaturated nitrile products are summarized in Scheme II. The former involves thermal β-lactam cleavage to

SCHEME II



the 1,4-dipolar species (A) with its delocalized anionic moiety. Isomerization of this primary dipole *via* the four-membered oxathiazete ring (B) to the nitrilium zwitterion C followed by elimination of SO_3 would lead to carbonium ion D, the progenitor of unsaturated ni-

(9) M. L. Wolfrom and T. M. Shenhan, *J. Amer. Chem. Soc.*, **81**, 1764 (1959).

trile products.[10] The cyclic mechanism E → F proposed involves precedented nucleophilic attack of DMF at the S site to give the iminium salt E,[5] followed by collapse of the β-lactam moiety to carbonium ion F. Loss of SO_3 and regeneration of DMF would lead to carbonium ion D. To account for the observed lack of stereoselectivity, β-lactam cleavage by both pathways to nitrilic carbonium ion D and its deprotonation to unsaturated nitriles must occur in step-wise fashion, albeit intermediate steps A → B → C → D ← F ← E may be synchronous.

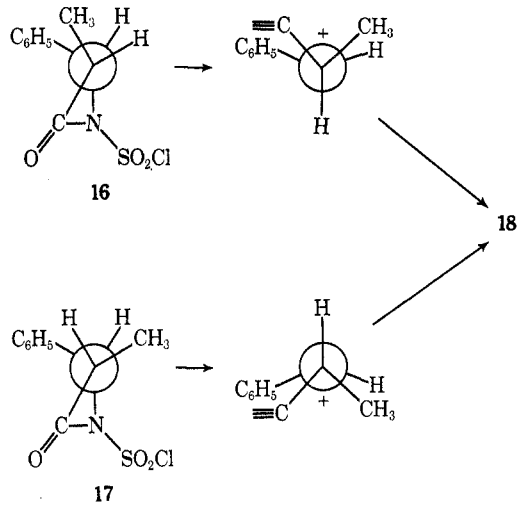
The formation of nitrile **2** and the predominance of **4**, from β-lactams **1** and **3**, respectively, suggests that when the conjugated nitrile is also the more substituted olefin, the preferred deprotonation of D is that which leads predominantly to α,β-unsaturated nitriles. The formation of **10** is in accord with the generalization that in simple hydrocarbons containing six-membered rings, endocyclic are far more stable than exocyclic double bonds.[11] A discernible pattern in the formation of equal amounts of nitrile products **7** and **8** from **7** is not evident. The formation of **8** is statistically favored over **7**; perhaps the relatively high acidity of the methine proton in **6** serves as an effective driving force in the deprotonation of D to the conjugated nitrile **7**.

The conversion of **21** to **23** presumably occurs *via* 1,4 addition of liberated HCl to intermediate 2-cyano-3-methyl-1,3-butadiene (**22**) which in turn would be a deprotonation product of D. This view of a dienic intermediate is supported by the actual isolation of the conjugated diene product **26** from **25**. Since the allylic, geminal methyl groups (R_1 and R_2 in **26**) apparently protect this double bond from further reaction, the results suggest that 1,4 addition of HCl to **22** (and its failure to do so in **26**) is initiated by protonation at the methylene carbon geminal to the nitrile function.

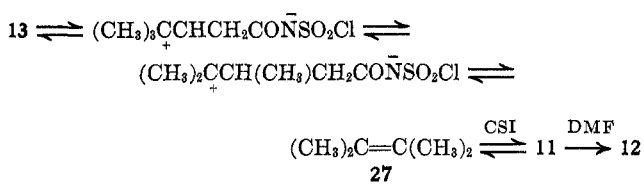
The formation of **18** from both **16** and **17** can be accounted for by deprotonation after the carbonium ion has assumed the most stable conformation; *i.e.*, the bulkier phenyl and methyl groups move farthest away from each other as the σ bond of the proton to be eliminated aligns trans to the vacant p orbital (Scheme III). If β-lactam cleavage and the deprotonation steps were synchronous, only **17** would lead to **18**.

The identity of nitrile product (**12**) resulting from **11** and **13** can be rationalized by a series of equilibria (Scheme IV) in which β-lactam **13** first rearranges, *via* the thermodynamically more stable olefin, tetramethylethylene (**27**), to β-lactam **11** followed by conversion to nitrile **12**. This rearrangement is reminiscent of the CSI-catalyzed rearrangement (slow) of 1,1,2,2-tetramethylcyclopropane to 2,3,3-trimethyl-1-butene followed by more rapid CSI addition to the formed olefin.[12]

SCHEME III



SCHEME IV

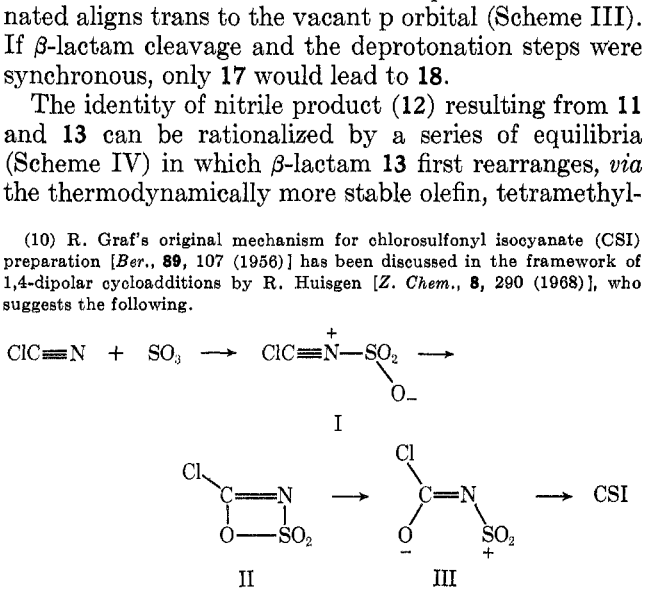


Experimental Section[13]

Reaction of β-Lactams with DMF.—The general procedure was as follows. The β-lactam was stirred at 70–80° with 3–4 mol equiv of DMF for 16–64 hr. The dark, viscous mixture was poured onto 50 ml of cold water and extracted continuously with 250 ml of pentane for 12 hr. The pentane extract was dried ($MgSO_4$), filtered, and evaporated. Distillation of the residue *in vacuo* afforded the nitrile product. Any variations in isolation procedure are noted under the appropriate β-lactam.

1-Chlorosulfonyl-4,4-dimethyl-2-azetidinone (**1**) (19.1 g, 0.10 mol) gave 2.4 g (30%) of **3-methyl-2-butenenitrile** (**2**). Vpc indicated the presence of a minor component as a shoulder on the main peak, presumably the β,γ-unsaturated nitrile. Nitrile **2** was obtained as colorless liquid: bp 39–41° (15.5 mm) [lit.[16] bp 141–142° (762 mm)]; ir (neat) 4.50 (conj C≡N) and 6.10 μ (C=C); nmr (neat) δ 1.88 (d, 3, J = 1.5 Hz, CH_3 trans to C≡N), 1.98 (s, 3, CH_3 cis to C≡N), and 5.08 (q, 1, J = 1.5 Hz, =CH).

(10) R. Graf's original mechanism for chlorosulfonyl isocyanate (CSI) preparation [*Ber.*, **89**, 107 (1956)] has been discussed in the framework of 1,4-dipolar cycloadditions by R. Huisgen [*Z. Chem.*, **8**, 290 (1968)], who suggests the following.



In this case, the primary 1,4 dipole is the nitrilium zwitterion (I) which proceeds to a new 1,4 dipole (III) *via* four-membered ring II. Our oxygen transfer step B → C is the reversal of II → III.

(11) H. C. Brown, J. H. Brewster, and H. Shecter, *J. Amer. Chem. Soc.*, **76**, 467 (1954); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(12) E. J. Moriconi, J. F. Kelly, and R. A. Salomone, *ibid.*, **33**, 3448 (1968).

(13) Boiling points are uncorrected. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60 spectrometer using TMS as an internal standard. Gas chromatograms were run on a Perkin-Elmer 880 instrument with a flame ionization detector and using a column packed with 10% SE-30 on Chromosorb W. Preparative vpc was accomplished on a Perkin-Elmer F 21 using a column packed with 18% QF-1 on Chromosorb W operating at temperature 125–135°. CSI was obtained from American Hoechst Corp. Fisher Scientific Corp. DMF was used without further purification. β-lactams **3**, **6**, **9**, **11**, **14**, **16**, **17**, **19**, **20**, **21**, and **25** were available from previous researches.[14,15]

(14) (a) E. J. Moriconi and J. F. Kelly, *J. Amer. Chem. Soc.*, **88**, 3657 (1966); (b) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).

(15) R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963).

(16) B. V. Ioffe and D. D. Tsitovich, *Dokl. Akad. Nauk SSSR*, **155**, 1348 (1964); *Chem. Abstr.*, **61**, 1849 (1964).

Anal. Calcd for C_5H_7N: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.84; H, 8.79; N, 16.92.

1-Chlorosulfonyl-4,4-diethyl-2-azetidinone (3)[15] (15.1 g, 0.07 mol) gave 5.2 g (71%) of **3-ethyl-2-pentenenitrile (4)** and **3-ethyl-3-pentenenitrile (5)** as colorless liquids in a 9:1 ratio by vpc: bp (of mixture) 68–69° (14.5 mm) [lit.[17] bp (of **4**) 66° (18 mm), lit.[18] bp (of **5**) 105–104° (72 mm)];[18] ir (neat) 4.46 (C≡N), 4.51 (conj C≡N), and 6.13 μ (C=C); nmr (neat) δ 1.02 (m, 9, CH_3), 1.60 (d, 3, J = 7 Hz, =$CHCH_3$), 2.18 (m, 6, CH_2CH_3), 3.05 (broad s, 2, CH_2CN), 5.07 (s, 1, =CHCN), and 5.41 (q, 1, J = 7 Hz, =$CHCH_3$).

Anal. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.86; H, 10.04; N, 13.02.

The isomeric mixture was separated by preparative gas chromatography to yield **4** [ir strong bands at 4.52 (conj C≡N) and 6.06 μ (C=C)] and **5** [ir 4.46 (strong C≡N) and 5.99 μ (weak C=C)]. Recovery from preparative vpc was so poor that samples available were insufficient for individual nmr analysis.

When 5.3 g (0.07 mol) of pyridine was added dropwise to a stirred mixture of 15.1 g (0.07 mol) of **3** and 10.0 g (0.13 mol) of DMF at 60° for 24 hr, the yield of nitrile product mixture (**4** + **5**) rose to 6.0 g (82%), bp 69–71° (15 mm).

Finally, careful addition of 15.6 g (0.21 mol) of DMSO to 15.1 g (0.07 mol) of **3** led to an exothermic reaction accompanied by rapid gaseous evolution. After several hours, the dark brown viscous product displayed no CN band in the infrared.

1-Chlorosulfonyl-3-ethyl-4,4-dimethyl-2-azetidinone (6)[14b] (10.0 g, 0.04 mol) gave 3.0 g (63%) of **2-ethyl-3-methyl-2-butenenitrile (7)** and **2-ethyl-3-methylenebutanenitrile (8)** as colorless liquids in a 1:1 ratio by vpc, bp (of mixture) 61–62° (14.5 mm).

Anal. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.01; H, 10.21; N, 12.71.

Preparative vpc afforded pure **7**: ir (neat) 4.53 (conj C≡N) and 6.10 μ (C=C); nmr (neat) δ 1.08 (t, 3, J = 7 Hz, CH_2CH_3), 1.83 (s, 3, CH_3 trans to C≡N), 2.03 (s, 3, CH_3 cis to C≡N), and 2.21 (q, 2, J = 7 Hz, CH_2CH_3).

Isomer **8** with the shorter retention time could not be completely separated from **7**. Its spectral data was inferred from that of the product mixture: ir (neat) 4.47 (C≡N) and 6.04 μ (C=C); nmr (neat) δ 1.07 (t, 3, J = 7 Hz, CH_2CH_3), 1.81 (s, 3, =CCH_3), 2.20 (q, 2, J = 7 Hz, CH_2CH_3), 3.22 (t, 1, J = 7 Hz, CHCN), 4.97 and 5.04 (two singlets each with fine splitting, 2, =CH_2).

1-Chlorosulfonyl-3-methyl-1-azaspiro[3.5]nonan-2-one (9)[14b] (6.0 g, 0.02 mol) gave 2.1 g (65%) of **2-(1-cyclohexenyl)propanenitrile (10)**: bp 98–99° (12 mm) [lit.[19] bp 113° (13 mm)]; ir (neat) 4.47 μ (C≡N); nmr (CCl_4) δ 1.35 (d, 3, J = 7 Hz, CH_3), 1.63 (m, 4, C-4,5 protons of cyclohexene moiety), 2.03 (m, 4, C-3,6 allylic protons), 3.15 (q, 1, J = 7 Hz, CH), and 5.75 (broad singlet with fine splitting, 1, =CH).

Anal. Calcd for $C_9H_{13}N$: C, 79.75; H, 9.69; N, 10.36. Found: C, 79.76; H, 9.62; N, 10.38.

A repetition of Rajzman's procedure[20] for the preparation of **10** in three steps from cyclohexanone and ethyl cyanoacetate led to a product, bp 114° (19 mm), whose nmr [(CCl_4) δ 1.62 (s, 6, CH_2), 1.85 (s, 3, CH_3), and 2.37 (m, 4, CH_2)] clearly indicate it to be the α,β isomer, **2-cyclohexylidinepropanenitrile**.

1-Chlorosulfonyl-3,3,4,4-tetramethyl-2-azetidinone (11)[14b] (11.3 g, 0.05 mol) gave 2.3 g (43%) of **2,2,3-trimethyl-3-butenenitrile (12)** as a yellow oil: bp 48.5–49° (14.5 mm) [lit.[21] bp 51.3–51.5° (19 mm)]; ir (neat) 4.46 (C≡N) and 6.04 μ (C=C); nmr (neat) δ 1.42 [s, 6, $C(CH_3)_2$], 1.83 (s, 3, CH_3), 4.92 (broad s, 1, vinyl H), and 5.10 (s, 1, vinyl H).

Anal. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.00; H, 10.44; N, 12.76.

Hydrogenation of **12** (2.6 g, 0.024 mol) in 50 ml of ethanol at 39 psi over 5% Pd–C for 4 hr ultimately afforded 2.0 g (77%) of **2,2,3-trimethylbutanenitrile**: bp 46–47° (15 mm) [lit.[22] bp 152° (760 mm)]; ir (neat) 4.47 μ (C≡N); nmr (neat) δ 1.00 [d, 6, J = 6.5 Hz, $CH(CH_3)_2$], 1.24 [s, 6, $C(CH_3)_2CN$], and 1.65 (m, 1, CH).

1-Chlorosulfonyl-4-*t*-butyl-2-azetidinone (13)[15] (25.8 g, 0.11 mol) also gave 2.49 g (20%) of **12**, identical in every respect with that obtained from **11**.

1-Chlorosulfonyl-4-phenyl-2-azetidinone (14)[15] (12.2 g, 0.05 mol) gave 1.48 g (23%) of *trans*-cinnamonitrile (**15**): bp 94–95° (2 mm); ir (neat) 4.51 (C≡N), 6.15 (C=C), and 10.35 μ (*trans* -CH=CH-); nmr (CCl_4) δ 5.74 (d, 1, J = 17 Hz, =CHCN), 7.20 (d, 1, J = 17 Hz, =CHC_6H_5), and 7.30 (s, 5, C_6H_5).

Anal. Calcd for C_9H_7N: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.97; H, 5.34; N, 10.76.

***cis*-3-Methyl-4-phenyl-2-azetidinone (16)**[14b] (13 g, 0.05 mol) and 8 ml (0.10 mol) of DMF in 25 ml of benzene were refluxed for 3 days. The dark viscous mixture was added to cold water and stirred until the benzene layer separated. The benzene moiety was washed twice with water, decolorized (Norit), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Distillation at 90–92° (1 mm) afforded 1.4 g (20%) of **α-methyl-*cis*-cinnamonitrile (18)**: lit.[23] bp 120° (14 mm); ir (neat) 4.51 (C≡N) and 6.15 μ (C=C); nmr (CCl_4) δ 2.06 (s, 3, CH_3), 6.80 (broad s, 1, =CH), 7.30 (m, 3, *meta*- and *para*-aromatic H), and 7.60 (m, 2, *ortho*-aromatic H). The analytical sample was prepared by preparative vpc.

Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.57; H, 6.43; N, 9.65.

Similarly, 6.5 g (0.02 mol) of ***trans*-3-methyl-4-phenyl-2-azetidinone**[14b] (**17**), 4 ml (0.05 mol) of DMF, and 15 ml of benzene, after refluxing for 2 days, gave 0.86 g (25%) of **18**, bp 88–90° (1 mm). The ir and nmr spectra of **18** obtained from **16** and **17** were superimposable.

***cis*- (19)** and ***trans*-1-Chlorosulfonyl-3,4-diethyl-2-azetidinone (20)**[14b] (2.2 g, 0.01 mol), each dissolved in 20 ml of benzene, were heated at 80° for 4 days with 5 ml of DMF. After extraction of DMF with H_2O, the organic layer was dried ($MgSO_4$) and filtered, and the benzene was removed by distillation *in vacuo*. The residual oil showed no nitrile absorption in the ir.

1-Chlorosulfonyl-3-methylene-4,4-dimethyl-2-azetidinone (21)[14] (21.0 g, 0.10 mol) gave 4.5 g (35%) of **4-chloro-2,3-dimethyl-*trans*-2-butenenitrile (23)**: bp 99.5–101° (13.5 mm); ir (neat) 4.51 (C≡N) and 6.10 μ (C=C); nmr (neat) δ 1.99 [s, 3, =$C(CH_3)CN$], 2.11 [s, 3, =$C(CH_3)CH_2Cl$], and 4.23 (s, 2, CH_2).

Anal. Calcd for C_6H_8NCl: C, 55.60; H, 6.22; N, 10.82; mol wt, 129. Found: C, 55.81; H, 6.31; N, 10.82; mol wt, 131.

Catalytic hydrogenation of **23** (1.02 g, 0.008 mol) in 30 ml of absolute ethanol over 5% Pd–C at 32 psi hydrogen pressure ultimately afforded **2,3-dimethyl-2-butenenitrile (24)**: bp 48–49° (14 mm) [lit.[8] bp 157° (766 mm)]; ir (neat) 4.50 (C≡N), 6.08 μ (C=C); nmr (neat) δ 1.82 (s, 6, *cis*-CH_3 groups) and 2.02 (s, 3, CH_3 cis to CN).

Anal. Calcd for C_6H_9N: C, 75.74; H, 9.54; N, 14.71. Found: C, 75.81; H, 9.73; N, 14.68.

The considerable discrepancy between our boiling point for **24** and the extrapolated literature value[8] led us to repeat the preparation of **24** from **3-methyl-2-butanone**. A solution of 65 g (1.0 mol) of KCN in 125 ml of water was added slowly to a cooled (ice bath) mixture of 102 g (1.0 mol) of acetic anhydride and 43 g (0.5 mol) of **3-methyl-2-butanone**. Stirring was continued for 16 hr at room temperature after which saturated Na_2CO_3 solution was added until the mixture was alkaline to litmus. The whole was extracted with three 100-ml portions of benzene. The combined extracts were washed with 30% aqueous $NaHSO_3$ and dried ($MgSO_4$), and the benzene was removed *in vacuo* (15 mm). The residual oil was distilled at 89–91° (11 mm) to yield 33.9 g (60%) of the **cyanohydrin**.

A solution of 15.6 g (0.14 mol) of this cyanohydrin in 100 ml of dry benzene was refluxed for 12 hr with 10 g of P_2O_5. The liquid was decanted from the solid material and the solvent distilled. Fractionation at 49–50° (14 mm) gave 10.5 g (79%) of a colorless liquid identical with **24**.

1-Chlorosulfonyl-4,4-dimethyl-3-isopropylidine-2-azetidinone[14] (**25**) (7.0 g, 0.03 mol) gave 1.6 g (43%) of **3-cyano-2,4-dimethyl-**

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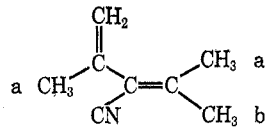

26

1,3-pentadiene (26): bp 71–74° (14.5 mm); ir (neat) 4.52 (C≡N), 6.08 and 6.14 μ (C=C); nmr (neat) δ 1.89 (split s, 6, a protons), 2.07 (s, 3, b protons), 4.87 (broad s, 1, vinyl proton), and 5.17 (m, 1, vinyl proton).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.33; H, 9.61; N, 11.34.

Registry No.—**2**, 4786-24-7; **4**, 5631-82-3; **5**, 26157-47-1; **7**, 26157-48-2; **8**, 26154-39-2; **10**, 26157-49-3; **12**, 4786-26-9; **15**, 1885-38-7; **18**, 26157-51-7; **23**, 26157-52-8; **24**, 4786-37-2; **26**, 26154-42-7; 2,2,3-trimethylbutanenitrile, 26154-43-8.

Phosphoramidate Analogs of Oligonucleotides[1]

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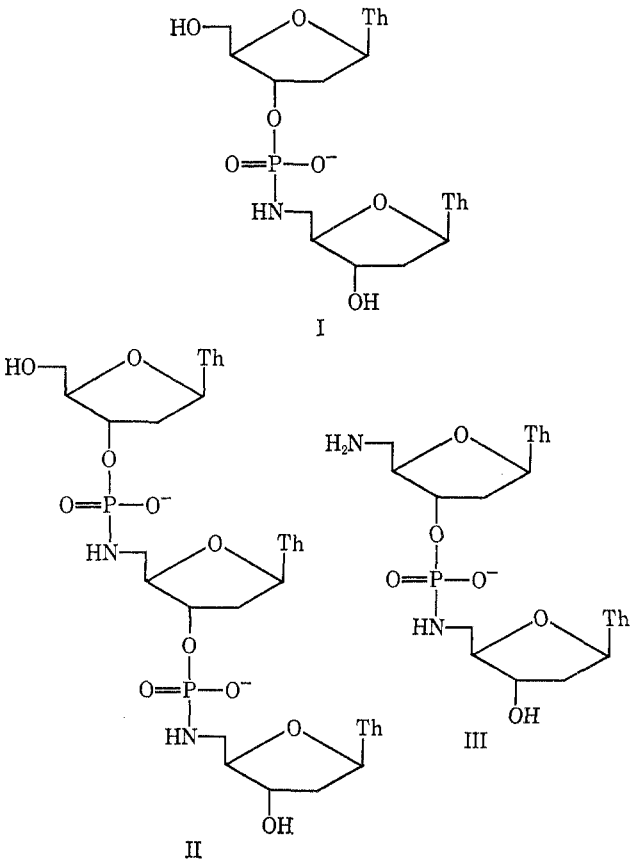
Some dinucleoside phosphate and trinucleoside diphosphate analogs that possess internucleotide phosphoramidate bonds [-OP(O)NH-] are described. These compounds are stable in neutral and alkaline solution, but they hydrolyze in acidic solutions and in solutions containing snake venom phosphodiesterase or spleen phosphodiesterase. A possible role for substances of this type in the synthesis of defined polynucleotides is suggested.

We describe in this paper the synthesis and some chemical properties of the oligonucleotide analogs thymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (Tp_NT, compound I), thymidylyl-(3′–5′)-5′-amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (Tp_NTp_NT, compound II), and 5′-amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine ($_NTp_NT$, compound III). These compounds were prepared as models to explore the accessibility and stability of polymers containing nucleoside units joined by O–P–N bonds. Our interest in this class of compounds was stimulated by the prospect that the stepwise chemical synthesis of such analogs might be more readily achieved than the synthesis of the natural polynucleotides and that the phosphoramidate analogs might serve as templates for enzymatic synthesis of defined polynucleotides from the nucleoside triphosphates and the polymerase enzymes.



I

II

III

The general synthetic approach was patterned after the phosphotriester method for oligonucleotides[3] as modified by Reese and Saffhill.[4] Thymidine was first protected by reaction with isobutyl chloroformate, a reagent that reacts selectively at the 5′ oxygen.[5] Treatment of the resulting ester, 5′-*O*-isobutyloxycarbonylthymidine, with phenyl phosphorodichloridate and pyridine in dioxane, followed by 5′-amino-5′-deoxythymidine[6] and triethylamine in dioxane, afforded the protected derivative, compound IV. This phosphoramidate was isolated in 83% yield by chromatography on silica gel. In agreement with expectations, the condensation of the phosphoryl monochloride with the amino group of 5′-amino-5′-deoxythymidine proceeded rapidly, being complete in less than 30 min. This feature is advantageous since it would facilitate the synthesis of a long chain poly(aminodeoxy nucleotide), both by reducing the time (relative to the time for synthesizing a natural polynucleotide *via* phosphoryl chlorides) and by eliminating the necessity for blocking the oxygen function at the 3′ position of the nucleosides.

One of the major questions concerning the utility of polynucleotide phosphoramidate analogs pertained to the stability of the internucleoside links. Simple phosphoramidates are known to be relatively labile; they hydrolyze readily in aqueous acid[7] and are suffi-

(1) Part XVI in series on Nucleotide Chemistry; for XV, see R. L. Letsinger, K. K. Ogilvie, and P. S. Miller, *J. Amer. Chem. Soc.*, **91**, 3360 (1969). This research was supported in part by a research grant (GM 10265) from the Division of General Medical Sciences of the National Institutes of Health.

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