bath temperature for 0.5 hr. After cooling, the mixture, which contained a precipitate, was neutralized to pH 6 with sodium hydroxide solution, and the precipitate was filtered off and dried. Recrystallization of the precipitate from acetone gave **3,3′-methylenebis(2-methyl-5-nitroindole)** (V) as bright orange-yellow needles (1.74 g., 40%), m.p. > 350°; reported 51%, m.p. 348–354° dec.[4]

The filtrate was made basic pH 10, giving a light yellow precipitate, which was filtered and dried. Recrystallization from methylene chloride–light petroleum (b.p. 60–68°) yielded **2-methyl-5-nitrogramine** as pale yellow needles (3.5 g., 60%), m.p. 173–175°; lit.[4] m.p. 173–175°.

2,3-Dimethyl-5-nitroindole (IV).—The preparation was carried out by nitration in concentrated sulfuric acid at 5° essentially according to the literature procedure,[6,10,11] except that no urea was used and sodium nitrate was substituted for the more expensive potassium nitrate. The yield was 66%, m.p. 189–190°; reported 60–65%,[9] m.p. 188–189°,[10] 190°[11]; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol[13]: 214 (4.29), 277 (4.30), 337 (3.95); ν_{NH} 3250 s, ν_{NO_2} 1518 mw or 1498 mw, 1312 vs cm.$^{-1}$ in Nujol.

5-Amino-2,3-dimethylindole (III). **A. From 2,3-Dimethyl-5-nitroindole.**—The reduction has been carried out previously with alkaline sodium hydrosulfite[6] in 52[7]–55[9]% yield and by Raney nickel-catalyzed hydrogen transfer from hydrazine in 91% yield.[8]

2,3-Dimethyl-5-nitroindole (1.15 g., 0.00605 mole) was dissolved in absolute ethanol (100 cc.) and hydrogenated over Raney nickel (1 g.) at 2 atm. and room temperature for 1 hr. The catalyst was filtered off and the ethanol evaporated under reduced pressure, leaving a pale yellow solid. Crystallization, with charcoal, from methylene chloride–light petroleum (b.p. 60–68°) yielded white flakes (0.78 g., 80%), m.p. 178.5–183°; lit.[6,8,9] m.p. 177–178°; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 234 (4.41), 285 (3.84), 304 diffuse infl. (3.69); ν_{NH} 3340 s, 3190 w cm.$^{-1}$ in Nujol.

B. **From 2-Methyl-5-nitrogramine.**—2-Methyl-5-nitrogramine (0.57 g., 0.00245 mole) was dissolved in absolute ethanol (100 cc.) and hydrogenated over Raney nickel (1 g.) at 2 atm. and 60° for 5.5 hr. Treatment as in part A gave a gray solid, which was sublimed at 160° (1 mm.), yielding white flakes (0.24 g., 61%), m.p. 178.5–183°. The mixture melting point with the sample described in part A was undepressed, and the infrared spectra of the two samples in Nujol were identical.

3,3′-Methylenebis(2-methyl-5-nitroindole) (V) **from 2-Methyl-5-nitrogramine and 2-Methyl-5-nitroindole.**—A solution of 2-methyl-5-nitrogramine (0.24 g., 0.00103 mole) and 2-methyl-5-nitroindole[4] (0.18 g., 0.00102 mole) in acetic acid (40 ml.) was stirred at room temperature for 1.5 hr. and then refluxed for 2 hr. The resulting mixture was cooled and the precipitate filtered and crystallized from acetone, yielding bright orange-yellow needles (0.25 g., 67%), m.p. > 350°; lit.[4] m.p. 348–354° dec. The mixture melting point with an authentic sample[4] did not depress below 350°, and the infrared spectra of the two samples in Nujol were identical.

2-Methyl-5-nitroindole-3-acetonitrile (VI).—A solution of 2-methyl-5-nitrogramine (0.50 g., 0.00214 mole) and sodium cyanide (0.50 g., 0.0102 mole) in aqueous 60% ethanol (80 ml.) was refluxed for 7.5 hr. The solid which had formed was filtered, dried, and crystallized from acetone, giving **3,3′-methylenebis(2-methyl-5-nitroindole)** (V) as bright orange-yellow needles (0.03 g., 8%), m.p. >350°. The mixture melting point with an authentic sample[4] did not depress below 350°, and the infrared spectra of the two samples in Nujol were identical.

The filtrate was diluted with water and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated. The residual yellow solid was crystallized with charcoal from methylene chloride–light petroleum (b.p. 60–68°), yielding, after concentration, **2-methyl-5-nitroindole-3-acetonitrile** as light yellow needles (0.15 g., 33%), m.p. 185–186°; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 205 (4.36), 266 (4.33), 326 (3.92); ν_{NH} 3280 m; $\nu_{C\equiv N}$ 2240 mw; ν_{NO_2} 1517 ms, 1335 s cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_9N_3O_2$ (215.21): C, 61.39; H, 4.22; N, 19.53. Found: C, 61.24; H, 4.26; N, 19.83.

2-Methyl-5-nitroindole-3-acetic Acid (VII).—A solution of 2-methyl-5-nitroindole-3-acetonitrile (0.40 g., 0.00186 mole) in concentrated hydrochloric acid (37.9%, 200 cc.) and ethanol (100 cc.) was refluxed for 60 hr. The resulting black solution was cooled and extracted with ether. The ether extract was then extracted with sodium bicarbonate solution until carbon dioxide was no longer evolved. The ether was dried over anhydrous magnesium sulfate and evaporated; there was no residue.

The sodium bicarbonate extract was acidified to pH 2 with hydrochloric acid, and the resulting mixture of precipitate and solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated. The residual yellow solid was crystallized with charcoal from hot water, yielding bright yellow needles (0.31 g., 71%), m.p. 240–241° dec., with gas evolution; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 211 (4.33), 273 (4.31), 333 (3.96); ν_{NH} 3250 m; ν_{OH} 2700 w; $\nu_{C=O}$ 1704 s; ν_{NO_2} 1506 m, 1333 s cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$ (234.21): C, 55.41; H, 4.30; N, 11.96. Found: C, 56.64; H, 4.49; N, 11.95.

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[13] Reported: 276 (4.25), 338 (3.90); A. Frasca, *Anales Asoc. Quim. Arg.*, **50**, No. 2, 1 (1962).

The Selective Hydrolysis of Steroidal Acetates on Alumina

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The importance of the selective reaction of a functional group in the presence of a similar moiety has been well demonstrated in steroid chemistry.[1] Among such reactions one that is not readily achieved is the selective hydrolysis of the ester of a primary alcohol in preference to the same ester of an unhindered secondary alcohol.[2] We wish to report a facile procedure that specifically effects this hydrolysis, offering a potentially superior alternative to selective esterification[3] and providing in good yield a group of compounds otherwise difficult to synthesize. This hydrolysis occurs readily on untreated alumina by the use of a modified chromatographic technique, incidentally affording ready separation of the pure monoester. Ester hydrolysis, a normal occurrence on alumina,[4] is demonstrated to proceed at a rate that allows clear distinction between the hydrolysis of primary and secondary acetates, thus affording a synthetically useful tool.

The chromatographic purification of pseudodiosgenin diacetate (**1a**) on alumina afforded the first example of selective acetate hydrolysis. A compound isolated in small amounts after elution of the pure diacetate was tentatively identified as the C-26 monohydroxy compound (**1b**) by inspection of the n.m.r. spectrum. Only a single acetate band (three protons) was seen; the C-3 α-proton signal at 275 c.p.s. ($\Delta\nu$ from tetramethylsilane at 60 Mc.) was unchanged; and, also, the doublet for the C-26 protons, found at 233 and 238 c.p.s. in the starting material, had been shifted to 205 and 210 c.p.s. Chemical evidence to support this structural assignment was obtained by acetylation of the new compound to the starting diacetate and also

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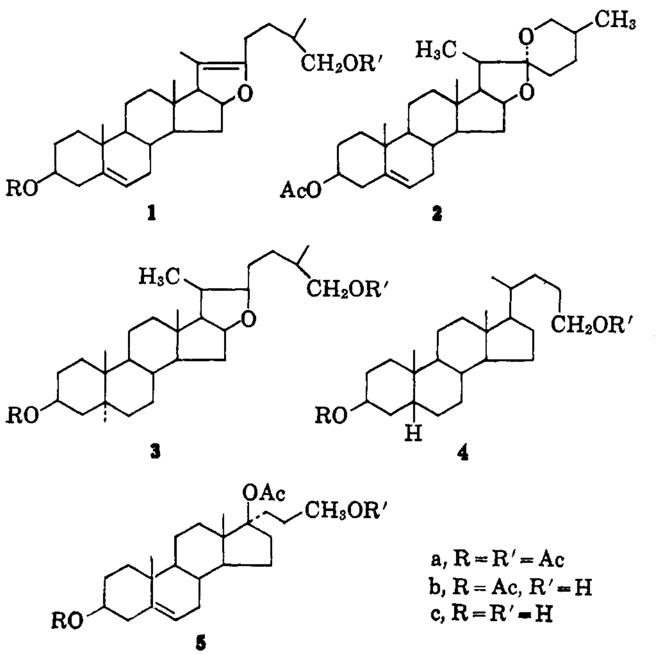
[1] For an excellent review see H. J. E. Loewenthal, *Tetrahedron*, **6**, 269 (1959).

[2] F. C. Uhle, *J. Am. Chem. Soc.*, **83**, 1460 (1961).

[3] R. T. Blickenstaffe and J. C. Chang, *ibid.*, **80**, 2726 (1958); I. Scheer, M. J. Thompson, and E. Mosettig, *ibid.*, **78**, 4733 (1956).

[4] The rapid hydrolysis of formates on alumina has been described: J. C. Chang and R. T. Blickenstaffe, *ibid.*, **80**, 2906 (1958), and R. H. Levin, *et al.*, *ibid*, **70**, 511 (1948). Only scattered examples of other ester hydrolyses exist; *e.g.*, E. Lederer and M. Lederer, "Chromatography," Elsevier Publishing Co., New York, N. Y., 1959, p. 61, and T. Reichstein and C. W. Shoppee, *Discussions Faraday Soc.*, **7**, 305 (1949).



1 2 3 4 5

a, R = R' = Ac
b, R = Ac, R' = H
c, R = R' = H

by mild acid-catalyzed cyclization to the known cyclopseudodiosgenin acetate 2.[5]

When the chromatogram of the diacetate **1a** was repeated and the column allowed to stand overnight before eluting the products, the yield of the monoacetate **1b** rose to 55%; the remainder of the product consisted mainly of starting material.

Several other polyacetates were subjected to this procedure in an effort to extend the generality of the reaction and to eliminate the possibility of intramolecular participation. Both dihydrotigogenin diacetate (**3a**) and cholanediol diacetate (**4a**) provided the respective C-3 monoacetates **3b** and **4b** on treatment with alumina. The structure in each case was determined by the n.m.r. spectrum.

A final hydrolysis was that of the triacetate **5a**. This triacetate, prepared by the reaction of the corresponding triol[6] with *i*-propenyl acetate, was allowed to stand on alumina for a three-day period. A simple elution sequence provided 85% of the monohydroxy compound **5b** as well as approximately 10% of the diol **5c**. The appearance of the latter material demonstrates the relatively slow but appreciable rate of hydrolysis of the secondary acetate under these conditions. Both the monoacetate **5b** and the diacetate **5c** were readily converted to the starting triacetate with acetic anhydride–pyridine.

This hydrolysis clearly is a result of the water obtained from the alumina, for similar results were obtained when the only other potential sources of water, the solvent and compound, were dried azeotropically. The yields of monoester obtained were sufficiently high that no studies were made to assess the relation of the activity (degree of hydration) of the alumina to the rate and yield of the hydrolysis. Attempts to hasten the reaction by stirring the diacetate **1b** in ether or benzene with alumina produced no better results.

A final point of interest arose from the inspection of the infrared spectra of the compounds prepared here. In each case, virtually no difference was found between the solution spectra of the mono- and diacetate, except in the hydroxyl region (2.7–2.9 μ). (The n.m.r. spectra and elemental analyses clearly distinguished each member of the pair.)

Experimental[7]

5α-Furosta-5,20(22)-diene-3β,26-diol 3-Monoacetate (1b).—A solution of 10 g. of 5α-furosta-5,20(22)-diene-3β,26-diol diacetate in 0.5 l. of benzene was poured on a column of 300 g. of Alcoa F-20 alumina.[8] The alumina was washed with 2 l. of benzene and allowed to stand overnight (still covered with benzene). After 20 hr. 2 l. of ether were passed over the adsorbent and this solution was combined with the initial benzene forerun. After evaporation of the solvent there remained 2.8 g. of crystalline residue (30%), shown by spectral examination to be essentially pure starting material **1a**. The column was then washed with 2 l. of ethyl acetate. Evaporation of the solvent afforded 5.2 g. of crystalline product (55%), m.p. 128–138°. Recrystallization of 1.0 g. of this material from acetone–petroleum ether (b.p. 60–68°) afforded 0.85 g. of the pure monoacetate **1b**, m.p. 136–138°; $[\alpha]_D$ −47°; λ_{max} 2.75, 5.79 μ; Δν 121 (C-3-OAc), 205 and 210 (C-26-H), 280 c.p.s. (C-3α-H).

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: 76.38; H, 9.61.

The only points of difference in the infrared spectra between the mono- and diacetate other than the hydroxyl absorption (2.7–2.9 μ) might easily be overlooked; minute reversals in the intensity of maxima at 6.81, 7.37, 11.18, and 11.95 μ distinguish the two.

When, instead of passing the solution of the diacetate over a column of alumina, the solution was stirred with a slurry of the alumina in ether or benzene, no appreciable change was seen in the rate of reaction.

Acetylation of the Monoacetate 1b.—Conversion of the monoacetate **1b** was readily effected by treatment with acetic anhydride in pyridine at room temperature overnight. The product was isolated by benzene extraction and was crystallized from aqueous methanol, affording the starting diacetate, **1a**, m.p. 97–99°, identical in the infrared with an authentic sample.

Cyclization of the Monoacetate 1b.—To a solution of 0.10 g. of monoacetate **1b** in 5 ml. of methanol was added 0.2 ml. of 10% aqueous hydrochloric acid. A precipitate formed immediately and was separated by filtration. The product was washed with water and dried, yielding 0.10 g. of cyclopseudodiosgenin acetate **2**, m.p. 188–191°. Both chloroform and potassium bromide infrared spectra were identical to an authentic sample.[9]

In some cases, the chloroform used for the infrared spectra contained sufficient acid to effect the cyclization of **1b**.

5α,22α-Furostane-3β,26-diol 3-Monoacetate (3b).—A solution of 0.80 g. of the diacetate **3a** was allowed to stand in benzene on 90 g. of Merck chromatographic alumina for 3 days. Washing the column with benzene afforded less than 0.10 g. of starting material. Elution with 5% ethyl acetate in benzene yielded 0.48 g. of the amorphous monoacetate **3b**; λ_{max} 2.75, 5.79 μ; Δν 199 (C-3-OAc), 205 and 210 (C-26-H), 2.75 c.p.s. (C-3α-H).

Anal. Calcd. for $C_{30}H_{50}O_5$: C, 75.60; H, 10.50. Found: C, 75.89; H, 10.39. The infrared spectra of the mono- and diacetates were identical except for the hydroxyl region (2.7–2.9 μ) and a small reversal in maxima at 7.23 μ.

Cholane-3β,24-diol 3-Monoacetate (4b).—A solution of 1.1 g. of the diacetate **4a** in 100 ml. of benzene was allowed to stand on a column of 180 g. of Merck chromatographic alumina. After 16 hr. the column was eluted with benzene, affording 0.23 g. of starting material (identification by infrared comparison). Elu-

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[5] J. B. Ziegler, W. E. Rosen, and A. C. Shabica, *J. Am. Chem. Soc.*, **77**, 1223 (1955); see also L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 825, for a discussion of the change in nomenclature of this compound.

[6] N. W. Atwater, R. H. Bible, Jr., E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *J. Org. Chem.*, **26**, 3077 (1961).

[7] We wish to thank Dr. R. T. Dillon and his staff for the analyses and spectra recorded here. The infrared spectra were run in chloroform. The n.m.r. spectra were determined in deuteriochloroform with tetramethylsilane as an internal standard using a Model A-60 spectrometer, Varian Associates, Inc., operating at 60 Mc. Rotations were taken in chloroform (1% solution). The melting points are uncorrected.

[8] Alumina columns employed were packed in petroleum ether (b.p. 60–68°) in a tube of such dimensions that the height to width ratio of adsorbent was between 4:1 and 6:1. Both sources of alumina (Merck, Alcoa) used exhibited the same pH (9.9) when slurried in water. No special care was taken to use freshly opened samples of alumina.

[9] We wish to thank Mr. R. Dexheimer for the preparation of this sample according to the method described in ref. 5.

tion with ethyl acetate afforded 0.75 g. of material that crystallized slowly from ether-petroleum ether (b.p. 28–38°) to yield 0.26 g. of the monoacetate **4b**, m.p. 92–94°; $[\alpha]_D$ +45°; λ_{max} 2.74, 5.79 μ.

Anal. Calcd. for $C_{26}H_{44}O_3$: C, 77.17; H, 10.96. Found: C, 77.35; H, 10.92.

A second crop of material, 0.15 g., m.p. 90–94°, also was obtained. The sole differences in the infrared of this compound as compared to starting material were maxima at 2.7–2.9 μ and minor intensity changes at 7.22, 10.71, and 11.29 μ.

3-(3β,17β-Diacetoxy-5-androsten-17α-yl)propyl Acetate (5a).—A slurry of 78 g. of 3-(3β,17β-dihydroxy-5-androsten-17α-yl)-propanol[6] in 0.8 l. of *i*-propenyl acetate and 1.9 g. of *p*-toluenesulfonic acid was heated at the boiling point with slow distillation of the solvent. The compound dissolved within 15 min. After 3 hr. the solution was cooled and filtered to remove insoluble inorganic material (a contaminant of the very insoluble starting material). The filtrate was washed twice with aqueous potassium bicarbonate and then with water, and the solution was concentrated to dryness. The resulting oil was crystallized from methanol yielding 54.5 g., m.p. 114–116°, of the triacetate **5a**. A second crop of 27 g., m.p. 112–114°, was obtained from aqueous methanol. Recrystallization of 1.5 g. of the first crop afforded 1.3 g. of the pure triacetate, m.p. 115–116°; $[\alpha]_D$ −76°; λ_{max} 5.78 μ; $\Delta\nu$ 220 (OAc), 222 (OAc), 223 (OAc), 243 c.p.s. (C-22-H).

Anal. Calcd. for $C_{28}H_{42}O_6$: C, 70.85; H, 8.92. Found: C, 71.10; H, 9.06.

3-(3β,17β-Diacetoxy-5-androsten-17-α-yl)propanol (5b) and 3-(3β-Hydroxy-17β-acetoxy-5-androsten-17α-yl)propanol (5c).—A solution of 80 g. of the triacetate **5a** in 1 l. of benzene was dried by the distillation of 100 ml. of solvent and was adsorbed on 2.5 kg. of Alcoa F-20 alumina. After 65 hr. the column was washed with 4 l. of benzene affording 2.0 g. of starting material (identification by infrared comparison). Ethyl acetate (10 l.) was passed through the column. On evaporation of the solvent 74 g. of crystalline residue remained. This was recrystallized from aqueous ethanol to afford 51 g. of the monohydroxy compound **5b**, m.p. 101–102°, and 11.5 g., m.p. 99–102°. Recrystallization of 1.1 g. of the first crop from petroleum ether (b.p. 60–68°) yielded 0.77 g. of pure material, m.p. 104–105°; $[\alpha]_D$ −85°; λ_{max} 2.74, 5.79 μ; $\Delta\nu$ 120 (OAc), 122 (OAc), 213, 218, and 223 c.p.s. (C-22-H).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.31; H, 9.26.

The only bands in the infrared distinguishing the monohydroxy compound from starting material were those at 2.7–2.9 μ and minor intensity changes at 6.91 and 9.12 μ.

Further elution of the column with 4 l. of methanol afforded 7.5 g. of material which was recrystallized from methanol–ethyl acetate to yield 2.7 g. of the dihydroxy compound **5c**, m.p. 200–204°. A further recrystallization from aqueous methanol yielded 1.35 g. of analytically pure material, m.p. 202–205°; $[\alpha]^{EtOH}_D$ −83°; λ^{KBr}_{max} 3.00, 5.78 μ.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.73; H, 9.74. Low chloroform solubility prevented obtention of an infrared spectrum of its solution.

Both the mono- and diacetates **5b** and **5c** were readily converted in good yields to the starting triacetate **5a** by treatment in acetic anhydride–pyridine at 100° for 20 min. The identification in each case was made by comparison of the infrared and n.m.r. spectra.

Isocyanides. III.[1,2] Electron Impact Study of Aliphatic Isocyanides

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Our interest in isocyanides has led us to study the isocyanide bond refraction[1] and solvent effects on the isocyanide stretching fundamental in the infrared.[2]

TABLE I

MASS SPECTRA OF ALIPHATIC ISOCYANIDES AND CYANIDES[a]

m/e	MeNC	MeCN	EtNC	EtCN	PrNC	PrCN	BuNC	BuCN
15	**8**	**1**	5	6	4	2	2	3
26	2	2	20	16	6	5	6	5
27	4	1	52	14	38	26	39	34
28	8	4	93	100	15	7	37	19
29			**100**	**3**	51	57	33	16
30			2		5	1	3	
37				1	4	3	1	2
38	13	10	5	2	5	3	3	3
39	20	19	8	2	17	8	19	15
40	49	55	29	4	10	4	7	4
41	*100*	*100*	2		100	100	100	100
42	3	3			44	3	9	5
43					**10**	**1**	56	97
44			2	1	1		3	4
50			2	2			1	1
51			9	9	2	2	2	2
52			15	11	3	3	2	3
53			3	7			2	2
54			33	61	25	2	9	54
55			*78*	*10*	2	1	43	21
56			4	1			25	3
57							**47**	
58							2	
68					11		2	1
69					*5*	<*1*		2
70						1		
82							2	4
83							<*1*	<*1*
84								1

[a] Peaks less than 1% of base peak omitted; molecular ions, italic; $M - 26$ ions, boldface.

The results of both studies could be interpreted consistently in terms of greater polarizability of the lone pair of electrons on the terminal carbon atom of the isocyanide group as compared with the nitrogen lone pair of the cyanide group. We now report a continuation of this work in comparing the behavior of aliphatic isocyanides in a mass spectrometer with the corresponding cyanides.

The fragmentation patterns for methyl, ethyl, *n*-propyl, and *n*-butyl isocyanides and cyanides are shown in Table I. The agreement between our results for cyanides and those recently reported by McLafferty[3] is satisfactory. The base peak of propyl and butyl isocyanides is at *m/e* 41 as for the corresponding cyanides. This indicates that β-bond cleavage is the principal mode of fragmentation in the isocyanides. McLafferty has already shown this to be the case in cyanides, and postulated a six-membered cyclic transition state. The identical geometry of the two species makes this transition state equally probable for the isocyanides. Ethyl isocyanide shows stronger peaks than ethyl cyanide at *m/e* 39, 40, and 41 (which are not base peaks), again demonstrating the importance of β-cleavage.

However, α-bond cleavage, which is of minor importance in cyanides, is very noticeable in isocyanides. This is seen by comparing the intensities of the $M - 26$ peaks (*m/e* 15, 29, 43, and 57, respectively). This indicates that the R–N bond of the isocyanide molecular ion is considerably weaker than the R–C bond of cyanide. It appears that the isocyanide molecular ion retains the destabilizing effect of the resonance of the molecule, which tends to place a negative charge on the

$$R-\overset{+}{N}=\overset{-}{C} \longleftrightarrow \overset{-}{R}=\overset{+}{N}=C$$

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[1] Part I, R. G. Gillis, *J. Org. Chem.*, **27**, 4103 (1962).

[2] Part II, R. G. Gillis, and J. L. Occolowitz, *Spectrochim. Acta*, **19**, 873 (1963).

[3] F. W. McLafferty, *Anal. Chem.*, **34**, 26 (1962).