Table I. Deamination of Arenimines to Arenes with Dichlorocarbene

arenimine	arene	mp, °C	yield, %
1a (X_{1-4} = F)	3a	108-110	85
1b (X_{1-4} = Cl)	3b	199-200	84
1c ($X_{1,3}$ = F; $X_{2,4}$ = Cl	3c	104-106	90
1d ($X_{1,2,4}$ = Cl; X_3 = H)	3d	91-92	85
5	6	209-210	73

under N_2 at −50 °C was added dropwise over 30 min *n*-butyllithium (2.25 M in hexane; 59 mL, 0.13 mol). The light yellow solution was allowed to warm to −35 °C and was then stirred at −35 to −25 °C for 1 h. Then freshly distilled *N*-methylpyrrole (22 g, 0.27 mol) was added in one portion, and the mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was cooled to 0–5 °C and extracted with cold 4 N HCl. The acidic extract was cooled, basified with NaOH (pellets), and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (K_2CO_3), and evaporated in vacuo to give crude **1b** as a white solid. Crystallization from MeOH–Et_2O gave 11 g (29%) of **1b** as colorless flakes in two crops, mp 155–156 °C. A second crystallization gave the analytical sample: mp 156–157 °C; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 4.8 (m, 2 H), 7.0 (m, 2 H); IR ($CHCl_3$) 2955 (s), 1350 (s), 1300 (s), 1270 (m), 1160 (m), 1115 (s), 915 (m), 850 (m), 690 cm^{-1} (s); mass spectrum, *m/e* (relative intensity) 295 (22), 269 (73), 254 (12), 217 (10), 194 (11), 181 (6), 160 (3), 147 (3), 120 (6), 98 (8), 42 (100).

Anal. Calcd for $C_{11}H_7NCl_4$: C, 44.78; H, 2.40; N 4.75; Cl, 48.07. Found: C, 44.69; H, 2.38; N, 4.81; Cl, 48.35.

9-Methyl-5,7-dichloro-6,8-difluoro-1,4-dihydronaphthalen-1,4-imine (1c). To a magnetically stirred solution of 1,3,5-trichloro-2,4,6-trifluorobenzene (16.8 g, 0.071 mol) in dry Et_2O (250 mL) under N_2 at −78 °C was added dropwise *n*-butyllithium (1.6 M in hexane; 45 mL, 0.072 mol). The solution was stirred for 1 h at −78 °C, treated at −78 °C over 30 min with freshly distilled *N*-methylpyrrole (15 g, 0.19 mol), and then stirred at −78 °C for 1 h. The mixture was then allowed to warm slowly to room temperature overnight. The usual workup gave 10.9 g (59%) of crude product which was distilled to afford **1c** as a colorless, low-melting solid: mp 41–42 °C; bp 95–96 °C (0.35 torr). Redistillation gave the analytical sample: bp 109 °C (0.25 torr); ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 4.8 (m, 2 H), 6.9 (s, 2 H); IR ($CHCl_3$) 2955 (s), 1460 (s), 1435 (s), 1410 (s), 1295 (m), 1150 (m), 1110 (m), 1060 (s), 870 (m), 840 (m), 810 cm^{-1} (s); mass spectrum, *m/e* (relative intensity) 261 (6), 235 (19), 219 (5), 185 (4), 162 (7), 149 (5), 123 (4), 99 (4), 80 (8), 42 (100).

Anal. Calcd for $C_{11}H_7NF_2Cl_2$: C, 50.41; H, 2.69; N, 5.35; Cl, 27.06. Found: C, 50.41; H, 2.73; N, 5.30; Cl, 26.92.

9-Methyl-5,6,8-trichloro-1,4-dihydronaphthalen-1,4-imine (1d). To a magnetically stirred slurry of 1,2,4,5-tetrachlorobenzene (21.6 g, 0.10 mol) in dry Et_2O (600 mL) under N_2 at −50 °C was added dropwise over 40 min *n*-butyllithium (2.28 M in hexane; 44 mL, 0.10 mol). The solution was stirred for an additional 35 min at −50 °C and then treated dropwise over 10 min with freshly distilled *N*-methylpyrrole (7.8 g, 0.096 mol). The solution was stirred at −50 to −35 °C for 5.5 h and then allowed to warm to room temperature overnight. The mixture was cooled to 0 °C and then treated slowly with cold 4 N H_2SO_4 (150 mL). The Et_2O layer was separated and discarded. The acid layer was extracted with several portions of Et_2O (discarded), cooled to 0 °C, and basified with cold 4 N NaOH. Extraction with Et_2O followed by drying (K_2CO_3) and concentration in vacuo afforded 11.6 g (46%) of crude **1d** as a brown oil which crystallized in a freezer. Sublimation at 0.5 torr gave 6.85 g (27%) of pure **1d**: mp 58–59.5 °C; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 4.8 (m, 2 H), 7.0 (m, 2 H), 7.1 (s, 1 H); IR ($CHCl_3$) 2960 (s), 1420 (s), 1315 (m), 1300 (m), 1275 (m), 1155 (m), 1110 (s), 860 (m), 850 (m), 710 cm^{-1} (m); mass spectrum, *m/e* (relative intensity) 259 (3), 233 (13), 217 (2), 183 (4), 160 (5), 147 (4), 123 (3), 109 (3), 98 (7), 80 (9), 42 (100).

Anal. Calcd for $C_{11}H_8NCl_3$: C, 50.71; H, 3.09; N, 5.38; Cl, 40.82. Found: C, 50.76; H, 3.14; N, 5.45; Cl, 40.85.

11-Methyl-1,2,3,4-tetrachloro-9,10-dihydroanthracen-9,10-imine (5). This was prepared from hexachlorobenzene and 2-methylisoindole[12] by using the procedure described for **1b** to give **5** as colorless crystals: mp 163 °C, after crystallization from acetone; ^1H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 5.2 (s, 2 H), 7.1 (m, 2 H), 7.4 (m, 2 H); IR (KBr) 2830 (m), 1355 (s), 1290 (m), 1260 (m), 1220 (m), 1090 (s), 795 (m), 730 cm^{-1} (s); mass spectrum, *m/e* (relative intensity) 345 (29), 330 (10), 316 (14), 310 (15), 308 (15), 282 (13), 280 (15), 246 (10), 174 (8), 91 (17), 42 (100).

Anal. Calcd for $C_{15}H_9NCl_4$: C, 52.21; H, 2.63; N, 4.06. Found; C, 53.05; H, 3.26; N, 4.11.

General Deamination Procedure. To a magnetically stirred solution of arenimine (2 mmol) in $CHCl_3$ (25 mL) at room temperature under N_2 was added 50% aqueous NaOH (3 mL) and benzyltriethylammonium chloride (0.2 mmol). The resulting mildly exothermic reaction was stirred at ambient temperature overnight and then was partitioned between 3 N HCl (35 mL) and $CHCl_3$ (50 mL). The organic layer was water washed, dried (Na_2SO_4), and concentrated in vacuo to afford the crude product which was purified as described below. Where possible the products were compared (TLC, IR, NMR) with those compounds prepared in our earlier study[1] or with commercial samples.

1,2,3,4-Tetrafluoronaphthalene (3a). The crude product was recrystallized from hexane to give **3a**: 85% yield; mp 108–110 °C (lit.[13] mp 110–111 °C).

1,2,3,4-Tetrachloronaphthalene (3b). The crude product was recrystallized from $CHCl_3$ to give **3b**: 84% yield; mp 199–200 °C (lit.[14] mp 198 °C).

1,3-Dichloro-2,4-difluoronaphthalene (3c). The crude product was sublimed at 80 °C (0.5 torr) to give **3c**: 90% yield; mp 103–104 °C (lit.[15] mp 103–104 °C).

1,2,4-Trichloronaphthalene (3d). The crude product was sublimed at 80 °C (0.5 torr) to give **3d**: 85% yield; mp 91–92 °C (lit.[16] mp 92 °C).

1,2,3,4-Tetrachloroanthracene (6). The crude product was recrystallized from MeOH–$CHCl_3$ (1:1) to give **6**: 73% yield; mp 209–210 °C (lit.[17] mp 217–219 °C).

Acknowledgment. This investigation was supported by Grant No. CA-14968 and CA-24422, awarded by the National Cancer Institute, DHEW. We also thank Merck Sharp and Dohme Research Laboratories and The Lilly Research Laboratories for their support of our research program and Dr. N. Ishikawa (Tokyo Institute of Technology) for a generous sample of 1,3,5-trichloro-2,4,6-trifluorobenzene.

Registry No. **1a**, 5875-75-2; **1b**, 26477-20-3; **1c**, 76137-28-5; **1d**, 76137-29-6; **3a**, 711-55-7; **3b**, 20020-02-4; **3c**, 27508-76-5; **3d**, 50402-51-2; **5**, 76137-30-9; **6**, 25283-02-7; chloropentafluorobenzene, 344-07-0; *N*-methylpyrrole, 96-54-8; hexachlorobenzene, 118-74-1; 1,3,5-trichloro-2,4,6-trifluorobenzene, 319-88-0; 1,2,4,5-tetrachlorobenzene, 95-94-3; 2-methylisoindole, 33804-84-1; dichlorocarbene, 1605-72-7.

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Nucleophilic Aromatic Substitution Reaction of Some 3-Nitroimidazo[1,2-*a*]pyridines with Thioglycolate Anion in DMF

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Received August 5, 1980

Imidazo[1,2-*a*]pyridines **1** undergo nucleophilic[1] and electrophilic[2] aromatic substitution reactions. Only a few

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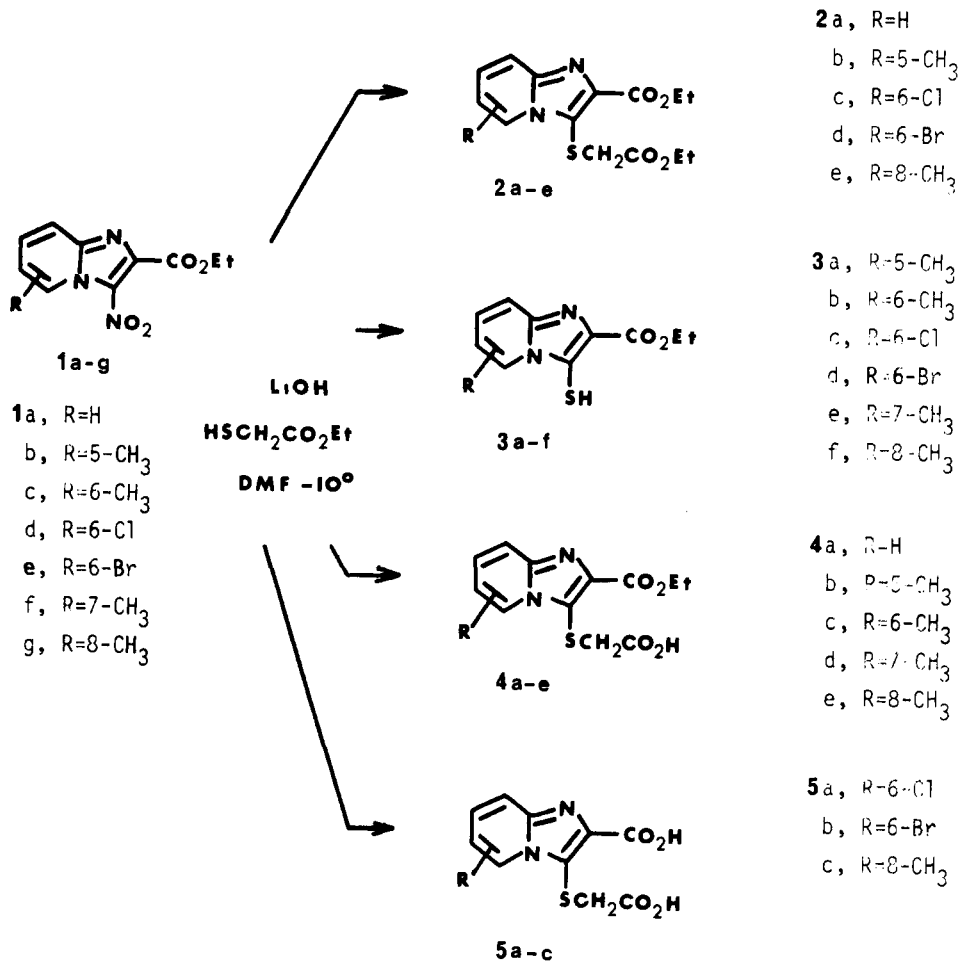
Scheme I

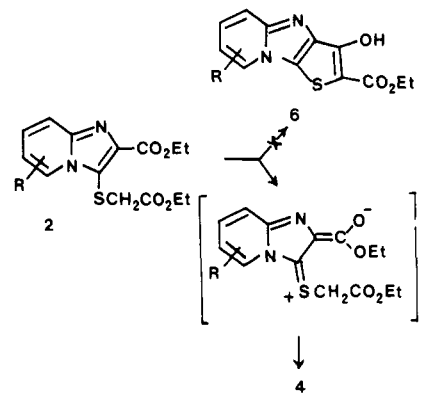


examples of nucleophilic substitution reactions can be found. However, when electron-withdrawing groups are present at the 2-position, 3-nitroimidazo[1,2-*a*]pyridines **1a–g** exhibit the desired reactivity toward the nucleophile ^-SR with displacement of nitro groups. This paper mainly describes the preparation of some thioimidazo[1,2-*a*]-pyridines by reaction of various 3-nitro compounds with ethyl thioglycolate anion.

Results and Discussion

Compounds **1a–g**, in rigorously dried DMF solution, were allowed to react with an equivalent amount of ethyl thioglycolate and excess lithium hydroxide at ice-bath temperature. The results are summarized in Scheme I. As expected, the ^1H NMR signals of the products **2a–e** (Table I) show a marked upfield shift of the ring proton signals, particularly H-5, from those of the starting materials **1a,b,d,e,g**, consistent with removal of the NO_2 group from C-3.[3] Attempts to obtain the expected tricyclic ester by a base-catalyzed cyclization were unsuccessful;[4] the major side reactions are hydrolyses of the diesters to give the mono- and dicarboxylic acids **4a–e** and **5a–c**, respectively.

Scheme II



Preferential hydrolysis of the glycolate ester function rather than of the formate ester is demonstrated by the alternate formation of **4a** from **1a** and methyl thioglycolate.[5]

In order to prepare the tricyclic ester **6**, for its potential immunostimulant activity, we repeated the reaction in a similar way with **2a,b** and LiOH in DMF. Under these

(1) (a) Paolini, J. P.; Robins, R. K. *J. Heterocycl. Chem.* **1965**, *2*, 53. (b) Paudler, W. W.; Pokorny, D. J.; Good, J. J. *Ibid.* **1971**, *8*, 37. (c) Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1976**, *41*, 3549. (d) *Ibid.* **1978**, *43*, 658. (e) *Ibid.* **1978**, *43*, 2900.

(2) (a) Matveev, V. K. *Izv. Akad. Nauk SSSR, Otd. Mat. Estestv. Nauk* **1936**, 1005. (b) Goldfarb, Y. L.; Kondakova, M. S. *J. Gen. Chem. USSR (Engl. Transl)* **1940**, *10*, 1055. (c) Kondakova, M. S.; Goldfarb, Y. L. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1946**, 523. (d) Paolini, J. P.; Robins, R. K. *J. Org. Chem.* **1965**, *30*, 4085. (e) Almirante, L.; Mugnaini, A.; De Toma, N.; Murmann, W. *Boll. Chim. Farm.* **1971**, *110*, 322. (f) Jacquier, R.; Lopez, H.; Maury, G. *J. Heterocycl. Chem.* **1973**, *5*, 755. (g) Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1975**, *40*, 2916. (h) Blewitt, H. L. In "Special Topics in Heterocyclic Chemistry"; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, 1977; Chapter II. (i) Teulade, J. C.; Grassy, G.; Girard, J. P.; Buochberg, S.; Chapat, J. P. *Eur. J. Med. Chem.—Chim. Ther.* **1978**, *13*, 271.

(3) Teulade, J. C.; Escale, R.; Grassy, G.; Girard, J. P.; Chapat, J. P. *Bull. Soc. Chim. Fr.* **1979**, 529.

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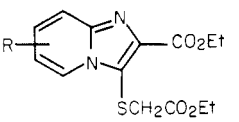
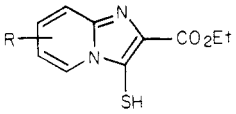
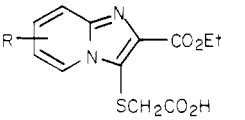
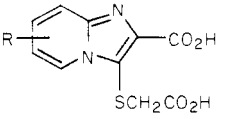
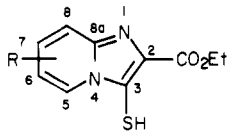
(5) The structure of **4** is demonstrated by the identity of the product **4a**, from **1a** with $NaSCH_2CO_2Me$ (^1H NMR), as the sole product.

Table I

compd	R	mp, °C	rel % yield	formula[a]	chemical shift,[b] δ
		Ethyl 2-Carbethoxyimidazo[1,2-*a*]pyridine-3-thioacetates (**2**): 			
2a	H	71-73	60	$C_{14}H_{16}N_2O_4S$	1.00 (3, CH_3), 1.46 (3, CH_3), 3.71 (2, SCH_2), 3.96 (2, OCH_2), 4.51 (2, OCH_2), 6.96 (1, H-6), 7.31 (1, H-7), 7.73 (1, H-8), 8.68 (1, H-5)
2b	5-CH_3	79-81	30	$C_{15}H_{18}N_2O_4S$	0.96 (3, CH_3), 1.46 (3, CH_3), 3.11 (3, CH_3-5), 3.70 (2, SCH_2), 3.93 (2, OCH_2), 4.50 (2, OCH_2), 6.61 (1, H-6), 7.18 (1, H-7), 7.61 (1, H-8)
2c	6-Cl	141-143	25	$C_{14}H_{15}ClN_2O_4S$	1.07 (3, CH_3), 1.47 (3, CH_3), 3.73 (2, SCH_2), 4.00 (2, OCH_2), 4.50 (2, OCH_2), 7.26 (1, H-7), 7.81 (1, H-8), 8.70 (1, H-5)
2d	6-Br	137-139	16	$C_{14}H_{15}BrN_2O_4S$	1.05 (3, CH_3), 1.45 (3, CH_3), 3.71 (2, SCH_2), 4.00 (2, OCH_2), 4.50 (2, OCH_2), 7.33 (1, H-7), 7.61 (1, H-8), 8.78 (1, H-5)
2e	6-CH_3	83-85	14	$C_{15}H_{18}N_2O_4S$	1.01 (3, CH_3), 1.46 (3, CH_3), 2.66 (3, CH_3-8), 3.66 (2, SCH_2), 3.95 (2, OCH_2), 4.51 (2, OCH_2), 6.86 (1, H-6), 7.13 (1, H-7), 8.51 (1, H-5)
		Ethyl 3-Mercaptoimidazo[1,2-*a*]pyridine-2-carboxylates (**3**): 			
3a	5-CH_3	210-212	10	$C_{11}H_{12}N_2O_2S$	1.20 (3, CH_3), 2.95 (3, CH_3-5), 4.03 (2, OCH_2), 6.66 (1, H-6), 7.28 (1, H-7), 7.65 (1, H-8)
3b	6-CH_3	190-192	32	$C_{11}H_{12}N_2O_2S$	1.30 (3, CH_3), 2.25 (3, CH_3-6), 4.21 (2, OCH_2), 7.18 (1, H-7), 7.61 (1, H-8), 7.78 (1, H-5)
3c	6-Cl	204-206	24	$C_{10}H_9ClN_2O_2S$	1.25 (3, CH_3), 4.08 (2, OCH_2), 7.35 (1, H-7), 7.75 (1, H-8), 8.30 (1, H-5)
3d	6-Br	219-221	16	$C_{10}H_9BrN_2O_2S$	1.33 (3, CH_3), 4.15 (2, OCH_2), 7.44 (1, H-7), 7.70 (1, H-8), 8.34 (1, H-5)
3e	7-CH_3	182-184	28	$C_{11}H_{12}N_2O_2S$	1.25 (3, CH_3), 2.43 (3, CH_3-7), 4.15 (2, OCH_2), 6.75 (1, H-6), 7.48 (1, H-8), 8.06 (1, H-5)
3f	8-CH_3	174-176	10	$C_{11}H_{12}N_2O_2S$	1.21 (3, CH_3), 2.66 (3, CH_3-8), 4.13 (2, OCH_2), 6.76 (1, H-6), 7.15 (1, H-7), 8.00 (1, H-5)
		2-Carbethoxyimidazo[1,2-*a*]pyridine-3-thioacetic Acids (**4**):[c] 			
4a	H	239-241	40	$C_{12}H_{12}N_2O_4S$	1.36 (3, CH_3), 3.71 (2, SCH_2), 4.36 (2, OCH_2), 7.15 (1, H-6), 7.48 (1, H-7), 7.71 (1, H-8), 8.69 (1, H-5), 8.10 (1, CO_2H)
4b	5-CH_3	203-205	60	$C_{13}H_{14}N_2O_4S$	1.34 (3, CH_3), 2.54 (3, CH_3-5), 3.69 (2, SCH_2), 4.35 (2, OCH_2), 6.82 (1, H-6), 7.33 (1, H-7), 7.56 (1, H-8), 7.50 (1, CO_2H)
4c	6-CH_3	231-233	68	$C_{13}H_{14}N_2O_4S$	1.33 (3, CH_3), 2.35 (3, CH_3-5), 3.65 (2, SCH_2), 4.32 (2, CH_2), 7.32 (1, H-7), 7.59 (1, H-8), 8.44 (1, H-5), 8.21 (1, CO_2H)
4d	7-CH_3	209-211	72	$C_{13}H_{14}N_2O_4S$	1.37 (3, CH_3), 2.38 (3, CH_3-7), 3.64 (2, SCH_2), 4.37 (2, OCH_2, 6.95 (1, H-6), 7.42 (1, H-8), 8.57 (1, H-5), 8.01 (1, CO_2H)
4e	8-CH_3	204-206	9	$C_{13}H_{14}N_2O_4S$	1.36 (3, CH_3), 2.46 (3, CH_3-8), 3.70 (2, SCH_2), 4.38 (2, OCH_2), 7.03 (1, H-6), 7.26 (1, H-7), 8.53 (1, H-5), 7.92 (1, CO_2H)
		2-Carboxyimidazo[1,2-*a*]pyridine-3-thioacetic Acids (**5**):[c] 			
5a	6-Cl	245-247	51	$C_{10}H_7ClN_2O_4S$	3.71 (2, SCH_2), 7.60 (2, H-7,8),[d] 8.76 (1, H-5), 6 (2, CO_2H)
5b	6-Br	256-258	68	$C_{10}H_7BrN_2O_4S$	3.69 (2, SCH_2), 7.60 (2, H-7,8), 8.93 (1, H-5), 8.5 (2, CO_2H)
5c	8-CH_3	233-235	67	$C_{11}H_{10}N_2O_4S$	2.54 (3, CH_3-8), 3.72 (2, SCH_2), 7.03 (1, H-6), 7.30 (1, H-7), 8.53 (1, H-5), 8.4 (1, CO_2H)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] Assignments of chemical shifts are based on peak areas and similarity of the splitting patterns to those of analogous compounds. Typical values of coupling constants (in hertz) are $J_{5,6}$ = 6-7.5, $J_{5,7}$ = 0-2, $J_{5,8}$ = 0-1, $J_{6,7}$ = 6.5-7.5, $J_{6,8}$ = 1.5-2.5, and $J_{7,8}$ = 8.5-9.5 H_z. [c] ^1H NMR in Me_2SO-d_6. [d] Center of overlapping multiplets.

Table II. ^{13}C Chemical Shifts[a] of Imidazo[1,2-a]pyridines 3a-f



	positions										
compd	C-2	C-3	C-5	C-6	C-7	C-8	C-8a	C=O	CH_2	CH_3	R
3a	139.59	111	128.26	116.79[b]	128.26	117.51[b]	148.65	161.89	61.17	14.24	21.98
3b	141.53	117.29	122.25	124.93	131.31	118.24	145.78	161.94	61.26	14.29	18.38
3c	142.68	117.29	122.98	123.75	129.98	119.66	145.32	161.35	61.44	14.24	
3d	142.34	117.14	132.04	110.23	125.12	119.84	145.37	161.3	61.44	14.2	
3e	141.78	116.92	123.89	117.33	139.73	117.47	147.24	161.85	61.21	14.2	21.43
3f	141.41	117.83	122.43	114.65	126.75	129.21	147.19	162.07	61.17	14.11	16.79

[a] Chemical shifts are in parts per million downfield from internal Me_4Si in Me_2SO-d_6. [b] Assignments may be interchanged.

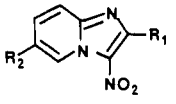
conditions, **2a,b** are hydrolyzed and gave thioacetic acids **4a,b** in 88% and 91% yields, respectively.

A reasonable explanation for the failure to observe condensation to the tricyclic ester would be that the susceptibility to nucleophilic attack of the CO_2Et group is decreased when it is attached to the π-excessive imidazole ring. The preferred direction of hydrolysis of the SCH_2CO_2Et group of **2a-e** would depend on its contribution to the resonance structure (Scheme II).

The structures of **3a-f** were established by the usual criteria of ^1H NMR (Table I) and ^{13}C spectroscopy (Table II). The five signals corresponding to the five carbon nuclei of the pyridine were readily assigned with off-resonance decoupling experiments and with the earlier observations.[3,6] Taking into consideration the well-known effects of the SH and CO_2Et groups,[7] we identified the chemical shifts of the imidazole peaks. Examination of the mass spectral fragmentation patterns of **3a-f** confirms the monomeric structures; peaks at higher m/e values are attributable to the disulfides **3c,d,f**.[8]

Interestingly, if **1a** is allowed to react with SHNa in DMF, the reduction of the nitro group is faster than the displacement, the lone product being the 3-amino-2-carbethoxyimidazo[1,2-a]pyridine **10** in 57% yield.

In order to explore the field of application and the factors governing the nucleophilic displacement of the nitro group, we investigated the effect of the structure of several 3-nitro derivates. The reactions of $NaSCH_2CO_2Et$ with **7-9** were carried out. The starting product was recovered unchanged for **7** and **8**, while **9** gave rise to a complex mixture of unidentified products.



7, $R_1 = R_2 = H$
8, $R_1 = CH_3$; $R_2 = H$
9, $R_1 = CO_2Et$; $R_2 = NO_2$

The unreactivity of **7** and **8** points to the need that a group at the 2-position would stabilize negative charge. The formation of 3-thio derivatives from 3-nitro compounds can be explained by the typical addition-elimination mechanism of nucleophilic aromatic substitution[9] (vs. a simple displacement mechanism). The displacement of the nitro group makes available compounds not easily accessible in other ways. Further studies are in progress.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by the Microanalytical Center, ENSCM, Montpellier. ^1H NMR spectra were taken on a Varian EM-390 spectrometer operating at 90 MHz. ^{13}C NMR spectra were obtained at about 26 °C, with proton-noise decoupling at 20.1 MHz, by using a Bruker WH-180. Chemical shifts are expressed relative to internal tetramethylsilane in $CDCl_3$ (or Me_2SO-d_6) at a concentration of about 5%. Mass spectra were recorded with a LKB 2091 spectrometer at 70 eV (θ (source) = 180°).

Ethyl 3-Nitroimidazo[1,2-a]pyridine-2-carboxylates 1a-e,g. Ethyl 3-nitroimidazo[1,2-a]pyridine-2-carboxylates **1a-e,g** were prepared as described previously.[2,3]

Ethyl 7-Methyl-3-nitroimidazo[1,2-a]pyridine-2-carboxylate (1f). Ethyl 7-methylimidazo[1,2-a]pyridine-2-carboxylate[10] (20.4 g, 0.1 mol) was dissolved in ice-cold, concentrated H_2SO_4 (100 mL), and HNO_3 (12 mL, d = 1.38) was added dropwise with stirring. The solution was left to stand at room temperature for 3 h and then poured onto ice (500 g). The yellow solid was filtered, rinsed with 200 mL of H_2O, and extracted with CH_2Cl_2. After being dried, the extract was evaporated. The residue was subjected to chromatography on silica gel with elution with CH_2Cl_2: 20.1 g (84%); mp 139-141 °C; ^1H NMR ($CDCl_3$) δ 1.43 (3, CH_3), 2.54 (3, CH_3-7), 4.52 (2, CH_2), 7.17 (1, H-6), 7.60 (1, H-8), 9.18 (1, H-5). Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.0; N, 16.8. Found: C, 52.9; N, 16.6.

General Procedure for Compounds 2a-e to 4a-c. To a well-stirred, cold solution (ice bath) containing 30 mmol of the substituted ethyl 3-nitroimidazo[1,2-a]pyridinecarboxylate and 4 mL of the ethyl thioglycolate in 60 mL of DMF was added slowly, portionwise, 2.5 g of lithium hydroxide. The mixture was stirred in the cold for 1 h and then at room temperature for 2 h. The solution was poured into ice-water, and the precipitated diester **2** was collected and chromatographed on silica gel, eluting with CH_2Cl_2. The aqueous layer, after extraction with three 100-mL portions of CH_2Cl_2, was acidified by using CH_3CO_2H. The solid was collected, washed with H_2O, and extracted with CH_2Cl_2. The insoluble was compound **4**. The extract was dried over sodium sulfate and concentrated. Chromatography on silica gel, eluting with CH_2Cl_2/EtOH (10/1), gave the pale yellow solid **3**. The diacid **5** precipitated when the aqueous solution was chilled at 0 °C overnight. Products **2a-e**, **3a-f**, **4a-e**, and **5a-c** are described in Tables I and II.

Attempts to Prepare 6 by Ring Closure of 2a. Method A. Treatment of 0.924 g (3 mmol) of **2a** with 0.2 g of lithium hy-

(6) (a) Pugmire, R. J.; Robins, M. J.; Grant, D. M.; Robins, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1887. (b) Pugmire, R. J.; Smith, J. C.; Grant, D. M. *J. Heterocycl. Chem.*, **1976**, *5*, 1057. (c) See reference 3.

(7) Ewing, D. F. *Org. Magn. Reson.* **1979**, *12*, 499.

(8) The RSSR were present in the reaction from **1d,e** and **1g**: **3c**, m/e 256, 258, 510, 512; **3d**, m/e 300, 302, 598, 600, 602; **3f**, m/e 235, 236, 470; **3a,b,e**, m/e 236.

(9) Miller, J. "Aromatic Nucleophilic Substitution"; Elsevier: London, 1968.

(10) This compound was prepared by the general method:[3] mp 128-130 °C; ^1H NMR ($CDCl_3$) δ 1.40 (3, CH_3), 2.33 (3, CH_3-7), 4.43 (2, CH_2), 6.64 (1, H-6), 7.36 (1, H-8), 8.03 (1, H-5), 8.1 (1, H-3).

droxide in 10 mL of DMF produce a pale white suspension which was warmed to 60 °C for 1 h. After the reaction mixture cooled, it was added slowly to 50 mL of ice-water. The solution was washed with CH_2Cl_2 (3 × 20 mL) and acidified by using CH_3CO_2H. The insoluble material was compound **4a** (0.80 g, 95%).

Method B. Similarly, **2a** in ethanol with sodium ethoxide at 50 °C for 1 h, followed by evaporation to dryness and trituration with aqueous CH_3COOH, gave **4a** as a white solid.

3-Nitroimidazo[1,2-*a*]pyridine (7) was prepared according to Paolini.[2d]

2-Methyl-3-nitroimidazo[1,2-*a*]pyridine (8) was prepared according to Hand.[1c]

Attempts to Displace the Nitro Group from 7 and 8. Treatment of 1.63 g (0.01 mol) of **7** with ethyl thioglycolate in 60 mL of DMF and 0.24 g of lithium hydroxide as in the general procedure produced a pale yellow solution which was poured into 200 mL of ice-cold water. The solid was collected and extracted with CH_2Cl_2. Evaporation of the solvent yielded the starting material (1.55 g, 95% recovery by ^1H NMR).

Similarly, the reaction of 1.77 g (0.01 mole) of **8** with $NaSCH_2CO_2Et$ and LiOH does not proceed (1.61 g, 91% recovery by ^1H NMR).

Attempts to Displace the Nitro Group from 9. Treatment of 2.80 g (0.01 mol) of **9** with ethyl thioglycolate in 100 mL of DMF and 0.24 g of lithium hydroxide produced a complex mixture of unidentified products.

3-Amino-2-carbethoxyimidazo[1,2-*a*]pyridine (10). To a stirred solution of **1a** (2.35 g, 0.01 mol) in DMF (20 mL) at −5 °C was added all at once a solution of 0.7 g of purified NaSH in 20 mL of DMF. The dark green solution was allowed to stand to room temperature about 10 min, and the stirring was continued for 30 min. The DMF solution was poured into 300 mL of ice-water. A solid (1.2 g) was collected by filtration and was subjected to chromatography on alumina. Elution with CH_2Cl_2 gave **10** (0.81 g). After the filtrate was evaporated, the resulting product (0.42 g) was treated with CH_2Cl_2 and was sujected to chromatography on alumina to give 0.35 g of additional **10**: 1.16 g total (56.6%); mp 210–212 °C; ^1H NMR ($CDCl_3$, relative to external Me_4Si) δ ~5.2 (NH_2), 2.81 (CH_3), 4.45 (CH_2), 6.71 (H-6), 7.06 (H-7), 7.48 (H-8), 7.76 (H-5).

Anal. Calcd for $C_{10}H_{11}O_2N_3$: C, 58.54; H, 5.36; N, 20.48. Found: C, 58.51; H, 5.37; N, 20.50.

Acknowledgment. We are indebted to Dr. W. W. Paudler and E. H. Hand, Department of Chemistry, University of Alabama, for their helpful discussions in the preparation of the manuscript and thank H. Viols for his technical assistance.

Registry No. 1a, 62223-44-3; **1b**, 67625-26-7; **1c**, 72721-16-5; **1d**, 67625-30-3; **1e**, 67625-29-0; **1f**, 76156-94-0; **1g**, 67625-34-7; **2a**, 76156-95-1; **2b**, 76156-96-2; **2c**, 76156-97-3; **2d**, 76156-98-4; **2e**, 76156-99-5; **3a**, 76157-00-1; **3b**, 76157-01-2; **3c**, 76172-94-6; **3d**, 76157-02-3; **3e**, 76157-03-4; **3f**, 76157-04-5; **4a**, 76157-05-6; **4b**, 76157-06-7; **4c**, 76157-07-8; **4d**, 76157-08-9; **4e**, 76157-09-0; **5a**, 76157-10-3; **5b**, 76157-11-4; **5c**, 76157-12-5; **10**, 76157-13-6; ethyl 7-methylimidazo[1,2-*a*]pyridine-2-carboxylate, 70705-33-8; ethyl thioglycolate, 623-51-8.

A New Synthesis of 7-Dehydrocholesterols

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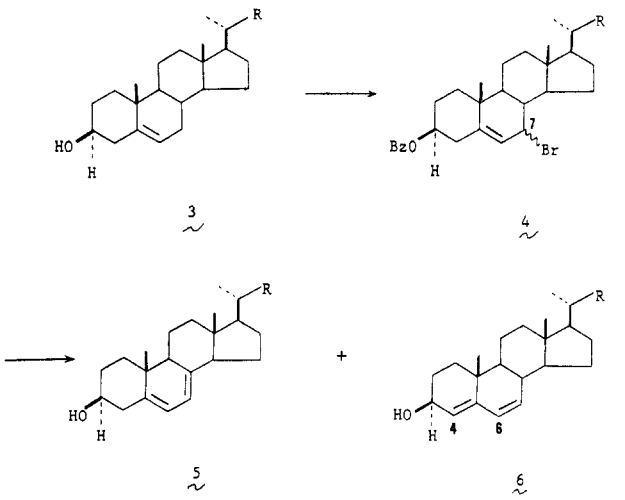
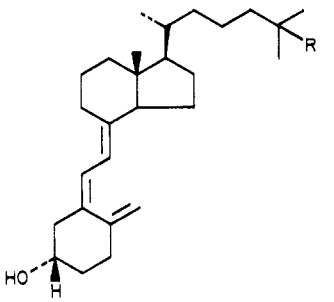
Received August 13, 1980

In conjunction with calcitonin and parathyroid hormone, vitamin D and its metabolites are largely responsible for the critical maintenance of calcium homeostasis.[1] The isolation and structural elucidation of a host of biologically active metabolites of vitamin D_3 (cholecalciferol) (1) have been the result of intense investigations begun in the early sixties,[2] highlighted by the landmark discovery of the first human metabolite, 25-hydroxy vitamin D_3 (**2**), by DeLuca.[3] These results soon triggered a corresponding effort to develop both total[4] and partial syntheses of all the known metabolites of vitamin D_3 as well as a number of analogues.[5] To date, all of the preparatively useful approaches to these compounds require the conversion of a cholesterol derivative such as **3** to its 7-dehydro counterpart **5** (Scheme I). Such a transformation was described in 1942 in the classical paper of Ziegler[6] which dealt with allylic bromination. Treatment of a suitable cholesterol ester with NBS afforded a 7-bromo derivative such as **4**, obtained as a mixture of epimers at C(7). The subsequent dehydrobromination and hydrolysis led to 7-dehydrocholesterol **5** along with a substantial quantity of the undesired 4,6-diene isomer **6**. The contaminant **6** has plagued this conversion despite almost 40 years of exhaustive developmental studies.[7] We report a process which affords

Scheme I





1, R = H
2, R = OH

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(4) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1979**, 4419–22 and leading references therein.

(5) See ref 1 for the various syntheses of the metabolites of vitamin D_3 (pp 95–110) and a number of analogues (pp 111–116).

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