than dithiols such as DTT and cannot reduce diselenide significantly (eq 7). The rate of thiol–disulfide interchange

$$2ME + AESe^{ox} \rightleftharpoons ME^{ox} + 2AESeH \quad (7)$$

reaction of cysteine (or *N*-acetylcysteine) with bis(2-hydroxyethyl) disulfide (ME^{ox}) is not enhanced in presence of 2-aminoethaneselenol ($^+H_3NCH_2CH_2SeH$) or 2-hydroxyethaneselenol ($HOCH_2CH_2SeH$) (Table I). The thiol–disulfide reactions involving monothiols and disulfides are not catalyzed by selenol because selenol is oxidized to diselenide by reaction with disulfide.

In the reactions involving strongly reducing dithiols and disulfides, the catalytic selenol can be generated from diselenide (RSeSeR) or selenocyanate (RSeCN).[18] The addition of diselenide or selenocyanate to the reaction mixture is more convenient than the addition of selenols because selenols are easily oxidized and are thus difficult to manipulate.

In conclusion, selenols catalyze the thiol–disulfide interchange reactions involving dithiols significantly in water. They are the first nonbiological materials that have even marginal utility as catalysts for this reaction.[19] We hypothesize, in the absence of any firm, relevant experimental evidence that this catalytic activity is attributable to their acidity ($pK_a \approx 7$, a number that probably provides a near-optimal combination of conversion of selenol to negatively charged selenolate nucleophile at pH 7 and useful nucleophilicity of this species) and to the weak solvation and high polarizability (and hence high nucleophilicity) of the selenolate ion. Thiolate–disulfide interchange reactions involving monothiols are, however, not accelerated in the presence of selenols. Selenols are oxidized to diselenides by noncyclic dialkyl disulfides. Their ability to catalyze reactions of eqs 1 and 2 is due to the ability of the dithiols to reduce diselenides to selenols.

The selenol precursors—diselenide or selenocyanate—can also be conveniently used to catalyze the thiol–disulfide interchange reactions involving strongly reducing dithiols.

Experimental Section

General. Selenocystamine hydrochloride ($AESe^{ox}$), potassium selenocyanate, 2-bromoethanol, dithiothreitol (DTT), cysteine (L-Cys), *N*-acetylcysteine (*N*-AcCys), and bis(2-hydroxyethyl) disulfide (ME^{ox}) were all purchased from Aldrich. Dihydroasparagusic acid (DHA) was prepared as described.[5] 2-Hydroxyethyl selenocyanate ($HOCH_2CH_2SeCN$) was prepared by a literature procedure.[17]

All flasks, quartz cuvettes, and NMR tubes were stoppered with rubber septa and were flushed with argon before use. All solutions were deoxygenated by bubbling argon through them for ~45 min. All transfers were done using gas-tight syringes.

Preparation of 2-Aminoethaneselenol ($^+H_3NCH_2CH_2SeH$). To a solution of selenocystamine hydrochloride (0.0028 g, 8.8 μmol) in deoxygenated ethanol (0.5 mL) was added sodium borohydride (0.0020 g, 53 μmol). The resulting solution was kept at room temperature under argon for 20 min until the solution became clear and no effervescence was seen. The solution was cooled in an ice bath and was quenched with glacial acetic acid (18 μL, 310 μmol). The concentration of 2-aminoethaneselenol was 40 mM by Ellman's assay.[20]

UV Assay for Catalysis of Thiol–Disulfide Interchange Involving DHA and ME^{ox} by 2-Aminoethaneselenol ($^+H_3NCH_2CH_2SeH$). Stock solutions of DHA and ME^{ox} (both 8 mM) were prepared from DHA (0.0131 g) in 10.8 mL of deoxygenated phosphate buffer (0.1 M in phosphate, pH 7.0, 2 mM in EDTA), and from ME^{ox} (0.0129 g) in 10.5 mL of deoxygenated phosphate buffer. In a quartz cuvette containing 1.5 mL of DHA stock solution and 30 μL of 2-aminoethaneselenol stock solution (40 mM) was added 1.5 mL of ME^{ox} stock solution, and the increase in absorbance at 330 nm was recorded. The initial concentrations in the cuvette were $[DHA] = [ME^{ox}] = c_{initial} = 4.0$ mM, $[^+H_3NCH_2CH_2SeH] = 0.4$ mM. The apparent rate constant (k^{obsd}) was calculated using the integrated form of the rate equation $d[DHA^{ox}]/dt = k^{obsd}[DHA][ME^{ox}]$: $k^{obsd} = (1/c_{final} - 1/c_{initial})/t$. For monitoring the reactions of DTT and ME^{ox}, the increase in absorbance at 310 nm was recorded.[2]

^1H NMR Assay for Catalysis of Thiol–Disulfide Interchange Involving DTT and ME^{ox} by 2-Aminoethaneselenol ($^+H_3NCH_2CH_2SeH$). Solutions of DTT (10 mM, 0.0031 g in 2 mL of deoxygenated D_2O buffer (50 mM in phosphate, pD 7.0)) and ME^{ox} (10 mM, 0.0046 g in 3 mL of deoxygenated D_2O buffer) were prepared. To an NMR tube was added $^+H_3NCH_2CH_2SeH$ (21 μL of a 11.8 mM solution in ethanol), and the solvent was removed in vacuo; to the NMR tube were added 0.25 mL of the DTT solution and 0.25 mL of the ME^{ox} solution, and the reaction was quenched after 1.5 min by addition of DCl (10 μL of a 37 wt % solution in D_2O). The initial concentrations in the NMR tube were $[DTT] = [ME^{ox}] = 5$ mM, $[^+H_3NCH_2CH_2SeH] = 0.5$ mM. The final concentrations of ME^{ox} and ME were determined by integration of the NMR peak areas. For the uncatalyzed reaction, 0.25 mL of DTT solution and 0.25 mL of ME^{ox} solution were mixed in an NMR tube, and the reaction was quenched after 5 min by addition of DCl (10 μL of a 37 wt % solution in D_2O).

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Registry No. DHA, 136202-27-2; DTT, 3483-12-3; L-Cys, 52-90-4; *N*-AcCys, 616-91-1; ME^{ox}, 1892-29-1; $^+H_3NCH_2CH_2SeH$, 116303-19-6; $(^+H_3NCH_2CH_2Se)_2$, 84250-77-1; $HOCH_2CH_2SeCN$, 115423-26-2.

(17) Kang, S. I.; Spears, C. P. *Synthesis* **1988**, 133-135.

(18) Selenols can be conveniently prepared by reduction of diselenide (RSeSeR) or selenocyanate (RSeCN) with sodium borohydride,[13,14] or with dithiothreitol (DTT).[15,16] Selenocyanates are conveniently prepared from alkyl bromide by reaction with potassium selenocyanate (KSeCN).[17] Selenocyanates are stable to chromatography on silica gel and are therefore useful intermediates in the synthesis of selenols.

(19) We believe that reduction of the disulfide groups of cystines in proteins by dithiothreitol in water would be accelerated by catalytic amounts of selenols, but we have not tested this belief experimentally.

(20) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70-77. Habeeb, A. F. S. A. *Methods Enzymol.* **1972**, *25*, 457-464.

Sigmatropic Rearrangements of Ammonium Benzylides: New Preparative and Mechanistic Aspects[1]

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Received September 7, 1990

Benzylammonium salts, when treated with a base, generate ylides, which undergo the Stevens [1,2] and/or Sommelet–Hauser [2,3] rearrangements.[2] The latter is an attractive method for the synthesis of aromatic compounds with ortho-located substituents.

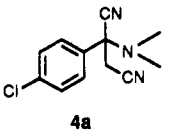
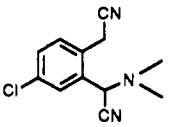
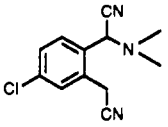
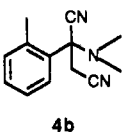
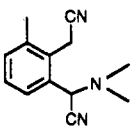
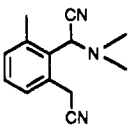
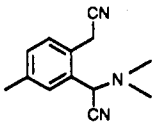
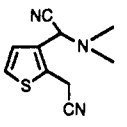
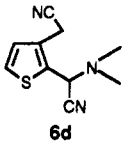
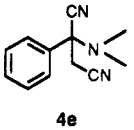
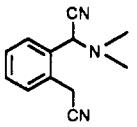
We report that the Sommelet–Hauser rearrangement of benzylides, generated from suitably substituted benzylammonium salts, is a new and convenient synthetic route leading to *o*-cyanomethylated derivatives of aromatic aldehydes. Furthermore, this reaction applied to ring-substituted benzylammonium salts allowed us to present a new mechanistic pathway.[3]

(1) Reactions of Organic Anions. 166. Part 165: Jończyk, A.; Balcerzak, P. *Tetrahedron Lett.* **1989**, *30*, 4697.

(2) Pine, S. H. *Org. React. (N.Y.)* **1970**, *18*, 403. Machida, J.; Shirai, N.; Sato, Y. *Synthesis* **1991**, 117 and references cited therein.

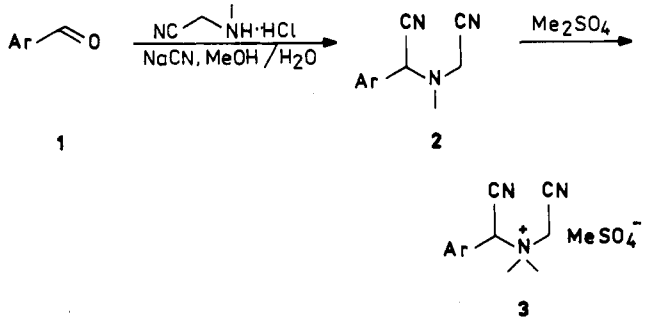
0022-3263/91/1956-6933$02.50/0

Table II. Amino Nitriles 4–6 from Salts 3

salt (Ar)	base/solvent system[a]	amino nitrile rearrangement [1,2]	[2,3]	[1,4]	product(s); yield,[b] %	ratio of products[c]
3a (4-ClC_6H_4)	A	 **4a**	 **5a**	 **6a**	**4a** + **5a**; 87	**5a**/**4a** ~ 92/8
	B				**4a** + **5a** + **6a**; 90	(**5a** + **6a**)/**4a** ~ 88/12; **5a**/**6a** ~ 54/46
	C				**5a**; 95	–
3b (2-MeC_6H_4)	A[d]	 **4b**	 **5b**	 **6b**	**4b** + **5b** + **6b**; 94	(**5b** + **6b**)/**4b** ~ 75/25; **5b**/**6b** ~ 81/19
	B				**5b** + **6b**; 90	**5b**/**6b** ≥ 95/5
	C				**4b** + **5b**; 61	**4b**/**5b** ~ 90/10
3c (4-MeC_6H_4)	B	–	 **5c**	–	**5c**; 98	–
	C	–		–	**5c**; 86	–
3d (2-thienyl)	B	–	 **5d**	 **6d**	**5d** + **6d**; 62	**5d**/**6d** ~ 24/76
	C	–			**5d** + **6d**; 70	**5d**/**6d** ~ 90/10
3e (C_6H_5)	A	 **4e**	 **5e** = **6e**		**4e** + **5e**; 94	**5e**/**4e** ~ 92/8
	B				**4e** + **53**; 98	**5e**/**4e** ~ 88/12

[a] A: 25% aqueous NaOH/PhH. B: solid K_2CO_3/DMF. C: 25% aqueous NH_3/CH_2Cl_2. [b] Yields of crude products (purity ≥ 90% by ^1H NMR spectra). [c] Calculated from ^1H NMR spectra. [d] PhMe instead of PhH was used.

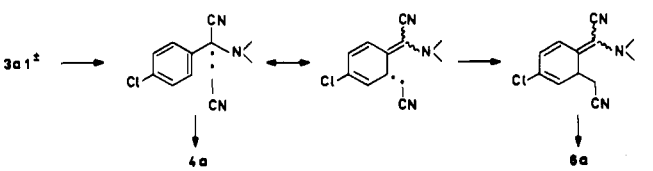
Scheme I



Thus, the stirring of salt **3a**, which was prepared from **1a** via **2a** according to Scheme I, with an excess of base (system A, 25% aqueous NaOH/benzene; system B, solid K_2CO_3/DMF; and system C, 25% aqueous NH_3/CH_2Cl_2) resulted in the formation of either a mixture of rearranged products **4a**, **5a**, and **6a** or single rearranged product **5a**. These compounds, from which crystalline **4a** was filtered off, after being treated with $CuSO_4$, afforded a mixture of aldehydes **7a** and **8a**. Their deformylation with chlorotris(triphenylphosphine)rhodium, as a catalyst,[4] resulted in the formation of nitriles **9a** and **10a**, the structures of which were correlated with the authentic samples (Scheme II, Tables II and III).

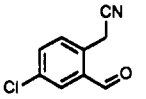
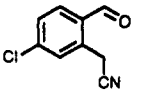
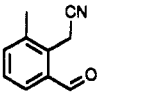
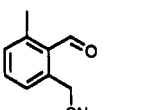
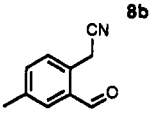
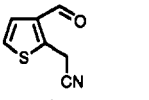
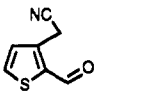
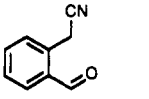
We explain, according to the literature,[2] the formation of products **4a** and **5a** in terms of [1,2] and [2,3] sigmatropic rearrangements of the ylides **3a1**$^{\pm}$ and **3a2**$^{\pm}$, respectively. On the other hand, we postulate the [1,4] sigmatropic rearrangement of the more stable ylide **3a1**$^{\pm}$ to account for the formation of product **6a** (Scheme III). The concerted mechanism is possible due to a six-electron aromatic transition state with suprafacial–suprafacial characteristics.[5,6] We have termed this type of reorganization of electron pairs as the "reverse" Sommelet–Hauser rearrangement. To the best of our knowledge, the latter rearrangement of ammonium benzylides has not hitherto been described. The formation of products of the Sommelet–Hauser rearrangement of benzylides has been explained so far in terms of a [2,3] mechanistic pathway.[2,9]

(3) Preliminary communication: Jończyk, A.; Lipiak, D.; Sienkiewicz, K. *Synlett* **1991**, 493.
(4) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99.
(5) Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1436.
(6) Alternatively, product **6a** as well as **4a** may result from a coupling process of mesomeric radicals. It has been stated that the [1,2][7] as well as [1,4][8] rearrangements of acyl-stabilized ammonium ylides normally involve a radical pair mechanism. In our case, the ratio of **5a**/**6a** depends on the base/solvent system used, and therefore the mechanism in Scheme II seems plausible.



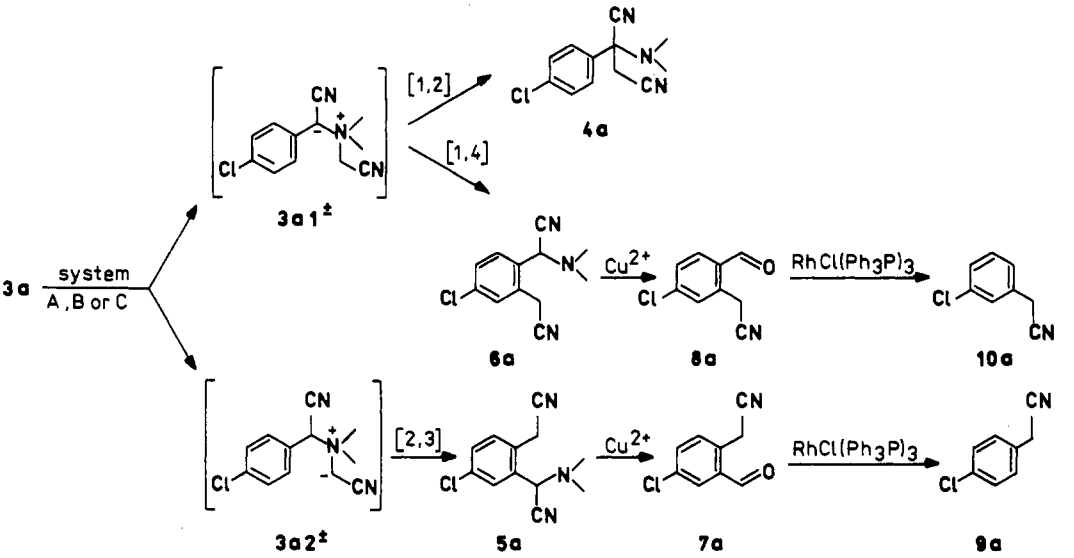
(7) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1009.
(8) Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *Ibid.* **1983**, 1049.
(9) A [1,4] rearrangement of benzylide generated from benzyltrimethylammonium salt was already considered, but it was discarded on the basis of the experimental data.[10] In our case the presence of two cyano groups in **3a1**$^{\pm}$ may favor such a rearrangement (Scheme III).

Table III. Aldehydes 7 and 8 from Amino Nitriles 5 and 6

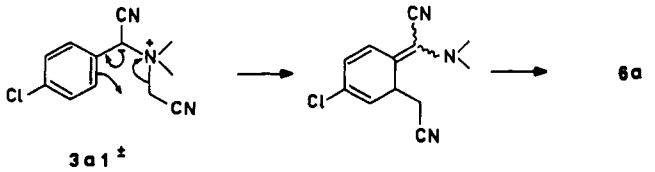
entry	amino nitriles formed under conditns A, B, or C	aldehyde(s)	product yield;[a] %	ratio of products[b]
1	**5a** + **6a** A	 **7a**	**7a**; 70	-
2	**5a** + **6a** B	 **8a**	**7a** + **8a**; 57 (78)	**7a**/**8a** ~ 55/45
3	**5a** C		**7a**; 80	-
4	**5b** + **6b** A	 **7b**	**7b** + **8b**; 59	**6b**/**8b** ~ 84/16
5	**5b** + **6b** B	 **8b**	**7b** + **8b**; 43	**7b**/**8b** ≥ 95/5
6	**5b** C		**7b**; 96	-
7	**5c** B	 **7c**	**7c**; 54	-
8	**5d** + **6d** B	 **7d**	**7d** + **8d**; (49)[c]	**7d**/**8d** ~ 10/90
9	**5d** + **6d** C	 **8d**	**7d** + **8d**; (63)[c]	**7d**/**8d** ~ 80/20
10	**4e** + **5e** A	 **7e**	**7e**; 70 (84)	-
11	**5e** B		**7e**; 55 (71)	-

[a] Yields of pure products; in parentheses, yields of crude products (purity ≥ 90% by ^{1}H NMR spectra). [b] Calculated from ^{1}H NMR spectra. [c] Calculated on **3d**.

Scheme II



Scheme III



A few other solvents with K_2CO_3, as well as a $KHCO_3$/DMF system, were tried for the generation of **3a**$^{\pm}$ from **3a** (Table IV, supplementary material). However, none of the base/solvent systems used allowed for the formation of product **6a** ([1,4] rearrangement). Even such a weak base as $KHCO_3$ induced generation of **3a1**$^{\pm}$ and its [1,2] rearrangement.

In order to collect more information on the above-mentioned processes, we have synthesized salts **3b–d** (Scheme I; Table I, supplementary material). Their treatment with system A, B, or C gave rise to mixtures of amino nitriles, the compositions of which depend on the base/solvent system used (Table II). In all but one case (salt **3c**), these mixtures contained products **6**, the formation of which we postulate via [1,4] rearrangement of the corresponding ylides. The data mentioned above indicate that the "reverse" Sommelet–Hauser rearrangement is fairly often encountered when benzylammonium salts are treated with a base. Finally, salt **3e**, unsubstituted in

(10) Jones, F. N.; Hauser, C. R. *J. Org. Chem.* **1961**, *26*, 2979.

the phenyl ring, was prepared and rearranged to give **5e** = **6e** as a main product. It is produced via either [2,3] or [1,4] rearrangements of isomeric benzylides (Table II).

Therefore, the data collected in this work do not allow us to design a base/solvent system which would induce the same rearrangement of ylides having different aromatic substituents.

All amino nitriles **5** and **6** were cleaved by means of $CuSO_4/EtOH/H_2O$ giving *o*-cyanomethylated aromatic aldehydes **7** and/or **8**. A proper choice of base/solvent system for rearrangement of ylides generated from **3** allows for the simple preparation of a single aldehyde via the reaction sequence described above (Table III).

In conclusion, we have introduced a new [1,4] sigmatropic ("reverse" Sommelet–Hauser) rearrangement of ammonium benzylides. Furthermore, we have described an easy access to synthetically attractive aromatic aldehydes, ortho substituted by a cyanomethyl group. The scope and limitations of these reactions, their mechanism, and the synthetic application of *o*-cyanomethylated aldehydes are currently being investigated.

Experimental Section

Melting points and boiling points are uncorrected. IR spectra were taken on a Perkin-Elmer Model 577 or a Perkin-Elmer 1600 FT/IR spectrometer. ^1H NMR spectra were recorded on a Tesla BS 267 A (100 MHz) or a Varian VXR 300 (300 MHz) spectrometer. Mass spectra were taken on a Finnigan Model 400 instrument with 70-eV EI. HPLC analyses were performed on a Du Pont 830 LC chromatograph with UV detector, equipped with Zorbax SIL column, with hexane/dioxane as eluting solvent. GC analyses were done on a GCHF 18.3 chromatograph, OV-17 (5%) on Chromosorb W-HP (80–100 mesh) column, or a Chrom 5 chromatograph, Carbowax 20000, 50-m steel capillary column, or Reoplex 400 (3%) on Chromaton N-AW (80–100) mesh) column.

Amino Nitriles 2a,b,d,e. (*N*-Methylamino)acetonitrile hydrochloride (2.93 g, 27.5 mmol), sodium cyanide (1.47 g, 30 mmol) in MeOH/water mixture (2:1, 18 mL), and aldehyde **1** (24.8 mmol; solid **1** was dissolved in a minimum amount of MeOH) were stirred at the temperature and for the time indicated in Table I. The mixture was diluted with water and extracted with CH_2Cl_2 (three times), and the organic phases were washed with aqueous $NaHSO_3$ and then water and dried ($MgSO_4$). The solvent was evaporated, and the residue was recrystallized or distilled to give the following products (Table I): **2a** (70%, EtOH), mp 50–51 °C; **2b** (77%, EtOH/hexane), mp 83–84 °C; **2d** (72%, EtOH/hexane), mp 58–60 °C; **2e** (87%), bp 108–109 °C (0.2 Torr).

Amino Nitrile 2c. (The reaction was carried out according to the literature[11].) A mixture of MeCN (5 mL), potassium cyanide (0.65 g, 10 mmol), (*N*-methylamino)acetonitrile hydrochloride (1.16 g, 11 mmol) and neutral Al_2O_3, type S (1.5 g), was sonicated in a laboratory ultrasonic cleaner (Itersonic, 100 W, 44 kHz) for 1 h. Then, aldehyde **1c** (0.6 g, 5 mmol) was added, and sonication was continued at 40 °C for 27 h. The mixture was filtered, the solid material was wahsed with CH_2Cl_2, the filtrate was concentrated, and the residue was crystallized from *i*-PrOH/hexane (3:2) to give 0.86 g (86%) of **2c**, mp 32–33 °C.

Salts 3a–e. Amino nitriles **2a–e** (10 mmol) and freshly distilled dimethyl sulfate (5.05 g, 40 mmol) were heated at the temperatures and for the times indicated in Table I. The mixture was cooled and diluted with dry ethyl ether (ca. 6–8 mL) or with dry ethyl acetate (ca. 6–8 mL). The crystals were filtered, washed with a small amount of ethyl acetate, dried, and stored in a desiccator, protected from light (Table I): **3a** (85%), mp 154–156 °C; **3b** (51%), mp 132–134 °C dec; **3c** (30%), mp 146–148 °C dec; **3d** (33%), mp 92–94 °C; **3e** (87%), mp 141–144 °C.

Rearrangements of the Salts 3a–e. Base/Solvent System A. A mixture of 25% aqueous NaOH (25 mL) and benzene (15 mL) was vigorously stirred at 3–5 °C, and the solid salt **3a** or **3e** (10 mmol) was added. Stirring was continued at 3–5 °C for 1 h, the mixture was diluted with water, the organic phase was separated, and the water phase was extracted with benzene. The combined organic extracts were washed with water and dried over $MgSO_4$, and the solvent was evaporated. The residue was analyzed by ^1H NMR.

4a + 5a: ^1H NMR ($CDCl_3$) δ 2.27 (s, 6 H, NMe_2, **5a**), 2.52 (s, 6 H, NMe_2, **4a**), 3.92 (s, 2 H, CH_2CN, **5a**), 3.98 (q, $^2J_{AB}$ = 11.27 Hz, 2 H, CH_2CN, **4a**), 7.33–7.63 (m, 3 H, Ar H, **5a**), 7.46 (s, 4 H, Ar H, **4a**). The ratio of **5a**/**4a** was calculated from the integrations of the signals of the CH_2CN protons (Table II). This mixture was diluted with EtOH (6 mL), cooled (ca. 0 °C), and filtered, and the solid was washed with EtOH to give 0.363 g (15.5%) of **4a**.

4a (EtOH): mp 128–130 °C. The filtrate was used for the preparation of **7a**.

4e + 5e: ^1H NMR ($CDCl_3$) δ 2.25 (s, 6 H, NMe_2, **5e**), 2.45 (s, 6 H, NMe_2, **4e**), 3.93 (s, 2 H, CH_2CN, **5e**), 3.93 (q, $^2J_{AB}$ = 11.30 Hz, 2 H, CH_2CN, **4e**), 4.92 (s, 1 H, CHCN, **5e**), 7.32–7.65 (m, 4 H, Ar H, **5e**), 7.43 (s, 5 H, Ar H, **4e**). The ratio of **5e**/**4e** was calculated from the integration of the signals of the NMe_2 protons (Table II). This mixture was used for the preparation of **7e**.

Toluene (5 mL) and 25% aqueous NaOH (4 mL) were vigorously stirred at −20 to −25 °C, and then salt **3b** (0.163 g, 0.5 mmol) was added. The reaction was carried out at this temperature for 0.75 h, the mixture was diluted with water, and the phases were separated. The water phase was extracted with benzene, and the organic phases were washed with water and dried over $MgSO_4$. The solvent was evaporated, and the residue was analyzed by ^1H NMR.

4b + 5b + 6b: ^1H NMR ($CDCl_3$) δ 2.28 (s, 6 H, NMe_2, **5b**), 2.33 (s, 6 H, NMe_2, **6b**), 2.34 (s, 6 H, NMe_2, **4b**), 2.41 (s, 6 H, Ar CH_3 **6b**), 2.43 (s, 3 H, $ArCH_3$, **5b**), 2.47 (s, 3 H, Ar CH_3, **4b**), 3.83 (q, $^2J_{AB}$ = 17.30 Hz, 2 H, CH_2CN, **5b**), 4.02 (q, $^2J_{AB}$ = 5.30 Hz, 2 H, CH_2CN, **4b**), 4.27 (s, 2 H, CH_2CN, **6b**), 4.79 (s, 1 H, CHCN, **6b**), 4.94 (s, 1 H, CHCN, **5b**), 7.23–7.56 (m, Ar H, **4b + 5b + 6b**). Ratios of (**5b + 6b**)/**4b** and **5b**/**6b** were calculated from the integration of the signals of the CH_2CN and CHCN protons, respectively (Table II). This mixture was diluted with EtOH (ca. 5 mL) and cooled (ca. 5 °C), and the solid was filtered off, affording 0.02 g (20%) of **4b**. The filtrate was used for the preparation of **7b** and **8b**.

Base/Solvent System B. DMF (15 mL) and salts **3a–e** (5.0 mmol) were stirred at 0 °C for **3a**,**e** or at −25 to −30 °C for **3b–d**, and then powdered K_2CO_3 (3.45 g, 25 mmol) was added. The mixture was vigorously stirred at 0 °C for 2 h (salts **3a** and **3e**), at −25 to −30 °C for 0.75 h (salts **3b** and **3c**), or at −25 to −30 °C for 1 h (salt **3d**) diluted with water, and extracted with CH_2Cl_2 (three times). Organic extracts were washed with water (three times) and dried with $MgSO_4$, the solvent was evaporated, and the residue was analyzed by ^1H NMR (Table II).

4a + 5a + 6a: ^1H NMR ($CDCl_3$) δ 2.27 (s, 6 H, NMe_2, **5a**), 2.28 (s, 6 H, NMe_2, **6a**), 2.52 (s, 6 H, NMe_2, **4a**), 3.92 (s, 2 H, CH_2CN, **5a**), 3.94 (s, 2 H, CH_2CN, **6a**), 3.98 (q, $^2J_{AB}$ = 11.27 Hz, 2 H, CH_2CN, **4a**), 4.90 (s, CHCN, **5a + 6a**), 7.33–7.68 (m, Ar H, **5a + 6a**), 7.46 (s, 4 H, Ar H, **4a**). The ratio of (**5a + 6a**)/**4a** was calculated from the integration of the signals of the CH_2CN protons. This mixture was diluted with EtOH, and the solid was filtered, to give 0.116 g (10%) of **4a**. The filtrate was used for the preparation of a **7a**/**8a** mixture.

5b + 6b: ^1H NMR spectrum as described above (lack of the signals of **4b**). This mixture was used for the preparation of **7b** and **8b**.

5c. This product was used for the synthesis of **7c**.

5d + 6d: ^1H NMR ($CDCl_3$) δ 2.29 (s, 6 H, NMe_2, **5d**), 2.32 (s, 6 H, NMe_2, **6d**), 3.79 (s, 2 H, CH_2CN, **6d**), 3.96 (q, $^2J_{AB}$ = 18.11 Hz, 2 H, CH_2CN, **5d**), 4.86 (s, 1 H, CHCN, **5d**), 5.00 (s, 1 H, CHCN, **6d**), 7.17 (q, $^3J_{AB}$ = 5.32 Hz, Ar H, **6d**), 7.22 (q, $^3J_{AB}$ = 5.32 Hz, Ar H, **5d**). The ratio of **5d**/**6d** was calculated from the integration of the signals of CH_2CN and CHCN protons. This mixture was used for the preparation of **7d** and **8d**.

4e + 5e: ^1H NMR spectrum as described above. This mixture was diluted with EtOH and a little hexane and cooled, and 0.1 g (10%) of **4e** was obtained by filtration.

4e (EtOH): mp 115–116 °C. The filtrate was used for the preparation of **7e**.

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Base/Solvent System C. CH_2Cl_2 (5 mL) and 25% aqueous NH_3 (5 mL) were stirred at −25 to −30 °C, and then salt **3a–d** was added. The mixture was stirred at −25 to −30 °C for 0.5 h (salt **3a**), for 0.75 h (salts **3b,c**), or for 1 h (salt **3d**) and diluted with water, and the phases were separated. The water phase was extracted with CH_2Cl_2 (three times), and the combined organic phases were washed with water and dried over $MgSO_4$. The solvent was evaporated, and the residue was analyzed by ^1H NMR (Table II).

5a. This product was used for the preparation of **7a**.

4b + 5b: ^1H NMR spectrum as described above (lack of the signals of **6b**). The ratio of **5b/4b** was calculated from the integration of the signals of the Ar CH_3 protons. This mixture was diluted with EtOH, the product **4b** was filtered, and the filtrate was used for the preparation of **7b**.

5c: ^1H NMR spectrum as described.

5d + 6d: ^1H NMR spectrum as described above. This mixture was used for the preparation of **7d** and **8d**.

Aldehydes 7 and 8. Crude products which resulted from the rearrangement of salt **3** (5 mmol) were dissolved in EtOH (20 mL; in some cases EtOH was already added in order to remove **4**), and $CuSO_4 \cdot 5H_2O$ (1.25 g, 5 mmol) dissolved in water (20 mL) was added. The mixture was gently refluxed until solid separated (ca. 5–10 min) and was then filtered; the filtrate was diluted with water and extracted with CH_2Cl_2 (three or four times). The organic extracts were washed with water, dried over $MgSO_4$, and concentrated to give crude aldehydes **7** and **8**, which were analyzed and purified (Table III).

7a + 8a. The ratio of **7a/8a** was determined by the integration of the signals of the CH_2CN protons in the ^1H NMR spectra. Pure **7a** was isolated from the reaction carried out under conditions A or C.

7a: bp (Kugelrohr) 100–130 °C (0.2 Torr); mp 50–52 °C.

8a. A sample of pure **8a** was isolated by preparative HPLC from the reaction carried out under conditions B.

Products **7a** and **8a** were deformylated,[4] affording 4-chlorophenylacetonitrile (**9a**) and 3-chlorophenylacetonitrile (**10a**), respectively, which were identified by comparison with authentic samples (GC, HPLC).

7b + 8b: ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H, Ar CH_3, **8b**), 2.47 (s, 3 H, Ar CH_3, **7b**), 3.70 (s, 2 H, CH_2CN, **8b**), 4.26 (s, 2 H, CH_2CN, **7b**), 7.44–7.67 (m, Ar H, **7b + 8b**), 9.94 (s, 1 H, CHO, **8b**), 10.06 (s, 1 H, CHO, **7b**). The ratio of **7b/8b** was calculated from the integration of the signals of the CH_2CN protons. GC/MS (one signal on GC): *m/e* (relative intensity) 159 (M^+, 32), 132 (100), 104 (47), 77 (33), 63 (12), 51 (17).

7b: isolated from the reaction carried out under conditions, B or C (Table III, entries 5 and 6); bp (Kugelrohr) 90–120 °C (0.02 Torr). Deformylation[4] of **7b** gave 2-methylphenylacetonitrile, identified by comparison with an authentic sample (GC).

7c: bp (Kugelrohr) 90–120 °C (0.02 Torr). Deformylation[4] of **7c** afforded 4-methylphenylacetonitrile, which was compared with an authentic sample (GC).

7d + 8d. The products decomposed during the attempted distillation: IR (film) 2250, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (s, 2 H, CH_2CN, **8d**), 4.33 (s, 2 H, CH_2CN, **7d**), 7.38 (q, $^3J_{AB}$ = 5.32 Hz, 2 H, Ar H, **7d**), 7.54 (q, $^3J_{AB}$ = 4.73 Hz, 2 H, **8d**), 9.91 (s, 1 H, CHO, **8d**), 10.00 (s, 1 H, CHO, **7d**). The ratio of **7d/8d** was calculated from the integration of the signals of the CH_2CN or CHO protons. Attempted deformylation[4] of this mixture failed.

7e: bp 92–93 °C (0.2 Torr); mp 36.5–38.5 °C.

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Registry No. **1a**, 104-88-1; **1b**, 529-20-4; **1c**, 104-87-0; **1d**, 98-03-3; **1e**, 100-52-7; **2a**, 135737-05-2; **2b**, 136262-88-9; **2c**, 136262-89-0; **2d**, 135737-06-3; **2e**, 135762-90-2; **3a**, 135737-02-9; **3b**, 136262-91-4; **3c**, 136262-93-6; **3d**, 135737-04-1; **3e**, 135737-00-7; **4a**, 135737-09-6; **4b**, 136262-94-7; **4e**, 135737-07-4; **5a**, 135737-10-9; **5b**, 136262-95-8; **5c**, 136262-97-0; **5d**, 135737-12-1; **5e**, 135737-08-5; **6a**, 135737-11-0; **6b**, 136262-96-9; **6d**, 135737-13-2; **7a**, 135737-15-4; **7b**, 136262-98-1; **7c**, 136263-00-8; **7d**, 135737-17-6; **7e**, 135737-14-3; **8a**, 135737-16-5; **8b**, 136262-99-2; **8d**, 135737-18-7; **9a**, 140-53-4; **10a**, 1529-41-5; (*N*-methylamino)acetonitrile hydrochloride, 5616-32-0; 4-methylphenylacetonitrile, 2947-61-7.

Supplementary Material Available: Reaction conditions for the preparation of **2** and **3** and their yields (Table I), rearrangements of **3a** under different conditions (Table IV), and characterization data (^1H NMR, IR, or MS spectra and elemental analyses) for compounds **2a–e**, **3a–e**, **4a,b,e**, **5a,c**, **7a–e**, and **8a,d** (5 pages). Ordering information is given on any current masthead page.

Synthesis of [4-(2-Guanin-8-ylethyl)benzoyl]glutamic Acid, a Guanine Analogue of DDATHF

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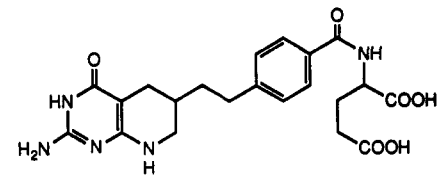
5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (1, DDATHF)[1] is the first member of a new class of folate antimetabolites



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whose site of action as a folate inhibitor, after intracellular polyglutamation by folylpolyglutamate synthetase,[1-3] has been shown to be glycinamide ribonucleotide formyltransferase (GARFT, E.C. 2.1.2.1) rather than dihydrofolate reductase (DHFR, E.C. 1.5.1.3). The remarkable potency and broad-spectrum antitumor activity of DDATHF, which is now in clinical trial, has stimulated an extensive structure–activity relationship study on this new agent for cancer chemotherapy.[4] One structural change which has not as yet been explored is contraction of the pyrazine "B" ring of the natural cofactor for GARFT,[5] and this paper describes the synthesis and biological evalutation of the novel guanine derivative **2**.

Application of the synthetic strategy developed for an efficient synthesis of DDATHF itself[6] to the guanine derivative **2** would involve a palladium-catalyzed coupling either of an 8-ethynylguanine derivative such as **3** with dimethyl (4-iodobenzoyl)glutamate (**4**) or of an 8-haloguanine derivative **5** with dimethyl (4-ethynylbenzoyl)-

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