Synthesis of Potential Anticancer Agents. XVIII. Nitrogen Mustards from 6-Substituted Coumarins[1,2]

ROBERT C. ELDERFIELD AND J. ROY

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48104

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A variety of alkylating agents has been prepared with 6-aminocoumarin or coumarin-6-carboxylic acid residues as the "carrier" moiety. Of these, 6-[3-bis(2-chloroethylamino)propionamido]coumarin showed some carcinostatic activity and 6-{*p*-[N,N-bis(2-methanesulfonoxyethyl)amino]benzylideneamino}coumarin showed pronounced activity against the Walker 256 carcinosarcoma. The latter also showed considerable activity against KB cells in cell culture cytotoxicity and some activity against leukemia L1210.

Since the concept of a pharmacologically active substance being composed of an active moiety and a carrier moiety was first put forward by Ing[3] a host of compounds carrying cytostatically active alkylating functions such as nitrogen mustards, methanesulfonates, aziridines, and epoxides, in combination with a carrier, have been synthesized. A number of reviews of this area have appeared.[4] However, coumarin does not appear to have been employed as the carrier moiety.

Coumarin and some of its hydroxylated derivatives, like other unsaturated lactones, *e.g.*, parasorbic acid and β-angelica lactone, have been shown[5] to be capable of suppressing germination of seeds at rather low concentrations. It is a differential phytocidal agent.[5] Derivatives of coumarin-3-carboxylic acid are reported to be sedative in small doses and hypnotic in large doses.[7] Among derivatives of this acid the diethyl amide has been effective in general nervous diseases and in various neurasthenic and hysterical ailments. Several hydroxylated arylcoumarins have shown estrogenic properties.[8] Buu-Hoi and co-workers[9] prepared a series of hydroxylated 3-arylcoumarins as potential carcinostatic and virustatic agents. Preliminary experiments on mice infected with influenza virus indicated that 3-(*p*-chlorophenyl)-8-hydroxycoumarin has some protective activity.

It therefore seemed to be of interest to couple an alkylating function with the coumarin nucleus. In this and the subsequent communication[10] we present the results of an exploration of the use of coumarin derivatives as carcinostatic agents.

It was originally planned to incorporate an alkylating function into both the aromatic and lactone rings of the coumarin molecule. The only two positions available in the lactone ring for this purpose are the 3 and 4 positions. Suitable 3-substituted precursors, *e.g.*, 3-aminocoumarin[11] and coumarin-3-carboxylic acid,[12] are known to be somewhat abnormal in their chemical behavior and preliminary investigations with these compounds did not appear to be promising. 4-Aminocoumarin and coumarin-4-carboxylic acid were not known at the time this investigation was initiated.[13] Therefore, syntheses were limited to coumarins bearing substituents on the aromatic ring. As there was no *a priori* reason to prefer one position for the substituent over another, 6-substituted coumarins were chosen because of the ready accessibility of the starting materials. In the succeeding communication[10] synthesis of representative 8-substituted coumarins carrying an alkylating function is described.

6-{*p*-[N,N-Bis(2-chloroethyl)amino]benzylideneamino}coumarin (**1**) was readily prepared by condensation of 6-aminocoumarin (**2**) (see Scheme I) with *p*-[N,N-bis(2-chloroethyl)amino]benzaldehyde (**3**) in absolute ethanol in the presence of a small amount of piperidine. In view of the much greater activity against the Dunning rat leukemia shown by *p*-[N,N-bis(2-methanesulfonoxyethyl)amino]benzaldehyde (**4**) compared to compound **3**[14] a similar condensation was attempted with **2** and **4**. The yellow granular product obtained, however, showed a lower sulfur and nitrogen content than that required by the expected product (**5**). Apparently, whereas the bischloroethyl group in **3** is stable to boiling ethanol, the bismethanesulfonoxyethyl group in **4** is partially hydrolyzed. However, when **2** and **4** were allowed to react in N,N-dimethylformamide at room temperature, 6-{*p*-[N,N-bis(2-methanesulfonoxyethyl)amino] benzylideneamino}coumarin (**5**) was obtained in 59% yield.

Condensation of 6-coumarylhydrazine (**6**) with **3** gave the *p*-[N,N-bis(2-chloroethyl)amino]benzaldehyde hydrazone (**7**). An analogous condensation of **6** with **4** in dimethylformamide at room temperature or boiling ethanol or chloroform gave only a viscous mass which could not be crystallized.

6-{3-[N,N-Bis(2-chloroethyl)amino]propionamido}-coumarin (**10**) as the hydrochloride was prepared essentially according to the procedure of Elderfield and LeVon.[15]

(1) This work was supported by Research Grant CA-02961 from the National Cancer Institute, National Institutes of Health, to the University of Michigan.

(2) For the preceding paper in this series, see R. C. Elderfield and D. Kodah, *Croat. Chem. Acta*, **36**, 33 (1964).

(3) H. R. Ing, *Trans. Faraday Soc.*, **39**, 372 (1943).

(4) W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. (Publishers) Ltd., London, 1962; J. P. Wheeler, *Cancer Res.*, **22**, 651 (1962); *Cancer Chemotherapy Rept.*, Suppl. 2 (Parts 1–3), 1 (1965).

(5) (a) R. Kuhn, D. Jerchel, F. Moewus, E. F. Möller, and H. Letré, *Naturwissenschaften*, **31**, 468 (1943); (b) H. Veldstra and E. Havinga, *Rec. Trav. Chim.*, **62**, 841 (1943); (c) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 954 (1946).

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(8) P. Giry and C. Mentzer, *Compt. Rend. Soc. Biol.*, **139**, 1055 (1945).

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(10) R. C. Elderfield and A. C. Meloan, *J. Med. Chem.*, **10**, 921 (1967).

(11) T. W. Lines, *J. Chem. Soc.*, **101**, 1758 (1912).

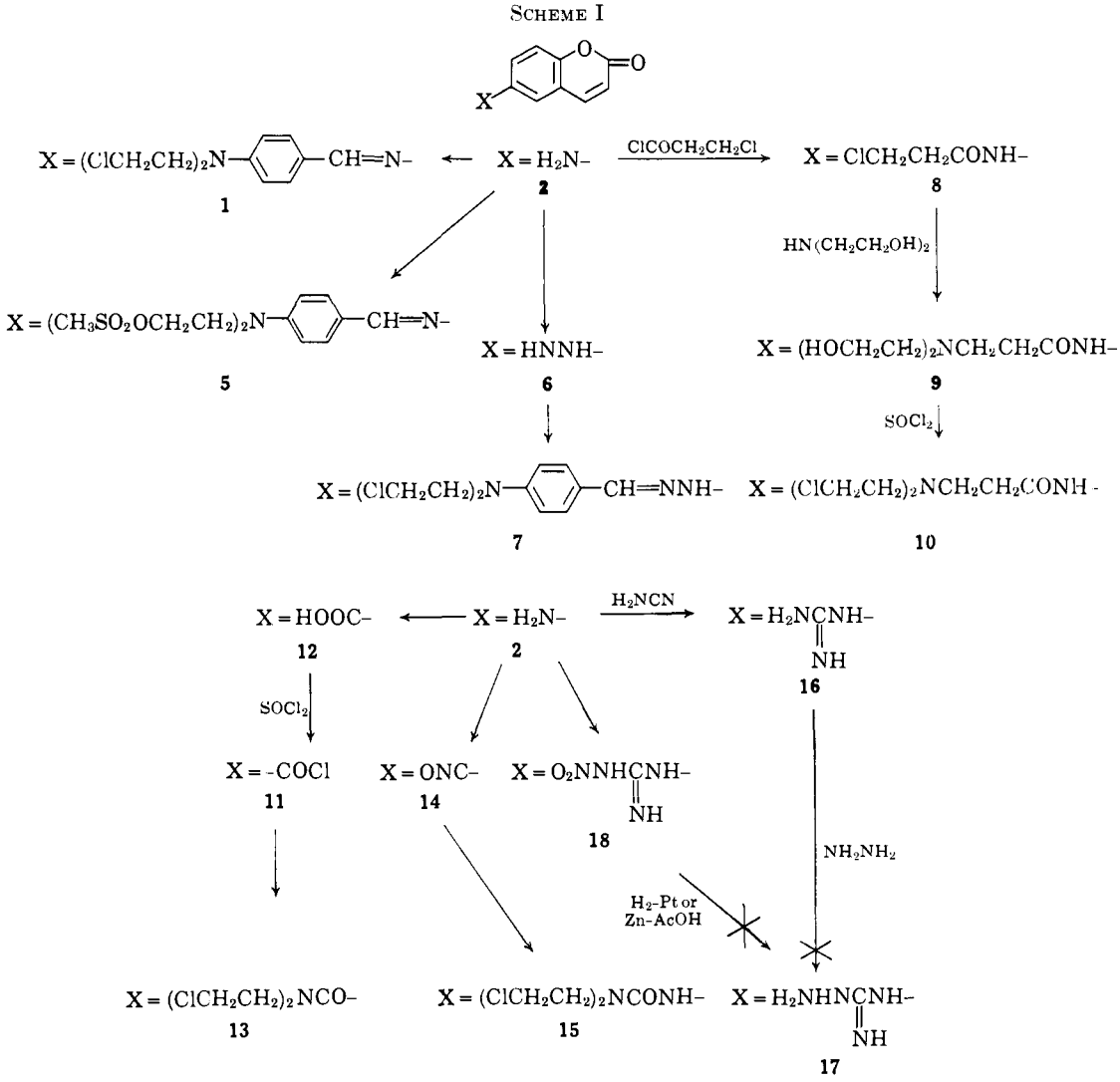
(12) S. Wawzonek in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p 195.

(13) Professor T. A. Geissman, of the University of California at Los Angeles, has recently informed one of us (R. C. E.) that he has succeeded in preparing a 4-aminocoumarin derivative.

(14) Private communication from Dr. Ralph L. Jones, Jr., Jackson Memorial Hospital, University of Miami, Miami, Fla., and from the Cancer Chemotherapy National Service Center, Bethesda, Md.

(15) R. C. Elderfield and E. F. LeVon, *J. Org. Chem.*, **25**, 1576 (1960).

SCHEME I



The preparation of coumarin-6-carbonyl chloride (**11**) from the acid (**12**) by refluxing with PCl_5 in $POCl_3$ has been reported by Dey and Dalal.[16] They describe it as a substance which began to shrink at 175° and melted completely at 182°. In our hands this procedure resulted only in recovery of **12**. However, when **12** was refluxed with $SOCl_2$ it was smoothly converted to the acid chloride (**11**) which melted at 131.5–132.5°. On reaction with N,N-bis(2-chloroethyl)amine **11** gave N,N-bis(2-chloroethyl)coumarin-6-carboxamide (**13**). No rearrangement of **13** was observed during recrystallization and the amide structure is supported by the infrared spectrum.

Coumaryl 6-isocyanate (**14**) has been prepared in about 22% yield by the action of phosgene on **2** as the free base.[17] By substituting the hydrochloride of **2** for the free amine we have increased the yield of **14** to 90%. Condensation of **14** with N,N-bis(2-chloroethyl)amine readily gave N,N-bis(2-chloroethyl)-N′-(6-coumaryl)urea (**15**).

In view of the known trypanocidal action of a number of guanidine derivatives[18] it was of interest to investigate the effect of incorporation of a guanidine function into the coumarin molecule. 6-Coumarylguanidine (**16**) was prepared by reaction of **2** with 50% aqueous cyanamide in ethanol.

Inasmuch as aminoguanidine appears to be less toxic than guanidine,[19] the preparation of N^1-(6-coumaryl)-N^3-aminoguanidine (**17**) was attempted. Although N^1-(6-coumaryl)-N^3-nitroguanidine (**18**) was obtained from **2** and N^1-methyl-N^1-nitroso-N^3-nitroguanidine by the general method of McKay and Wright,[20] reduction of **18** to **17** either by zinc dust and acetic acid or catalytically over PtO_2 failed. Finally reaction of **16** with hydrazine[21] failed to yield **17**.

Biological Evaluation.—The coumarin derivatives have been evaluated for cell culture cytotoxicity.[22,23] The results are shown in Table I. Further evaluations against experimental animal tumors[22] are summarized in Table II.

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(17) B. B. Dey and T. R. Seshadri, *J. Indian Chem. Soc.*, **8**, 293 (1931).

(18) E. M. Lourie and W. Yorke, *Ann. Trop. Med. Parasitol.*, **31**, 435 (1937); H. King, E. M. Lourie, and W. Yorke, *Lancet*, **233**, 136 (1937); S. R. Safir, S. Kushner, L. M. Brancone, and Y. Subbarow, *J. Org. Chem.*, **13**, 924 (1948), *inter alia*.

(19) V. A. Conard and R. L. Shriner, *J. Am. Chem. Soc.*, **55**, 2867 (1933).

(20) (a) A. F. McKay and G. F. Wright, *ibid.*, **69**, 3028 (1947); (b) A. F. McKay, *ibid.*, **71**, 1968 (1949).

(21) R. Phillips and J. F. Williams, *ibid.*, **50**, 2465 (1928).

(22) The evaluations were done through the facilities of the Cancer Chemotherapy National Service Center.

(23) These growth inhibition studies were carried out by the procedure of Eagle and Foley[24] as modified by the Cancer Chemotherapy National Service Center.[25]

(24) H. Eagle and G. E. Foley, *Cancer Res.*, **18**, 1017 (1958).

(25) *Cancer Chemotherapy Rept.*, **1**, 63 (1959).

TABLE I
CELL CULTURE CYTOTOXICITY

Compd	ED_{50},[a] μg/ml
10·HCl	25
7	11
13	20
1	11
16	1000×10^2
5	<1
15	54

[a] The concentration required to inhibit the growth of KB cells in culture to 50% of controls.[24]

TABLE II
WALKER 256 CARCINOSARCOMA

Compd	Dose, mg/kg sc	Tumor weight, g Test	Control	T/C	Wt loss[a]
10·HCl	3.80	0.0	5.3	0	−34
	1.90	0.0	5.3	0	−19
	0.95	0.3	5.3	5	−5
	0.47	4.3	5.3	81	0
7	170	6.5	6.4	101	−7
	100	3.0	6.4	46	0
	50.0	4.2	6.4	65	−3
	25.0	4.0	6.4	62	4
13	100	0.0	6.4	0	−6
	50.0	4.5	6.4	70	−5
	25.0	2.3	6.4	35	−1
1	200	5.8	5.3	109	5
	100	5.5	5.3	103	9
	50.0	4.9	5.3	92	2
	25.0	7.8	5.3	147	4
5	4.70	0.0	5.3	0	−19
	2.35	0.0	5.3	0	0
	1.17	1.0	5.3	18	5
	0.58	5.0	5.3	94	2
5	96.0[b]	0.3	7.2	4	−9
	24.0[b]	0.9	8.8	10	4
	12.0[b]	0.8	8.8	9	0
	6.00[b]	1.3	8.8	14	5
	3.00	4.0	8.8	45	7
	48.00[b]	0.0	5.0	0	−12
15	200	1.5	5.3	28	−16
	100	5.5	5.3	103	−4
	50.0	4.1	5.3	77	−2
	25.0	4.5	5.3	84	5

[a] Average weight increment of the test animals minus the average increment of control animals. [b] Administered intramuscularly.

Compound **16** showed T/C of 76 in one test against Sarcoma 180, of 82 against Carcinoma 755, and 94% (increase in survival time) against leukemia L1210.

Compound **5** showed T/C (increase in survival time) against leukemia L1210 of 148% at 24.0 mg/kg, 136% at 12.0 mg/kg, 140% at 6.00 mg/kg, 130% at 3.00 mg/kg, and 129% at 48.0 mg/kg.

Experimental Section[26]

6-{*p*-[N,N-Bis(2-chloroethyl)amino]benzylideneamino}coumarin (1).—A solution of 1.6 g of 6-aminocoumarin[27] and 2.7 g of *p*-[N,N-bis(2-chloroethyl)amino]benzaldehyde (**3**) in 40 ml of absolute ethanol containing 5 drops of piperidine was refluxed for 6 hr. After treatment with decolorizing carbon, the solution was concentrated under reduced pressure. On cooling, 2.4 g of light yellow plates separated which on recrystallization from absolute ethanol melted at 142–143°.

Anal. Calcd for $C_{20}H_{18}Cl_2N_2O_2$: C, 61.70; H, 4.66; Cl, 18.22; N, 7.20. Found: C, 61.77; H, 4.69; Cl, 18.10; N, 7.21.

6-{*p*-[N,N-Bis(2-methanesulfonoxyethyl)amino]benzylideneamino}coumarin (5).—A solution of 1.6 g of 6-aminocoumarin and 3.65 g of *p*-[N,N-bis(2-methanesulfonoxyethyl)amino]benzaldehyde[28] in 25 ml of DMF containing 5 drops of piperidine was stirred at room temperature for 6 hr. On addition of 100 ml of absolute ethanol and refrigeration overnight, 3 g of greenish yellow material separated and was collected, washed with absolute ethanol, and dissolved in $CHCl_3$. After treatment with decolorizing carbon and concentration, hot absolute ethanol was added to the solution from which yellow needles separated on cooling. Further recrystallization from chloroform–ethanol gave analytically pure material, mp 136.5–138°.

Anal. Calcd for $C_{22}H_{22}N_2O_8S_2$: C, 51.95; H, 4.75; N, 5.51; S, 12.61. Found: C, 51.97; H, 5.08; N, 5.51; S, 12.74.

***p*-[N,N-Bis(2-chloroethyl)amino]benzaldehyde 6-Coumarinylhydrazone (7).**—A solution of 1.76 g of 6-coumarinylhydrazine[29] and 2.7 g of **3** in 50 ml of absolute ethanol containing 5 drops of piperidine was heated under reflux. After 6 hr solid material separated from the light brown solution. On cooling 3.6 g of material was collected. Recrystallization from absolute ethanol gave the hydrazone as dull red granules, mp 157–158°.

Anal. Calcd for $C_{20}H_{20}Cl_2N_4O_2$: C, 59.41; H, 4.74; Cl, 17.54; N, 10.39. Found: C, 59.42; H, 4.80; Cl, 17.58; N, 10.25.

6-(3-Chloropropionamido)coumarin (8).—To a stirred solution of 3.2 g of **2** in 25 ml of $CHCl_3$ containing 2 ml of pyridine, 2.5 ml of 3-chloropropionyl chloride was added during 15 min while the temperature was held at 5°. The solution was allowed to come to room temperature and then was refluxed gently for 30 min. The cooled mixture was made basic with ice-cold Na_2CO_3 solution and stirred in an ice bath for 30 min. The dirty white solid was collected, washed thoroughly with water, and recrystallized from absolute ethanol (charcoal) to give 4 g of small white needles, mp 192.5°.

Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; Cl, 14.09; N, 5.57. Found: C, 57.42; H, 4.11; Cl, 14.20; N, 5.61.

6-[3-Bis(2-hydroxyethyl)aminopropionamido]coumarin (9).—A solution of 5 g of **8** and 4.25 g of iminodiethanol in 100 ml of absolute ethanol was refluxed for 48 hr, most of the ethanol was removed under reduced pressure, and the residue was taken up in ethyl acetate. After washing the solution with saturated NaCl solution and drying, removal of the solvent left 6 g of a thick viscous material which solidified to a white mass on refrigeration but could not be recrystallized.

For characterization 1.6 g of the crude product was converted to the picrate in 95% ethanol. On the basis of the picrate isolated the yield of **9** was about 90%. The picrate was recrystallized from 95% ethanol and formed canary yellow needles, mp 160–160.5°.

Anal. Calcd for $C_{22}H_{23}N_5O_{12}$: C, 48.09; H, 4.22; N, 12.75. Found: C, 48.30; H, 4.26; N, 12.79.

6-[3-Bis(2-chloroethyl)aminopropionamido]coumarin (10).—Crude **9** (5.25 g) was cooled in an ice bath and 10 ml of ice-cold $SOCl_2$ was added in one portion. After standing 1 hr in the ice bath, the mixture was left at room temperature overnight. Removal of the excess $SOCl_2$ under reduced pressure left a light brown powder which on recrystallization from absolute ethanol gave 5 g of the hydrochloride of **10** as clusters of small white needles, mp 183.5°.

Anal. Calcd for $C_{16}H_{19}Cl_3N_2O_3$: C, 48.81; H, 4.86; Cl, 27.02; N, 7.11. Found: C, 48.53; H, 5.07; Cl, 27.29; N, 7.23.

It was not possible to obtain the gummy, hygroscopic free base (**10**) in crystalline form.

Coumarin-6-carbonyl Chloride (11).—Coumarin-6-carboxylic acid[26] (270 mg) was refluxed with 3 ml of $SOCl_2$ for 3 hr. Removal of excess $SOCl_2$ under reduced pressure left a quantitative yield of the acid chloride. Two recrystallizations from benzene–petroleum ether (30–60°) gave analytically pure material, mp 131.5–132.5°.

Anal. Calcd for $C_{10}H_5ClO_3$: C, 57.57; H, 2.42; Cl, 17.00. Found: C, 57.64; H, 2.59; Cl, 16.89.

Coumarin-6-[N,N-bis(2-chloroethyl)]carboxamide (13).—A suspension of 2 g of N,N-bis(2-chloroethyl)amine hydrochloride

(26) Melting points are uncorrected and were taken on a Thomas–Hoover Unimelt melting point apparatus. Microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(27) G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **85**, 1230 (1904).

(28) R. C. Elderfield, R. N. Prasad, and T. K. Liao, *J. Org. Chem.*, **27**, 573 (1962).

in 25 ml of benzene was shaken with a solution of 0.5 g of NaOH in 10 ml of water. The benzene layer was washed once with water and dried (Na_2SO_4), concentrated to half its volume, and chilled to 5°. To the well-stirred chilled solution a benzene solution of coumarin-6-carbonyl chloride (from 0.9 g of the acid) was added dropwise. A white solid began to separate within a few minutes and, after addition of the acid chloride was complete, the mixture was stirred in the cold bath for 30 min and at room temperature for 30 min, refluxed for 1.5 hr, and allowed to stand overnight at room temperature. After collection of 0.78 g of bis(2-chloroethyl)amine hydrochloride, the light yellow filtrate was treated with decolorizing carbon, concentrated, and left at room temperature for 2–3 hr. The filtered solution was heated just to boiling and carefully diluted with petroleum ether (30–60°). On cooling 1.25 g (83%) of the chloroamide separated as clusters of shiny white plates. Similar recrystallization raised the melting point to 111–112°. The infrared spectrum (KBr disk) showed amide absorption at 1647 cm^{-1} indicating that no rearrangement had occurred.

Anal. Calcd for $C_{14}H_{13}Cl_2NO_3$: C, 53.52; H, 4.17; Cl, 22.57; N, 4.46. Found: C, 53.60; H, 4.16; Cl, 22.50; N, 4.57.

6-Coumaryl Isocyanate (14).—Dry HCl was passed through a solution of 6 g of 6-aminocoumarin in 150 ml of dry toluene until precipitation of the hydrochloride was complete. After refluxing for 30 min dry $COCl_2$ was passed through the gently boiling suspension (hood and NaOH trap). Solution of the hydrochloride was essentially complete after 3 hr. On concentration to about 75 ml and filtering from a trace of solid, 6.3 g (90%) of the isocyanate separated as shiny white plates. Recrystallization from benzene raised the melting point to 166–167°, lit.[17] mp 163°.

Anal. Calcd for $C_{10}H_5NO_3$: C, 64.17; H, 2.69; N, 7.48. Found: C, 64.25; H, 2.62; N, 7.60.

N^1,N^1-Bis(2-chloroethyl)-N^3-(6-coumaryl)urea (15).—To a stirred suspension of 6-coumaryl isocyanate (1.9 g) in 100 ml of dry benzene a benzene solution of bis(2-chloroethyl)amine (from 2.0 g of the hydrochloride) was added. After refluxing for 6 hr the mixture was stirred for an additional 12 hr at room temperature. A granular brown solid (3.0 g) separated and was recrystallized from ethyl acetate to give the urea as clusters of fine white needles, mp 136–137°.

Anal. Calcd for $C_{14}H_{14}Cl_2N_2O_3$: C, 51.08; H, 4.29; Cl, 21.54; N, 8.51. Found: C, 50.92; H, 4.36; Cl, 21.60; N, 8.61.

6-Coumarylguanidine (16).—6-Aminocoumarin hydrochloride (12.9 g) was added to a solution of 16.5 g of 50% aqueous hydrogen cyanamide[29] in 150 ml of ethanol and the suspension was heated to boiling with stirring. Solution of the solid occurred within 10 min and immediately thereafter solid material separated. After refluxing with stirring for 4.5 hr and standing overnight at room temperature, 10.0 g of yellowish white granular material was collected and washed with ethanol. Water was added dropwise to a boiling suspension of the material in ethanol until it was all in solution. On treatment with decolorizing carbon and concentration of the solution, the hydrochloride of the guanidine, mp 296–297° dec, separated.

Anal. Calcd for $C_{10}H_{10}ClN_3O_2$: C, 50.11; H, 4.21; Cl, 14.80; N, 17.54. Found: C, 50.32; H, 4.34; Cl, 14.74; N, 17.61.

The free guanidine liberated from the hydrochloride melted at 208–209°. It was insoluble in common solvents and could not be recrystallized.

N^1-Nitro-N^3-(6-coumaryl)guanidine (18).—A suspension of 3.2 g of 6-aminocoumarin and 3.2 g of N^1-methyl-N^1-nitroso-N^3-nitroguanidine[20b] in 50 ml of 50% aqueous ethanol was refluxed with stirring for 1 hr. Solution was rapid and after 15 min solid separated from the red solution. After cooling 4.0 g of light brown material was collected with absolute ethanol and recrystallized from glacial acetic acid by chilling to give white granular crystals, mp 234°.

Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.25; N, 22.58. Found: C, 48.62; H, 3.42; N, 22.38.

(29) Aero Cyanamide from Cyanamid of Canada Ltd., Montreal, Canada.

Synthesis of Potential Anticancer Agents. XIX. Nitrogen Mustards from 7-Hydroxycoumarin Derivatives[1,2]

ROBERT C. ELDERFIELD AND A. C. MEHTA

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48104

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7-Hydroxycoumarin derivatives when subjected to the Mannich reaction with iminodiethanol gave the expected eight Mannich bases which were in turn converted to nitrogen mustards. 7-Hydroxycoumarin-4-acethydrazide on reaction with representative 4-[N,N-bis(2-chloroethyl)amino]benzaldehydes gave the benzylidene mustards. The compounds prepared have been evaluated against cell cultures and experimental animal tumors.

In view of the suggestive experimental antitumor activity shown by certain coumarin nitrogen mustard derivatives,[2] it seemed advisable to explore possible cytotoxic properties of such coumarin derivatives somewhat further. Since there appeared to be no *a priori* reason to select one type of structure over others, accessibility of starting materials was the controlling factor in selection of compounds for synthesis. In this paper we present the synthesis of nitrogen mustards derived from 7-hydroxycoumarins and from 7-hydroxycoumarin-4-acetic acid together with the results of pharmacological evaluation of the cytotoxicity of the candidate compounds.

7-Hydroxycoumarin (**1a**) and its 4-methyl (**1b**) and 4-phenyl (**1c**) derivatives were subjected to the Mannich reaction with formaldehyde and iminodiethanol giving the 7-hydroxy-8-[N,N-bis(2-hydroxyethyl)aminomethyl]coumarins (**2a–c**) (see Table I). Optimum yields of **2a** and **2b** were obtained by the procedure of Cromwell[3] in which the hydroxycoumarin is heated with an activated stock solution of the reagent for 6 hr. Conventional Mannich reaction conditions gave better results in the preparation of **2c** but a 60-hr period of refluxing was required.

The Mannich reaction with **1b** and a variety of amines has been reported by Desai[4] who obtained either the expected product or a 7,8-(*m*-oxazino)coumarin depending on the nature of the secondary amine. It was assumed that the aminomethyl group entered the 8

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(2) For the preceding paper in this series, see R. C. Elderfield and J. Roy, *J. Med. Chem.*, **10**, 918 (1967).

(3) N. H. Cromwell, *J. Am. Chem. Soc.*, **68**, 2634 (1946).

(4) R. B. Desai, *J. Org. Chem.*, **26**, 5251 (1961).