Mixed Bifunctionality. Antitumor Properties of 2-Chloroethyl Sulfide Derivatives of Polynuclear Aromatic Hydrocarbons[1]

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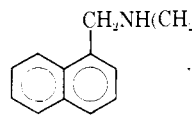
A high degree of specificity has been demonstrated in the relationships between the structure and antitumor activity of 2-chloroethyl sulfide derivatives of several polycyclic aromatic hydrocarbons. The sulfur mustards of 9,10-dimethylanthracene were found to be particularly potent compounds. The presence of a salt-forming group in the alkylating side chain resulted in enhanced molar activity. The coincidence of intense cytotoxic activity in both the acridine and anthracene derivatives supports a mechanism of action that involves the spatial configuration of the carrier component as well as covalent binding by the alkylating moiety.

The discovery of a series of heterocyclic monofunctional nitrogen mustards displaying pronounced antitumor activity[2] was followed by the synthesis of a parallel group of monofunctional sulfur mustards.[3] Comparisons of the two groups of compounds showed antitumor activity to be present in a wider spectrum of the sulfur mustards of aromatic heterocyclic moieties than in the corresponding monofunctional nitrogen mustard derivatives.[3]

This finding led to the investigation of a series of polynuclear aromatic hydrocarbon groups, sterically analogous to the heterocyclics and well known to possess significant cytotoxic activity, as possible potentiators of monofunctional alkylating agents. The initial assumption that incorporation of a naphthalene nucleus (I) would give a model inactive compound, thus forming a base line from which to progress to three- and four-ring potentiating nuclei, proved incorrect; this compound met our criterion of activity in



I

the Ehrlich ascites tumor system by causing an increase of more than 80% in the mean survival time of treated mice.[2,3] Substitution of the *p*-chlorophenyl radical for the naphthyl group in I resulted in loss of activity.

Increases in antitumor activity were noted as structural alterations were made in the direction of the more complex polynuclear carcinogens (Table I); the quantitative data given there will be discussed under Biological Results.

In order to provide comparisons with Seligman's hemisulfur mustard derivative of 7-methylbenz[*a*]anthracene,[4] the corresponding derivatives of the same classes of aryl groups (lacking the salt-forming amino group) were made, as listed in the second section of Table I. These chemicals are completely hydrophobic, but may be expected to have moderate lipid solubility; the dosages necessary for display of biological activity are considerably higher than those for the corresponding ionic compounds, as would be expected.

The synthesis of the nonbasic chloroethyl sulfides involved alkylation of sodiomercaptoethanol and replacement of the hydroxy group in the intermediate (see Table II) by reaction with an equimolar quantity of thionyl chloride in dioxane solution.[5] Excess thionyl chloride led in some cases to cleavage of the arylmethyl-sulfur bond, and also, in the case of the anthryl derivative, to nuclear chlorination, presumably in the *meso* position, although a proof of structure by independent synthesis was not undertaken.

Experimental Section

Melting points were taken in open capillary tubes in a Hershberg apparatus using total immersion thermometers and are reported as uncorrected values. All of the 2-chloroethyl compounds carrying basic side chains were prepared by the action of excess $SOCl_2$ on their hydroxy precursors.[2,3]

The first stage in their synthesis was the attachment of the aminopropanol residue, either by reaction with the arylaldehyde and catalytic reduction (method I), or by direct reaction of the amino alcohol with the chloromethylated hydrocarbons (method II). The latter method gave an impure product, and usually a distillation was necessary to remove the disubstituted impurity. The intermediates were converted in excess $SOCl_2$[2,3] to the chloropropyl derivatives, which were used to alkylate mercaptoethanol. Replacement of the hydroxyl group with chlorine produced the alkylating agents in Table I. Data on the intermediate compounds are given in Tables II and III.

N-(3-Chloropropyl)-*p*-chlorobenzylamine Hydrochloride.—To a stirred solution of 21 g of 3-(*p*-chlorobenzylamino)-1-propanol[6] in 40 ml of 1:1 chloroform–hexane was added 40 ml of $SOCl_2$, in portions. After standing overnight at room temperature, the solvent was removed *in vacuo*, and the residue was decomposed with ethanol, crystallized, and filtered from ethanol. The yield was 27.7 g (slightly greater than theoretical), mp 209–211°. A sample recrystallized from ethanol gave the analytical sample reported in Table II.

N-[3-(2-Hydroxyethylmercapto)propyl]-*p*-chlorobenzylamine Hydrochloride.[7]—A solution of 25.2 g (100 mmoles) of the previous compound in about 400 ml of hot 95% ethanol was added to a stirred solution of 10 ml of mercaptoethanol in 229 ml of 1 *N*

(1) Supported by Research Grants CA 02975 and CA 06927 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) (a) R. K. Preston, R. M. Peck, E. R. Breuninger, A. J. Miller, and H. J. Creech, *J. Med. Chem.*, **7**, 471 (1964); (b) R. M. Peck, E. R. Breuninger, A. J. Miller, and H. J. Creech, *ibid.*, **7**, 480 (1964).

(3) R. M. Peck, A. P. O'Connell, and H. J. Creech, *ibid.*, **9**, 217 (1966).

(4) A. M. Seligman, M. Milden, and O. M. Friedman, *Cancer*, **2**, 701 (1949). When given as a single intraperitoneal injection of 5.0 mg in oil, this compound gave positive antitumor results in mammary adenocarcinoma, negative results in myelogenous leukemia, and questionable results in Sarcoma 37. For a 20-g mouse, this is comparable to three doses of approximately 250 μmoles/kg, the dosage units used in Table I.

(5) W. T. Hunter, J. S. Buck, F. W. Gubitz, and C. H. Bolen, *J. Org. Chem.*, **21**, 1512 (1956).

(6) Prepared by method I; bp 91–95° (15 μ); previously prepared by method II and reported to boil at 127–132° (0.8 mm) by A. R. Surrey, S. O. Wiuthrop, M. K. Rukwid, and B. F. Tullar, *J. Am. Chem. Soc.*, **77**, 633 (1955).

(7) The only fundamental departure from this procedure is the case in which the free base of the product is crystalline and simple dilution of the concentrated reaction mixture precipitates the product which is recrystallized from ethanol.

Table I

Antitumor Activity and Analytical Information

Aryl radical	Side chain	Salt	Antitumor activity[b] Range, μmoles/kg	Degree	Yield, %	Mp, °C	Calcd, % C	H	S	Cl	Found, %[a] C	H	S	Cl
p-Chlorophenyl	$ClH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	75–100	1.3	61	179–181	15.80	5.77	10.19	33.78	16.02	5.60	10.36	33.52
1-Naphthyl	$ClH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	125	1.9	76	131–133	58.18	6.11	9.72	21.12	58.21	6.11	9.76	21.50
2-Methyl-1-naphthyl	$ClH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	60–80	2.1	87	143.5–145	59.33	6.73	9.31	20.59	59.37	6.79	9.51	20.56
4-Methyl-1-naphthyl	$ClH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	100–200	2.2	61	166–169	59.33	6.73	9.31	20.59	59.33	6.76	9.18	20.37
9-Anthryl	$CH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	30–70	2.5	50	132–135	63.22	6.25	8.42	18.14	62.55	6.32	8.38	18.60
9-Phenanthryl	$CH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	20–75	2.5	99	155–156	63.22	6.25	8.42	18.14	63.27	6.18	8.25	18.82
10-Methyl-9-anthryl	$CH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	1.0–31	2.6	80	167–169	63.95	6.39	8.11	17.97	63.48	6.46	7.78	18.32
10-Methyl-9-phenanthryl	$CH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	8–40	2.1	55	153–155	63.95	6.39	8.11	17.97	63.72	6.62	8.10	18.03
7-Benz[*c*]anthryl	$CH_2NH(CH_2)_3SCH_2CH_2Cl$	HCl	14–60	2.1	68	73–75	67.00	5.86	7.45	16.16	66.79	6.02	7.16	16.41
2-Naphthyl	$CH_3SCH_2CH_2Cl$	...	250–400	1.8	39	42–45	66.00	5.53	13.55	14.96	66.61	5.54	12.79	15.58
2-Methyl-1-naphthyl	$CH_3SCH_2CH_2Cl$	...	250–400	1.8	45	87–88.3	67.10	6.02	12.79	14.13	67.31	6.21	12.65	14.05
9-Anthryl	$CH_3SCH_2CH_2Cl$	...	150–1600	2.2	79	118.5–120.5	73.19	5.27	11.18	12.37	71.35	5.30	10.96	12.56
10-Methyl-9-anthryl	$CH_3SCH_2CH_2Cl$	...	6–800	2.3	72	137.5–139.5	71.88	5.70	10.66	11.78	72.00	5.31	10.63	12.09

[a] Values are either single analyses or averages of checks. [b] See section on Biological Results.

Table II

Substituted Hydroxyethyl Sulfides

Aryl radical	Side chain	Salt	Yield, %	Mp, °C	Calcd, % C	H	S	Cl	Found, %[a] C	H	S	Cl
p-Chlorophenyl	$ClH_2NH(CH_2)_3SCH_2CH_2OH$	HCl	70	117.5–118.5	48.65	6.16	10.82	23.93	48.87	6.64	10.85	21.15
1-Naphthyl	$ClH_2NH(CH_2)_3SCH_2CH_2OH$	...	61	185 (25 μ)[d]	60.80	7.69	11.65		70.18	7.76	11.27	
2-Methyl-1-naphthyl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	HCl	77	86–88	62.70	7.42	9.84	10.88	62.34	7.50	9.87	11.18
4-Methyl-1-napothyl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	HCl	68	111–113	62.70	7.42	9.84	10.88	63.12	7.42	9.86	11.22
9-Anthryl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	HCl	62	127–129	66.40	6.68	8.86	9.80	65.99	6.92	8.61	10.16
9-Phenanthryl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	HCl	82	122–124 dec[b]	66.40	6.68	8.86	9.80	66.51	6.76	8.60	9.51
10-Methyl-9-anthryl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	...	78	91–95	74.33	7.43	9.41		73.91	7.97	9.34	
10-Methyl-9-phenanthryl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	...	90	87–92	74.33	7.43	9.41		73.56	7.53	9.88	
7-Benz[*c*]anthryl	$CH_3NH(CH_2)_3SCH_2CH_2OH$	HNO_3	60[c]	138–140 dec	65.78	5.98	7.32		65.44	6.10	7.18	
2-Naphthyl	$CH_3SCH_2CH_2OH$[d]	...	85	53–56	71.53	6.46	11.68		70.77	6.34	14.54	
2-Methyl-1-naphthyl	$CH_3SCH_2CH_2OH$	...	77	48–50	72.38	6.94	13.80		72.06	6.94	13.90	
9-Anthryl	$CH_3SCH_2CH_2OH$[e]	...	85	96–97	76.07	6.01	11.96		76.67	6.09	11.70	
10-Methyl-9-anthryl	$CH_3SCH_2CH_2OH$[f]	...	61	124–126.5	76.55	6.43	11.36		76.64	5.95	10.98	

[a] Values are either single analyses or averages of checks. [b] Recrystallized from dilute HCl. [c] Yield of hydrochloride, mp 74–77°, which was used in the next reaction. [d] Previously prepared by another method by A. H. Weinstein and R. M. Pierson, *J. Org. Chem.*, **23,** 554 (1958), who reported mp 52–53.5°. [e] The required 9-chloromethylanthracene was prepared according to ref 5. [f] The required 9-chloromethyl-10-methylanthracene was prepared according to J. L. Adelfang and G. H. Daub, *J. Am. Chem. Soc.*, **80,** 1405 (1958). [g] Boiling point.

methanolic NaOH. The mixture was heated and concentrated on the steam cone for 1 hr, diluted with 200 ml of ether, and let stand overnight. After filtration of 10.9 g of NaCl (93% of the theoretical), the mixture was concentrated and the residue was heated 1 hr in a crystallizing dish on the steam cone and then partitioned between ether and water. The organic layer was washed and then extracted with 90 ml of 1 *N* HCl. The extract plus a small water wash was concentrated *in vacuo* and the residue was crystallized from ethanol–acetone. The yield was 20.7 g (70%), mp 147.5–148.5° (Table II).

3-(10-Methyl-9-anthrylmethylamino)-1-propanol (Method I).—A mixture of 5.0 g of 10-methylanthracene-9-carboxaldehyde and 1.75 g of 3-amino-1-propanol in 50 ml of absolute ethanol was refluxed for 2 hr (an additional 0.2 g of amino alcohol was added after 1 hr), cooled, diluted to a faint turbidity, and cooled overnight to give 5.2 g of the the anil, mp 97–98° (Table II). A suspension of 5.1 g of the anil and 300 mg of PtO_2 catalyst in 20 ml of alkali-distilled ethanol was shaken 8 hr under 3.5 kg/cm² of hydrogen; the suspension became a pale yellow and hydrogen uptake ceased. The mixture was diluted with an equal volume of water and cooled overnight. The mixed solid was filtered and stirred with dilute acetic acid, and the insoluble material was removed by filtration. The filtrate was made alkaline to give 4.1 g of impure base. Recrystallization from dilute ethanol gave 2.4 g, mp 84–86°; a further recrystallization from benzene–petroleum ether (bp 30–60°) gave 1.8 g, mp 91–93°. A sample was converted to the nitrate for analysis (Table II).

3-(4-Methyl-1-naphthylmethylamino)-1-propanol (Method II).—A solution of 15 g of 1-chloromethyl-4-methylnaphthalene in ethanol–benzene was added with stirring to 25 g of 3-amino-1-propanol in 25 ml of ethanol. The mixture was refluxed for 1 hr, concentrated to two-thirds volume, and cooled; 6.3 g of 50% aqueous NaOH was added with stirring. The precipitated NaCl was removed by filtration, the filtrate was concentrated, and the residue was distilled twice *in vacuo* in a modified von Braun flask to give 12.4 g (68.5%) of product, bp 134–136° (20 μ), neut equiv 235 (calcd 229.5).

Attempted Synthesis of 9-Anthrylmethyl 2-Chloroethyl Sulfide in Excess Thionyl Chloride.—To 20 ml of stirred $SOCl_2$ was added 2.05 g of 2-(9-anthrylmethylthio)ethanol (Table II). The mixture was allowed to stand at room temperature overnight, excess $SOCl_2$ was removed *in vacuo*, and the crystalline residue was filtered from hexane and washed with a little ethanol. It weighed 1.4 g, mp 158–167°. Recrystallization from benzene–petroleum ether gave 1.0 g, mp 173–174°. *Anal.* Calcd for $C_{17}H_{15}ClS$ (the desired product): C, 71.19; H, 5.27; Cl, 12.37; S, 11.18. Found: C, 69.32, 69.59; H, 3.64, 3.85; Cl, 27.22, 26.91; S, none. Calcd for $C_{15}H_{10}Cl_2$: C, 69.02; H, 3.86; Cl, 27.15. This corresponds to x-chloro-9-chloromethylanthracene. The same compound was isolated from a similar $SOCl_2$ reaction with 9-hydroxymethylanthracene.

Biological Results

Because of their unique suitability, albino mice (ICR Swiss) bearing Ehrlich ascites tumors were employed for the quantitative determinations of the activities of these compounds. The procedures have been described in detail in previous publications;[2,3] they are based on the exceptional capability of certain analogs of the nitrogen and sulfur mustards to prolong by a severalfold factor the survival time of mice that have been inoculated intraperitoneally with several million ascites tumor cells.

Table III

Precursors to Compounds in Table II

R	Method[c]	Salt	Yield, %	Mp or bp (μ), °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, %[a] C	Found, %[a] H	Found, %[a] N	Found, %[a] Cl
Chloropropylamine Derivatives, $RCH_2NH(CH_2)_3Cl$												
p-Chlorophenyl		HCl	95	210.5–212.3	47.17	5.54	5.50	41.77	47.38	5.75	5.67	41.08
1-Naphthyl		HCl	65	175.5–176.5	62.25	6.35	5.18	26.23	62.36	6.55	4.85	25.97
2-Methyl-1-naphthyl		HCl	82	144–146[b]	63.41	6.74	4.92	24.92	63.25	6.96	4.96	24.58
4-Methyl-1-naphthyl		HCl	66	204–205.3	63.41	6.74	4.92	24.92	63.96	6.81	4.85	24.92
9-Anthryl		HCl	60	190–192	67.50	5.98	4.37	22.13	67.18	6.48	4.36	22.09
9-Phenanthryl		HCl	100	224–225	67.50	5.98	4.37	22.13	67.48	6.24	4.31	22.41
10-Methyl-9-anthryl		HCl	41	200.5–201.5	68.28	6.34	4.19	21.20	68.33	6.43	4.09	20.81
10-Methyl-9-phenanthryl		HCl	50	223–225	68.28	6.34	4.19	21.20	68.39	6.24	4.21	21.11
7-Benz[*a*]anthryl		HCl	47	213–214.5	71.32	5.72	3.78	19.14	70.84	6.23	3.79	18.96
3-Amino-1-propanol Derivatives, $RCH_2NH(CH_2)_3OH$												
1-Naphthyl	II	...	53	122–132 (60)				215.5[i]				220[i]
2-Methyl-1-naphthyl	II	HNO_3	78[d]	178–179.5	61.65	6.90	9.59		62.89	6.92	9.38	
4-Methyl-1-naphthyl	II	...	69	131–135 (20)				229.5[i]				235[i]
9-Anthryl	I	...	65	81–82	81.50	7.23	5.28		81.61	7.32	5.51	
9-Phenanthryl	I	...[e]	75	80–82	81.50	7.23	5.28		81.34	7.22	4.80	
10-Methyl-9-anthryl	I	HNO_3	35	185.5–187	66.48	6.48	8.18		66.80	6.99	8.15	
10-Methyl-9-phenanthryl	II[f]	...	45	101–113[g]	81.74	7.58	5.01		81.23	7.69	4.90	
7-Benz[*a*]anthryl	I[h]	...	64	86–90	83.80	6.72	4.44		84.66	6.42	4.11	
Iminopropanol Derivatives, $RCH{=}N(CH_2)_3OH$												
9-Anthryl			55	115.5–116.5	82.10	6.51	5.32		82.38	6.43	5.33	
9-Phenanthryl			52	82.5–84	82.10	6.51	5.32		82.14	6.51	5.28	
10-Methyl-9-anthryl			81	97–98	82.37	6.91	5.05		83.32	6.82	4.52	
7-Benz[*a*]anthryl			81	110–114	84.38	6.11	4.47		85.03	6.12	4.12	

[a] Values are either single analyses or averages of checks. [b] Melt resolidifies and remelts at 171–172°. [c] See Experimental Section. [d] Over-all yield of salt; the free base was obtained in 83% yield and boiled at 110–125° (15 μ). The salt was obtained by addition of concentrated $NaNO_3$ to a solution of base in dilute acetic acid. [e] The nitrate was also obtained and used as a purification step, mp 153–155°. [f] The chloromethyl precursor of this compound was prepared according to S. Hauptmann, *Chem. Ber.*, **93**, 2604 (1960). [g] Sample prepared by sublimation *in vacuo* at 110° (10 μ). [h] This compound was also isolated in lower yield *via* method II. [i] Neutralization equivalent.

The results of the tests are expressed in terms (a) of the degree of activity against the tumors and (b) of effective range of the compound that caused at least an 80% increase in the survival time over that of the controls. The dosages of compounds are presented as the number of micromoles per kilogram of body weight of the mouse. The effective range runs from the minimum dosage producing the desired action, through an optimum level for maximum influence on survival time, and up to the highest dosage still producing the desired antitumor effect despite concomitant toxic activity. The ratio of the highest to the lowest dosages is, therefore, an expression of therapeutic index; the lowest effective dosage is a measure of the molar activity of the compound.

All experiments were terminated at the conclusion of a period (usually 48 days) that was three times the mean survival time of the control mice. In our experience with nitrogen mustards, nearly all of the mice surviving this period could be expected to live more than 15 weeks without signs of ascites tumor development. If all the mice in the treated group lived to the time of sacrifice, a maximum value of 3.0 was assigned as the degree of antitumor activity. A value of 1.0 was recorded when the mean survival time of the experimental group did not exceed that of the control group. The value for the degree of activity of an effective compound as recorded in Table I represents the average of the two minimum values of 1.8, obtained at the lowest and highest dosages, and the values found at 3–8 intermediate dosages. Consequently, a highly effective compound will display an average value of 2.2–2.5; values of 1.8–2.1 indicate a moderately active compound capable of prolonging the survival time of the mice bearing ascites tumors by a factor of two.

Judged by these criteria, the most potent compounds are those that display (1) the highest degree of antitumor activity, (2) the widest effective range, and (3) the lowest initial dosage producing an 80% increase in survival time. Only a very limited number of the sulfur mustard and the monofunctional nitrogen mustard derivatives have been found to be as effective as the bifunctional nitrogen mustards in causing prolongation of the survival time of mice with ascites tumors. Our previous studies[2,3,8] have demonstrated that for potent antitumor activity only one 2-chloroethyl group is necessary provided the molecule contains a specific heterocyclic component, such as acridine or benz[*c*]acridine.

It is evident from the information in Table I that incorporation of certain polycyclic aromatic hydrocarbons into the side chains containing the sulfur mustard moiety also produces compounds with pronounced effectiveness against ascites tumors. The 10-methyl-9-anthryl derivative with the basic side chain displayed a molar activity and a wide dosage range equal to those of the acridine sulfur mustards described earlier;[3] furthermore, it was discovered to be unusually effective against the ascites form of Sarcoma 37. An examination of the table shows that the first series of compounds containing the basic side chain exhibited more pronounced antitumor effects at considerably lower dosage levels than the corresponding sulfur mustards with the simpler side chain. Other trends are indicated, namely, the general increase in antitumor effectiveness as the polycyclic component becomes more complex and the increased molar activity caused by the presence of a methyl substituent in each of the aromatic nuclei. It is conceivable that a rela-

(8) H. J. Creech, E. Breuninger, R. F. Hankwitz, Jr., G. Polsky, and M. L. Wilson, *Cancer Res.*, **20**, 471 (1960).

tionship exists between the carcinogenic and the antitumor potentialities of the aryl component. Studies by Cook and Kennaway[9] have shown that 9,10-dimethylanthracene is a moderately active carcinogen in mice, whereas benz[*a*]anthracene and 10-methylphenanthrene exhibit no more than slight carcinogenic activity. Since certain methyl-substituted benz[*a*]-anthracenes are potent carcinogens, we propose to synthesize the sulfur and nitrogen mustard derivatives of several of these polycyclic aromatic compounds and determine the existence of any carcinogenic–carcinostatic correlations.

Cross-linking ability is generally considered to be a requirement for a tumor-inhibiting alkylating agent. This condition is fulfilled by the bifunctional nitrogen and sulfur mustards. Several of our monofunctional mustards have also displayed pronounced antitumor activity; these have contained a specific polycyclic component, such as a derivative of acridine or anthracene. It is probable that these half-mustards also exert their action by a bifunctional mechanism, one phase of which involves the reaction of the 2-chloroethyl group with the guanine moiety of deoxyribonucleic acid, as shown by Lawley and Wallick,[10] or with some other essential constituent. It seems reasonable that cross-linking can be completed by intercalation of the polycyclic component between the base pairs in deoxyribonucleic acid, a process proposed by Lerman[11] for the acridine nucleus and by Boyland and Green[12] for the polynuclear hydrocarbons.

(9) J. W. Cook and E. L. Kennaway, *Am. J. Cancer*, **39**, 381 (1940); E. L. Kennaway, N. M. Kennaway, and F. L. Warren, *Cancer Res.*, **2**, 157 (1942).

(10) P. D. Lawley and C. A. Wallick, *Chem. Ind. (London)*, 633 (1957); P. D. Lawley *Proc. Chem. Soc.*, 240 (1957); P. Brookes and P. D. Lawley, *Brit. Med. Bull.*, **20**, 91 (1964).

(11) L. S. Lerman, *J. Cellular Comp. Physiol.*, **64**, Suppl. 1, 1 (1964).

(12) E. Boyland and B. Green, *Brit. J. Cancer*, **16**, 507 (1962); *J. Mol. Biol.*, **9**, 580 (1964).

Acetylenic Carbamates. A New Class of Potential Oncolytic Agents

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A series of 1,1-diaryl-2-propynyl carbamates is described. Unlike the previously reported 1,1-dialkyl-2-propynyl carbamates, this series was found to have potent antitumor effects against various tumor systems in mice. Oral as well as parenteral activity of these compounds is demonstrated. Structure–activity relationships are discussed.

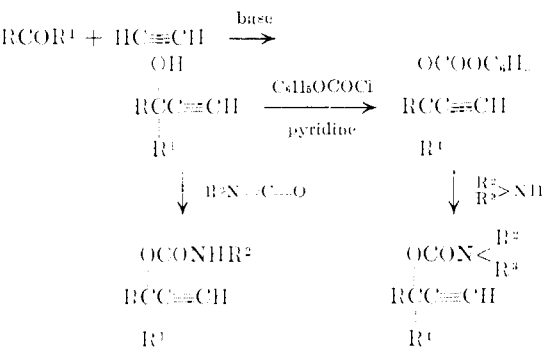
An investigation of the intramolecular reactions of acetylenic compounds[1-3] led to the synthesis of 1,1-diphenyl-2-propynyl carbamate. This compound showed interesting activity in our cancer screen. On this basis, a series of diaryl carbamates was investigated for antitumor activity. In contrast to that reported for 1,1-dialkyl-2-propynyl carbamates,[4,5] these were void of any hypnotic properties. However, unlike the 1,1-dialkyl compounds, this series demonstrated repeatable activity against a series of mouse neoplasms.

Since these compounds were most active against the myelogenous leukemia C1498 and the plasma-cell tumor X5563, these tumors were used to evaluate the relative efficacy of the compounds as antitumor agents. Although most of the carbamates showed activity in these tests, certain variations in structure appeared to promote optimum antitumor effects.

Although the preliminary activity of these compounds was established by the intraperitoneal route of therapy, other routes were explored. The oral activity was of particular interest, inasmuch as it is more desirable to administer oncolytic agents for clinical use by the oral route. Studies were carried out and comparisons made by both the intraperitoneal and oral routes. More extensive studies are in progress including delayed therapy experiments, broad-spectrum tumor studies, tissue localization in mice, hemopoetic effects, and general toxicological effects.

Chemistry.—The preparation of the carbamates by a modified procedure described by Mehta and Catlin[1] is outlined in Scheme I. The 1,1-diaryl-2-propyn-1-ols,

Scheme I



prepared by well-known procedures from diaryl ketones, were treated with phenyl chloroformate using pyridine as an acid acceptor in dichloromethane to give the phenyl carbonate intermediate. In the presence of an amine, this intermediate was converted to the carbamate and phenol. The crude products were purified by crystallization to give yields of 5–30%. No effort was made to obtain optimum yields. The N-monosubstituted carbamates could be prepared directly from the 2-propyn-1-ols using an alkyl isocyanate. The allyl carbamates were obtained by catalytic hydrogenation of the appropriately substituted 2-propynyl carbamates.

(1) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **28**, 2465 (1963).

(2) N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **27**, 2927 (1962).

(3) N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **29**, 1851 (1964).

(4) M. D. Mehta and E. R. Catlin, U. S. Patent 3,062,870 (Nov 6, 1962).

(5) W. Keil, R. Muschaweck, and E. Radenbacher, *Arzneimittel-Forsch.*, **4**, 177 (1954).