tionship exists between the carcinogenic and the antitumor potentialities of the aryl component. Studies by Cook and Kennaway⁹ have shown that 9.10dimethylanthracene 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

(9) J. W. Cook and E. L. Kennaway, Am. J. Concer, **39**, 381 (1940); E. L. Keonaway, N. M. Kennaway, and F. L. Warren, *Concer Res.*, **2**, 157 (1912).

mustards have also displayed pronounced antitumor activity; these have contained a specific polycyclic component, such as a derivative of aeridine or anthraeene. 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 guamine 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 Lerman¹¹ for the aeridine nucleus and by Boyland and Green¹² for the polynuclear hydrocarbons.

 (10) P. 1). Leadey and C. A. Wallick, Chem. Ind. (London), 653 (1957).
 P. D. Lawley Proc. Chem. Soc., 290 (1957); P. Broukes and P. 1). Leadey, Brit. Mod. Built, 20, 91 (1964).

(11) L. S. Lerman, J. Cellubar Comp. Physiot., 64, Suppl. 1, 1 (1964).

(12) E. Boyhard and B. Green, Brit. J. Cancer. 16, 507 (1962); J. Moi Riol., 9, 589 (1994).

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 immer 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 compounds¹⁻³ 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 Catlin⁴ is outlined in Scheme I. The 1,1-diaryl-2-propyn-1-ols.

Semigraph I

$$\begin{array}{cccc} & & & & & & & \\ RCOR^{4} + \Pi C = C \Pi & & & & \\ OH & & & & & \\ OH & & & & & \\ RCC = C \Pi & & & & \\ RCC = C \Pi & & & & \\ RCC = C \Pi & & & & \\ & & & & \\ & & & & & \\ & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\$$

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. Ocg. 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, $ib(d_s, \mathbf{29}, 1851)(1964)$.

 ⁽¹⁾ M. D. Meloa and E. R. Catlin, P. S. Patent 3,062,870 (Nov 6, 1962).
 (5) W. Keil, R. Muschaweck, and E. Rademacher, Accurimittel-Fusich, 4, 177 (1954).

All products mentioned above are listed in Table I.

Pharmacological Methods.—Because of the obvious physical limitations, only two of the 21 experimental tumor systems maintained in these laboratories were employed for preliminary antitumor testing of this series of compounds. The two systems were selected because of their responsiveness to the carbannates, and the fact that both are used to predict useful candidates for clinical evaluation. Those carbannates showing a high degree of potency against these two systems were then subjected to more extensive studies.

One of the tumors, X5563, is a slow-growing, plasmacell tumor, the other, an atypical, myelogenous leukemia known as C1498. Procedures for animal-tumor testing in our laboratories have been previously described by Johnson, et al.⁶ However, in brief, for the solid tumor, a tumor fragment was implanted subcutaneously by trocar in C₃H mice and after 72 hr, treatment was initiated and continued until a total of 10 injections had been given. Two-dimensional measurements were taken after the tenth injection; the activity is reported as a comparison of the tumor sizes of test animals to that of saline controls. A 100% activity would mean that no measurable tumor was present in the test animals at the end of the treatment period. This plasma-cell tumor exhibits some of the same characteristics associated with multiple myeloma in man, including the presence of an abnormal protein found in the serum from animals bearing the disease.

The other test system, the myelogenous leukenia, is maintained in C-57B1/6 mice in the solid form. The test animals are injected with a tumor cell homogenate. Inoculation was by the intraperitoneal route at known, standard-cell concentrations. Inoculated animals usually survive for 14–18 days. Treatment was initiated 24 hr after inoculation, and a total of ten treatments with the compound was given. Activity was determined by prolongation of life of treated animals vs. that of saline controls. Those living for 45 days were considered "cured" and were designated as indefinite survivors. These were not calculated in the per cent activity. This tumor system is naturally resistant to many known clinically useful anticancer agents.

The insolubility of the carbamates in most vehicles used for antitumor testing, acacia, saline, sesame oil, and carboxymethylcellulose, did not prevent their effectiveness as antitumor agents. Suspensions of the carbamates using 1:10 dilutions of Emulphor²⁷ were used successfully throughout the series.

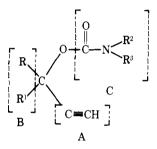
Prior to testing the compounds against the tumor systems, subacute toxicity studies were conducted using normal Swiss ICR mice. Compounds were administered daily at four different levels for 5 days. Antitumor testing was then initiated at the maximum tolerated level and at two lower levels, usually one-half and one-fourth of the high dose. Dose-response studies on the compounds demonstrating the most potent antitumor properties in the primary screen were then undertaken. In this study, dose levels were given that usually determined the minimum effective dose, and then dosage was increased until evidence of toxicity was seen. The toxic effects were noted by early deaths of the test animals and weight loss as compared to con-

(6) I. S. Johnson, et al., Cancer Res., 20, 1016 (1960).

(7) Emulphor[®] is a polyoxyethylated fatty acid available from General Aniline Film Corp., Melrose Park, Ill.

trol animals. Visual observations of the general appearance of the animals such as lack of mobility and rough coat were helpful in determining toxicity of the compound tested. The dose levels for maximum antitumor effects were obtained from the dose-response results. These are reported in Table I. For those compounds not included in the extended tests, the best activities indicated by the initial screen are reported.

Structure-Activity Relationships.—Antitumor activity against the X5563 and C1498 systems was found for almost all of the 1,1-diaryl-2-propynyl carbamates tested. However, for maximum potency, certain structural requirements were found to be necessary. To help in assessing the importance of each functional portion of the molecule, the carbamate structure was divided into three main areas—the ethynyl (A), the 1,1 substituents (B), and the carbamoyl portion (C) and the effect of structural changes on antitumor ac-



tivity is discussed separately for the three areas. The activity discussed here will refer to the results reported in Table I.

The acetylenic group (A) of the molecule was found to be essential to obtain potent antitumor effects. Reduction of this group to the ethylenic derivative gave compounds with much less activity (compare 82 and 83 with 20 and 24, respectively). Substitution on the terminal position of the triple bond did not appear to alter the antitumor effect significantly (compare 79 and 80 with 4).

One of the important features of portion B was that \mathbf{R} and \mathbf{R}^1 must both be aromatic groups for the carbamates to show significant antitumor effects. Compounds that deviated from these requirements such as 1, 2, and 3 showed little if any effects. When R and R^1 were both phenyl, compounds with varying degrees of potencies were obtained depending upon substituents on the remainder of the molecule. Although the effects of substituents on these phenyl groups upon potency were of a lesser degree, certain variations in this area were more beneficial than others. In general, halogen substitution on the phenyl rings gave compounds that demonstrated good antitumor effects. Of the group, chloro, bromo, and iodo, the *p*-chlorophenyl derivatives were the most beneficial in promoting antitumor activity. Of particular interest were the fluorophenyl derivatives (52, 54, 58, and 59), since they were the most potent of the halophenyl compounds. Other substitution on the phenyl ring such as methyl, nitro, trifluoromethyl, and phenyl did not seem to enhance activity. When R was phenyl and R^1 was heteroaromatic (72 and 76), less potent compounds were obtained. However, when R^1 was α - or β -naphthyl, potency was retained (68-70). The same was true when the R and R^1 were joined together forming the fluorenvl moiety (77 and 78).

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TABLE 1

ACETYLENIC CARBAMATES AND THEIR ANTITUMOR ACTIVITIES

Rª - oCuŃRª

RCC=CH

111

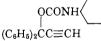
					10						
Compil)	110	1.1.4	M_{10}		\sim , calculated \sim	found	Dose,"	Tamor	
ηa.	R	$\mathbf{R}_{\mathbf{J}}$	\mathbb{R}^2	R®	°C	Formula	$C = \Pi$	C = 11	mg/kg	X 5563	C1408
۱۴	CH_3	$C1C11_2$	11	11	66-68	$C_6 H_5 CINO_2$	44.59 - 1.99	44.32 - 5.26	60	0.5	
2	$C_6 \Pi_5$	C Ha	11	11	40-42	C_1 : H ₂ : NO ₂	69.82 - 5.85	69.98 ± 5.89	4.5	0	$\Omega^{\prime\prime}$
3	C611;	11	11	11	86-88 ⁷	C ₁₀ H ₉ NO ₂	68.56 5.18	68.43 5.14	30	0	n
-1	CsH5	$C_{6}H_{5}$	H	11	138-140	Cl6Hr3NO2	76.47 5.22	76,48 5.49	37.5	83 (6)	
5* 62	C6115 C6115	C6115 C6115	CHa Cella	11 11	151 - 152 108 - 109	C17H15NO2 C18H17NO2	76.96 5.96 77.39 6.13	$76.98 ext{ 5.81} \\ 77.22 ext{ 6.21}$	$\frac{15}{30}$	64 (10) 97 (81	$\frac{113}{115} \frac{(1)}{(2)}$
-	C6H5	C6H5	CH2CH2CH2	ü	56-98	C ₁₉ H ₆₅ NO ₂	78.33 5.88	78.45 6.08	18	100 (9)	109(2)
8	Colls	Cells	CH₂C≡CH	11	125-127	C19H15NO2	78.87 5.22	78.91 5.31	15	98 (8)	81
9	Colle	Ca115	Cyclopropyl	11	118-120	C ₁₉ H ₁₅ NO ₂	78.33 5.88	78.60 6.07	15	0	39
10	Calls	(6115	CH2CH2OH	11	110-112	CisHinNO2	73.20 5 8D	73.24 - 6.04	15	0	0
11	C6115	Cella	$C11_2C_611_5$	11	103 - 105	C2311+9NO2	80.91 5.60	81.16 - 5.84	30	0	a -
12	CeH5	Celle	$CH_2CH_2C_6H_5$	11	121 - 123	$\mathrm{C}_{21}\mathrm{H}_{21}\mathrm{N}\mathrm{O}_2$	81.10 - 5.95	81.10 - 6.08	60	47 (9)	20
13	$C_{h}\Pi_{b}$	CoHs	Cyclopentyl	11	142 - 145	$C_{21}H_{21}NO_{3}$	78.97 - 6.63	78.69 - 6.75	15	67 (6)	157(3)
11	C ₆ H ₅	C6115	Cyclohexyl	11	160161	C 29H28NO2	79.25 6.95	79.40 7.12	7.5	96 (7)	183
15	C ₆ H ₅	CsH5	Cycloheptyl	11 11	162-165	C 23 H 25 N O 2	79.50 7.25	79.63 7.48	15	100 (7)	138
$\frac{16}{17}$	C ₆ H ₅	C6H5 C6H5	Cyclooctyl CH2CH2CH2N(CH3)2	11	148 - 150 98 - 100	C24H27NO2 C21H24N2O2	79.74 7 53 74.97 7.19	$79.47 7.48 \\ 74.91 7.47$	$\frac{30}{15}$	$\begin{array}{c} 100\ (7) \\ 62\ (7) \end{array}$	77 (1)
189	C6115 C6115	Collo	4-ClC6H)	11	89-90 89-90	C22H16CINO2	73.02 1.15	72.87 + 4.51	150	-30(10)	45 36
19	C6116	Calls	NH2	11	107 - 109	C16H14N2O2	$72 \ 16 \ 5.29$	72.10 - 5.46	30	0	20
20	Cully	Calls	CH ₃	C 113	102-104	CisHinNO2	77.30 0.13	77.58 6.18	15	65 (10)	68
21	C6115	C6115	$-(CH_2)_4-$		164-166	C27H13NO2	78.66 11-27	78.90 6.53	15	100 (8)	133
22	$C_6 \Pi_5$	$C_6 \Pi_5$	-C112C112OCH2C11	<u>.</u>	143-144	$C_{20}H_{10}NO_8$	74.74 ± 5.00	74.92 - 6.32	15	99 (9)	74
23	$C_6 H_6$	C6115	-(CH ₂) _b -		158 - 160	$\mathrm{C}_{2t}\mathrm{H}_{21}\mathrm{N}\mathrm{O}_2$	78.97 ± 6.63	78.81 - 6.79	150		0
24	$1-ClC_6H_4$	Cella	11	11	140-142	C16He2CINO2	67.25 ± 1.23	$67.27{\pm}4.41$	40	100 (9)	101
250	4-CIC6H4	C6H5	CHis	11	153~155	C ₁₇ H ₁₄ CINO ₂	08.11 1.70	08.26 - 4.74	30	(16-18)	(0, (1))
26	4-ClC6114	C6H5	CH2CH==CH2	11	10610/1	C19H16CINO3	70.04 1.95	69.86 5.24	30	87(2)	182 (2)
27	4-ClC6ll4	Calls	Cyclohexyl	H C Ha	156 125 197	CasHasCINOs	$71.82 \pm 0.03 \\ 68.90 \pm 5.13$	71.89 6.02	$\frac{75}{30}$	100(5)	49 (7)
28 29	4-ClC6H4 4-ClC6H4	C6115 C6115	-(CH2)4-	(113	135 - 137 101 - 92	C18H16CINO2 C29H14CINO2	70.69 5.33	68.91 - 5.41 - 70.31 - 5.88	30	100 (8) {14 (10]	$\frac{62}{129(7)}$
30	3-ClC6H4	CoH5	11	н	113-115	CielligCINO:	67.25 4.23	67.09 4.41	611	0 0	0
314	3-CIC6H4	Cells	CH3	11	141-142	C ₁₇ H ₁₄ CINO ₂	68.11 1.70	67.96 - 4.92	90	100 (7)	98
32	3-CIC6H4	Colla	Clls	CH_3	97-99	C-sH ₁₆ CINO ₂	68.90 5.13	68.52 - 5.01	90	100 (9)	76
33	2-ClC6H4	$C_6 \Pi_b$	n	н	169 - 171	C161112C1NO2	67.25 ± 4.23	67.48 4.19	<u>ព</u> 0	82 (51	Ū.
34	$2-C4C_{6}H_{4}$	C6115	C H3	CH_3	154 - 156	$C_{18}H_{16}CINO_2$	68/90 - 5.13	68.91 - 5.12	90	65(7)	21
35	$4-ClC_6ll_4$	4-ClC6H4	11	Ħ	131-133	$C_{16}H_{t1}Cl_2NO_3$	60.02 - 3.46	60.19 3.66	60	93(6)	60
36#	4-C1C6114	4-ClC6114	C 113	11	173 - 174	$C_{17}H_{18}Cl_2NO_2$	04.01 3.92	60.98 3.91	24	100 (9)	(111(1))
37	4-CIC6114	4-ClC6H4	CH_3	CH_3	162 - 164	C18H15Cl2NO2	62.08 ± 4.34	62.16 - 4.59	60	100 (8)	81
:18	3,4-Cl ₂ C ₆ H ₃	C6115	11	Н	167 - 169	Cr6Hr1Cl2NO2	$60.02 \pm .16$	60.34 3.64	150	24(10)	D
29	3,4-Cl ₂ C ₆ Hs	CeH5	C11 ₃	CH_3	157 - 159 199 - 199	CisH ₁₅ Cl ₂ NO ₂	62.08 + 1.34	62.19 4.50	150	7-1 (8)	11
-10 -11	3,4-Cl ₂ C ₆ H ₃	C5H5 C5H5	- (C112)4 11	11	$121 - 123 \\ 163 - 165$	$C_{20}H_{17}Cl_2NO_2$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	64.25 4.81	150 300	0	26
-12	2,1-Cl2C6H3 2,4-Cl2C6H3	C6H5	CH2	CHa	157~159	C16H11Cl2NO2 C18H15Cl2NO2	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	60.28 - 3.70 - 62.31 - 4.49	150	0	0 0
43	3,4-Cl2C6H3	4-CIC6H4	н	11	154-156	CisHoClaNO2	54.19 2.84	54.42 3.01	150	58 (10)	a a
11	2,4-Cl2C6H3	4-C1C6f14	H	11	145146	CisHigClaNO2	51.19 2.84	51.35 3.01	ĠŬ	0	0
45	4-BrC6114	C6115	н	11	141-143	Ci6H12BrNO2	58.20 - 3.66	58.39 - 3.83	60	95 (9)	120(1)
-162	4-BrC6H4	Calla	$C11_3$	11	149-151	$C_{17}H_{14}BrNO_3$	50.32 ± 09	59.50 - 1.30	60	100 (8)	82(2)
17	4-BrC ₆ H ₁	C6115	Cyclohexyl	11	190 - 165	$C_{22}H_{22}BrNO_{2}$	61.08 ± 5.37	04.13 - 5.41	150	39 (3)	145
48	d-BrC6H4	Cells	CH3	$C\Pi_{\delta}$	147-149	CallieBrNO7	60.35 1.50	60, 64 - 1, 61	30	87 (8)	71
-19	4-BrC6H4	C5H5	-(CH ₂) ₄ -		102-104	CallisBrNO2	62.51 + 1.72	152.58 1.79	30	100(9)	56
50	3-BrC6H4	C ₆ H ₅	11	11 ('H₃	$127 \cdot 129$	C36H32BrNO2	58.20 3.66	58.30 - 3.80 - 60.42 - 4.61	100 150		37
51 52	3-BrC6H4	C6115 C6115	CH3 11	11	111~113 99 -1 01	CisH ₁₀ BrNO2 CisH22FNO2	60,35 4.50 71,36 4.49	-60.42 4 61 71.40 4.27	50	100 (8)	71 107 (15
52 53	4-FC6H4 4-FC6H4	C6115 C6115	n CH₂C≡CH	11	121-123	CisHj4FNO2	71.25 1.59	71.48 4.59	15	50 (10)	
54	4-FC6114	C6H6	Cyclohexyl	n	168-170	C22H22FNO2	75,19 6.31	75.43 6.41	10	100 (2)	98 (1)
55	4-FC6H4	C ₆ H ₅	CH_4	CH3	121 - 123	C15I116FNO2	72.71 5.42	72.77 5.42	15	100 (10)	207 (6)
56	4-FC6114	C6115	~(CH2)4-		131-133	CmH18FNO2	74.28 - 5.61	74.43 5.84	20	100 (91	143 (6)
57	4-FC ₆ H ₄	$1-1$ C 6 11_4	11	11	121 - 123	C6ffhfF2NO2	66.90 - 7.86	66.91 - 1.14	35	100 (7)	94 (3)
58	$4 - FC_0H_4$	4 - F C $_{6}$ H $_{4}$	Cyclohexyl	11	177-179	$C_{22}H_{31}F_2NO_2$	71.53 ± 5.72	71.52 ± 5.93	ā	100 (8)	146
59 FO	4-FC6H4	4-FC6H4	Clla	CH^{s}	144~146	CisCi6F2NO2	68.56 -1.80	68.52 4.52	15	100 (9)	100
60	4-FC6H4	4-FC6H4	-(C11 ₂) ₄ -		143-145	$C_{20}H_{17}F_2NO_2$	70.37 5.01	70.67 5.39	30	100 (6)	0
61 62	4-1C6H4 4-CF2C6H4	C6115 C6115	11 11	11 11	$144-146 \\ 143-145$	CialligINO2 CialligF3NO2	50 95 3.20 63 95 3.79	51,22 3,35 63,86 3,85	$\frac{45}{150}$	100 (10)	100 - 0
63	4-CF3C6H4	Cella	CH:	$\frac{1}{C}$	176-178	CialliaFaNO2	65.70 1.64	65.84 + 4.81			
64	4-02NC6H4	Celle	11	n	165-167	CiallioN2O4	64.85 4.08	65.02 ± 1.14	60	a	• • •
65	1-CH4C6H4	Calls	н	n	128-130	CitllisNO:	76.96 5 70	76.84 5.41	15	é.	0
66	4-C6H5C6H4	C6H5	11	11	154 - 156	C22H 3 NO2	75.98 5.43	80.32 - 5.17	45	· · ·	141 (3)
67	-1-C6H5C5H4	C6115	CH_3	CH_3	145~147	$\mathrm{C}_{24}\mathrm{H}_{21}\mathrm{NO}_2$	81.10 5.95	81.16 5.99	60		81
68	2-CheH7	Calls	n	11	163 - 165	C2nH15NO2	79.71 - 5.02	79.88 5.03	12.5	100(51	85
69 - 0	$2 - C_{tr} H_7$	Cells	CHa	CH_1	111-113	CarHasNOa	80.21 5.81	80.11 5.95	30	100 (8)	164 (7)
70	$2 - C_m \Pi_7$	$C_{\delta}\Pi_{\delta}$	(CH2)4	11	83-85	CarHaNOa	81,10 5.95 Th T1 5.00	81.21 6.12	45	100 (7)	151 (1)
71 72	1-C ₁₀ H7 2-Cr11/N	Cella Cella	11 11	11 11) 57~159 331~135	Carllis NO2 Carlla NaCa	75 71 -5 0271 41 -4 80	79,98 5.09 71,80 5,16	- 30 150	100 (5) 100 (2)	72 0
12 739	2-C5114N 2-C5114N	Cells Cells	C11a	11	112-115	CasHa2N2O2 CasHa2N2O2	72.16 5.30	71.80 $3.1072.20$ 5.60	60	100(2) 92(7)	0
7.19	2-CallaN 2-CallaN	Cells	C 113 CB115	11	$112 \cdot 113 \\ 119 \cdot 120$	CarliaN ₂ O ₂ CarliaN ₂ O ₂	76.81 4.91	76.88 5.02		912 (F) 	·.
75	2-CsHiN 2-CsHiN	Cells Cells	CBD5 CD5	n Culs	110 - 120 121 - 125	CarHieNeO CarHieNeO	10.81 4.91 72 81 5.75	72.85 6.00	60	50 (8)	Ú.
70	2-C5414.8 2-C4H5S	Calls	0 115 11	H H	$121 \cdot 120$ $114 \cdot 115$	Chi HiaNO ₁ S	605(30)(4), 82	61559 4.92	300		a
.0	- (1113)3		••	••	*** ****	1. THE R. LEWIS CO.		an ne tree			

TABLE I (Continued)

TABLE 1 (Continued)										
Compd no.	Structure	Mp. °C	Formula	∼% calco C]	d— H	<i>−</i> % fo C	und— H	Dose, ^a	Tumor	
								mg/kg	X5563	C1498
770	HCEC OCONHCH _a	153-154	$C_{17}H_{18}NO_2$	77.55 4	.97	77.26	5.13	10	47 (10)	29
78	$HC \equiv C \longrightarrow OCON(CH_3)_2$	182-183	$C_{18}H_{16}NO_2$	77.96 5	.45	78.24	5.57	18	100 (8)	77
79	$(C_{6}H_{4})_{2}CC \equiv CCH_{3}$ OCONH ₂	147-149	$\mathrm{C}_{17}\mathrm{H}_{15}\mathrm{NO}_2$	76.96 5	.96	76.74	5 .6 5	60	27 (10)	28
80	(C₀H₅))CC≡CBr OCSNHCH₀	150-152	$\mathrm{C}_{16}\mathrm{H}_{12}\mathrm{BrNO}_2$	58.20 3	. 66	58.89	3.69	45	80 (6)	66
81	$(C_{\delta}H_{\delta})_{2}CC \equiv CH$ OCON(CH_{2})_{2}	135-136	$C_{i7}H_{i5}NO_{5}$	h				60	25 (10)	0
82	$(C_6H_5)_2CCH=CH_2$ OCONH ₂	102–104	$\mathrm{C}_{15}\mathrm{H}_{19}\mathrm{NO}_{2}$	76.84 6	. 81	77.21	6.83	30	43 (6)	0
83	p-ClC6H4C(C6H5)CH=CH2 OH	111-113	C16H14ClNO2	66.68 4	.90	66.97	5.03	7.5	0	39
84	$p\text{-ClC}_{6}H_{4}\dot{C}(C_{6}H_{6})C \equiv CH$ $OCOOC_{6}H_{6}$	47-48	$C_{15}H_{11}ClO$	74.23 4	. 56	74.23	4.86	60	0	0
85^i	(C ₆ H _δ) ₂ CC≡CH	76-78	$C_{22}H_{16}O_{3}$	80.47 4	.91	80.75	5.20	60	35 (9)	0

^a A total of ten treatments were given, by daily injections intraperitoneally, at each dose level indicated, and the reported activities of these compounds against the two systems are the results of a specific dose-response test for each compound and should be considered in a qualitative manner in comparing relative potencies. Activity must be greater than 20% to be considered significant. Myleran at 30 mg/kg inhibited the X5563 system 100% and did not inhibit the C1498 system. HN_2 at 0.15 mg/kg did not inhibit the X5563 system but gave a 34% prolongation of life against the C1498 system. Cytoxan (cyclophosphamide) at 50 mg/kg inhibited the X5563 system 100% and the C1498 system 39%. ^b Those compounds with R² and R³ being hydrogen were made by method A as described in the Experimental Section. The compounds with one or both R² and R³ being alkyl were prepared by method B. ^c Lit.⁴ mp 66-68°, ^d The number given is the per cent inhibition of the tumor, and the number in parentheses indicates total survivors out of ten at the end of the treatment period. ^c The number given is the per cent prolongation of life of treated animals vs. saline controls and the number in parentheses is the number of animals surviving for 45 days from date of inoculation and are considered cures. These animals are not calculated in the per cent activity. ^f W. Logemann, et al. [Farmaco (Pavia), Ed. Sci., **8**, 406 (1953)] report mp 87°. ^g Made by method C as described in Experimental Section. ^h Anal. Calcd: N, 4.98. Found: N, 5.18. ⁱ Intermediate described in method A recrystallized from benzene-petroleum ether (bp 35-60°).

TABLE II INTRAPERITONEAL VS. ORAL TREATMENT USING COMPOUND 14



Tumor system	Dose level, mg/kg ^a	Route of admin	Av wt change, T/C	% activity	Indefi- nite sur- vivors				
C1498	7.5	Ip	-1.5/1.9	61	0				
	10.0	Ip	-0.4/1.9	83	1				
	12.0	Ip	-2.8/1.9	98	3				
	15.0	Ip	-2.7/1.9	0	7				
	15.0	Oral	-3.6/0.5	107	1				
	20.0	Oral	-2.6/0.5	99	2				
	25.0	Oral	-3.7/0.5	35	4				
X5563	7.5	$_{\rm Ip}$	-0.9/2.0	92					
	10.0	Ip	-1.2/2.0	95					
	12.0	Ip	-3.1/2.0	100					
	15.0	\mathbf{Oral}	-2.0/1.2	97					
	20.0	Oral	-2.2/1.2	100					
	25.0	\mathbf{Oral}	-2.7/1.2	100					
a The dose was administered once daily for 10 days									

^a The dose was administered once daily for 10 days.

Definite requirements also have been demonstrated for the "C" portion of the carbamates. If this portion was hydrogen, *e.g.*, the 1,1-diaryl-2-propyn-1-ols, no significant antitumor effect was found. This was true for the phenylcarbonate intermediate 85 and the thiocarbamate 81. It could therefore be concluded that the carbamoyl portion O=CN < is necessary to produce compounds with significant activity. A comparison of the R^2 and R^3 substituents revealed that they could be varied widely with high potency being maintained. These variations included compounds where R^2 and R^3 were hydrogen, the N-methyl, N-allyl, N-propynyl, and N,N-dimethyl derivatives, and compounds where the substituents with the nitrogen formed a pyrrolidine ring. However, the N-phenyl derivative (18) was much less effective.

When R^2 was hydrogen and R^3 cyclohexyl (14), very high potency was found. This group was particularly effective when R and R¹ were *p*-fluorophenyl (58). Also, other N-cycloalkyl groups such as cyclopentyl, cycloheptyl, and cyclooctyl (13, 15, and 16) gave compounds of high potency.

Intraperitoneal vs. Oral Treatment.—In Table II, a comparison of intraperitoneal and oral administration of compound 14 against the X5563 and C1498 systems is given. In both systems, it appears that an equivalent antitumor effect can be seen using oral doses approximately twice that used by the intraperitoneal route. Other carbamates have also demonstrated this type of oral activity.

Experimental Section⁸

1,1-Diaryl-2-propyn-1-ols were prepared by known procedures $^{\rm g}$ from the appropriately substituted benzophenones and were

⁽⁸⁾ All melting points were determined using a Mel-Temp melting point apparatus and are uncorrected.

⁽⁹⁾ K. Campbell, B. Campbell, and L. Eby, J. Am. Chem. Soc., 60, 2882 (1938),

purified by distillation or crystallization. In some cases, the crude products were used.

1,1-Diaryl-2-propynyl N,N-Disubstituted Carbamates. The following specific examples represent the three methods used for making the carbamates listed in Table 1. They are designated as methods A, B, and C.

Method A. 1-(4-Bromophenyl)-1-phenyl-2-propynyl Carbamate, A solution of 57.4 g (0.2 mole) of 1-(4-bromophenyl)-1phenyl-2-propyn-1-ol and 40 ml of pyridine in 200 ml of CH₂Cl₂ was cooled to 0° and 31.3 g (0.2 mole) of phenyl chloroformate was added dropwise with stirring over 30 min. Stirring and cooling were continued for 4 hr. Tee water (200 ml) and 500 ml of ether were added, and the organic layer was separated and washed with excess $5_{11}^{(*)}$ HCl, saturated NaHCO₃, and water. After drying (MgSO₄), the solution was added dropwise to 400 ml of liquid NH₃ over a 15-min period. The resulting mixture was stirred for 16 hr and washed with $5_{11}^{(*)}$ NaOH solution. After drying over MgSO₄, the solvent was removed and the residue was crystallized from henzene-petrolenm ether (hp) 35-60° : A white, rrystalline solid was obtained: yield 6.5 g (25) () tsee Table 1, 45).

Method B. 1-(4-Bromophenyl)-1-phenyl-2-propynyl 1-Pyrrolidinecarboxylate. The same procedure was used as above to make the phenyl carbonate intermediate on a 0.1 mole scale. The effert CH_2Cl_2 solution of the intermediate was added to 50 ml of pyrrolidine in an equal volume of effect, and the mixture was stirred for 16 hr at room temperature and washed with excess 5^{++}_{-+} HCl then 5^{++}_{-+} NaOH solution. After drying, the solvent was removed at reduced pressure. The residue was crystallized from henzene-petroleum ether in a yield of 20^{++}_{-+} (Table 1, 49). Method C. 1,1-Diphenyl-2-propynyl N-Methylcarbamate. A submition of 0.4 mole of 4.1-diphenyl-2-propyn-1-ol, 0.25 mole of methyl isocyanate, and 4 g of triethylenediamine in 200 ml of CHCL, was left for 4 days at room temperature. All of the low-hoiling biaterials were removed at reduced pressure and the residue was recrystallized twice from henzene petroleum ether. The product was obtained in a 30%, yield (Table 1, 5).

1.1-Diphenylallyl N.N-dimethylcarbamate. A solution of 27.9 g of 1.4-diphenyl-2-propynyl N.N-dimethylcarbamate in 200 ml of 4; t benzeae petrolenin ether (hp 85/100°) was hydrogenated at 40 psi using 0.5 g of 5% Pd BaSO₁ and 0.5 g of KO11 mult 1 equiv of hydrogen was taken up. The catalyst was filtered and the solvent was removed at reduced pressure. The residue was erystallized twice from petroleum ether; yield 27%, (Tahle I, 82).

In a similar manner, 1-(4-chlorophenyl)-1-phenyl-2-propyryl carbamate was hydrogenated to <math>1-(4-chlorophenyl)-1-phenylallyl carbamate (Table I, 83).

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The 6-Deoxytetracyclines. VII. Alkylated Aminotetracyclines Possessing Unique Antibacterial Activity

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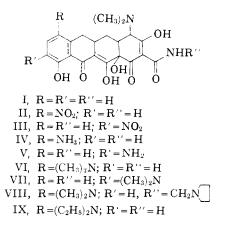
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The reductive methylation of 7-nitro-6-demethyl-6-deoxytetracycline gives 7-dimethylamino-6-demethyl-6-deoxytetracycline (VI). Similarly, reductive alkylation of other nitro- or aninotetracyclines forms related derivatives. An *in vitro* spectrum of VI is presented and its unique activity against tetracycline-resistant staphylococci is discussed.

Nitration of 6-demethyl-6-deoxytetracycline (I) in strong acid results in electrophilic substitution at the 7 and 9 positions.¹ Subsequent reactions of these substances to form amino, diazonium, and further transformation products have been the subject of previous papers from these and other laboratories.²

In the course of new investigations into the chemistry of these modified antibioties in the hope of further enhancing the pronounced antibacterial activity possessed by several members of this series, or to find new types of antibacterial activity (*i.e.*, broadened spectrum of activity) we had occasion to examine the reductive alkylation of these substances.

Reductive methylation of 7- or 9-nitro- (II or III) or -amino-6-demethyl-6-deoxytetracycline (IV or V) in methoxy ethanol under restricted pH conditions using 10% palladium-on-char coal catalyst at atmospheric pressure, gave 7- or 9-dimethy lamino-6-



demethyl-6-deoxytetracycline (VI or VII) and their 4-epimers. These compounds could be purified using liquid–liquid partition chromatography on neutral (acid-washed) diatomaceous earth. The reaction was

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