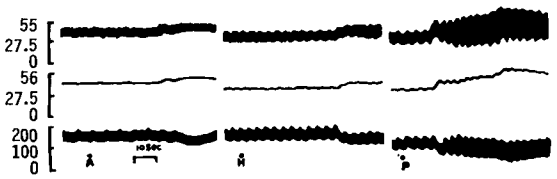

Figure 6—*Polygraph records showing, from below upward, the effects of himachalol and papaverine on blood pressure, mean femoral blood flow, and pulsatile femoral blood flow in an anesthetized cat. Key: A, control response to 0.25 ml of alcohol alone 30 sec after intravenous injection; H, hypotension and increase in the mean and pulsatile femoral blood flow 30 sec after intravenous injection of 5 mg/kg of himachalol dissolved in 0.25 ml of alcohol; and P, marked hypotension and increase in the mean and pulsatile femoral blood flow following injection of papaverine (2 mg/kg iv).*

There is a qualitative difference in the effect of the two compounds on guinea pig bronchial muscle. Himachalol causes constriction of bronchial muscle and papaverine causes relaxation. The constriction caused by himachalol cannot be blocked by pyrilamine, an antihistaminic agent, and, therefore, it seems unlikely that the constriction is due to release of histamine (Fig. 5). It is also unlikely that pulmonary congestion caused by himachalol would bring about bronchoconstriction by diminishing air inflow through bronchial tubes since papaverine causes greater vasodilation but does not cause any increase in bronchial resistance. Bronchoconstriction probably is the result of a directly stimulating action of himachalol in some unknown way.

Himachalol, like papaverine, produces systemic hypotension and peripheral vasodilation. The hypotensive effect is not mediated by cholinergic or histaminic receptor sites since the hypotension remains unaffected following pretreatment with atropine and pyrilamine. A stimulation of β-adrenergic receptors by himachalol can also be ruled out due to the absence of any tachycardia or relaxant effect on the bronchial musculature. The hypotension is unlikely to be due to a cardiac effect either, since there is no significant effect on heart rate in intact animals and only a mild inhibitory effect on the isolated auricle. The hypotension, therefore, appears to result mainly from a decrease in the peripheral resistance due to vasodilation caused by a direct relaxant action on the vascular smooth muscle.

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Possible Antineoplastic Agents I

A. U. DE ˣ and D. PAL

Abstract □ A few thalidomide and glutarimide derivatives were synthesized. Several compounds possessed significant antineoplastic activity against Ehrlich ascites carcinoma in Swiss albino mice.

Keyphrases □ Thalidomide derivatives—6-alkyl-2-[3′- or 4′-nitrophthalimido]glutarimides synthesized and screened as possible antineoplastic agents □ Glutarimide derivatives—6-alkyl-3-phenylglutarimides synthesized and screened as possible antineoplastic agents □ Antineoplastic agents, potential—synthesis and screening of thalidomide and glutarimide derivatives

The teratogenic effect of thalidomide (2-phthalimidoglutarimide, I) has been well established in humans and animals (1). To account for this manifestation, Faigle *et al.* (2) isolated a number of suspected metabolites of thalidomide and showed them to be derived from D-glutamic acid, an unnatural amino acid, in place of L-glutamic acid, the natural amino acid. They also pointed out the similarity between *N*-(*O*-carbobenzoxyl)glutamic acid, a metabolite of thalidomide, and folic acid. All of these observations led them to conclude that the metabolites of thalidomide might act as vitamin antagonists or antimetabolites. Since then, a number of claims and counterclaims on the antiglutamine, antifolic, and antivitamin activities of thalidomide have been made, the objective being to utilize thalidomide as a possible antineoplastic agent.

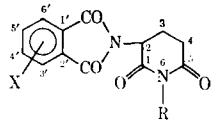


Table I—Antineoplastic Activity of 6-Alkyl-2-[3′- or 4′-nitrophthalimido]glutarimides (II) in Ehrlich Ascites Carcinoma

Compound	R	X	Cells Injected into Each Animal	Average Number of Cells per Milliliter in Control (C)	Average Number of Cells per Milliliter in Test (T)	T/C of Cells	Percent Inhibition of Ascitic Cells, (1 − T/C) × 100	Average Weight of Ascitic Fluid in Control (C), g	Average Weight of Ascitic Fluid in Test (T), g	T/C of Ascitic Fluid	Percent Inhibition of Ascitic Fluid, (1 − T/C) × 100
II*a*	H	H	2.65×10^6	366.3×10^6	200.8×10^6	0.5480	45.20	0.8	0.32	0.40	60.00
II*b*	Methyl	H	2.65×10^6	366.3×10^6	25.45×10^6	0.06947	93.053	0.8	0.5	0.625	37.50
II*c*	Ethyl	H	2.65×10^6	366.3×10^6	6.6×10^6	0.01801	98.199	0.8	0.4	0.50	50.00
II*d*	*n*-Propyl	H	2.65×10^6	366.3×10^6	48.0×10^6	0.1310	86.90	0.8	0.26	0.325	67.50
II*e*	*n*-Butyl	H	2.65×10^6	366.3×10^6	126.0×10^6	0.3440	65.60	0.8	0.2	0.25	75.00
II*f*	*n*-Pentyl	H	2.3625×10^6	282.32×10^6	205.4×10^6	0.7276	27.24	1.225	0.68	0.555	44.50
II*g*	*n*-Hexyl	H	2.3625×10^6	282.32×10^6	4.7×10^6	0.01665	98.335	1.225	0.06	0.04898	95.102
II*h*	H	3′-Nitro	2.3625×10^6	282.32×10^6	9.28×10^6	0.03287	96.713	1.225	0.1	0.08162	91.838
II*i*	H	4′-Nitro	2.3625×10^6	282.32×10^6	8.55×10^6	0.03029	96.971	1.225	0.08	0.0653	93.47
Mitomycin (as standard)			2.3625×10^6	282.32×10^6	0	0	100.00	1.225	0	0	100.00

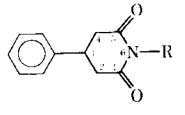
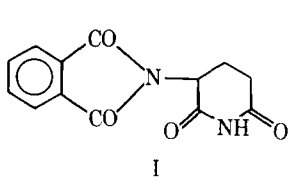


Table II—Antineoplastic Activity of 6-Alkyl-3-phenylglutarimides (V) in Ehrlich Ascites Carcinoma

Compound	R	Cells Injected into Each Animal	Average Number of Cells per Milliliter in Control (C)	Average Number of Cells per Milliliter in Test (T)	T/C of Cells	Percent Inhibition of Ascitic Cells, (1 − T/C) × 100	Average Weight of Ascitic Fluid in Control (C), g	Average Weight of Ascitic Fluid in Test (T), g	T/C of Ascitic Fluid	Percent Inhibition of Ascitic Fluid, (1 − T/C) × 100
V*a*	H	1.715×10^6	212.0×10^6	4.4×10^6	0.02076	97.924	0.667	0.1	0.1409	85.91
V*b*	Methyl	1.715×10^6	212.0×10^6	10.0×10^6	0.04718	95.282	0.667	0.09	0.1349	86.51
V*c*	Ethyl	1.715×10^6	212.0×10^6	13.34×10^6	0.06294	93.706	0.667	0.12	0.1799	82.01
V*d*	*n*-Propyl	1.56×10^6	565.2×10^6	17.38×10^6	0.03075	96.925	0.734	0.12	0.01635	98.365
V*e*	*n*-Butyl	1.56×10^6	565.2×10^6	21.95×10^6	0.03884	96.116	0.734	0.1	0.01362	98.638
V*f*	*n*-Pentyl	1.5×10^6	564.0×10^6	91.2×10^6	0.1617	83.83	0.7	0.2	0.2857	71.43
V*g*	*n*-Hexyl	1.5×10^6	564.0×10^6	216.75×10^6	0.3844	61.56	0.7	0.2	0.2857	71.43
V*h*	Phenyl	1.5×10^6	564.0×10^6	54.35×10^6	0.09636	90.364	0.7	0.6	0.8572	14.28
Mitomycin (as standard)		1.56×10^6	565.2×10^6	0	0	100.00	0.734	0	0	100.00



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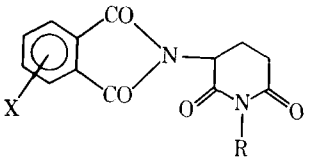

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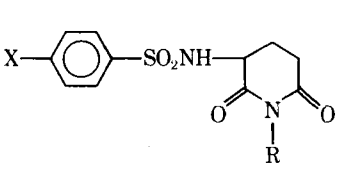

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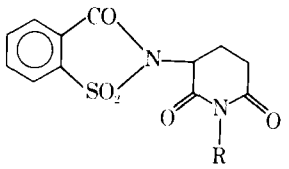

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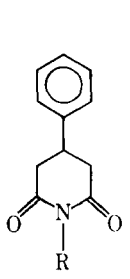

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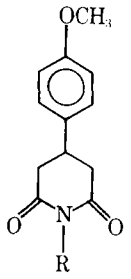

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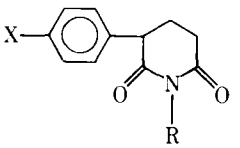


VII

DISCUSSION

The teratogenic activity of thalidomide has been viewed by many as the manifestation of its cytostatic activity and has been tested against a wide variety of experimental tumors including Ehrlich ascites, carcinoma, sarcoma, HeLa cell cancer, myeloma, and lymphoma (3–13). Although the results have not been very encouraging, thalidomide has been reported to limit the manifestation and growth of certain tumors. It has also been shown to possess a specific antiproliferative effect (4) necessary for their arrest.

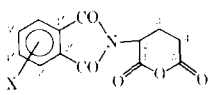
These observations are not unexpected, because Pastac (14) pointed out the analogy between the growth regulators of plant tissues and those of animals. In the former case, the growth regulators are derived from phthalic acid and naphthylamine, while in the latter thalidomide is derived from phthalic acid and glutamic acid. It was also observed (15) that folic acid-dependent embryological tumors might be susceptible to thalidomide. Besides this, there are two significant similarities between thalidomide and several alkylating agents. Thalidomide and these alkylating agents cause teratogenesis (16); furthermore, these alkylating agents, in general, alkylate DNA (17), whereas thalidomide acylates DNA and RNA in the fetus (18).

Although work with thalidomide as a possible antineoplastic agent is abundant, its derivatives have not been investigated extensively. This situation prompted the synthesis and biological evaluation of a few derivatives (II–IV). Derivative II was chosen to bring about changes both in the phthalimide and glutarimide portions of the original molecule, while derivatives of types III and IV include a sulfonamide group either in the straight chain or cyclic part of the molecule so as to result in appreciable antineoplastic activity.

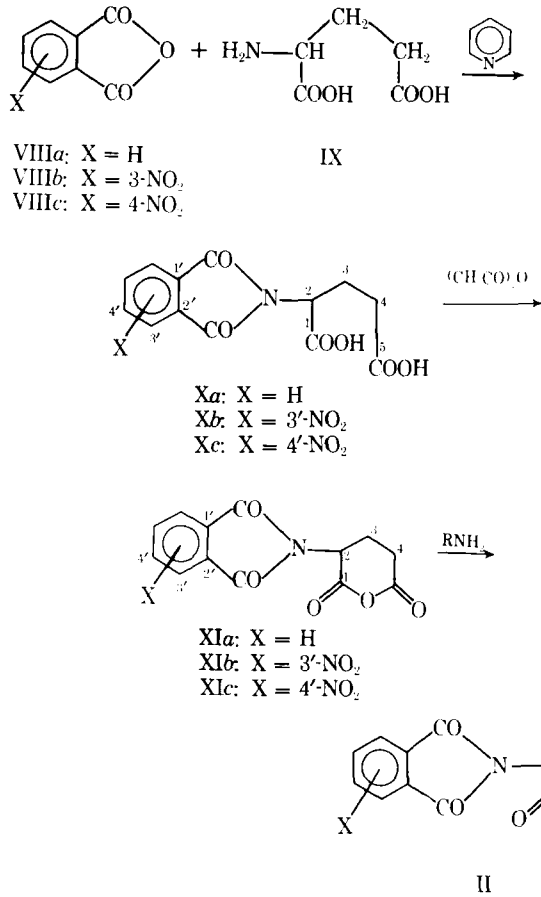
The antineoplastic antibiotics, cycloheximide and streptovitacin A, like thalidomide, are characterized by the presence of a glutarimide moiety in their structures. Therefore, the synthesis and biological evaluation of a few derivatives of the types V–VII were also undertaken.

This article describes the synthesis and activity of II and V; the synthesis and activity of other derivatives will be communicated subsequently with molecular orbital indexes calculated and a regression model built on the glutarimide moiety for the quantitative structure–activity relationships in this class of compounds.

Table III—2-[3′- or 4′-Nitrophthalimido]glutaric Anhydrides (XI)



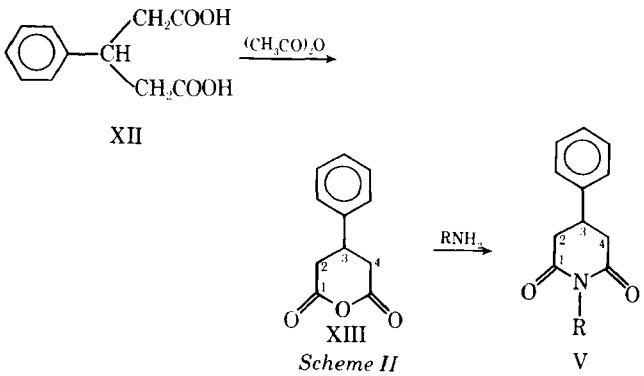
Compound	X	Melting Point	Yield, %
XI*a*	H	195–197°	76
XI*b*	3′-Nitro	213–215°	64
XI*c*	4′-Nitro	221–223°	60



Scheme I

EXPERIMENTAL

Chemistry—Phthalic anhydride and its 3- and 4-nitro derivatives (VIII) (19) were condensed with glutamic acid (IX) in the presence of pyridine to the diacids (X) and subsequently treated with acetic anhydride to furnish the anhydrides (XI) (20). Conversion of the diacids (X*b* and X*c*) to the corresponding anhydrides (XI*b* and XI*c*) was accomplished under mild conditions to avoid unnecessary decomposition. Attempts to remove any excess pyridine and acetic anhydride under reduced pressure with heating re-



Scheme II

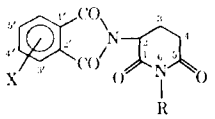


Table IV—6-Alkyl-2-[3′- or 4′-nitrophthalimido]glutarimides (II)

Compound	R	X	Yield, %	Melting Point	Boiling Point	Formula	Analysis, % Calc.	Found
II*a*	H[a]	H	70	258–260°	—	$C_{13}H_{10}N_2O_4$	C 60.47 H 3.88 N 10.85	60.81 4.32 10.57
II*b*	Methyl[b]	H	42	131–133°	—	$C_{14}H_{12}N_2O_4$	C 61.76 H 4.41 N 10.29	62.12 4.88 10.70
II*c*	Ethyl[b]	H	46	75–77°	—	$C_{15}H_{14}N_2O_4$	C 62.94 H 4.90 N 9.79	62.57 5.27 9.43
II*d*	*n*-Propyl	H	60	66–68°	—	$C_{16}H_{16}N_2O_4$	C 64.00 H 5.33 N 9.33	63.82 5.27 9.32
II*e*	*n*-Butyl	H	64	29–31°	135–137°/ 2 mm	$C_{17}H_{18}N_2O_4$	C 64.97 H 5.73 N 8.92	65.01 6.22 8.56
II*f*	*n*-Pentyl	H	60	19–21°	110–112°/ 1 mm	$C_{18}H_{20}N_2O_4$	C 65.85 H 6.10 N 8.54	66.28 6.45 8.72
II*g*	*n*-Hexyl	H	65	34–36°	100–102°/ 0.9 mm	$C_{19}H_{22}N_2O_4$	C 66.67 H 6.43 N 8.19	66.62 6.91 8.31
II*h*	H	3′-Nitro	30	262–264° dec.	—	$C_{13}H_9N_3O_6$	C 51.49 H 2.97 N 13.86	51.13 3.41 14.18
II*i*	H	4′-Nitro	27	278–280° dec.	—	$C_{13}H_9N_3O_6$	C 51.49 H 2.97 N 13.86	51.24 3.35 13.84

[a] Lit. (24) mp 271° and (25) mp 244°. [b] Purified by sublimation.

sulted in considerable decomposition and, consequently, were avoided.

The anhydrides (XI) were treated with ammonia (21) or the respective amines to give the desired imides (II) (Scheme I). Conversion of the anhydrides (XI*b* and XI*c*) to the corresponding imides (II*h* and II*i*) with ammonia was accomplished with considerable decomposition, lowering the yield appreciably. 3-Phenylglutaric acid (XII) (22) was converted to 3-phenylglutaric anhydride (XIII) with acetic anhydride (19) and subsequently treated with ammonia (21) and various amines to furnish the desired imides (V) (23) (Scheme II).

Biological Evaluation—Several groups of Swiss albino mice, each containing five healthy animals of the same sex and approximately the same age and body weight (18–20 g), were selected at random and kept in different cages under identical conditions. One group served as the control; the others were the test groups.

The mice were marked by cutting the fur at different parts of the body, with individual weights being recorded at the same time. Ehrlich ascites carcinoma cells, collected from the donor mice, were suspended in sterile isotonic saline, and the number of living cells per milliliter of this suspension was counted. A fixed number of the viable cells was implanted into the intraperitoneal cavity of each mouse. In this instance, the tumor cells multiplied relatively freely and ascites developed. A day of incubation was allowed to establish the disease before drug administration.

From the 2nd day of transplantation up to the 8th day, a suitable dose of the drug suspension, usually 50 mg/kg ip in buffered isotonic saline (pH 7.2), was injected to the test groups. The weight of each mouse was recorded every alternate day to assess the toxicity, activity, and other specificity of the screening program. Thus, seven consecutive doses were administered. On the 9th day, food and water were withheld for 6 hr before the testing operation started.

Fluid from the peritoneal cavity of each mouse of both the control and test groups was drawn by a sterile syringe, diluted to a suitable volume with sterile ice-cold isotonic saline, and preserved in an ice bath. The total number of living cells per milliliter of fluid of each mouse was separately counted with trypan blue indicator; only the dead cells took the stain. The individual weight of each animal was recorded before sacrificing. The peritoneal cavity was dissected and the fluid was sucked by cotton or filter papers; the weight of each mouse after sacrifice was recorded.

The evaluation of test compounds was made by comparing the cell counts and tumor weights of the test groups with those of the control. Mitomycin was used as a standard in these tests at a dose of 1 mg/kg in buffered isotonic saline (Tables I and II).

Activity—Antineoplastic potency of the synthesized compounds (II and V) is recorded in Tables I and II. Significant activity was observed. In the thalidomide series, appreciable activity was observed in the *n*-hexyl (II*g*) and nitro (II*h* and II*i*) derivatives based on live cell counts and tumor weights as the activity parameters. In the glutarimide series, maximum activity was observed in a simple and known compound (V*a*). The other significantly active compounds in this series were the methyl, ethyl, *n*-propyl, and *n*-butyl derivatives (V*b*–V*e*).

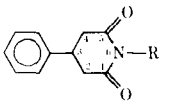
Syntheses[1]—*2-[3′- or 4′-Nitrophthalimido]glutaric Anhydrides (XIb and XIc)*—A suspension of the anhydrides (VIII*b* and VIII*c*, 20 mmoles) and L-glutamic acid (IX, 20 mmoles) in dry pyridine (12 ml) was refluxed on an oil bath for about 6 hr. Only the clear solution was transferred, by decantation, to a conical flask. Acetic anhydride (9 ml) was added to this clear solution. The solution was refluxed on a very low flame for 10 min or heated on a water bath for 1 hr and kept in the cold overnight. The anhydride crystals were filtered and washed with ether to give the product. The anhydrides were crystallized from dry ethyl acetate (Table III).

2-[3′- or 4′-Nitrophthalimido]glutarimides (II h and II i)—The appropriate anhydride (XI*b* or XI*c*) was heated at about 220–240° in an oil bath until it melted. Then dry ammonia gas was bubbled through the molten mass for about 15 min and the whole mass became tarry. The mass was cooled and crystallized from 90% ethanol with charcoal treatment, yielding 27–30% (Table IV).

6-Alkyl-2-phthalimidoglutarimides (II b–II g)—A mixture of 2-phthalimidoglutaric anhydride (XI*a*, 1 mole) and the corresponding amine (1.2 moles) was heated in a sealed tube for 8 hr in an oil bath at 210–220°. The imides were purified by sublimation

[1] All melting points are uncorrected.

Table V—6-Alkyl-3-phenylglutarimides (V)



Compound	R	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
V*a*	H	85	173–174°	$C_{11}H_{11}NO_2$	C 69.84 H 5.82 N 7.41	70.12 6.23 7.29
V*b*	Methyl	64	138–140°	$C_{12}H_{13}NO_2$	C 70.94 H 6.40 N 6.90	71.32 6.71 7.25
V*c*	Ethyl	62	86–88°	$C_{13}H_{15}NO_2$	C 71.89 H 6.91 N 6.45	71.58 7.30 6.76
V*d*	*n*-Propyl	72	104–106°	$C_{14}H_{17}NO_2$	C 72.73 H 7.36 N 6.06	73.02 7.48 6.17
V*e*	*n*-Butyl	76	112–114°	$C_{15}H_{19}NO_2$	C 73.47 H 7.76 N 5.71	73.81 7.45 5.38
V*f*	*n*-Pentyl	72	79–81°	$C_{16}H_{21}NO_2$	C 74.13 H 8.11 N 5.41	74.49 8.43 5.42
V*g*	*n*-Hexyl	68	88–90°	$C_{17}H_{23}NO_2$	C 74.71 H 8.42 N 5.13	74.89 8.26 4.87
V*h*	Phenyl	70	188–190°	$C_{17}H_{15}NO_2$	C 76.98 H 5.66 N 5.28	76.63 6.02 5.33

or by crystallization from water or dilute ethanol or were distilled *in vacuo* (Table IV).

6-Alkyl-3-phenylglutarimides (*V*)—Dry ammonia gas was bubbled through the molten 3-phenylglutaric anhydride (XIII) to furnish the imide (V*a*). A mixture of the anhydride (XIII, 1 mole) and the respective amine (1.2 moles) was heated in a sealed tube for 8 hr in an oil bath at 150–160° to furnish the crude imides (V*b*–V*h*), which were purified by crystallization from water or dilute ethanol with charcoal treatment (Table V).

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