tive values of π. Substituents which contribute to the lipophilic nature of the molecule should therefore be sought.

These data were also analyzed by the method of Free and Wilson.[8] By subjecting our data to multiple linear regression analysis[9] the contribution of each substituent to the antitumor activity of the molecule was determined (Table II). In order to estimate the value of $C \cdot T$ at the maximum tolerated dose for each compound, the contribution of each substituent in the 5 positions of the two rings is added to the base activity, 1.116. Since $C \cdot T$ at the maximum tolerated dose should be as large as possible for good antitumor activity the results indicate the desirability of having in the amine moiety, Me groups at the 2, 3, and 4 positions, OH groups in the 2, 3, and 4 positions, CO_2H at the 4 position, and NO_2 in the 5 position. Substitution in the aldehyde moiety is desirable especially for OH in the 2 position; in this case the substituent effect of the 2-OH is very certain since it is substantiated by 13 compounds.

Acknowledgments.—Grateful acknowledgment is made of the valuable assistance of Paul Mooney, Charles Capshew, and Joyce Wan in the preparation of these compounds, the staff of the Oklahoma State University Computing Center in making the correlations, and the staff of the Research Foundation of Oklahoma State University in preparing this report.

(8) S. M. Free, Jr., and J. W. Wilson, *J. Med. Chem.*, **7**, 395 (1964).

(9) The computer program used for this purpose was a modified version of the multiple regression program contained in IBM's SYSTEM/360 Scientific Subroutine Package. This program was maintained on tape and required only a few seconds of computation time on the IBM 360/50 computer.

Antineoplastic Research. 1. Pyrazole and Pyrimidine Derivatives of Dehydrocycloheximide Analogs[1]

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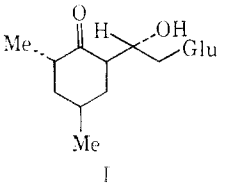
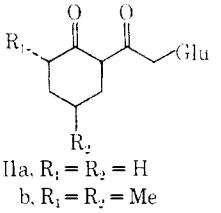
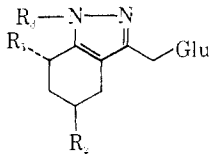
Cycloheximide[2] (I), a product of *Streptomyces griseus* cultures, is well known for its ability to inhibit protein biosynthesis.[3] This biological action as well as that of emetine, anisomycin, and others is attributed to the stereochemical relationships between the N and O atoms of the molecule.[4] It has also been demonstrated that this relationship can be affected by a change in the substitution pattern or stereochemistry at many of the other positions in the molecule.[5]



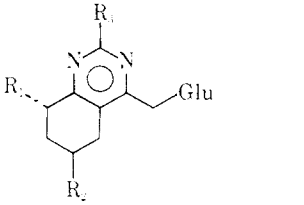
I



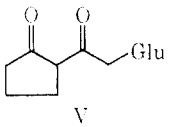
IIa, $R_1 = R_2 = H$
b, $R_1 = R_2 = Me$
c, $R_1 = H$; $R_2 = Me$
d, $R_1 = Me$; $R_2 = H$



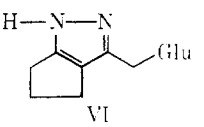
IIIa, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = C_6H_5$
c, $R_1 = R_2 = Me$; $R_3 = H$
d, $R_1 = H$; $R_2 = Me$; $R_3 = H$
e, $R_1 = H$; $R_2 = Me$; $R_3 = C_6H_5$
f, $R_1 = Me$; $R_2 = R_3 = H$



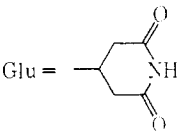
IVa, $R_1 = R_2 = H$; $R_3 = NH_2$
b, $R_1 = R_2 = H$; $R_3 = SH$
c, $R_1 = R_2 = Me$; $R_3 = NH_2$
d, $R_1 = Me$; $R_2 = H$; $R_3 = NH_2$



V



VI



In order to establish further points about the structure–activity relationships of these molecules we have undertaken a program directed toward the synthesis of several modified glutarimide antibiotics. During the course of these studies we had occasion to prepare a a few dehydrocycloheximide type compounds II which could also be converted into a variety of heterocyclic compounds through the 1,3-diketone system. Even though we would be destroying the essential stereochemical features, the combination of the salient parts of cycloheximide with heterocyclic systems appeared attractive for its biological potential.

The required 1,3-diketones II and V were prepared from the enamine of the appropriately substituted ketone and the acid chloride of 2-(β-glutarimido)acetic acid according to the acylation procedure developed by Johnson, *et al.*,[6] in their elegant total synthesis of cycloheximide. Though Struck and coworkers[7] had prepared diketones IIa,c,d by a similar method, we found the Johnson modifications generally gave much better yields. Dehydrocycloheximide (IIb) was more easily prepared by the Jones' oxidation of cycloheximide (I) at ambient temperature.[8]

The pyrazole derivatives III and VI were easily formed by the action of hydrazine and phenylhydrazine on the 1,3-diketones. Although we have indicated the

(1) This work was aided by Grant T-474 from the American Cancer Society and Grant 67-16 from its Illinois Division.

(2) Actidione®.

(3) For recent reports see B. S. Baliga, A. W. Pronczuk, and H. N. Munro, *J. Biol. Chem.*, **244**, 4480 (1969); A. Geller, F. Robustelli, S. H. Barondes, H. D. Cohen, and M. E. Jarvik, *Psychopharmacologia*, **14**, 371 (1969); J. A. Burdman and L. J. Journey, *J. Neurochem.*, **16**, 493 (1969); S. D. J. Yeh and M. Shils, *Biochem. Pharmacol.*, **18**, 1919 (1969).

(4) A. P. Grollman, *Science*, **157**, 84 (1967); *Proc. Nat. Acad. Sci. U. S.*, **56**, 1867 (1966).

(5) H. D. Sisler and M. R. Siegel, in "Antibiotics," Vol. I, D. Gottlieb and P. D. Shaw, Ed., Springer-Verlag, New York, N. Y., 1967, p 283.

(6) F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Amer. Chem. Soc.*, **88**, 149 (1966). We have assigned the stereochemistry at C-2 as depicted because of the arguments presented by these workers.

(7) R. F. Struck, H. S. Schaeffer, C. A. Krauth, R. T. Kemp, Y. F. Shealy, and J. A. Montgomery, *J. Med. Chem.*, **7**, 646 (1964).

(8) Yields were generally 70–80% decidedly better than the CrO_3-HOAc method originally used by E. C. Kornfield, R. G. Jones, and T. V. Parke [*J. Amer. Chem. Soc.*, **71**, 150 (1949)].

stereochemistry of the heterocyclic derivatives at C-2 to be the same as the corresponding ketone, the hydrazines could have isomerized the methyl moiety during the condensation reaction. Use of semicarbazone or thiosemicarbazone resulted also in pyrazoles. All of the pyrazoles IIIa,c,d,f and VI exhibited uv maxima at 225–227 mμ, which shifted to 231–235 mμ in acidified alcohol. The phenylpyrazoles IIIb,e had a maximum at 253 mμ, which was not affected by acidification. No attempt was made to ascertain the exact location of the phenyl ring.

The pyrimidines IV were best prepared by melting an intimate mixture of the 1,3-diketones and guanidine carbonate or thiourea. Use of the standard base- or acid-catalyzed condensation conditions resulted only in the destruction or the recovery of diketone. The aminopyrimidines had double maxima of 230 and 303 mμ, which could be shifted by acid to 226 and 312 mμ, respectively. Thiourea product IVb had peaks at 233 and 286 mμ.

Preliminary evaluation of IIIa–e, IVd, V, and VI in the leukemia 1210 system[9] by single- and multiple-dose injections indicated the compounds to be neither active nor toxic. In the Walker 256 test system four doses of 400-mg total showed that IIIa,b decreased tumor weight only slightly.

Survey of a few representative compounds as IIId,e, and V in the paw edema antiinflammatory test and for androgenic–anabolic activity disclosed no significant activity.

Experimental Section

Pyrazole Formation.—The appropriate 1,3-diketone and $NH_2NH_2 \cdot H_2O$ or $C_6H_5NHNH_2$ (1 mol equiv) in EtOH (30–35 ml/g of diketone) was refluxed for 6 hr. The soln was cooled to 5° for 16 hr, and the product then collected. If insufficient product crystallized, the volume of EtOH was reduced *in vacuo* and additional material collected. The product was then recrystd from the appropriate solvent to give an analytical sample. Data for pyrazoles III and VI are listed in Table I.

TABLE I
DATA FOR NEW COMPOUNDS

Compd	Mp,[a] °C	Recrystn solvent[b]	Yield, %[c]	Formula	Analyses[d]
IIIa	254–255	A	89	$C_{13}H_{15}N_3O_2$	C, H, N
b	204–208	A	90	$C_{19}H_{21}N_3O_2$	C, H, N
c	199–202	B	60	$C_{15}H_{21}N_3O_2$	C, H, N
d	117–118	A	75	$C_{14}H_{19}N_3O_2$	C, H
e	190–192	A	62	$C_{20}H_{23}N_5O_2$	C, H, N
f	185–186	A	55	$C_{14}H_{19}N_3O_2$	C, H, N
IVa	255–257[e]	A	37	$C_{14}H_{18}N_4O_2$	N
b	260–265	C	69	$C_{14}H_{17}N_3O_2S$	N
c	198–200	A	24	$C_{16}H_{22}N_4O_2$	C, H, N
d	234–235	A	30	$C_{15}H_{20}N_4O_2$	N
V	119–120	D	20	$C_{12}H_{15}NO_4$	C, H, N
VI	233–236	A	57	$C_{12}H_{15}N_3O_2$	C, H, N

[a] Melting points were taken on a Fisher–Johns apparatus and are uncorrected. [b] A, EtOH; B, MeOH; C, H_2O; D, CH_2Cl_2. [c] Yields are based on material which could be crystallized directly from the reaction and had mp 0–4° lower than the analytical sample. [d] New compounds had the expected ir spectra. All analyses indicated by only the elemental symbol were within ±0.4% of the theoretical value. [e] A change in crystal structure occurs at 184–187°.

(9) We wish to thank Dr. H. B. Wood of the Drug Development Branch, Cancer Chemotherapy National Service Center for providing the anticancer assays.

Pyrimidine Formation.—An intimately ground mixture of diketone and guanidine carbonate or thiourea (1 mol equiv) was heated in an oil bath to 160–180°. The mixture liquified, then solidified upon continued heating. This change was accompanied by the release of H_2O vapor. The solid was added to a few milliliters of boiling H_2O to remove the unreacted urea. After collecting the H_2O treated product, it was recrystd from EtOH or H_2O to give the desired pyrimidine. Yields and physical data for the pyrimidines IV are in Table I.

Halogenated 1-(4-Aminobenzylidene)indenes[1,2]

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1-(4-Dimethylaminobenzylidene)indene (I) and a number of its analogs have been found active against subcutaneous Walker 256 tumors, intramuscular Walker 256 tumors, and Lymphoma 8.[3,4,5] Moreover, I appeared to cause mammary tumors, especially in female rats. In order to determine whether halogen atoms *ortho* to the amino group would reduce the carcinogenic activity, we have prepared the compounds listed in Table I and submitted then for testing. The results obtained indicate that most of the *ortho*-halogenated compounds have activity against the Walker tumors in one or both types of test. Some of the compounds seem more effective in the single dose test, possibly because they are slower in absorption or activation than the unhalogenated compounds. When compared on a molar basis the bromo compounds appeared to be somewhat more effective than the fluoro, chloro, or iodo compounds. It is interesting to note that the *m*-chloro compound was inactive. A similar effect of a halogen atom in this position has been observed in the 4-(4-dimethylaminostyryl)quinoline series. A halogen atom at the 2 or 3 position of the indene portion of the molecule also prevented antitumor activity.

Base-catalyzed condensation of the halogenated aminobenzaldehyde with indene seemed to go smoothly, but isolation and purification of the desired products required patient attention, as did preparation of the halogenated aldehydes.

Experimental Section

Equal molar quantities of aldehyde and indene were dissolved separately in hot EtOH and then combined in preparing the halogenated 1-(4-aminobenzylidene)indenes. After KOH in EtOH was added dropwise in excess until a color change occurred, the solution was allowed to reflux about 30 min, then cooled, and filtered.

3-Fluoro-4-dimethylaminobenzaldehyde was prepared from *N,N*-dimethyl-*o*-fluoroaniline according to the method of Campaigne and Archer.[6] 3-Chloro-4-dimethylaminobenzaldehyde

(1) This investigation was supported by Public Health Service Research Grants No. CA-03717-07, -10, and -11 from the National Cancer Institute.

(2) Presented at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., December 6, 1968.

(3) C. T. Bahner, H. Kinder, D. Brotherton, J. Spiggle, and L. Gutman, *J. Med. Chem.*, **8**, 390 (1965).

(4) R. M. Folk and M. A. Sheridan, *Proc. Amer. Assn. Cancer Res.*, **9**, 23 (1968).

(5) F. J. C. Roe, R. L. Carter, and N. A. Barron, *Nature*, **222**, 383 (1969).

(6) E. Campaigne and W. L. Archer, *Org. Syn.*, **33**, 27 (1953).