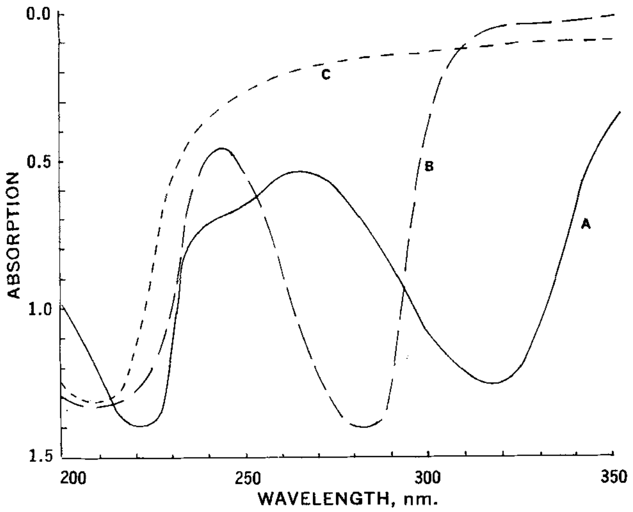


Figure 1—*Changes in UV absorption spectra of aqueous and methanolic solutions of* Ia *on exposure to light. All solutions are 1 × 10^{-4} mole/l. Key: Curve A, UV spectrum of* Ia *in water prior to exposure to light (the spectrum in methanol is essentially the same); Curve B, methanolic solution after exposure to light for 24 hr.; and Curve C, aqueous solution after exposure to light for 24 hr.*

(s, 3, O—CH_3), 5.3 (d, 1, J = 3.5 Hz., H—C4), 7.0 (d, 1, J = 3.5 Hz., H—C3), and 6.2 (s, 1, N—H).

Anal.—Calc. for $C_{10}H_{15}NO_3$: C, 60.88; H, 7.68; N, 7.10. Found: C, 61.03; H, 7.68; N, 7.07.

REFERENCES

(1) H. E. Paul and M. F. Paul, in "Experimental Chemotherapy," vol. II, Academic, New York, N. Y., 1964, chap. 7.

(2) K. Hirano, S. Yoshina, K. Okamura, and I. Suzuka, *Bull. Chem. Soc. Japan*, **40**, 2229(1967).

(3) F. Yoneda and Y. Nitta, *Chem. Pharm. Bull.*, **12**, 1264 (1964).

(4) E. Boyland and B. E. Speyer, *Biochem. J.*, **119**, 463(1970).

(5) L. J. Powers and G. E. Bass, to be published.

(6) H. R. Snyder, Jr., *J. Med. Chem.*, **10**, 737(1967).

(7) S. Gronowitz, G. Sorlin, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi*, **19**, 483(1962).

(8) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p. 99.

(9) D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, **22**, 323 (1957).

(10) F. Feigl, "Qualitative Analysis by Spot Tests," 3rd ed., Elsevier, New York, N. Y., 1946, p. 248.

ACKNOWLEDGMENTS AND ADDRESSES

Received March 15, 1971, from the *Department of Molecular and Quantum Biology, College of Pharmacy, University of Tennessee Medical Units, Memphis, TN 38103*

Accepted for publication April 21, 1971.

The author thanks Doctor Frederic C. Chang of this Department for his helpful suggestions during the preparation of this manuscript.

COMMUNICATIONS

Benzene Analogs of Triazenoimidazoles

Keyphrases ☐ Triazenoimidazoles, benzene analogs—synthesis, antileukemic activity ☐ Triazenobenzamides—synthesis, light stability, antileukemic activity ☐ Antileukemic activity—triazenoimidazoles, benzene analogs

Sir:

The fact that 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (I*a*) (NSC-45388) increased survival time in mouse lymphatic leukemia L-1210 and inhibited other neoplasma (1) led to the synthesis of similar triazenoimidazole amides (2–6), triazenoimidazole esters (I*b*) (7), heterocyclic ring analogs (8–11), and certain phenyltriazenes with *para*-attached chains selected for presumed carrier properties (12). Benzene analogs (II–IV) of the triazenoimidazole amides and esters, as well as similar *para*-substituted derivatives (V–VIII), were also synthesized for antineoplastic evaluation; investigations of such derivatives were further stimulated by demonstrations of clinical activity by Compound I*a* (13). This communication is a preliminary account of some of the structural changes made in the aryl moiety and of antileukemic activity by certain of these derivatives.

The *p*-benzamides (V), the *o*- and *p*-benzoates (IV and VII), and the *p*-benzamidines (VIII) were prepared by diazotizing the appropriate aromatic amine derivative and coupling with an aliphatic amine by the general procedure described for certain other phenyltriazenes (12). The *o*- and *p*-benzoic acid hydrazides (III and VI) were obtained by treating the analogous esters (IV and VII) with hydrazine. Since it is well known that diazotization of 2-aminobenzamides gives 1,2,3-benzotriazin-4(3*H*)-ones (14), the *o*-benzamides (II) were synthesized by first isolating *o*-carbamoylbenzenediazonium tetrafluoroborate [m.p. 114–115° dec., IR band at 2290 cm.$^{-1}$ (N_2^+)]. Calc. for $(C_7H_6N_3O)^+BF_4^-$: C, 35.78; H, 2.57; N, 17.88. Found: C, 35.77; H, 2.61; N, 17.75. Coupling with aliphatic amines was then performed in anhydrous media to minimize intramolecular cyclization to 1,2,3-benzo-

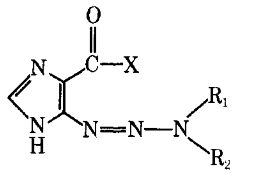
Table I—Increases in Survival Time in L-1210 Tests[a]

Compound	Dose, mg./kg., and Schedule[b]	Survival Time, T/C^c, %
o-(3,3-Dimethyl-1-triazeno)-benzamide (II, $R_1 = R_2 = CH_3$)	225, A	139
	150, A	127,162,150[d]
	100, A	137
o-(3-Butyl-3-methyl-1-triazeno)-benzamide (II, R_1 = *n*-C_4H_9, $R_2 = CH_3$)	200, A	150,144
	200[e], A	108,137
	133[e], A	122,126
	89[e], A	108,134
p-(3,3-Dimethyl-1-triazeno)-benzamide (V, $R_1 = R_2 = CH_3$)	100, B	146
	75, B	144
	60, B	121
	50, B	132
p-(3,3-Dimethyl-1-triazeno)benzoic acid hydrazide (VI, $R_1 = R_2 = CH_3$)	100, B	129
	75, B	134
	50, B	119
Ethyl *p*-(3-butyl-3-methyl-1-triazeno)-benzoate (VII, R_1 = *n*-C_4H_9, $R_2 = CH_3$)	400, B	137
	200, B	92
p-(3,3-Dimethyl-1-triazeno)-benzamidine (VIII, $R_1 = R_2 = CH_3$)	52, A	128
	35, A	133

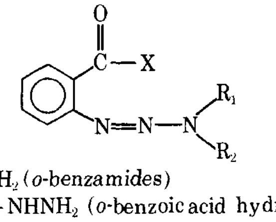
[a] Explanations of testing *versus* L-1210 are given in *References 11* (Footnotes *a–d* of Table I) and *17*. [b] Schedule A = daily administration of the stated dose on Days 1–9 (q.d. 1–9); Schedule B = administration on Days 1–30 or to death. [c] Ratio in percent of average survival time of treated mice (*T*) with L-1210 leukemia to untreated leukemic control mice (*C*). [d] Results of three separate tests. [e] Two separate dose–response tests. The value of *T/C* at 200 mg./kg./day in the first test in comparison with the *T/C* ratio in three other tests at this dose indicates that the first dose–response test was anomalous.

triazin-4(3*H*)-one. The following compounds[1] are illustrative of several derivatives that have been prepared with the Structures II–VIII.

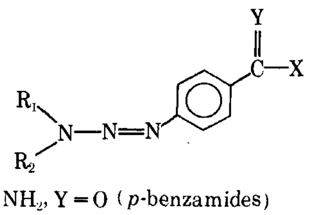
Benzamides—Compound II, $R_1 = R_2 = CH_3$: m.p. 124–126° (ethyl acetate–cyclohexane); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 242 (10.7), 280–290 (sh), and 318 nm. (12.8) at pH 7 and 13. Calc. for $C_9H_{12}N_4O$: C, 56.23; H, 6.29; N, 29.15. Found: C, 56.18; H, 6.50; N, 29.50. Compound II, R_1 = *n*-C_4H_9, $R_2 = CH_3$: m.p. 83–86°



Ia: X = NH_2, $R_1 = R_2 = CH_3$
Ib: X = OR



II: X = NH_2 (*o*-benzamides)
III: X = —$NHNH_2$ (*o*-benzoic acid hydrazides)
IV: X = OCH_3 (*o*-benzoates)



V: X = NH_2, Y = O (*p*-benzamides)
VI: X = —$NHNH_2$, Y = O (*p*-benzoic acid hydrazides)
VII: X = OC_2H_5, Y = O (*p*-benzoates)
VIII: X = NH_2, Y = NH (*p*-benzamidines)

(cyclohexane); $UV_{max.}$ 242 (10.6), 280–290 (sh), and 320 nm. (13.4) at pH 7 and 13. Calc. for $C_{12}H_{18}N_4O$: C, 61.51; H, 7.74; N, 23.92. Found: C, 61.58; H, 7.80; N, 23.97. Compound V, $R_1 = R_2 = CH_3$: m.p. 171–172° (ethanol–ethyl acetate–hexane); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 221 (10.6) and 322 nm. (21.6) at pH 7. Calc. for $C_9H_{12}N_4O$: C, 56.23; H, 6.29; N, 29.15. Found: C, 56.42; H, 6.15; N, 29.05. Compound V, R_1 = *n*-C_4H_9, R_2 = CH_3: m.p. 101–102° (ethanol–hexane). Calc. for $C_{12}H_{18}N_4O$: C, 61.51; H, 7.74; N, 23.92. Found: C, 61.62; H, 7.64; N, 23.97.

Benzoic Acid Hydrazides—Compound III, R_1 = $R_2 = CH_3$: m.p. 128° (ethanol); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 223 (11.6), 247 (sh), 296 (sh), and 316 nm. (12.5) at pH 7. Calc. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.80. Found: C, 52.06; H, 6.46; N, 34.06. Compound III, $R_1 = CH_3$, R_2 = cyclohexyl; m.p. 110° (ethanol–hexane); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 225 (11.3), 250 (sh), 297 (sh), and 321 nm. (14.1) at pH 7. Calc. for $C_{14}H_{21}N_5O$: C, 61.07; H, 7.69; N, 25.44. Found: C, 61.25; H, 7.65; N, 25.71. Compound VI, $R_1 = R_2 = CH_3$: m.p. 136–137° (ethanol–hexane). Calc. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.80. Found: C, 51.96; H, 6.13; N, 33.77. Compound VI, R_1 = *n*-C_4H_9, R_2 = CH_3; oil that solidified after storage at low temperature; m.p. 37°. Calc. for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.10. Found: C, 57.66; H, 7.56; N, 27.94.

Benzoates—Compound IV, $R_1 = R_2 = CH_3$[2]: oil purified by chromatography on magnesia–silica gel (Florisil), elution with cyclohexane–acetone; $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 235 (10.7), 278 (9.8), and 312 nm. (10.8) at pH 7. Calc. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.87; H, 6.33; N, 20.28. Compound IV, R_1 = *n*-C_4H_9, $R_2 = CH_3$: pale-yellow oil (purified by chromatography on Florisil, elution with petroleum ether–acetone); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 235 (10.6),

[1] Solvents used for recrystallization are given in parentheses after the melting points.

[2] This compound was reported by Elks and Hey (15), who stated that their specimen did not give satisfactory analytical data. It also was used in studies of benzyne formation (16).

280 (9.9), and 312 nm. (11.1) at pH 7 and 13. Calc. for $C_{13}H_{19}N_3O_2$: C, 62.62; H, 7.68; N, 16.86. Found: C, 62.78; H, 7.92; N, 17.15. Compound VII, R_1 = *n*-C_4H_9, R_2 = CH_3: oil, n_D^{25} 1.5799. Calc. for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.64; H, 7.92; N, 15.99.

Benzamidines—Compound VIII, $R_1 = R_2 = CH_3$: m.p. 113° dec. (hexane–chloroform); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 226 (10.9) and 327 nm. (22.4) at pH 7. Calc. for $C_9H_{13}N_5$: C, 56.52; H, 6.85; N, 36.63. Found: C, 56.32; H, 6.59; N, 36.53. Compound VIII, R_1 = methyl, R_2 = cyclohexyl: m.p. (hydrochloride) 235° dec. (ethanol–ethyl acetate); $UV_{max.}$ ($\epsilon \times 10^{-3}$) at 228 (12.0) and 333 nm. (25.0) at pH 7. Calc. for $C_{14}H_{21}N_5 \cdot HCl$: C, 56.84; H, 7.50; N, 23.68; Cl, 12.00. Found: C, 56.64; H, 7.43; N, 23.59; Cl, 12.0.

In standard tests against mouse lymphoid leukemia L-1210, *o*-(3,3-dimethyl-1-triazeno)benzamide, the analogous *o*-(3-butyl-3-methyl-1-triazeno) derivative, and *p*-(3,3-dimethyl-1-triazeno)benzamide increased lifespan by 40–60%. Dosages of these compounds that prolonged survival time are summarized in Table I; additional data in Table I indicate that a benzoic acid hydrazide, a benzoate ester, and a benzamidine also cause modest increases in lifespan. Although additional testing is required to delineate the degree and scope of activity of Compounds II–VIII, the available biological data indicate that at least some of the derivatives represented by Structures II–VIII can cause significant increases in average survival time of mice bearing leukemia L-1210. Previously, it was reported (18) that certain benzenoid triazenes, which lack the amide or carboxyl-type groups and which are inhibitory to certain experimental tumors (18–20), are not active against lymphatic leukemia L-1210.

The stability to sunlight of the benzamide analog (II, $R_1 = R_2 = CH_3$) of I*a* and of *p*-(3,3-dimethyl-1-triazeno)benzamide (V, $R_1 = R_2 = CH_3$) is a point of additional interest. In a prior study (11), it was shown that I*a* decomposes more rapidly in direct sunlight than does its pyrazole analog, 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide. Solutions (4×10^{-5} *M*) of the two dimethyltriazenobenzamides and of the pyrazole analog in 50% aqueous ethanol were placed side-by-side in direct sunlight which passed through window glass and through the Pyrex glass of the containers. Under the prevailing exposure conditions, the UV absorbance of the pyrazole analog decreased by 40% within 3 hr. and by 85% within 10 hr., whereas the UV spectra of the two benzamide derivatives were unchanged during the same periods.

(1) Y. F. Shealy, J. A. Montgomery, and W. R. Laster, Jr., *Biochem. Pharmacol.*, **11**, 674(1962).

(2) Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2150(1962).

(3) Y. F. Shealy and C. A. Krauth, *J. Med. Chem.*, **9**, 34(1966).

(4) Y. F. Shealy and C. A. Krauth, *Nature*, **210**, 208(1966).

(5) Y. F. Shealy, C. A. Krauth, S. J. Clayton, A. T. Shortnacy, and W. R. Laster, Jr., *J. Pharm. Sci.*, **57**, 1562(1968).

(6) K. Hano, A. Akashi, I. Yamamoto, S. Narumi, and H. Iwata, *Gann*, **59**, 207(1968).

(7) Y. F. Shealy, C. A. Krauth, R. F. Pittillo, and D. E. Hunt, *J. Pharm. Sci.*, **56**, 147(1967).

(8) Y. F. Shealy and C. A. O'Dell, *J. Med. Chem.*, **9**, 733(1966).

(9) C. W. Noell and C. C. Cheng, *ibid.*, **12**, 545(1969).

(10) Y. F. Shealy and C. A. O'Dell, *J. Pharm. Sci.*, **59**, 1358 (1970).

(11) *Ibid.*, **60**, 554(1971).

(12) Y. F. Shealy, C. A. Krauth, C. E. Opliger, H. W. Guin, and W. R. Laster, Jr., *J. Pharm. Sci.*, **60**, 1192(1971).

(13) J. K. Luce, W. G. Thurman, B. L. Isaacs, and R. W. Talley, *Cancer Chemother. Rep., Part 1*, **54**, 119(1970).

(14) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, in "The Chemistry of Heterocyclic Compounds," vol. 10, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, chap. 1.

(15) J. Elks and D. H. Hey, *J. Chem. Soc.*, **1943**, 441.

(16) J. Nakayama, O. Simamura, and M. Yoshida, *Chem. Commun.*, **1970**, 1222.

(17) Cancer Chemotherapy National Service Center, *Cancer Chemother. Rep.*, **25**, 1(1962).

(18) J. H. Burchenal, M. K. Dagg, M. Beyer, and C. C. Stock, *Proc. Soc. Exp. Biol. Med.*, **91**, 398(1956).

(19) D. A. Clarke, R. K. Barclay, C. C. Stock, and C. S. Rondestvedt, Jr., *ibid.*, **90**, 484(1955).

(20) K. Sugiura, *Gann*, **50**, 251(1959).

Y. FULMER SHEALY
C. ALLEN O'DELL
JOE D. CLAYTON
CHARLES A. KRAUTH
Kettering-Meyer Laboratories
Southern Research Institute
Birmingham, AL 35205

Received April 9, 1971.
Accepted for publication June 11, 1971.
This work was supported by Chemotherapy, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Contract PH43-64-51; biological testing was performed under the terms of Contract PH43-65-594 and under the supervision of Dr. F. M. Schabel, Jr., and Dr. W. R. Laster, Jr.

Assessment of Compression Characteristics of Powders

Keyphrases □ Powders—compression characteristics □ Tablets—compression characteristics □ Compression properties—powders, tablets

Sir:

The characterization of the compression properties of powders by the "modulus of pressing," *i.e.*, the slope of the log of the applied pressure against the log of the relative density of the compact, has been criticized by Jones (1). As an alternative, he suggested that a plot of the power expended in pressing a powder against the volume displacement would show differences in the pressing qualities of various powders (1). Rather than using the power in forming the tablet, *i.e.*, the energy expended in unit time, we consider that the work done in forming the tablet, *i.e.*, the force times the distance moved by the punch, would be a more useful characterization.

Varsano and Lachman (2) described how the work done in forming a tablet can be obtained from the area under the load/displacement curves when powders are compressed at a constant rate on an Instron physical