Synthesis of 5-(3,3-Disubstituted-1-triazenyl)imidazole-4-carbonitriles

Y. FULMER SHEALY [x] and C. ALLEN O'DELL

Abstract □ The 3,3-dimethyl-, 3-*n*-butyl-3-methyl-, 3-(2-hydroxyethyl)-3-methyl-, 3,3-bis(2-fluoroethyl)-, and 3,3-bis(2-chloroethyl)-1-triazenyl derivatives of imidazole-4-carbonitrile were prepared from 5-diazoimidazole-4-carbonitrile, a stable compound which produced a mass spectrum consistent with its structure. In contrast to the corresponding carboxamides, none of the triazenylimidazole-4-carbonitriles were active against lymphatic leukemia L-1210 in mice. Like the analogous carboxamide, the bis(2-chloroethyl)triazene readily cyclizes to the 1,2,3-triazolinium chloride.

Keyphrases □ Triazenylimidazoles—derivatives of imidazole-4-carbonitrile, synthesis □ Diazoimidazolecarbonitrile—synthesis and stability □ Triazenes—synthesis of 5-(3,3-disubstituted-1-triazenyl)imidazole-4-carbonitriles, screened against leukemia L-1210 □ Antileukemia activity—triazenylimidazolecarbonitriles screened

The effect of structural modifications on the antineoplastic activity of triazenes may be evaluated by varying the substituents on either the terminal nitrogen atom or the aryl (or heteroaryl) moiety. When the primary amide group of 5-(3,3-dimethyl-1-triazenyl)imidazole-4-carboxamide (I*a*) was replaced by ester groups (1–3), activity was retained. However, the esters, with the exception of the methyl ester (I*b*), were somewhat less effective against L-1210 lymphoid leukemia than was I*a*, and some of the ester analogs (I*c*) with terminal substituents identical with those of active congeners (I*d*) of I*a* did not show significant activity. Further alteration of the imidazole moiety of imidazole triazenes was effected by replacing the amide group of I*a* and a few of its active congeners (I*d*) with a nitrile group.

DISCUSSION

5-Aminoimidazole-4-carbonitrile (II) (4, 5) was prepared by dehydrating 5-aminoimidazole-4-carboxamide with phosphorus oxychloride (Scheme I) (6). The amino nitrile was diazotized in aqueous solution, and 5-diazoimidazole-4-carbonitrile (III) was isolated (80–90% yield) by extraction with ethyl acetate and was easily recrystallized. The IR spectrum included identifying bands at 3100 (imidazole CH), 2240 (CN), and 2185 (diazo group, strong) cm^{-1}. The mass spectrum of this diazoheterocycle was readily obtained and included prominent peaks arising from the molecular ion (*m/e* 119), loss of nitrogen (*m/e* 91), and loss of nitrogen and HCN (*m/e* 64), as well as metastable ions of *m/e* 69.6 (119 → 91) and 45.0 (91 → 64).

Coupling of III with the appropriate amine in ethyl acetate (or in ethyl acetate–ethanol) furnished the dimethyltriazenyl (IV*a*), *n*-butylmethyltriazenyl (IV*b*), and (2-hydroxyethyl)methyltriazenyl (IV*c*) derivatives. Reactions of III with bis(2-fluoroethyl)amine in aqueous solution or with bis(2-chloroethyl)amine in methylene chloride gave the bis(2-fluoroethyl)triazenyl (IV*d*) and bis(2-chloroethyl)triazenyl (IV*e*) derivatives, respectively. Triazenes IV*a*, IV*b*, and IV*d* were also obtained by diazotizing II and allowing the coupling reaction to proceed *in situ*.

Material isolated after reaction of III with bis(2-chloroethyl)amine contained 10–40% of the isomeric 1,2,3-triazolinium salt (V) as well as the triazene (IV*e*). Washing the isolated material with water reduced the amount of V to 5–10%. The triazolinium salt was isolated from the aqueous filtrate and was also prepared by stirring a mixture of IV*e* and aqueous methanol. The IR spectra of the triazenes (IV*d*–IV*e*) included a medium strong band at 1495–1500 cm^{-1}, whereas the triazolinium salt (V) produced a strong band at 1510 cm^{-1}. Although the analogous amide (NSC-82196) may be stored in the solid state at −15 to −20° for prolonged periods (7), triazene IV*e* slowly cyclizes to V under comparable conditions. The amount of V in a specimen of IV*e* stored at −15 to −20° had increased from about 10% to about 30% after 50 days. The hydrochloride of IV*e*, as well as the free base, cyclized to V rapidly in dimethyl sulfoxide solution.

The bis(2-fluoroethyl)triazene (IV*d*) was readily isolated and purified without the difficulties accompanying the obtainment of IV*e*. However, a UV absorption study showed that IV*d* changes rapidly at approximately pH 13 and indicated that the triazolinium fluoride analogous to V was formed. There was also evidence of a slower—presumably analogous—change in phosphate buffer.

All of the triazenes (IV*a*–IV*e*) and the diazoimidazole (III) were tested against lymphatic leukemia L-1210 in mice on the dosage schedules of Day 1, Days 1, 5, 9, and Days 1–9. Newly prepared specimens of IV*e* were used in these tests, and all compounds were injected within 5 min of the preparation of suspensions or solutions. No significant antileukemic activity was observed in any of these tests (Table I); in contrast, all of the corresponding imidazolecarboxamides (I*a* and I*d*) analogous to IV*a*–IV*e* are active against L-1210 leukemia (8–10). Except for the bis(2-fluoroethyl)triazene (IV*d*), triazenes IV*a*–IV*e* either were nontoxic (at doses up to 400 mg/kg) or were less toxic than the amide analogs. Although the failure of IV*e* to show activity may be due to its lability, the absence of observed activity by the remaining triazenes—and, perhaps, IV*e*—must be ascribed to replacement of the primary amide group by the nitrile group.

EXPERIMENTAL[1]

During all operations employed in the preparation, isolation, and purification of the triazenes (IV*a*–IV*e*) and the diazo derivative (III), the compounds were routinely protected from light. Specimens were routinely stored at 5° except for the bis(2-haloethyl)triazenyl derivatives, which were stored at −15 to −20°.

5-Aminoimidazole-4-carbonitrile (II) (4, 5)—This compound was prepared by the method of Suzuki *et al.* (6), except that the period of heating 5-aminoimidazole-4-carboxamide hydrochloride in phosphorus oxychloride was shortened to 2 hr to improve the yield (yields 40–50%); IR: 2220 and 2210 (CN) cm^{-1}; mass spectrum (direct-probe inlet temperature of 40°): *m/e* 108 (M), 81 (M − HCN), and 54 (81 − HCN).

5-Diazoimidazole-4-carbonitrile (III)—A solution of 5.20 g

[1] UV spectra were recorded with a Cary model 17 or model 14 spectrophotometer. UV maxima are in nanometers; sh = shoulder. Solutions for UV determinations were prepared by diluting a 5-ml aliquot of an ethanol solution (water for V) to 50 ml with 0.1 *N* HCl, phosphate buffer (pH 7), or 0.1 *N* NaOH; absorption maxima are reported as being at pH 1, 7, or 13, respectively. IR spectra were recorded with a Perkin-Elmer model 621 or model 521 spectrometer from samples in KBr disks. NMR spectra were determined with a Varian model A-60A spectrometer for observing proton resonance at 60 MHz. Chemical shift data (δ) are in parts per million downfield from tetramethylsilane, the internal reference. Mass spectral data were taken from low-resolution spectra determined with a Hitachi-Perkin-Elmer RMU-7 double-focusing instrument (70-ev electrons); M = molecular ion. Melting temperatures were determined in capillary tubes heated in a Mel-Temp apparatus and are not corrected. Unless otherwise indicated, TLC was performed on plates of silica gel H in chloroform–methanol (9:1) and spots were detected by: *(a)* UV light (254 and 365 nm) and *(b)* UV light (254 nm) after spraying the chromatogram with an optical whitening agent (Ultraphor WT, BASF Colors and Chemicals, Inc., Charlotte, N.C.). The quantity applied is shown parenthetically at appropriate places in the procedures.

Table I—Tests of 5-(3,3-Disubstituted-1-triazenyl)imidazole-4-carbonitriles against L-1210 Leukemia[a]

Compound	Dose, mg/kg[b] Day 1	Days 1, 5, 9	Days 1–9	Results[c]
IV*a*	400	400, 200, 100	200 (−2.8), 100	I, NT
			400 (6/6)	T
IV*b*	400 (6/6)			T
	300, 150, 75	300, 150, 75	300, 150, 75	I, NT
IV*c*	400, 200, 100	400, 200, 100	400[d], 200, 100	I, NT
IV*d*	150 (5/6)	75 (5/6)	37 (6/6)	T
	75 (−2.6)	37 (−2.7), 18	18 (−3.2), 9 (−1.9)	I, NT
IV*e*	400, 200, 100	400, 200, 100	400, 200, 100	I, NT
III	25 (4/6)			T
	12 (−2.0)	12 (−1.9)	12 (−3.5)	I, NT
		6 (−2.1), 3	6 (−1.9), 3	I, NT

[a] Tests were performed in accordance with protocols of the National Cancer Institute (11). These compounds were administered intraperitoneally in saline containing polysorbate 80 (Tween 80); the suspensions or solutions were prepared no more than 5 min prior to injection. [b] Numbers in parentheses give data either for deaths (treated/total) on or before Day 5 or for the difference (ΔW) in weight change (negative numbers, grams) on Day 5. Values for ΔW that were positive or were less than −1.8 g in magnitude are not shown. ΔW = average change in weight of treated mice minus average change in weight of control mice. [c] This summary of results applies to all of the doses listed on the same line in columns 2–4. I = inactive, T = toxic, and NT = nontoxic according to protocol criteria. [d] ΔW = −1.8 g.

(48 mmoles) of II in 50 ml of 2 *N* hydrochloric acid was added, dropwise, during 45 min to a stirred solution of 3.32 g (48 mmoles) of sodium nitrite in 50 ml of water at 0–5°. The red solution was stirred at 0–5° for 45 min and then extracted with ethyl acetate (5 × 100 ml). The organic solution was dried with magnesium sulfate, treated with activated charcoal, and concentrated *in vacuo* to a crystalline residue. The residue was triturated with cyclohexane, washed on a filter with cyclohexane, and dried *in vacuo* at 56° for 0.5 hr and at room temperature for 3 hr; the yield was 4.85 g (85%), mp 96–99°.

A specimen was recrystallized by treating a warm ethyl acetate solution of crude material with activated charcoal, diluting the hot filtrate with cyclohexane, and cooling the mixture, mp 97–100°; IR [medium and strong (s) bands in 3600–1000-cm^{-1} region]: 3100 (imidazole CH), 2240 (CN), 2185 s (diazo), 1465, 1425 s, 1320, 1285, 1260, 1225 s, 1150 s, and 1105 cm^{-1}; UV: λ_{max} 270 (sh) and 309 (ϵ 9000) nm in 0.1 *N* HCl; mass spectrum (direct-probe inlet temperature of 40°): *m/e* 119 (M), 91 (M − N_2), 69.6 (metastable, 119 → 91), 64 (91 − HCN), and 45.0 (metastable, 91 → 64).

Anal.—Calc. for C_4HN_5: C, 40.34; H, 0.85; N, 58.81. Found: C, 40.31; H, 1.17; N, 58.65.

5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carbonitrile (IV*a*)—To a solution of 10 ml of anhydrous dimethylamine, 80 ml of ethyl acetate, and 10 ml of ethanol at 0° was added, portionwise and with stirring, 1.5 g of the diazoimidazole (III). Stirring at 0° was continued for 1 hr, and the solvents were evaporated *in vacuo*. The solid residue was triturated with ethyl acetate–cyclohexane (1:1), washed with ethyl acetate, and dried *in vacuo* at 56°; the yield was 1.98 g (87%), mp 186–189° dec.

A solution of the product in 100 ml of hot ethanol was treated with activated charcoal, filtered, diluted with 100 ml of cyclohexane, and stored at 5°; the yield of recrystallized IV*a* was 1.25 g (55%), mp 187–189° dec. (inserted at 100°, 3°/min); TLC: 1 spot (20 or 40 μg); IR: 2225 (CN) cm^{-1}; UV: λ_{max} 225 (ϵ 11,200) and 326 (ϵ 15,300) nm in phosphate buffer (pH 7) and 235 (ϵ 15,500) and 333 (ϵ 11,600) nm in 0.1 *N* NaOH; NMR (CF_3COOD): δ 3.48 (s, CH_3), 3.78 (s, CH_3), and 8.63 (s, imidazole CH).

Anal.—Calc. for $C_6H_8N_6$: C, 43.89; H, 4.91; N, 51.20. Found: C, 43.54; H, 4.82; N, 51.08.

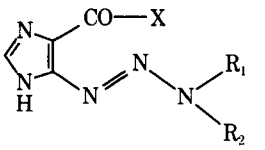
5-(3-Butyl-3-methyl-1-triazenyl)imidazole - 4-carbonitrile (IV*b*)—A solution of 173 mg of sodium nitrite in 4 ml of water was added slowly to a solution of 250 mg of the aminonitrile (II), 8 ml of water, and 2 ml of 2 *N* HCl at 0–5°. The mixture was stirred at 0–5° for 0.5 hr, filtered to remove a small amount of precipitate, and treated with sulfamic acid to decompose excess nitrite. Butylmethylamine (2 ml) was added to the cold solution, and the mixture was stirred for 1 hr at 0–5° and filtered to separate a precipitate (255 mg). Recrystallization of the crude product from a mixture of ethyl acetate (5 ml) and cyclohexane (12 ml) afforded white needles; the yield was 200 mg (42%), mp 103–105° dec. (inserted at 80°, 2°/min); TLC: 1 spot (40 or 80 μg); IR: 2225 (CN) cm^{-1}; UV: λ_{max} 226 (ϵ 11,600) and 328 (ϵ 15,600) nm in phosphate buffer (pH 7) and 236 (ϵ 16,600) and 334 (ϵ 11,500) nm in 0.1 *N* NaOH.

Anal.—Calc. for $C_9H_{14}N_6$: C, 52.41; H, 6.84; N, 40.75. Found: C, 52.71; H, 7.08; N, 40.62.

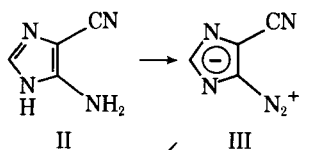
5-[3-(2-Hydroxyethyl)-3-methyl - 1-triazenyl]imidazole-4-carbonitrile (IV*c*)—This compound was prepared from III (476 mg) and *N*-methylethanolamine (1 ml) in ethyl acetate (20 ml) by the procedure used for IV*a* except that the reaction was carried out at room temperature. Sufficient methanol was added to dissolve a gummy material which precipitated in the reaction mixture, the solution was treated with activated charcoal, and the filtrate was concentrated *in vacuo* to a syrup. Stirring the residue with ethyl acetate (15 ml) containing methanol (1 ml) gave a crystalline solid (670 mg) which was recrystallized from ethyl acetate–cyclohexane (or, on a larger scale, from ethyl acetate–ethanol–cyclohexane); the yield was 570 mg (72%), mp 153–155° dec. (inserted at 60°, 3°/min); TLC: 1 spot (40 or 80 μg); IR: 2220 (CN) cm^{-1}; UV: λ_{max} 225 (ϵ 11,300) and 327 (ϵ 15,600) nm in phosphate buffer (pH 7) and 235 (ϵ 15,500) and 333 (ϵ 11,900) nm in 0.1 *N* NaOH.

Anal.—Calc. for $C_7H_{10}N_6O$: C, 43.28; H, 5.19; N, 43.28. Found: C, 43.24; H, 5.11; N, 43.19.

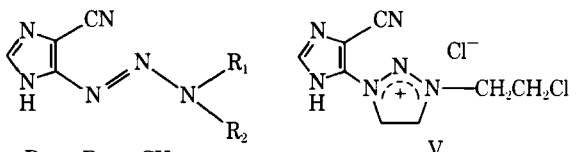
5-[3,3-Bis(2-fluoroethyl) - 1-triazenyl]imidazole-4-carboni-



Ia: X = NH_2, R_1 = R_2 = CH_3
Ib: X = OCH_3, R_1 = R_2 = CH_3
Ic: X = OR, R_1 = CH_3, R_2 = alkyl
Id: X = NH_2, R_1 = CH_3, R_2 = alkyl



II III



IVa: R_1 = R_2 = CH_3
IVb: R_1 = CH_3, R_2 = n-C_4H_9
IVc: R_1 = CH_3, R_2 = CH_2CH_2OH
IVd: R_1 = R_2 = CH_2CH_2F
IVe: R_1 = R_2 = CH_2CH_2Cl

V

Scheme I

trile (IV*d*)—A solution of 4.56 g of bis(2-fluoroethyl)amine hydrobromide (12), 20 ml of water, and 12 ml of 2 *N* aqueous sodium hydroxide was prepared at 0° and added in one portion to a solution of 1.0 g of the diazo derivative (III) in 30 ml of water at 0–5°. An orange precipitate formed immediately. The mixture was stirred at 0–5° for 15 min, and the precipitate was separated by filtration, washed thoroughly with water, and dried *in vacuo* at 55° for 45 min and at room temperature for 3 hr; the yield was 1.45 g, mp 125–128° dec.

A warm solution of the product in ethyl acetate (56 ml) was treated with activated charcoal, filtered, diluted with cyclohexane (20 ml), and chilled; the yield of recrystallized IV*d* was 1.2 g (62%), mp 129–131° dec. (inserted at 75°, 3°/min); TLC, 1 spot [40 μg, silica gel H, chloroform–methanol (95:5), detection by I_2, UV, and UV + whitening agent]; IR (KBr): 2220 (CN) cm^{-1}; UV: λ_{max} 226 (ε 9600) and 323 (ε 15,000) nm in 0.1 *N* HCl, 226 (ε 11,400) and 328 (ε 14,200) nm in phosphate buffer (pH 7), and unstable in 0.1 *N* NaOH; mass spectrum (direct-probe inlet temperature of 200°): *m/e* 228 (M), 120 [M − $N(CH_2CH_2F)_2$], 108 [$(FCH_2CH_2)_2N$+], and 92 (120 − N_2).

Anal.—Calc. for $C_8H_{10}F_2N_6$: C, 42.10; H, 4.42; N, 36.83. Found: C, 42.07; H, 4.43; N, 36.52.

A 10-ml aliquot of an ethanol solution of IV*d* was diluted to 200 ml with 0.1 *N* NaOH, and UV spectra of aliquots were determined at intervals up to 2.5 hr. The spectrum changed rapidly and within 20 min was essentially identical with that of V in 0.1 *N* NaOH: λ_{max} 234 (ε 10,500), 307 (ε 4200), and 412 (ε 13,300) nm.

5-[3,3-Bis(2-chloroethyl) - 1-triazenyl]imidazole-4-carbonitrile (IV*e*)—A solution of bis(2-chloroethyl)amine free base was prepared from 8.96 g of the hydrochloride and 150 ml (2 × 75 ml) of methylene chloride by the procedure described previously (7). To this solution at 15° was added 2.0 g of the diazoimidazole (III); the solution was stirred for 15 min, treated with activated charcoal, filtered, and diluted with 150 ml of cyclohexane. An oil precipitated and solidified when the mixture was chilled. The crystalline product was collected by filtration, washed with methylene chloride–cyclohexane (1:1), and dried *in vacuo* at room temperature; the yield was 3.97 g, mp 195–197° dec. (inserted at 70°, 3°/min).

The crude product was stirred in 50 ml of water in the dark for 5 min, separated by filtration, washed with water, and dried *in vacuo;* the yield was 3.76 g (86%); NMR (CF_3COOD): δ 4.17 (center of A_2B_2 multiplet, CH_2CH_2Cl) and 8.73 (s, imidazole CH). The NMR spectrum showed that this specimen was about 90% IV*e* and about 10% V (δ 5.1, 8.2). NMR analyses showed that the amount of V increased to about 15% after this specimen was kept for 20 days at −15 to −20° and that the amount of V in another specimen stored similarly had increased from about 10% to about 30% after 50 days. The melting temperature, 196–198° dec. (inserted at 70°, 3°/min), was the same as that of the triazolinium chloride (V). When a specimen was inserted at 130°, it melted immediately, resolidified, and remelted at 196–198° dec.

Anal.—Calc. for $C_8H_{10}Cl_2N_6$: C, 36.79; H, 3.86; N, 32.19. Found: C, 36.51; H, 3.65; N, 32.16.

The IR spectra of typical specimens of IV*e* containing 5–10% of V included the following bands in the 1600–1200-cm^{-1} region: 1570 m, 1510 sh, 1495 m, 1450 s, 1420 m, 1395 ms, 1375, 1355 ms, 1335 ms, 1285 ms, 1275, 1265 ms, 1220, and 1210 sh. A medium strong band at 1100 cm^{-1} and medium bands at 1160 and 1140 cm^{-1} were in a region where V showed only weak bands (at 1180, 1170, and 1135 cm^{-1}); other prominent bands in the spectra of IV*e* were at 2230 s (CN), 955, and 650 cm^{-1}. The shoulder at 1510 cm^{-1} in the spectra of specimens of IV*e* was probably due to the presence of the triazolinium salt (V). Attempts to correlate the results of NMR assays of IV*e* samples containing different amounts (5–40%) of V with IR spectra indicated that IV*e* was sometimes partly converted to V during the preparation of the potassium bromide disk.

A hydrochloride of IV*e* was prepared as follows. A mixture of 350 mg of IV*e*, 20 ml of ether, and 40 ml of methanol was filtered, the filtrate was treated with an excess of hydrogen chloride, the turbid mixture was filtered, and the filtrate was concentrated to a syrup *in vacuo*. Evaporation of several portions of ether from the residue converted it to a crystalline solid, which was washed with several portions of ether and dried *in vacuo;* the yield was 280 mg. The NMR spectra (CF_3COOD) of the hydrochloride and the free base were identical.

Anal.—Calc. for $C_8H_{10}Cl_2N_6 \cdot HCl$: C, 32.29; H, 3.73; N, 28.24. Found: C, 32.52; H, 3.48; N, 28.58.

1-(2-Chloroethyl)-3-(5-cyanoimidazol-4-yl)-Δ^2-1,2,3-triazolinium Chloride (V)—Another experiment performed by the procedure described for the reaction of III and bis(2-chloroethyl)amine afforded a crude product that contained (NMR analysis) about 40% of the 1,2,3-triazolinium salt (V). A suspension of this material (2.9 g) in 40 ml of water was stirred in the dark for 5 min. The insoluble fraction (1.88 g) was separated by filtration and was shown by NMR analysis to be the bis(2-chloroethyl)triazene (IV*e*), containing about 10% of V. The filtrate was treated with activated charcoal, filtered, and lyophilized.

The residual, yellow crystalline solid was triturated with ethyl acetate and dried *in vacuo* at 56°; the yield was 640 mg, mp 197–199° dec. (inserted at 70°, 3°/min); UV: λ_{max} 232 (ε 13,100), 252 (plateau), and 345 (ε 8800) nm in 0.1 *N* HCl; 233 (ε 11,300), 277 (ε 3750), and 375 (ε 8300) nm in phosphate buffer (pH 7); 233 (ε 10,500), 305 (ε 4200), and 410 (ε 13,600) nm in 0.1 *N* NaOH; IR (1600–1200-cm^{-1} region): 1575 ms, 1510 s, 1460 ms, 1440, 1420 s, 1365, 1350, 1325, 1300, 1280 s, 1270 s, and 1210 cm^{-1}; also medium strong IR bands at 3120, 2510 (broad), 2230 (CN), 930, and 865 cm^{-1}; NMR (CF_3COOD): δ 4.38 (center of A_2B_2 multiplet, CH_2CH_2Cl), 5.12 (multiplet approaching singlet, CH_2CH_2), and 8.25 (s, imidazole CH).

Anal.—Calc. for $C_8H_{10}Cl_2N_6$: C, 36.79; H, 3.86; Cl, 27.16; N, 32.19. Found: C, 36.71; H, 3.78; Cl, 27.18; N, 32.41.

Compound V was also prepared by stirring isolated IV*e* in 90% methanol; several days were required to complete the cyclization because of the sparing solubility of IV*e*.

REFERENCES

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

(2) Y. F. Shealy, C. A. O'Dell, and C. A. Krauth, Canadian pat. 871,699 (May 25, 1971).

(3) C. A. Krauth, Y. F. Shealy, and C. A. O'Dell, U.S. pat. 3,649,613 (Mar. 14, 1972).

(4) J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.*, **87**, 4976(1965).

(5) *Ibid.*, **88**, 3829(1966).

(6) K. Suzuki, T. Saito, T. Meguro, I. Kumashiro, and T. Takenishi, Japanese pat. 6910 (1967); through *Chem. Abstr.*, **68**, 68995(1968).

(7) Y. F. Shealy, C. A. Krauth, L. B. Holum, and W. E. Fitzgibbon, *J. Pharm. Sci.*, **57**, 83(1968).

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

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

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

(11) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1(1972).

(12) G. R. Pettit and R. L. Smith, *Can. J. Chem.*, **42**, 572(1964).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 26, 1974, from the *Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, AL 35205*

Accepted for publication November 14, 1974.

Supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Contracts NIH-NCI-C-71-2021 and PH43-64-51. Testing against L-1210 leukemia was performed under the supervision of Dr. F. M. Schabel, Jr., and Dr. W. R. Laster, Jr., and was supported by Contracts NIH-NCI-C-71-2098 and PH43-65-594 with the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

Elemental analyses and spectrometric determinations were performed by members of the Molecular Spectroscopy Section of this Institute under the supervision of Dr. W. C. Coburn, Jr.

[x] To whom inquiries should be directed.