

no reference to the use of *A. cannabinum* for the treatment of cancer, a milky bitter juice obtained from the fresh plant has been used against warts and condylomas.¹¹

We have noted with considerable interest the recent report that, of more than 150 steroids tested for cytotoxic activity against KB, the most active compounds all contain an α,β -unsaturated lactone ring.¹² Studies are in progress in these laboratories which are aimed at evaluation of the importance of the γ -lactone ring, the 19-oxo function, the glycosidic moiety, and other structural features to the cytotoxicity of cardenolide derivatives.

Experimental¹³

Separation into Main Fractions.—The aqueous alcoholic extract (150 g.) of the roots of *Apocynum cannabinum* (Meer Corp.) was partitioned between water (500 ml.) and four 250-ml. portions of chloroform. The resulting aqueous layer was freeze-dried to yield 112.5 g. of aqueous extract (A). The chloroform solution, after drying over anhydrous sodium sulfate, was evaporated under reduced pressure to yield 25.3 g. of chloroform solubles (C). The interfacial insolubles after drying yielded 9.2 g. of solid (B).

The chloroform-soluble fraction (C) was dissolved in methanol (250 ml.) and treated with excess 10% methanolic lead acetate solution. The precipitate was removed by centrifugation and the centrifugate was freed from excess lead by treatment with hydrogen sulfide. The precipitate, after resuspending in methanol (250 ml.), was regenerated by separate treatment with hydrogen sulfide. Evaporation of the two solutions under reduced pressure yielded 12.7 g. of the nonprecipitated (D) and 12.0 g. of precipitated material (E). (See Scheme I for flow sheet.)

Isolation of the Glycosides.—The nonprecipitated material was further fractionated by adsorption chromatography on a silicic acid (Mallinckrodt)-Celite 545 (Johns Manville) (3:1, 500 g.) column, 40 × 5 cm. Fraction D (12.7 g.), dissolved in chloroform (150 ml.), was added to the column and washed on with a further 100 ml. of chloroform. The column was then eluted with 1% methanol in chloroform to yield a yellow waxy solid (F, 2.60 g.) and a yellow oil (G, 0.72 g.). Elution was continued with 3% methanol in chloroform to yield a yellow crystalline solid (H, 3.75 g.), a yellow waxy solid (I, 0.34 g.), and another yellow crystalline material (J, 0.86 g.). The solvent was changed to 5% methanol in chloroform to yield a brown oil (K, 0.50 g.) and two yellow oil fractions (L, 0.69 g., and M, 0.76 g.). The material remaining on the column was removed using methanol to yield a fawn solid (N, 1.19 g.).

Fraction L (0.69 g.) was crystallized from methanol-ether to yield 230 mg. of colorless needles of apocannoside (P), m.p. 134–137° (lit.⁹ m.p. 122–132°); $[\alpha]_D^{25} -8^\circ$ (*c* 0.91, CHCl₃); $\lambda_{\text{max}}^{\text{alc}}$ 216 μ (ϵ 12,600); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.83, 3.41, 5.63, 5.76, 5.84, and 6.20 μ . The acetate was obtained from acetone-ether as colorless prisms, m.p. 182–184° (lit.⁹ m.p. 175–185°), $[\alpha]_D^{25} +4^\circ$ (*c* 1.04, CHCl₃).

The residual oil (445 mg.) obtained from the above crystallization of apocannoside was rechromatographed on a silicic acid (Mallinckrodt)-Celite 545 (Johns Manville) (3:1, 12 g.) column as previously described. The fraction containing apocannoside was rechromatographed on silica gel thin layer plates using 10% methanol in chloroform as solvent. The apocannoside band (R_f 0.60–0.65) was removed and eluted with methanol to yield 36 mg. of crystalline apocannoside. The remaining silica gel was also washed with methanol and the residue after removal of the methanol was combined with the apocannoside-

free material obtained from the column, yielding residual apocannoside-free oil (O, 328 mg.).

Fraction M (0.76 g.) was crystallized from methanol-ether, yielding 255 mg. of colorless needles of cynarin (R), m.p. 143–144° (lit.⁹ 138–148°); $[\alpha]_D^{25} +38^\circ$ (*c* 1.07, CHCl₃); $\lambda_{\text{max}}^{\text{alc}}$ 216 μ (ϵ 9800); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.87, 3.40, 5.62, 5.76, 5.85, and 6.19 μ .

Acid hydrolysis yielded aglycone which was obtained from methanol-water as colorless prisms, m.p. 150–152°, $[\alpha]_D^{25} +42^\circ$ (*c* 1.2, MeOH). This sample also had the same R_f as that of an authentic sample of strophanthidin on thin layer chromatography on silica gel using 10% methanol in chloroform. The infrared spectrum in Nujol was essentially superimposable with that of the authentic sample of strophanthidin.

The residual oil (489 mg.) obtained from the above crystallization of cynarin was rechromatographed on a silicic acid (Mallinckrodt)-Celite 545 (Johns Manville) (3:1, 12 g.) column as previously described. The fraction containing cynarin was chromatographed on silica gel thin layer plates using 10% methanol in chloroform as solvent. The cynarin band (R_f 0.40–0.48) was removed and eluted with methanol to yield 162 mg. of crystalline cynarin. The remaining silica gel was also washed with methanol and the residue after removal of the methanol was combined with the cynarin-free material obtained from the column, yielding residual cynarin-free oil (Q, 233 mg.).

The Oral Progestational Activity of the 3-Ketals of Certain 17-Acetoxy- and 17-Alkylprogesterones

MARTIN J. WEISS, JOHN F. POLETTO, GEORGE R. ALLEN, JR.,
ROBERT E. SCHAUB, AND IRA RINGLER

*Lederle Laboratories Division, American Cyanamid Company,
Pearl River, New York*

Received June 20, 1964

In the course of our studies¹ in the 17-alkylprogesterone series we observed that in most instances the 3-ethylene ketal derivative was at least as effective in the oral Clauberg assay as the parent ketone and in some instances even showed enhanced activity.² To investigate further this interesting observation we prepared the 3-ketals of a variety of known active 17-acetoxyprogesterones, namely 17-acetoxyprogesterone³ and its 6 α -methyl,⁵ 6-dehydro,^{6,7} 6-dehydro-6-methyl,⁸ and 6-chloro-6-dehydro⁹ derivatives. In addition, the 3-ketals of 6-dehydro-17-ethylprogesterone¹⁰ and its 6-chloro derivative¹⁰ were prepared.

The various ketals (Table I) were obtained by direct ketalization, according to the usual technique,¹¹ of

(1) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poleto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(2) In a previous report from this laboratory [W. S. Allen, H. M. Kissman, S. Mauer, I. Ringler, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 133 (1962)] we noted the glucocorticoid activity of various 20-ketalized corticoids.

(3) Although the preparation of the 3-ethylene ketal of 17-acetoxyprogesterone has been reported,⁴ no biological activity was noted.

(4) C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Am. Chem. Soc.*, **79**, 6303 (1957).

(5) J. C. Babcock, E. S. Gussell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *ibid.*, **80**, 2904 (1958).

(6) R. Sciacchi, *Gazz. chim. ital.*, **91**, 545 (1961).

(7) Prepared by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzquinone of the corresponding Δ^4 -3-ketone according to the procedure of H. J. Ringold and A. Turner [*Chem. Ind. (London)*, 211 (1962)] (see Experimental).

(8) (a) P. DeRuggieri, C. Ferrari, and C. Gandolfi, *Ann. Chim. (Rome)*, **49**, 1371 (1959); (b) H. J. Ringold, J. Perez Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959).

(9) H. J. Ringold, E. Baires, A. Bowers, J. Edwards, and J. Zderic, *ibid.*, **81**, 3485 (1959).

(10) M. J. Weiss, R. E. Schaub, J. F. Poleto, G. R. Allen, Jr., and C. Pidacks, *Steroids*, **1**, 608 (1963); R. Deghenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963).

(11) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(11) H. Boeillon-Limousin, "Manuel des Plantes Medicinales Coloniales et Exotiques," J. B. Baillièrre et fils, Paris, 1903. We thank Dr. J. L. Hartwell for calling this reference to our attention.

(12) J. E. Pike, J. E. Grady, J. S. Evans, and C. G. Smith, *J. Med. Chem.*, **7**, 348 (1964).

(13) Melting points have been corrected for stem exposure. Values of $[\alpha]_D$ have been approximated to the nearest degree. Infrared spectra were determined on a Beckman infrared 5A spectrophotometer. Ultraviolet absorption spectra were determined in 95% ethanol on a Beckman DK 2A recording spectrophotometer.

TABLE I
 VARIOUS 3-KETALS

No.	Name	Yield, % ^a	M.p., °C. (recrystn. solvent) ^b	[α] _D , deg. ^c	Formula	C, %		H, %		Cl, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1	17-Acetoxy-3-ethylenedioxy-6-methylpregn-5-en-20-one	61	185-187 (A-B)	-55	C ₂₅ H ₃₈ O ₄	72.52	72.61	8.90	9.32
2	17-Acetoxy-3-(1,2-dimethylethylenedioxy)-6-methylpregn-5-en-20-one	41	188-192 (C-D)	-49	C ₂₅ H ₄₂ O ₄	73.32	73.32	9.23	9.55
3	17-Acetoxy-3-ethylenedioxy-pregna-4,6-dien-20-one	77	231-234 (E)	+37	C ₂₅ H ₃₄ O ₄	72.43	71.67	8.27	8.30
4	17-Acetoxy-3-ethylenedioxy-6-methylpregna-4,6-dien-20-one	6 ^d	217-219 (E)	+41	C ₂₅ H ₃₈ O ₄	72.86	72.51	8.47	8.63
5	17-Acetoxy-6-chloro-3-ethylenedioxy-pregna-4,6-dien-20-one	54	205-206 (C-F)	+18.6	C ₂₅ H ₃₂ ClO ₄	66.87	66.88	7.41	7.58	7.90	7.90
6	17-Acetoxy-6-chloro-3-(methyl-ethylenedioxy)pregna-4,6-dien-20-one	24 ^e	192-194 (D-F)		C ₂₆ H ₃₆ ClO ₄	67.44	67.65	7.62	7.51	7.66	7.96
7	17-Acetoxy-6-chloro-3-(1,2-dimethylethylenedioxy)pregna-4,6-dien-20-one	21	168-170 (G)		C ₂₇ H ₃₇ ClO ₄	67.98	68.23	7.82	8.22	7.43	7.62
8	17-Ethyl-3-ethylenedioxy-pregna-4,6-dien-20-one	38	166-168 (C-F)	+63	C ₂₅ H ₃₆ O ₄	78.08	78.01	9.44	9.59
9	6-Chloro-17-ethyl-3-ethylenedioxy-pregna-4,6-dien-20-one	50	176-178 dec. (A-B)	+36	C ₂₅ H ₃₂ ClO ₄	71.66	71.44	8.42	8.63	8.46	8.62
10	6-Chloro-17-ethyl-3-(1,2-dimethylethylenedioxy)pregna-4,6-dien-20-one	55	156-158 (E)	+49	C ₂₇ H ₃₆ ClO ₄	72.54	72.72	8.79	9.06	7.93	8.08
11	17-Acetoxy-6-chloro-3-ethylenedioxy-pregna-4-en-20-one ^f	33	245-246 (D-F)	+73	C ₂₅ H ₃₂ ClO ₄ S ₂ ^g	62.40	62.98	6.92	6.97

^a Yield of good quality material. ^b Corrected analytical melting point determined in open capillary tubes on a Mel-Temp apparatus. Recrystallization solvents: A = acetone, B = petroleum ether (b.p. 60-70°), C = methylene chloride, D = ether, E = methanol, F = petroleum ether (b.p. 30-60°), G = isopropyl ether. ^c All rotations were determined in chloroform solutions in dm. tubes at a concentration of 0.9-1.1% with the exception of entry 5, which was determined at 0.43%. $\lambda_{\text{max}}^{\text{CH}_2\text{OH}}$ (6-unsubstituted $\Delta^{4,6}$ -3-ketals): 232-233 m μ (ϵ 22,000-25,000), 238-239 (23,000-27,000), 246-247 (15,000-18,000); for the 6-methyl $\Delta^{4,6}$ -3-ketal (entry 4): 236 m μ (ϵ 20,800), 242 (22,700), 250 (15,400); for the 6-chloro $\Delta^{4,6}$ -3-ketals: 237-238 m μ (ϵ 19,000-21,000), 243 (21,000-24,000), 252-253 (15,000-16,000); in all instances the center peak of the triad was the major peak; for the 6-chloro- $\Delta^{4,6}$ -3-thioketal (entry 11): 248 m μ (ϵ 18,600), 270 (12,200). The infrared spectra in all instances confirmed the loss of the conjugated 3-ketone and the retention of the 20-ketone. ^d Eluted from silica gel with benzene-ether (10:1). ^e Eluted from silica gel with benzene-ether (95:5). ^f See ref. 13. ^g Anal. Calcd.: S, 13.33. Found: S, 13.15.

the parent 17-acetoxy- and 17-alkylprogesterones. As has been noted previously,^{1,4} the presence of the 17-substituent effectively hinders ketalization of the 20-carbonyl group and a preferential 3-ketalization is smoothly achieved. That $\Delta^{4,6}$ -3-ketones will undergo ketalization has already been reported.¹² Ketalization was carried out with ethanediol, butane-2,3-diol, propane-1,2-diol, and also with ethane-1,2-dithiol.¹³

Progestational Evaluation.—The various ketals and their parent ketones were assayed for progestational activity by the oral Clauberg procedure¹⁴; these activities are listed in Table II. It is apparent that the ketals have an order of activity similar to that shown by the parent ketones. In certain instances the activity even appears to be somewhat enhanced. Thus, the 3-ethylene ketals of 17-acetoxypregesterone and 17-ethylprogesterone are about 3-4 times as active as the parent 3-ketones. Also, the ketals of 6-chloro-6-dehydro-17-acetoxypregesterone are as much as 2-3 times as active as the parent compound. On the other hand, the 3-ethylene ketal of 6-dehydro-6-methyl-17-acetoxypregesterone has only about half the activity of the parent ketone.

The structure-activity relationship resulting from variations in the ketal moiety of these molecules was investigated only briefly. With the ketals of 6-chloro-6-dehydro-17-acetoxypregesterone, small varia-

tions in activity were noted. The ethylenethio ketal in this series was either inactive or at best considerably less active than the parent.

With regard to the question as to whether these ketals are active *per se* or undergo conversion to the active parent ketones, we have no pertinent evidence to report.¹⁵ However, it is of interest to note that one ketal, that of 17-ethylprogesterone, was inactive when administered by the subcutaneous route, although the ketal of 6-dehydro-17-ethylprogesterone was substantially active when assayed by this route of administration.

Experimental¹⁶

17-Acetoxypregna-4,6-diene-3,20-dione.⁷—A solution of 2 g. of 17-acetoxypregna-4-ene-3,20-dione and 1.34 g. of recrystallized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 65 ml. of purified dioxane was saturated with HCl. After 30 min. the solution was filtered, the mother liquor was diluted with methylene chloride washed with water, 1% aqueous NaOH solution, and saline solution, dried (MgSO₄), and evaporated to dryness leaving a solid. Several recrystallizations from acetone gave white crystals, yield 871 mg. (44%); m.p. 220-221° (lit.⁶ m.p. 227-228°); [α]_D²⁵ +6° (c 0.5, CHCl₃); $\lambda_{\text{max}}^{\text{CH}_2\text{OH}}$ 283 m μ (ϵ 23,000); $\lambda_{\text{max}}^{\text{KBr}}$ 5.73, 5.78, 6.02, 6.14, 6.26, 7.93 μ .

Anal. Calcd. for C₂₅H₃₀O₄: C, 74.56; H, 8.16. Found: C, 74.29; H, 8.59.

17-Acetoxy-6-methylpregna-4,6-diene-3,20-dione.⁷—In the manner described above 3.865 g. (10 mmoles) of 17-acetoxy-6 α -methylprogesterone⁵ was treated with 2.73 g. (12 mmoles) of

(12) G. J. Fonken, *J. Org. Chem.*, **26**, 2549 (1961).

(13) The ethylenedithio ketal was prepared by the procedure previously reported by J. W. Ralls and B. Riegel [*J. Am. Chem. Soc.*, **76**, 4479 (1954)] for the thioketalization of Δ^4 -3-ketones.

(14) All Clauberg assays were carried out under the supervision of Dr. E. Shipley of the Endocrine Labs., Madison, Wis., according to the McPhail modification [M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1934)].

(15) One of the ketals (17-acetoxy-6-chloro-3-ethylenedioxy-pregna-4,6-dien-20-one) was checked for stability in tragacanth, the administration vehicle used in the Clauberg assay, and found to be stable (see Experimental).

(16) Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are corrected.

TABLE II
ORAL PROGESTATIONAL ACTIVITY OF KETALS AND
CORRESPONDING KETONES

Compl.	Relative potency ^a	Endometrial response	Total dose, mg.
17-Acetoxyprogesterone	1	3.0 2.3 1.5	20 10 5
3-ethylene ketal ³	3		
6 α -Methyl-17-acetoxyprogesterone ⁵	60	1.6 3.6	0.1 0.4
3-ethylene ketal		2.2 2.5 3.0	0.1 0.2 0.4
3-(1,2-dimethylethylene) ketal		1.2	0.1
6-Dehydro-17-acetoxyprogesterone ⁵	26		
3-ethylene ketal	25		
6-Dehydro-6-methyl-17-acetoxyprogesterone ⁸	200		
3-ethylene ketal	114		
6-Chloro-6-dehydro-17-acetoxyprogesterone ⁹	190	3.1	0.08
3-ethylene ketal	320		
3-methylethylene ketal	430		
3-(1,2-dimethylethylene) ketal	520		
3-ethylenethio ketal		0	0.08
17-Ethylprogesterone ^{1,10}	0.5		
3-ethylene ketal	2	0 0	1.0 s.c. 3.0 s.c.
17-Propylprogesterone ^{1,10}	2		
3-ethylene ketal ¹	3		
6-Dehydro-17-ethylprogesterone ¹⁰	5	0.5 1.2 3.7 1.5 1.8 1.2 3.8 3.8 4.0	0.5 1.0 5.0 0.5 1.0 2.0 5.0 0.5 s.c. 1.5 s.c.
3-ethylene ketal			
6-Chloro-6-dehydro-17-ethylprogesterone ¹⁰	60	0.5 2.6	0.04 0.16
3-ethylene ketal	52		
3-(1,2-dimethylethylene) ketal		0.2 3.2	0.04 0.16

^a All values are based on data obtained by the present authors.¹⁴ Relative potencies were determined by plotting dose-response data on semilog paper. Where a dose-response effect was not observed or where a complete evaluation was not obtained, the activity is indicated in terms of the endometrial response to a given total dose (mg.). This response (or lack thereof) is measured in terms of 0 to 4, the latter number indicating the highest activity.

2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 100 ml. of dioxane saturated with HCl. The product was recrystallized from acetone-hexane to give 1.922 g. (50%) of white crystals, m.p. 213-215° (lit.¹⁵ m.p. 218-220°), $[\alpha]_D^{25} +19^\circ$ (*c* 1.0, CHCl₃) (lit.¹⁵ $[\alpha]_D +11^\circ$, CHCl₃), $\lambda_{max}^{CH_2OH}$ 289 m μ (ϵ 24,000).

General Ketalization Procedure.—The following preparation of 17-acetoxy-3-ethylenedioxyprogna-4,6-dien-20-one is illustrative. A solution of 400 mg. of 17-acetoxypregna-4,6-diene-3,20-dione,⁶ 20 mg. of *p*-toluenesulfonic acid and 20 ml. of ethyl-

one glycol in 100 ml. of reagent grade benzene was stirred vigorously at reflux for 5 hr. The water formed was removed by means of a Dean-Stark tube. The cooled solution was poured into 100 ml. of 5% aqueous sodium carbonate solution. The organic phase was separated, diluted with ether, washed with saline and water, dried (MgSO₄), and evaporated to dryness under reduced pressure. The resulting solid was triturated with ether and collected to give 346 mg. (77%) of product, m.p. 220-225° (see Table I). The various 3-ketals prepared by this procedure are listed in Table I.

17-Acetoxy-6-chloro-3-ethylenedioxyprogna-4,6-dien-20-one.¹⁵—A mixture containing 95 mg. of 17-acetoxy-6-chloropregna-4,6-diene-3,20-dione,⁹ 2 ml. of acetic acid, 26 mg. of 1,2-ethanedithiol, and 30 mg. of *p*-toluenesulfonic acid was kept at room temperature for 1 hr. and then was poured into water with stirring. The precipitated solids were filtered, washed well with water, and dissolved in chloroform. After drying over anhydrous sodium sulfate, the chloroform solution was evaporated to dryness to give the product (see Table I).

Stability of 17-Acetoxy-6-chloro-3-ethylenedioxyprogna-4,6-dien-20-one in Tragacanth.—Subject ketal (100 mg./ml.) was suspended in 10 ml. of tragacanth (pH 5.4, from the same source as that used for assay purposes). Aliquots of this suspension were taken 0, 3, and 5 days after preparation. These aliquots were extracted three times with equal volumes of chloroform, the total volume was adjusted to 50 ml., and the ultraviolet spectrum was determined. In all instances approximately 95% of steroid could be accounted for as ketal, which was confirmed by paper chromatography with a methanol-water-heptane (4:1:5) system. Samples of the chloroform extract partitioned for 90 min. on Whatman paper No. 3 each exhibited a single ultraviolet-absorbing spot, with a degree of migration identical with that of concurrently partitioned standard ketal and different from that of parent ketone. (Parallel experiments with this ketone, 17-acetoxy-6-chloropregna-4,6-diene-3,20-dione showed that this ketone also is absorbed into the chloroform layer.)

Acknowledgments.—We wish to thank Mr. J. Nocera and Dr. J. Fedrick of the Preparations Group of these laboratories for a supply of 17-acetoxy-6-chloro-6-dehydroprogesterone, Mr. C. Pidacks and staff for the partition chromatographic work, Mr. W. Fulmor and staff for the spectroscopic and polarimetric data, and Mr. L. Brancone and staff for the micro-analytical data.

Studies on Methylglyoxal Bis(guanylhyazone)¹ Analog. III. Trifluoromethylglyoxal Bis(guanylhyazone)² and 1,2-Bis(guanidinoamino)propane^{3,4}

EUGENE G. PODREBARAC AND C. C. CHENG

Midwest Research Institute, Kansas City, Missouri 64110

Received April 3, 1964

In view of the antileukemic activity of methylglyoxal bis(guanylhyazone) (I) and the complete lack of activity of closely related homologs⁵ and structural analogs,⁶ it appears that steric factors play a

- (1) According to *Chemical Abstracts*, the name for this compound is 1,1'-[(methyl)ethanediyldenedinitrilo]diguanidine.
- (2) 1,1'-[(Trifluoromethyl)ethanediyldenedinitrilo]diguanidine.
- (3) 1,1'-[(Methylethylene)diimino]diguanidine.
- (4) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract SA-43-ph-3025.
- (5) E. G. Podrebarac, W. H. Nyberg, F. A. French, and C. C. Cheng, *J. Med. Chem.*, **6**, 283 (1963).
- (6) (a) F. Baiocchi, C. C. Cheng, W. J. Haggerty, Jr., L. R. Lewis, T. K. Liao, W. H. Nyberg, D. E. O'Brien, and E. G. Podrebarac, *ibid.*, **6**, 431 (1963). (b) Butane-1,3-dione bis(guanylhyazone) sulfate, originally reported by Burness,⁷ was found to be inactive in L-1210 system.
- (7) D. M. Burness, *J. Org. Chem.*, **21**, 97 (1956).