Methylglyoxal Bis(guanylhydrazone) Analogs VI. Methylglyoxal Bis(guanylhydrazone) Pamoate

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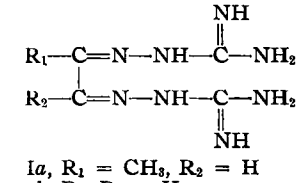
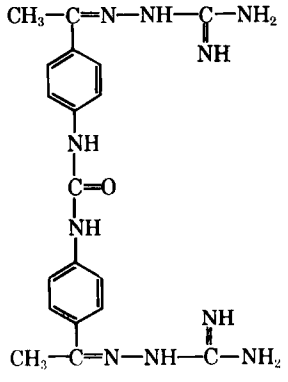
The pamoate of methylglyoxal bis(guanylhydrazone) was prepared. This compound, on a molar basis, is more active and less toxic than the corresponding dihydrochloride salt against leukemia L-1210.

THE ANTITUMOR ACTIVITY of methylglyoxal bis(guanylhydrazone),[1] [methyl-GAG, *Ia*], against leukemia L-1210 in mice and adult acute myelocytic leukemia (1, 2) in man is now well known. This drug, however, was found to be quite toxic (3, 4).



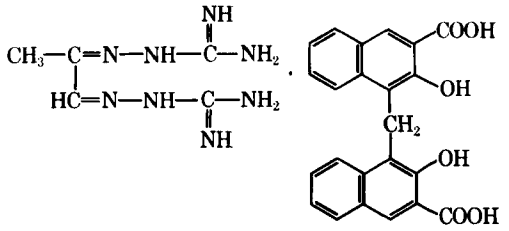
Ia, $R_1 = CH_3$, $R_2 = H$
b, R_1, $R_2 = H$
c, $R_1 = CH_2OH$, $R_2 = H$
d, R_1, $R_2 = CH_3$

Subsequent work revealed that, except for the unmethylated compound *Ib* which is almost as active (1) as *Ia*, other modifications of the basic structure failed to yield compounds active against leukemia L-1210 (5–9). The reported activity of hydroxymethyl-GAG (*Ic*) was proved to be erroneous since the originally synthesized *Ic* (10) was found to be actually hydrated methyl-GAG (11–13). The authentic hydroxymethyl-GAG did not show the expected activity (11–13). Although the compound 4,4′-diacetyldiphenylurea bis(guanylhydrazone) [DDUG, II], was found to have marked activity against leukemia L-1210 (14), no cross-resistance between methyl-GAG and DDUG was observed (14–16). In addition, a structurally related compound, dimethyl-GAG (*Id*), is entirely devoid of antileukemia activity (6). Compound II is believed to be an analog of the terephthalanilide-type (15).



II

In view of the aforementioned information, an attempt was made to modify the absorption and excretion pattern, rather than the basic structure, of *Ia*. Since salts of pamoic acid, due to their very limited solubility, are known to provide slow release of basic drugs and thus maintain a low level of drug in the blood stream,[2] the pamoate salt of methyl-GAG (III) was prepared in this laboratory.



III

The title compound was readily obtained by the reaction of methylglyoxal bis(guanylhydrazone) dihydrochloride and the disodium salt of pamoic acid. Equivalent amounts of pure starting materials gave desired product of analytical purity in 91% yield.

Preliminary tests of III indicated activity in the 9KB primary screen. Tests in the leukemia L-1210 system revealed that, on a molar basis, compound III is much more active and less toxic than the corresponding dihydrochloride salt (see Table I). For comparison, pamoic acid or its sodium salt possessed no anticancer activity against either sarcoma 180, carcinoma 755, or leukemia L-1210 in mice (21).

That compound III is more than a simple acid-base compound was demonstrated by titration studies. The addition of two equivalents of base to an aqueous suspension of the compound, even after prolonged stirring, failed to yield a solution (a solution was obtained after the addition of four equivalents of base). Since these conditions should give freely water-soluble materials—the free base of methyl-GAG and the disodium salt of pamoic acid—it appears that the phenolic functions of the pamoic acid may play an important role in the composition of III. As such, the pamoic acid salt of methyl-GAG is very different from the simple methyl-GAG salts.

EXPERIMENTAL

One mole (257 g.) of the purified dihydrochloride

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[1] According to *Chemical Abstracts*, the name for this compound is 1,1′-[(methyl)ethanediylidenedinitrilo]diguanidine.

[2] In the treatment of malaria, intramuscular injection of an oil suspension of cycloguanil pamoate was found to curtail the effects of malaria in man for extended periods (17–19). In cancer chemotherapy study, it was reported that the pamoates of various alkylating agents had significantly better actions in prolonging the survival time of mice with ascites tumors than their corresponding hydrochloride salts (20).

TABLE I—COMPARISON OF ANTILEUKEMIA ACTIVITY OF THE DIHYDROCHLORIDE AND PAMOATE OF METHYLGLYOXAL BIS(GUANYLHYDRAZONE) AGAINST LEUKEMIA L-1210 IN MICE[a]

Dose (i.p.), mg./kg.	Survivors	Cures	Animal Wt. Diff.	Percent T/C[b]
	Me-GAG·2HCl			
400.0	0/7			
200.0	5/7		−3.8	89
100.0	7/7		−2.0	144
60.0	6/6		−2.3	168
60.0	6/6		−1.2	138
60.0	5/6		−1.4	114
40.0	6/6		−0.1	139
25.0	6/6		−1.2	160
25.0	6/6		−0.5	135
18.0	6/6		−0.4	115
16.0	6/6		−0.8	124
11.1	6/6		−0.3	118
	Me-GAG·Pamoate			
1000.0	10/10		−1.6	208
800.0	10/10		−1.2	170
800.0	10/10	1	−2.4	257
400.0	10/10		−1.7	196
200.0	10/10		−1.3	157
200.0	10/10	1	−1.6	264
100.0	10/10		−1.1	210
50.0	10/10		−0.8	166
25.0	9/9		−1.2	136
19.0	6/6		0.3	123
15.6	6/6		−1.8	135
12.0	6/6		−1.7	125
7.8	6/6		−1.1	116

[a] Biological testing was performed by contract screeners of CCNSC. [b] T/C = survival time: test/control.

salt of methyl-GAG was dissolved in 2,500 ml. of distilled water and the solution warmed to 80°. A disodium pamoate solution was prepared by dissolving 1 mole of disodium pamoate monohydrate (450 g.) in 2,800 ml. of distilled water. The solution was warmed to 70°, treated with Norite, then filtered (still had red-brown color).

The Me-GAG·2HCl solution was stirred vigorously at 80–90° while the disodium pamoate solution at 70° was added portionwise during approximately 45 min. A solid began to separate immediately. The reaction mixture was stirred at 90° for 1 hr. then filtered. The filter cake was washed well with hot water then dried in a vacuum oven at 80–85° at approximately 20 mm. for 20 hr. to give 536 g. (91% yield) of the pamoate salt of methylglyoxal bis(guanylhydrazone), m.p. 262–263° dec.; $\lambda_{max.}^{pH\ 1}$ 282 mμ (ε 61,800); 273 mμ (ε 63,600). $\lambda_{max.}^{pH\ 11}$ 327 mμ (ε 34,100); 235 mμ (ε 94,200). Minor absorption peaks at 300 and 288 mμ and a shoulder at 277 mμ were noted in pH 11.

Anal.—Calcd. for $C_{23}H_{28}N_8O_6 \cdot H_2O$ (mol. wt. 590.6): C, 56.94; H, 5.12; N, 18.97; H_2O, 3.05. Found: C, 56.98; H, 4.71; N, 19.27; H_2O, 3.00.

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Keyphrases

Methylglyoxal bis(guanylhydrazone) pamoate—synthesis
Antileukemic activity—methylglyoxal bis(guanylhydrazone) pamoate
UV spectrophotometry—structure