to give 1.9 g (60%) of yellow liquid **52**.

Acknowledgment. The authors wish to express their appreciation to Mrs. C. J. Jelatis, Mrs. J. J. Boudreau, and Mr. D. B. Holtzclaw for their assistance in the biological evaluation of these compounds.

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Anticoccidial 1-Substituted 4(1*H*)-Pyridinone Hydrazones

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4-Chlorobenzaldehyde 1-(4-chlorophenyl)-4(1*H*)-pyridinylidene hydrazone fluorosulfonate (**4**) was found to have excellent anticoccidial activity in chickens. The synthesis and biological evaluation of related analogues are presented. Presumably **4** shares a common mechanism of action with robenidine (**25**) since it was not active on a robenidine tolerant strain of *E. tenella*. Structural comparisons of the two molecules are presented.

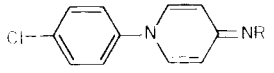
As part of our continuing search for bioactive molecules, some 1-substituted 1,4-dihydro-4-iminopyridines were synthesized for screening. One derivative, 4-chlorobenzaldehyde 1-(4-chlorophenyl)-4(1*H*)-pyridinylidene hydrazone fluorosulfonate (**4**), showed broad-spectrum anticoccidial activity in chickens. Structure–activity relationships within the series were explored through the synthesis and testing of some close analogues.

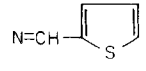
Chemistry. The 1,4-dihydro-4-iminopyridines which were prepared in this study are listed in Tables I and II. Syntheses of a few 1-aryl-1,4-dihydro-4-iminopyridines had been accomplished previously.[1] The methods used involved the arylation of 4-aminopyridine with reactive aryl halides or aryliodonium halides. In the present work we developed a more general route beginning with the reaction of substituted anilines with chelidonic acid. In a typical example, reaction of 4-chloroaniline with chelidonic acid gave via decarboxylation of the intermediate chelidamic acid, 1-(4-chlorophenyl)-4(1*H*)-pyridinone (**23**).[2] Alkylation of **23** with methyl fluorosulfonate afforded the intermediate **24** which on reaction with hydrazine yielded 1-(4-chlorophenyl)-4(1*H*)-pyridinone hydrazone fluorosulfonate (**2**). Compound **2** readily condensed with 4-chlorobenzaldehyde to give **4**. A series of aldehydes and 4-chloroacetophenone was similarly allowed to react with **2** yielding analogous hydrazones. Reaction of **24** with ammonia gave 1-(4-chlorophenyl)-4(1*H*)-pyridinimine (**1**). Condensation of 4-hydrazinopyridine[3] with 4-chlorobenzaldehyde gave 4-chlorobenzaldehyde 4-pyridylhydrazone (**19**) which was alkylated with methyl iodide or 4-chlorobenzyl chloride to yield the 1-alkyl derivatives **20** and **22**.

Biological Activity. Tables I and II list the compounds which were investigated in this study. Table I summarizes results of variations of the lead structure **4** at the 4 position and Table II presents the results of variations at the 1 position.

Compounds were evaluated for anticoccidial activity in chickens[4] carrying an infection of either *E. acervulina* or *E. tenella* by standard assay methods indicated in the footnotes of Tables I and II. All but one of the active compounds showed activity against both species of coccidia, but there was a trend toward higher activity against *E. tenella* throughout the series. The most potent group of monosubstituted compounds **4**, **6**–**8**, **10**, and **11** contained halogen or halogen-like groups in the 4 position. Analogues containing unsubstituted phenyl (**3**), 2-chlorophenyl (**5**), or substituted 4-aminophenyl (**12**, **13**) were inactive. Likewise, replacement of the methylidyne

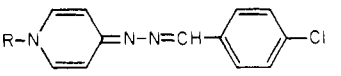
Table I. Chemical and Anticoccidial Properties of 1-(4-Chlorophenyl)-4(1*H*)-pyridinone Hydrazone Analogues and Derivatives



No.	R	Method[a]	% yield[b]	Recrystn solvent	Mp, °C	Formula	Analyses	Anticoccidial act. *E. acervulina*[c]	Anticoccidial act. *E. tenella*[d]
1	H	B	89	MeOH	204-206	$C_{11}H_9N_2Cl \cdot HFSO_3$	C, H, N, Cl	I	I
2	NH_2	B	93	MeOH	174-176	$C_{11}H_{10}N_3Cl \cdot HFSO_3$	C, H, N, Cl	I	I
3	N=CHC$_6$H$_5$	C	96	EtOH-H_2O	206-208	$C_{18}H_{14}N_3Cl \cdot HFSO_3$	C, H, N, Cl	I	I
4	N=CH-C$_6$H$_4$-*p*-Cl	C	94	EtOH-H_2O	252-253	$C_{18}H_{13}N_3Cl_2 \cdot HFSO_3$	C, H, N, Cl	0.0125	0.003
4a	N=CH-C$_6$H$_4$-*p*-Cl	D	100	EtOH-H_2O	165-166	$C_{18}H_{13}N_3Cl_2$	C, H, N, Cl		
		E	90						
5	N=CH-C$_6$H$_4$-*o*-Cl	C	95	EtOH-H_2O	247-249	$C_{18}H_{13}N_3Cl_2 \cdot HFSO_3$	C, H, N, Cl	I	I
6	N=CH-C$_6$H$_4$-*p*-Br	C, D	98	EtOH-H_2O	173-174	$C_{18}H_{13}N_3ClBr$	C, H, N	0.005	0.0025
7	N=CH-C$_6$H$_4$-*p*-F	C, D	96	EtOH-H_2O	135-136	$C_{18}H_{13}N_3ClF \cdot 0.25H_2O$	C, H, N	0.025	0.0125
8	N=CH-C$_6$H$_4$-*p*-CF_3	C, D	92	EtOH-H_2O	143-145	$C_{19}H_{13}N_3ClF_3 \cdot 0.5H_2O$	C, H, N	0.0125	0.0125
9	N=CH-C$_6$H$_4$-*p*-CH_3	C, D	98	EtOH-H_2O	162-164	$C_{19}H_{16}N_3Cl \cdot 0.25H_2O$	C, H, N	I	I
10	N=CH-C$_6$H$_4$-*p*-CN	C, D	97	EtOH-H_2O	192-193	$C_{19}H_{13}N_4Cl \cdot 0.5H_2O$	H, N; C[e]	0.025	0.025
11	N=CH-C$_6$H$_4$-*p*-SCH_3	C, D	93	EtOH	164-165	$C_{19}H_{16}N_3ClS$	C, H, N	0.025	0.025
12	N=CH-C$_6$H$_4$-*p*-N(CH_3)$_2$	C, D	90	EtOH	188-189	$C_{20}H_{19}N_4Cl$	H, N; C[f]	I	I
13	N=CH-C$_6$H$_4$-*p*-NHC(=O)CH_3	C	98	EtOH	266-268	$C_{20}H_{17}N_4ClO \cdot HFSO_3$	C, H, N, Cl, S	I	I
14	N=CH-C$_6$H$_4$-*m*,*p*-Cl_2	E	80	EtOH-H_2O	177-179	$C_{18}H_{12}N_3Cl_3 \cdot 0.5H_2O$	C, H, N	0.005	0.0025
15	N=CH-C$_6$H$_4$-*o*,*p*-Cl_2	C, D	95	EtOH-H_2O	164-165	$C_{18}H_{12}N_3Cl_3$	C, H, N	0.025	0.006
16		C	97	EtOH-H_2O	185-187	$C_{16}H_{12}N_3ClS \cdot HFSO_3$	C, H, N, Cl	I	I
17	N=CH—CH=CH-C$_6$H$_4$-*p*-Cl	C, D	65	EtOH-H_2O	172-173	$C_{20}H_{15}Cl_2N_3$	H, N; C[g]	0.025	0.0125
18	N=C(CH_3)-C$_6$H$_4$-*p*-Cl	C, D	79	EtOH-H_2O	189-190	$C_{19}H_{15}N_3Cl_2$	C, H, N	I	I

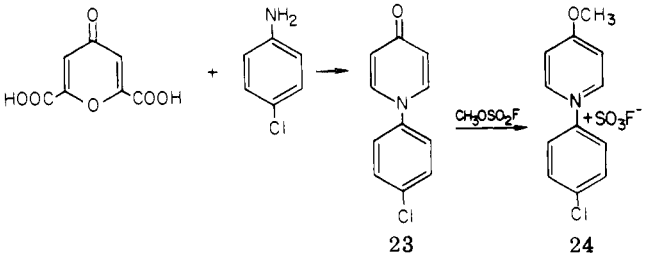
[a] See Experimental Section. [b] Yield figures refer to method C when both methods C and D are indicated. Yields for method D were essentially quantitative. [c] Adaptation to a single bird *E. acervulina* assay of the method of E. F. Rogers, R. L. Clark, H. J. Becker, A. A. Pessolano, W. J. Leanza, E. C. McManus, F. J. Andriuli, and A. C. Cuckler, *Proc. Soc. Exp. Biol. Med.*, 117, 488 (1964). Results are given as the lowest percentage of compound in the test diet which results in control of the coccidial infection or as inactivity (I) at 0.1%, the highest level tested. [d] Method of A. C. Cuckler, L. R. Chapin, C. M. Malanga, E. F. Rogers, H. J. Becker, R. L. Clark, W. J. Leanza, A. A. Pessolano, T. Y. Shen, and L. H. Sarett, *Proc. Soc. Exp. Biol. Med.*, 98, 167 (1958). [e] C: calcd, 66.77; found, 66.28. [f] C: calcd, 68.47; found, 68.01. [g] C: calcd, 65.23; found, 64.73.

Table II. Chemical and Anticoccidial Properties of 4-Chlorobenzaldehyde 1-Substituted 4(1H)-Pyridinylidene Hydrazones

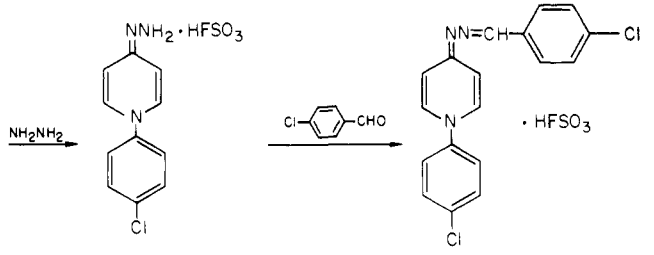


No.	R	Method[a]	% yield	Recrystn solvent	Mp, °C	Formula	Analyses	Anticoccidial act.[b] E. acervulina	Anticoccidial act.[b] E. tenella
19	H	E	92	EtOH-H_2O	215-217	$C_{12}H_{10}ClN_3$	H, N, Cl; C[c]	0.05	0.025
20	CH_3	F	67	EtOH-H_2O	130-132	$C_{13}H_{12}ClN_3$	C, H, N, Cl	I	I
		D	100						
21	C_6H_5	A, B, C	20[d]	EtOH	188-190	$C_{18}H_{14}N_3Cl\cdot HFSO_3$	C, H, N	I	I
22	Cl-C_6H_4-CH_2-	F	87	EtOH	269-271	$C_{19}H_{15}N_3Cl_2\cdot HCl$	C, H, N, Cl	I	I
		D	100						
25	Robenidine							0.0008	0.003

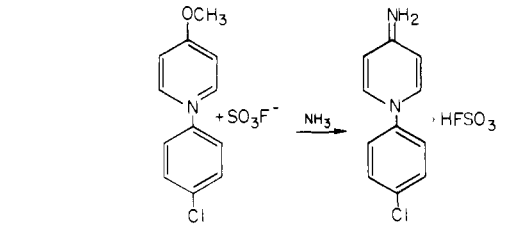
[a] See Experimental Section. [b] See footnotes c and d, Table I. [c] C: calcd, 62.21; found, 62.67. [d] Overall yield for three steps.



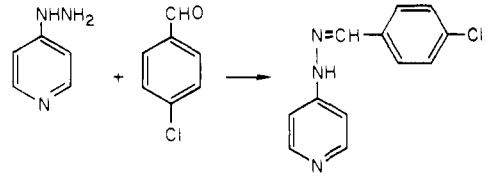
23 24



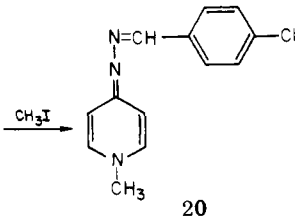
2 4



24 1



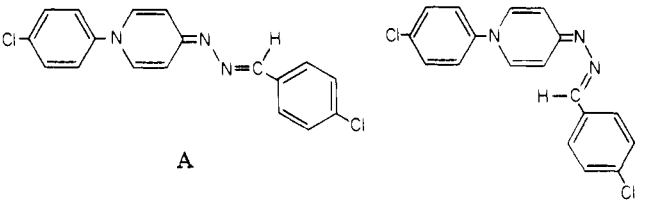
19



20

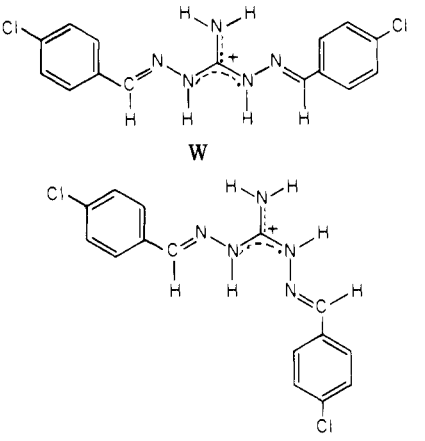
hydrogen of 4 by a methyl group (18) led to abolition of activity. The 2,4-dichlorophenyl analogue 15 and the 3,4-dichlorophenyl analogue 14 were highly active. Lengthening of the carbon chain to the 4-chlorocinnamylidene derivative 17 gave a less active compound. Replacement of the 4-chlorophenyl group in the 1 position

Chart I. E Configurations of Compound 4a



A B

Chart II. Two Conformations of the Robenidine Cation[a]

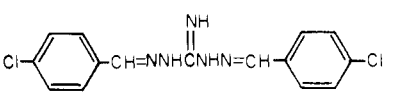


W S

[a] "W" and "S" refer to the patterns formed by the N-N-C-N-N substructure.

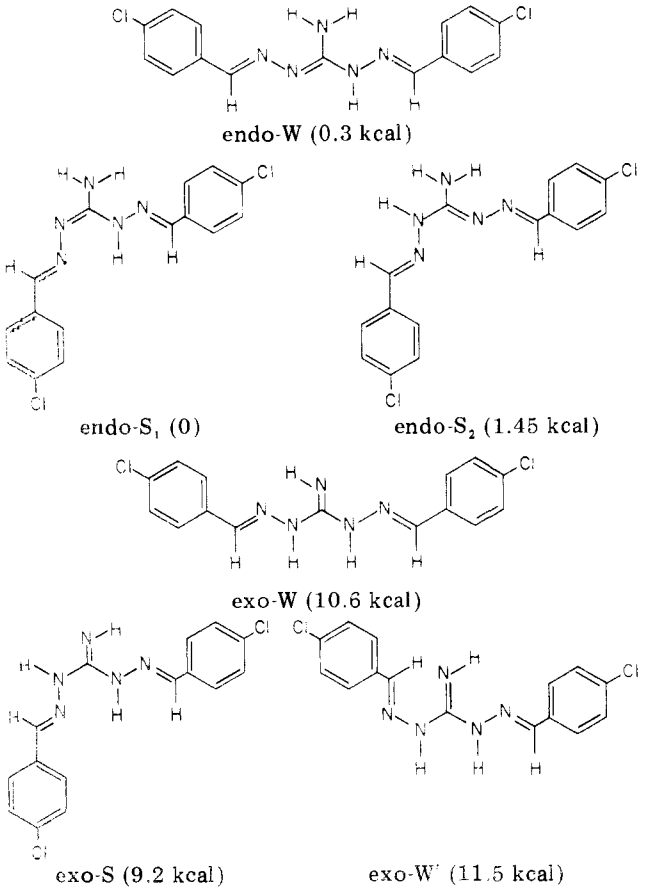
by methyl (20), phenyl (21), or 4-chlorobenzyl (22) gave inactive compounds but, surprisingly, replacement by hydrogen (19) retained some activity.

During the course of characterizing the biological properties of 4, it was discovered that 4 was completely inactive against a robenidine (25)[5] tolerant strain of *E. tenella* at levels of 0.025, 0.0125, 0.006, and 0.003% in the diet. A comparison of 4 with robenidine (25) against sensitive strains was also made and may be examined by comparing data in Tables I and II. The two compounds were equipotent on our laboratory strain of *E. tenella* but against the *E. acervulina* strain robenidine (25) was much more active. The most potent compounds reported from the current study, especially against *E. acervulina*, were 6 and 14 which are 4-bromo- and 3,4-dichlorobenzaldehyde derivatives, respectively.



robenidine (25)

Chart III. Six Conformations of *exo*- and *endo*-Imino Tautomers of Robenidine (Free Base) (25)[a]



[a] Relative energies by CNDO calculation[6] are indicated.

Conformational Studies. Since robenidine (**25**) and 4 display a biological cross resistance and since there are obvious structural similarities, we examined the possibility that conformational analysis would reveal a common bioactive structural pattern. Both compounds **25** and **4a** are weak bases whose pK_a values are 6.8 and 7.8, respectively, as determined from their UV spectra in 1:1 MeOH–H_2O over the pH range 2–12. Because these pK_a values are close to 7, we felt it necessary to consider the structures of both the protonated and free base forms of 4 and **25** as being potentially important biologically.

Assignment of an *E* configuration to **4a** as shown in Chart I was relatively straightforward with ^{13}C NMR. The key value was the one bond coupling of the benzal hydrogen with its carbon. The observed value of 161 Hz is quite close to the reported 163 ± 1 Hz for (*E*)-acetaldoxime and distinct from the 177 ± 1 Hz given for the *Z* form of the same oxime.[6] Of the two *E* conformations, the more extended form A is preferred to avoid serious crowding of the benzylidene proton with the C-3 proton of the dihydropyridine ring in B. The protonated form of A is expected to resemble A quite closely but with slight elongation of the C_4-imino nitrogen bond.

To our knowledge the conformation of robenidine (**25**) has not been reported. For its cation we again made *E* configurational assignments at the hydrazone functionalities based on the coupling constant of 162–163 Hz for the benzal hydrogens. We assumed the robenidine cation would be planar for maximum resonance stabilization. A systematic examination of possible conformations led us to conclude that conformations W and S shown in Chart II would be of low energy. These conformations are equally favored according to CNDO calculations which indicated

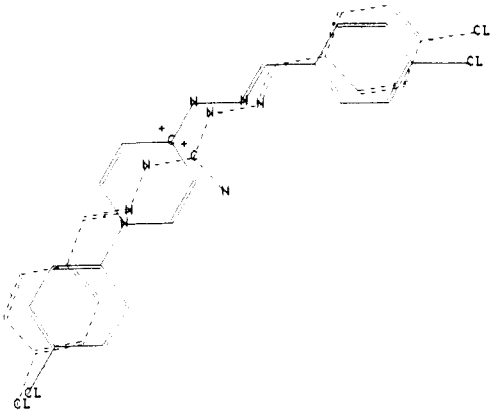


Figure 1. Superposition of compound 4 (solid lines) with the robenidine cation in conformation W. The average distance deviation was 0.73 Å for superposition of 22 atoms.

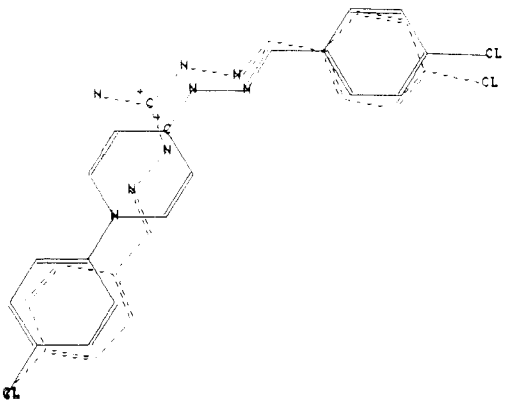


Figure 2. Superposition of compound 4 (solid lines) with the robenidine cation in conformation S. The average distance deviation was 0.58 Å for 22 atoms superposed.

that the W conformation was more stable than the S conformation by an insignificant 0.14 kcal/mol.[7]

In the case of robenidine free base (**25**), all three planar conformations of the *endo*-imine tautomer are substantially lower in energy than any *exo*-imine tautomers (Chart III). The endo S_1, W, and S_2 conformations are close enough in energy that all have to be considered potentially bioactive forms. The exo-W′ conformation was of special interest to us since it and **4a** are virtually superimposable. However, we do not believe that this conformation is biologically significant since CNDO calculations indicate it to be about 10 kcal/mol higher in energy than the low-energy conformations noted above.

Qualitative resemblances of **4** in the A conformation with robenidine (**25**) cation in conformations W and S can be seen in Figures 1 and 2. These figures are photographs taken from computer terminal displays. Superpositions have been made by a best-fit calculation using a molecule comparison program.[8] The average deviation data indicate a slight preference for the superposition of **4** with the S conformation of the robenidine cation. The same slight preference also applies to the superposition of **4a** with the endo-S free base conformers of **25**.

In conclusion, although our calculations do not permit an unambiguous assignment of a bioactive conformation to robenidine (**25**), structural similarities are apparent of the low-energy conformers with **4**. We believe that the cross resistance of robenidine (**25**) and **4** can be explained on this basis.

Experimental Section

Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Elemental analyses

were determined at the Merck Sharp & Dohme Research Laboratories by Mr. Jack Gilbert and his associates. Where analyses are indicated only by symbols of elements, they are within ±0.4% of the theoretical values. Proton NMR spectra were recorded on a Varian Model T-60 spectrometer using tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer.

General Methods. Method A. 1-(4-Chlorophenyl)-4-methoxypyridinium Fluorosulfonate (24). A solution of 18.7 g (0.091 mol) of carefully dried 1-(4-chlorophenyl)-4(1*H*)-pyridinone (**23**)[2] in 160 mL of dimethoxyethane was heated to reflux. Without further external heating, 14.2 g (0.123 mol) of methyl fluorosulfonate was added gradually. The mixture boiled vigorously during the addition and crystalline product started to separate. After the addition was complete, the mixture was stirred at room temperature for 1 h and then cooled to 10 °C. The product was filtered, washed with cold dimethoxyethane and Et_2O, and dried in vacuo: yield 28.0 g (96.5%); mp 182–185 °C; NMR (Me_2SO-d_6) δ 4.26 (s, 3 H, CH_3O), 6.27 (d, 2 H, β-pyridyl H), 6.32 (s, 4 H, aromatics), 7.62 (d, 2 H, α-pyridyl H). Anal. C, H, N, Cl.

Method B. 1-(4-Chlorophenyl)-4(1*H*)-pyridinone Hydrazone Fluorosulfonate (2). To a suspension of 3.2 g (0.01 mol) of **24** in MeOH (20 mL) was added 0.4 g of anhydrous hydrazine. The mixture was heated to boiling for a few minutes and the resulting clear orange solution was kept overnight at room temperature. The orange crystals of **2** obtained in two crops weighed 2.97 g (93%). This product was recrystallized from MeOH (Table I).

Method C. 4-Chlorobenzaldehyde 1-(4-Chlorophenyl)-4(1*H*)-pyridinylidene Hydrazone Fluorosulfonate (4). To a solution of 2.4 g (7.5 mmol) of **2** in EtOH (35 mL) and H_2O (30 mL) was added a solution of 1.27 g (9 mmol) of *p*-chlorobenzaldehyde in EtOH (5 mL). After heating the reaction mixture on the steam bath for 3 min, the mixture was concentrated to remove most of the EtOH, cooled, and filtered: yield 3.1 g (94%). Recrystallization from EtOH–H_2O gave mp 252–253 °C (Table I).

Method D. Conversion of Compound 4 to Free Base 4a. A sample of **4** was partitioned between CH_2Cl_2 and 2 N NaOH. The organic layer was concentrated to dryness and the residue recrystallized from EtOH–H_2O: mp 165–166 °C (Table I).

Method E. Direct Formation of 4a. To a solution of 2.4 g (7.5 mmol) of **2** in 15 ml of 0.5 N NaOEt in EtOH at 30 °C was added 1.27 g (9 mmol) of *p*-chlorobenzaldehyde. After stirring at 30–35 °C for 0.5 h the solution was refrigerated. The yield of **4a** in two crops was 2.3 g (90%) which was recrystallized from EtOH–H_2O (Table I).

Method F. 4-Chlorobenzaldehyde 1-Methyl-4(1*H*)-pyridinylidene Hydrazone (20). A mixture of 2.31 g (0.01 mol) of 1-[(4-chlorophenyl)methylene]-2-(4-pyridyl)hydrazine (**19**), 2.5 g (0.018 mol) of CH_3I, and EtOH (20 mL) was refluxed for 20 h. On cooling 3.2 g of **20**·HI (86%) was obtained. The salt was converted to free base **20** by method D (Table II).

Acknowledgment. The computer program used to superimpose the structures discussed in this paper was developed by J. D. Andose and M. Pensack. Determinations of pK_a values were by Dr. George B. Smith. Dr. Graham Smith performed some of the molecular modeling calculations.

Supplementary Material Available: A listing of atomic coordinates used for structures **4** and **25** (4 pages). Ordering information is given on any current masthead page.

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Hydrophobicity of Several Rhodium(II) Carboxylates Correlated with Their Biologic Activity[1]

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Rhodium(II) carboxylates differ greatly in antitumor activity and toxicity depending on the properties of the carboxylate group (methoxyacetate, propionate, butyrate, etc.) involved. The solubility characteristics of rhodium(II) carboxylates correlate well with both the antitumor activity and toxicity that these compounds display. The amount of rhodium which is adsorbed by tumor cells in vitro also correlates with the partition coefficient of the rhodium(II) compounds studied. Survival and toxicity studies show rhodium(II) pentanoate to possess the highest therapeutic index against the Ehrlich ascites tumor strain and also show that lengthening the carboxylate R chain beyond the pentanoate reduces the drugs' therapeutic efficacy.

Recently, our laboratories reported on the antitumor activity of some selected rhodium(II) carboxylates (Figure 1).[2,3] Survival studies on Swiss mice bearing the Ehrlich ascites tumor showed that the series, rhodium(II) acetate and rhodium(II) propionate, exhibited increasing toxicity and antitumor activity when compared on a millimoles per kilogram basis.[4] An earlier study showed that rhodium(II) acetate in combination with arabinosylcytosine gave significant increases in survival times and 50-day "cures" of BDF_1 mice bearing the L1210 ascites tumor.[5] Since rhodium(II) acetate and propionate differ only by the length of the carbon chain, yet vary significantly in antitumor activity and toxicity, it seemed reasonable to hypothesis that an increase in lipophilicity might correlate with an increase in antitumor activity. In the study reported here, this hypothesis was tested using a number of