In certain runs the mp was much wider indicating that some of the stilbene had already formed. Such mixts were as suitable to use in the following procedure as pure **13**.

2′-Methylthio-4-nitrostilbene (14).—A soln of 5.8 g of **13** in DMSO (40 ml) was refluxed for 24 hr then boiled down to 10 ml, cooled, and poured into 50 ml of H_2O to give 4.9 g (90%), mp 108–110°. One recrystn (EtOH, Darco) gave 4.3 g (80%) of the product, mp 109.5–110°. *Anal.* ($C_{15}H_{13}NO_2S$) C, H, N.

2′-Methylthio-4-stilbenamine (15).—Hydrazine hydrate (100%) and Pd/C (5%) reduction of 1.5 g of **14** (1 hr) was followed by evapn to near dryness. Addn of petr ether (bp 30–60°) with stirring, gave a light brown ppt, 1.2 g (93%), mp 62–65°. One recrystn from EtOH–petr ether (bp 30–60°) gave an anal. sample, mp 65–66°. *Anal.* ($C_{15}H_{15}NS$) N.

***N*-4-(2′-Methylthiostilbenyl)acetamide (16).**—Acetylation gave the amide, mp 162–162.5°. *Anal.* ($C_{17}H_{17}NOS$) C, H, N, S; mol wt.[9]

3′-Methylthio-4-nitrostilbene (17).—3-Methylthioaniline [tech, Aldrich, redistd at 156.5–157° (16 mm)] (4.2 g, 0.03 mole) was mixed with HCl (7.8 ml), DMSO (2 ml), and H_2O (15 ml). The mixt was stirred at 0–5° while a soln of $NaNO_2$ (2.1 g, 0.03 mole) in H_2O (5 ml) was added dropwise in 15 min. After stirring at 0° for 30 min, the soln was added in one portion to a stirred mixt of *p*-nitrocinnamic acid (mp 287.5–290° dec) (5 g, 0.025 mole), DMSO (50 ml), and Me_2CO (100 ml) at 0°. This was immediately followed by addn of anhyd NaOAc (8 g) and $CuCl_2 \cdot 2H_2O$ (5.1 g, 0.03 mole, in 8 ml of H_2O) with continuous stirring at 0° for 2 hr, then at 25° for 18 hr. The mixt was then dild with H_2O (350 ml). The solvent and some oily material were removed by steam distn. The residue was filtered off and extd with boiling C_6H_6 (200 ml). The insol *p*-nitrocinnamic acid was recovered by alk extn (3.8 g). The C_6H_6 ext was washed with 5% NaOH and H_2O and dried ($MgSO_4$). Evapn and column chromatog (Al_2O_3–C_6H_6) gave the product (1.8 g). Recrystn from EtOH gave orange crystals, 1.5 g (90%, based on the amt of *p*-nitrocinnamic acid consumed), mp 117–119°. One recrystn (EtOH) gave an anal. sample, mp 118–119°. *Anal.* ($C_{15}H_{13}NO_2S$) C, H, N.

3′-Methyl-4-stilbenamine (18).—Hydrazine hydrate (100%) and Pd/C (5%) reduction of **17** gave the amine, mp 111–112° (EtOH–H_2O). *Anal.* ($C_{15}H_{15}NS$) C, H.

***N*-4-(3′-Methylthiostilbenyl)acetamide (19).**—Acetylation (Ac_2O in AcOH) and recrystn (EtOH) gave the amide, mp 133–134°. *Anal.* ($C_{17}H_{17}NOS$) C, H, N, S; mol wt.[9]

4-Methylthiobenzaldehyde (20).—To a soln of KSMe, prepd by dissolving 26.4 g of powd KOH in 240 ml of EtOH and adding 20 g of MeSH at 0°, 56 g of *p*-chlorobenzaldehyde was added, and the mixt was refluxed for 3 hr, dild with 400 ml of H_2O, and extd with CCl_4. The org layer was sepd and dried (Na_2SO_4), and the solvent distd off to give 52 g (85.5%) of the aldehyde, bp 163–165° (22 mm) [lit.[12,13] bp 99–100° (1.3 mm), 153° (17 mm)].

1-(4-Methylthiophenyl)-2-(4-nitrophenyl)ethanol (21).—Compd **20** (7.6 g, 0.05 mole) and *p*-nitrotoluene (6.85 g, 0.05 mole) were combined as described for **2**. The mixt was poured into dil HCl and extd with C_6H_6 (300 ml), and the ext was dried (Na_2SO_4). After evapn of the solvent, addn of 150 ml of cyclohexane gave 2.7 g (20%) of 4′-methylthio-4-nitrostilbene, mp 172–174°. Evapn of the filtrate to near dryness gave 6.4 g (44%) of **21**, mp 121–122°. Recrystn (EtOH) gave an anal. sample with the same mp. *Anal.* ($C_{15}H_{15}NO_3S$) C, H, N, S.

4′-Methylthio-4-nitrostilbene (22).—A soln of 2 g of **21** in DMSO (10 ml) was refluxed for 3 hr, cooled to room temp, and dild (H_2O) to give, after recrystn (PhMe), 1.6 g (86%) of the product, mp 172–174°. Mmp with the first product in the previous reaction gave no depression. Recrystn (PhMe) gave an anal. sample, mp 173–174°. *Anal.* ($C_{15}H_{13}NO_2S$) C, H, N, S. This product can also be obtained in high yield from the crude mixed product of the foregoing procedure.

4′-Methylthio-4-stilbenamine (23).—Hydrazine hydrate (100%) and Pd/C (5%) reduction of **22** gave the amine (97%), mp 168–169° (EtOH). *Anal.* ($C_{15}H_{15}NS$) C, H, N, S.

***N*-4-(4′-Methylthiostilbenyl)acetamide (24).**—Acetylation of **23** gave the amide, mp 242.5–243.5°. Recrystn from EtOH–Me_2CO (1:1) gave mp 243–244°. *Anal.* ($C_{17}H_{17}NOS$) C, H, N, S.

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Antitumor Activities and Rates of Hydrolysis of Schiff Bases

ERNEST M. HODNETT* AND JOSEPH TAI

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

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Although some Schiff bases have shown activity against a variety of animal tumors,[1] many of these compounds hydrolyze rapidly in neutral aq solution near room temp.[2] We have prepared 11 aromatic Schiff bases with electron-withdrawing substituents in order to increase their resistance to hydrolysis and thereby improve their antitumor activities. New compounds are listed in Table I with some of their properties.

The hydrolysis rates of these Schiff bases were determined in H_2O buffered at pH 7.0 since cellular and intercellular fluids generally have a pH close to 7. At this pH the rate-controlling step in the hydrolysis of most of these compounds is the addition of a molecule of water to the Schiff base[3] and the kinetics of the reaction becomes pseudo first order in the Schiff base. Assuming that

$$\mathrm{RCH{=}NR' + H_2O} \underset{k'}{\overset{k}{\rightleftharpoons}} \mathrm{RCHO + R'NH_2} \qquad (1)$$

the integrated and simplified rate expression is[4]

$$\frac{x_e}{k(2a - x_e)} \ln \frac{ax_e + x(a - x_e)}{a(x_e - x)} = t \qquad (2)$$

where a = initial concn of Schiff base, $a - x$ = concn of Schiff base at time t, and $a - x_e$ = concn of Schiff base at equilibrium. The plot of log $[ax_e + x(a - x_e)]/[a(x_e - x)]$ *vs.* time should be a straight line for which the slope is $k(2a - x_e)/2.3x_e$. The rate constants were calcd by use of eq 2 and the best one was selected by the method of least squares. Since salicylaldehyde, one of the products of the reaction, oxidizes in H_2O solution under these conditions its absorption in the uv would change gradually. The absorbance of salicylaldehyde at equilibrium was calcd by the method of Guggenheim[5] assuming a first-order oxidation of the salicylaldehyde. Since only the first part of each reaction was used to calculate the rate the slow oxidation of salicylaldehyde did not affect these results. The reaction rate constants for these reactions, given in Table II, indicate

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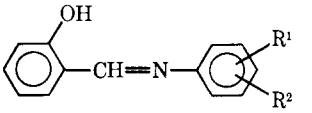
TABLE I
NEW SCHIFF BASES OF SALICYLALDEHYDE



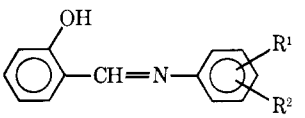
R¹	R²	Formula[a]	Mp, °C	Yield, %	C=N stretch, cm⁻¹	E₂ band, nm
2-CF_3	H	$C_{14}H_{10}NOF_3$	62.5–63.5	81.5	1617	272
4-CH_3	H	$C_{14}H_{10}NOF_3$	104.5–105.5	83	1622	273
3-CF_3	6-Cl	$C_{14}H_9NOClF_3$	91–93	87	1619	275
4-CN	H	$C_{14}H_{10}N_2O$	118–121	69	1615	280
4-$NHCOCH_3$	H	$C_{15}H_{14}N_2O_2$	162–164	61	1615	270
2-$COCH_3$	H	$C_{15}H_{13}NO_2$	164–166	60	1615	255

[a] All compds were analyzed for N. [b] In KBr pellets. The ir spectra of 131 aromatic Schiff bases exhibit absorption at 1613–1639 cm^{-1} in solid KBr and 1618–1645 cm^{-1} in $CHCl_3$. M. Nakamura, K. Komatsu, Y. Gondo, K. Ohta, and Y. Ueda, *Chem. Pharm. Bull.*, **15**, 585 (1967).

that Schiff bases with electron-withdrawing substituents generally hydrolyze more slowly than the unsubstituted compound at pH 7.0.

These Schiff bases have been tested in the L1210 lymphoid leukemia of mice[6] by the Cancer Chemotherapy National Service Center with the results shown in Table II. Unfortunately none of these compounds have significant activity (T/C greater than 1.25) in this tumor system. The increased stabilities of these compounds do not improve their activities in L1210 mouse leukemia.

TABLE II
RATES OF HYDROLYSIS AND ANTITUMOR ACTIVITIES



R¹	R²	L1210 leukemia of mice[a] Dose, mg/kg	L1210 leukemia of mice[a] T/C,[b] %	Rates of hydrolysis, sec^{-1} $10^5 \times k$	Reference
H	H	125	94	137.	*c*
2-$COCH_3$	H	400	96	4.67	*d*
3-$COCH_3$	H	400	98	97.1	*e*
4-$COCH_3$	H	400	100	73.7	*f*
2-CF_3	H	400	94	7.75	*d*
3-CF_3	H	400	100	240.	*g*
4-CF_3	H	400	90	4.40	*d*
3-CF_3	6-Cl	400	106	54.0	*d*
2-$CONH_2$	H	400	98	101.	*h*
4-CN	H	400	103	73.0	*d*
4-$NHCOCH_3$	H	400	97	48.3	*d*

[a] The screening data were supplied through the kindness of Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md. Assays were performed according to CCNSC specifications as reported in ref 6. [b] Effectiveness against L1210 leukemia of mice is measured by the length of life of leukemic mice (C) as compared to the length of life of leukemic mice having daily doses of the compound being tested (T). [c] T. J. Lane and A. J. Kandathil, *J. Amer. Chem. Soc.*, **83**, 3782 (1970). [d] This work. [e] B. M. Krasovitskii, B. M. Bolotin, and R. N. Nurmukhametov, *Zh. Obshch. Khim.*, **34**, 3786 (1964). [f] F. Mattu, *Gazz. Chim. Ital.*, **81**, 891 (1951). [g] P. M. Maginnity and J. L. Eisenmann, *J. Amer. Chem. Soc.*, **74**, 6119 (1952). [h] T. A. K. Smith and H. Stephen, *Tetrahedron*, **1**, 38 (1957).

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Experimental Section

Synthesis of Compounds.—Each compd was prepd by refluxing equimolar quantities of salicylaldehyde and the aromatic amine in abs EtOH. The crystals which formed on cooling were sepd and recrystd. Each compd was analyzed for N and sent to the CCNSC for testing.

Rates of Reaction.—Samples were weighed, dissolved in a few drops of EtOH, and then quickly dild at time zero with a large vol of aq buffer (prepd from 0.01 *M* KH_2PO_4 and adjusted to pH 7.0 with 0.01 *M* NaOH soln) in order to make a soln approx 10^{-4} *M*. The uv spectrum was then recorded for a sample of this soln held at 25° as soon as possible and at intervals of 5–10 min for 2–3 hr. The wavelength showing the greatest change in absorbance was selected and the absorbances at various times recorded. The absorbances were used to determine the concns of the Schiff bases.

Acknowledgment.—Grateful acknowledgment is made of the valuable assistance of the Cancer Chemotherapy National Service Center for providing the antitumor screening data on these compounds.

Potential Antitumor Agents. 1. Analogs of Camptothecin

J. A. BEISLER

Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

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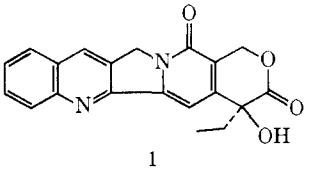
Camptothecin (1), an unusual pentacyclic alkaloid, was isolated from *Camptotheca acuminata* and identified as the antitumor factor in the alcohol extracts of the stem wood of the tree.[1] Since this rare alkaloid has pro-



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vided encouraging clinical results in the treatment of patients with advanced solid tumors,[2] a synthesis program

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