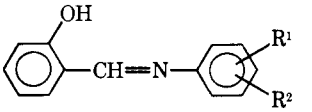
TABLE I
NEW SCHIFF BASES OF SALICYLALDEHYDE



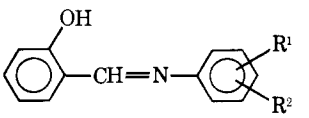
R¹	R²	Formula[a]	Mp, °C	Yield, %	C=N stretch, cm⁻¹	E_2 band, nm
2-CF_3	H	$C_{14}H_{10}NOF_3$	62.5–63.5	81.5	1617	272
4-CH_3	H	$C_{14}H_{10}NOF_3$	104.5–105.5	83	1622	273
3-CF_3	6-Cl	$C_{14}H_9NOClF_3$	91–93	87	1619	275
4-CN	H	$C_{14}H_{10}N_2O$	118–121	69	1615	280
4-$NHCOCH_3$	H	$C_{15}H_{14}N_2O_2$	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).

(6) *Cancer Chemother. Rep.*, **25**, 1 (1962).

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

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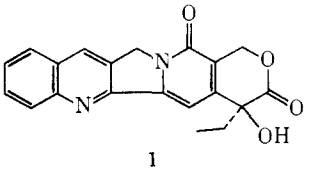
Camptothecin (**1**), an unusual pentacyclic alkaloid, was isolated from *Camptotheca acuminata* and identified as the antitumor factor in the alcohol extracts of the stem wood of the tree.[1] Since this rare alkaloid has pro-



1

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

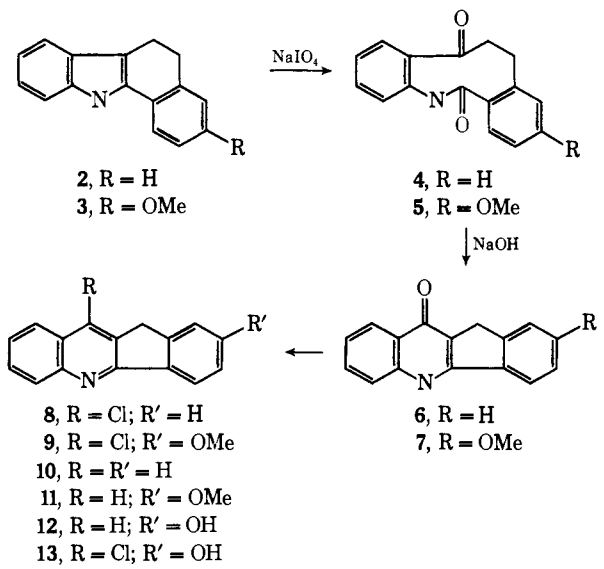
(1) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).

(2) J. A. Gottlieb, A. M. Guarino, J. B. Call, V. T. Oliverio, and J. B. Black, *Cancer Chemother. Rep. (Part 1)*, **54**, 461 (1970).

for the purpose of producing analogs of **1** was initiated in this laboratory.

Chemistry.—A rational synthetic approach might be patterned after the apparent biosynthesis[3] of **1** from indolic precursors. Thus, the quinoline portion of **1**, as well as analogs of **1**, could be formed by an oxidation of the indolic double bond followed by a Camps intramolecular condensation[4] and reduction of the resulting 4-quinolone.

As model systems, two benzocarbazoles (**2** and **3**) were selected, not only to demonstrate the feasibility of these transformations, but also to provide an initial series of analogs. Accordingly, the indolic double bond was smoothly oxidized to give the ketolactams **4** and **5** *via* the convenient $NaIO_4$ method[5] affording, after treatment with base, the quinolones **6** and **7**. Reduction of the latter intermediates was accomplished in two steps by reaction with $POCl_3$–PCl_5 followed by hydrogenolysis of the chloroquinoline derivatives **8** and **9**. All reactions were attended by high yields.



Biological Results.—Compds **9** and **10** as HCl salts were tested for antitumor activity against L-1210 lymphoid leukemia. Compds **12** and **13** were similarly tested, but as HBr salts. All of the compds were inactive and generally of low toxicity. Data are recorded in Table I.

TABLE I

SCREENING RESULTS AGAINST L-1210 LYMPHOID LEUKEMIA[a]

No.[b]	Dose, mg/kg	Survivors	Animal weight diff ($T - C$)	Average test	Evaluation control	T/C,[c] %
9	400	10/10	−0.6	9.1	9.1	100
	200	10/10	−0.2	8.8	9.1	96
	100	10/10	0.1	8.5	9.1	93
10	400	3/6	−1.2	8.3	9.1	
	300	5/6	0.1	8.6	8.5	101
	150	6/6	0.8	8.3	8.5	97
12	400	10/10	−0.1	8.5	9.1	93
	200	10/10	0.0	8.9	9.1	97
	100	10/10	−0.1	8.7	9.1	95
13	400	10/10	−0.5	8.5	9.1	93
	200	10/10	−0.4	8.9	9.1	97
	100	10/10	−0.2	9.0	9.1	98

[a] Host, BDF_1 and CDF_1 mice; vehicle, saline; route, ip; single administration; evaln after 60 days; tissue, ascitic fluid; level, 10^5 cells. [b] Numbers correspond to the numbered structural formulas. [c] Ratio of mean survival time of test animals (T) to control animals (C).

Experimental Section

Elemental microanalyses were performed by Dr. W. C. Alford and his associates of this laboratory; where analyses are indicated only by elemental symbols, the anal. results obtained for those elements were within ±0.3% of the theor values. Melting points were determined using a Kofler micro hot stage and were not corrected. Ir spectra were recorded with a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were measured in $CDCl_3$ with a Varian Model A-60 (Me_4Si). The Hitachi-Perkin-Elmer RMU-6 mass spectrometer was operated at 80 eV to obtain the mass spectra.

3-Methoxy-5,6-dihydro-11*H*-benzo[*a*]carbazole (**3**) was synthesized from 6-methoxy-1-tetralone and phenylhydrazine in glacial AcOH soln according to the method of Rogers and Corson.[6] After washing the product several times with 70% aq MeOH, 59% of white needles were obtd: mp 173–174° (MeOH); ir ($CHCl_3$) 3470, 1605, 1586, 1589 (indolic bands) cm^{-1}; mass spectrum m/e 249 (m^+), 204 (base). *Anal.* ($C_{17}H_{15}NO$) C, H.

3,4:8,9-Dibenzo-1-azacyclonona-3,8-dien-2,7-dione (**4**).—The oxidation of 5.93 g of 5,6-dihydro-11*H*-benzo[*a*]carbazole[6] (**2**) in 240 ml of MeOH was carried out following the procedure of Dolby and Booth[5] with 14 g of $NaIO_4$ in 90 ml of H_2O. After stirring at room temp for 25 hr the reaction mixt was poured into H_2O (1 l.) and extd with CH_2Cl_2. The dried (Na_2SO_4) exts gave crude crystals which were recrystd (PhH–MeOH) to yield 5.81 g (85% of large prisms: mp 152–153° (the melt crystallizes over 155–160° and does not remelt below 300°); ir ($CHCl_3$) 3375 (NH), 1670 (PhNHCO and PhCO) cm^{-1}. *Anal.* ($C_{16}H_{13}NO_2$) C, H, N.

3,4-(3-Methoxybenzo)-8,9-benzo-1-azacyclonona-3,8-dien-2,7-dione (**5**) was prepd in the same way as **4** in 89% yield after recrystn (PhH–MeOH): mp 167–169° (melt crystallizes on contd heating); ir ($CHCl_3$) 3370, 1668 cm^{-1}. *Anal.* ($C_{17}H_{15}NO_3$) C, H.

10-Chloro-11*H*-indeno[1,2-*b*]quinoline (**8**).—Periodic swirling slowly dissolved 3.0 g of ketolactam **4** in 175 ml of 2 *N* NaOH. The soln was left at room temp overnight then the 4-quinolone (**6**) was pptd with concd HCl, collected by vacuum filtration, washed several times with H_2O, and dried in a 95° oven.

Without further purification, the quinolone was combined with 60 ml of $POCl_3$ and 5 g of PCl_5 and refluxed for 5 hr. After concg by distn, the residue was poured over ice chips. After making the hydrolysate basic with NaOH, the product was removed by CH_2Cl_2 extn. The crude cryst material was recrystd from EtOAc (charcoal) to give 2.32 g (77%) of **8**: mp 158–159°; ir (CS_2) 3065, 2900, 1620, 1370, 838 cm^{-1}; nmr δ 8.3–7.2 (m, 8 H, arom), 3.9 (s, 2 H, CH_2); mass spectrum m/e 253 and 251 (M^+), 216 (Base, M − Cl). *Anal.* ($C_{16}H_{10}NCl$) C, H, Cl.

2-Methoxy-10-chloro-11*H*-indeno[1,2-*b*]quinoline (**9**) was prepd from 4.0 g of ketolactam **5** as described for **8**. After recrystn from EtOAc, 3.29 g (82%) of **9** was obtained: mp 172–173°; ir ($CHCl_3$) 2963, 2842, 1610, 1368, 838 cm^{-1}; nmr δ 8.2–6.8 (m, 7 H, aromatic), 3.87 (s, 2 H, CH_2), 3.82 (s, 3 H, OCH_3). *Anal.* ($C_{17}H_{12}ClNO$) C, H, Cl.

11*H*-Indeno[1,2-*b*]quinoline (**10**).—A slurry of 2.18 g of chloride **8** and 400 mg of 10% Pd/C in 250 ml of MeOH was hydrogenated at room temp and pressure for 2 hr. The reaction soln was filtered, and by successive concns of the filtrate, 1.99 g (91%) of **10**·HCl was obtd: mp 180–183° subl. *Anal.* ($C_{16}H_{11}N$·HCl) C, H, Cl.

Basification of an aq soln of the hydrochloride followed by CH_2Cl_2 extn provided the free base **10** which was recrystd from MeOH: mp 170–171° (lit.[7] mp 166–167°); ir (CS_2), 3055, 2895, 1624, 1392 cm^{-1}; nmr δ 8.5–7.4 (m, 9 H, arom), 3.86 (s, 2 H, CH_2).

2-Methoxy-11*H*-indeno[1,2-*b*]quinoline (**11**).—Using a procedure similar to that described above for the prepn of **10**, 3.09 g of methoxychloride **9** was converted to 2.35 g (87%) of **11**: mp 167–168° subl; ir ($CHCl_3$) 2963, 2842, 1609, 1396 cm^{-1}; nmr

(3) M. Shamma, *Experientia*, **24**, 107 (1968).
(4) B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Amer. Chem. Soc.*, **73**, 2641 (1951), and ref cited therein.
(5) L. J. Dolby and D. L. Booth, *ibid.*, **88**, 1049 (1966).
(6) C. U. Rogers and B. B. Corson, *ibid.*, **69**, 2910 (1947).
(7) E. Noelting and H. Blum, *Ber.*, **34**, 2467 (1901).

δ 8.2–6.8 (m, 8 H, arom), 3.80 (s, 3 H, OCH_3), 3.77 (s, 2 H, CH_2). *Anal.* ($C_{17}H_{13}NO$) C, H.

2-Hydroxy-11*H*-indeno[1,2-*b*]quinoline (12).—To a stirring hot sol of 1.20 g of **11** in 35 ml of glacial HOAc was slowly added 25 ml of 48% HBr. The resulting yellow soln was refluxed and stirred for 45 hr and cooled, and the product was collected by vacuum filtration. The microcryst needles thus obtd were washed several times with H_2O and dried giving 1.48 g (97%) of **12**·HBr which sublimes but does not melt below 320°. Recrystn from *i*-PrOH–MeOH afforded the analytic sample. *Anal.* ($C_{16}H_{11}NO$·HBr) C, H.

The free base was obtained by dissolving the hydrobromide in 1 *N* NaOH and pouring the basic soln into coned NH_4Cl. Filtration and recrystn from EtOH–H_2O gave cryst **12**: mp 299–301° dec; ir (KBr) 3525 (phenolic OH) cm^{-1}; mass spectrum *m/e* 233 (base, M^+). *Anal.* ($C_{16}H_{11}NO$) C, H.

2-Hydroxy-10-chloro-11*H*-indeno[1,2-*b*]quinoline (13) was prepd from **9** in 92% yield as described for **12.** Recrystn of **13**·HBr from DMF gave pure material: mp >320° subl. *Anal.* ($C_{16}H_{10}ClNO$·HBr) C, H.

Acknowledgment.—The author wishes to express his appreciation to Dr. H. B. Wood, Drug Development Branch, National Cancer Institute, for his interest in this work and for making the screening data available.

Gentamicin Antibiotics. 4.[1] Some Condensation Products of Gentamicin C_2 with Aromatic and Aliphatic Aldehydes[2]

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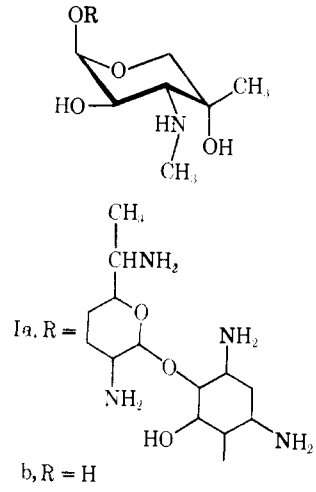
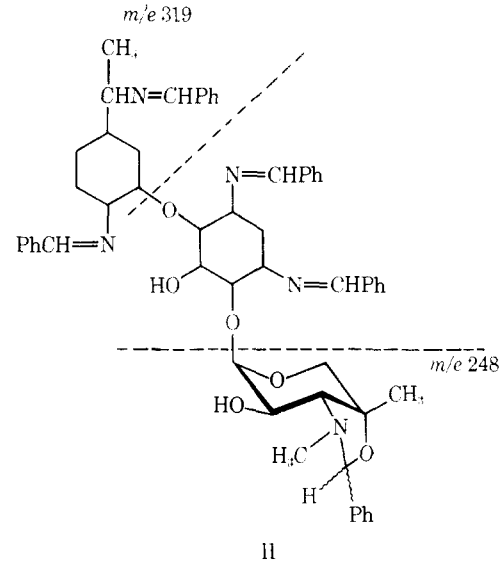
Received September 27, 1970

The gentamicins are a family of broad-spectrum antibiotics belonging to the aminoglycoside group. The isolation,[3] biological properties,[4a–d] and chromatographic separation[5a,b] of the gentamicins have been published and a recent communication[6] from our laboratory has described the gross structures of the components of the gentamicin C complex. One member of the complex, gentamicin C_2 was shown to possess structure Ia. In common with the other gentamicins, Ia is not absorbed to any great extent when given orally in man and, given parenterally, it is rapidly excreted in the urine requiring relatively frequent dosing in order to maintain effective blood levels. It seemed reasonable that a lipophilic derivative of the antibiotic, from which the parent compound could be regenerated *in vivo*, might provide oral absorption or longer duration of action when given parenterally. Such a derivative could be formed by condensation of the primary amino groups with aldehydes, a



procedure described previously for the related antibiotic kanamycin.[7]

Gentamicin C_2 reacted readily with BzH in EtOH on gentle heating to give a colorless, crystalline benzylidene derivative. Microanal. of this material indicated that 5 aldehyde groups—not 4 as expected—had been incorporated into the molecule. Low-resolution mass spectrometry of this compound surprisingly gave a strong molecular ion at *m/e* 903 consistent with condensation of 5 aldehyde residues with elimination of 5 moles of H_2O. The recent determination of the L-arabino absolute stereochemistry for garosamine[8a,b] (Ib) enables this result to be interpreted in terms of the formation of the novel oxazolidine (II). This was sub-



II

stantiated by the appearance in the mass spectrum of intense peaks at *m/e* 319 (cleaved purpurosamine fragment) and *m/e* 248 (cleaved garosamine fragment). Formation of the oxazolidine was confirmed by examination of the ^1H nmr spectrum (60 MHz, $CDCl_3$) which contained a 1-proton singlet at δ 5.0 corresponding to the benzylic proton of the oxazolidine system and indicating further that oxazolidine formation proceeds stereospecifically.

(1) Part 3: D. J. Cooper, M. D. Yudis, H. M. Mangliano, P. J. L. Daniels, R. D. Guthrie, and S. T. Bukhari, submitted for publication.

(2) Presented in part before the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, MEDI 052.

(3) M. J. Weinstein, G. M. Luedemann, E. M. Oden, and G. H. Wagman, *Antimicrob. Ag. Chemother.*, 1 (1963).

(4) (a) M. J. Weinstein, G. H. Wagman, E. M. Oden, and J. A. Marquez, *J. Bacteriol.*, **94**, 789 (1967); (b) J. Black, B. Calesnick, D. Williams, and M. J. Weinstein, *Antimicrob. Ag. Chemother.*, 138 (1963); (c) M. J. Weinstein, G. M. Luedemann, E. M. Oden, and G. H. Wagman, *ibid.*, 816 (1965); (d) J. A. Waitz and M. J. Weinstein, *J. Infect. Dis.*, **119**, 355 (1969).

(5) (a) G. H. Wagman, J. A. Marquez, and M. J. Weinstein, *J. Chromatogr.*, **34**, 210 (1968); (b) H. Maehr and C. P. Schaffner, *ibid.*, **30**, 572 (1967).

(6) D. J. Cooper, H. M. Mangliano, M. D. Yudis, and T. Tranhiel, *J. Infect. Dis.*, **119**, 342 (1969).

(7) A. Fujii, K. Maeda, and H. Umezawa, *J. Antibiot.*, **21**, 340 (1968).

(8) (a) D. J. Cooper, M. D. Yudis, R. D. Guthrie, and A. M. Prior, *J. Chem. Soc. C*, 960 (1971); (b) W. Meyer zu Reckendorf and E. Bischof, *Tetrahedron Lett.*, 2375 (1970).