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Synthesis of Potential Antineoplastic Agents XXVI: 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]2-quinolizinone Derivatives

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Received May 23, 1977, from the **Department of Chemistry, University of Missouri–Kansas City, Kansas City, MO 64110,* and the ‡*Department of Chemistry, Clarkson College of Technology, Potsdam, NY 13676.* Accepted for publication September 22, 1977.

Abstract □ A number of 3-alkyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]2-quinolizinones and 2-substituted 3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizines were prepared and submitted for antineoplastic and anticonvulsant screening.

Keyphrases □ Benzo[*a*]quinolizines, various substituted—synthesized, evaluated for antineoplastic and anticonvulsant activity □ Antineoplastic activity—evaluated in various substituted benzo[*a*]quinolizines □ Anticonvulsant activity—evaluated in various substituted benzo[*a*]quinolizines □ Structure–activity relationships—various substituted benzo[*a*]quinolizines evaluated for antineoplastic and anticonvulsant activity

During work directed toward the synthesis of analogs of emetine (I), 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-ethyl-2*H*-benzo[*a*]2-quinolizinone (II) was synthesized (1). The hydrochloride salt of II was active in the L-1210 lymphoid leukemia system.

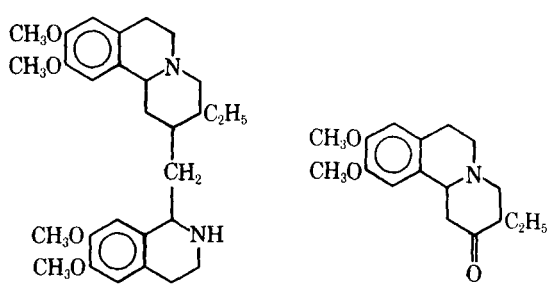
DISCUSSION

To determine the effect of structure on the antineoplastic activity of II hydrochloride, a series of related compounds was prepared. The compounds investigated fall into two categories: analogs in which the ethyl group of II has been replaced by a series of other alkyl groups (III*a*–III*i* and V, Table I) and analogs in which the carbonyl group of II has been replaced by other groups (IV*a*–IV*i*, VI, and VII, Table II).

The compounds in Table I were prepared by reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline and the appropriate Mannich bases (1). New compounds, including the dimer V, are discussed under *Experimental*. All known compounds had melting points in agreement with reported values (2–4).

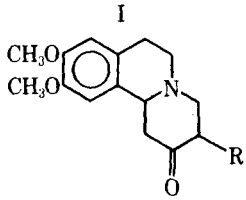
Compounds IV*a*–IV*c* were prepared by the method of Openshaw and Whittaker (5), as was the propyl analog VI. The oxime (IV*d*) (6) and IV*e* and IV*f* (7) were prepared by previously reported methods. The preparation of the remaining compounds in Table II is reported under *Experimental*.

The compounds in Tables I and II were screened through the Drug Evaluation Branch of the National Cancer Institute in the L-1210 lymphoid leukemia or P-388 lymphocytic leukemia systems. None of the compounds with groups in place of the 2-carbonyl possessed any significant antineoplastic activity (Table II). A number of the analogs in Table

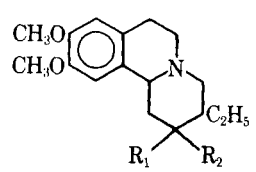


I

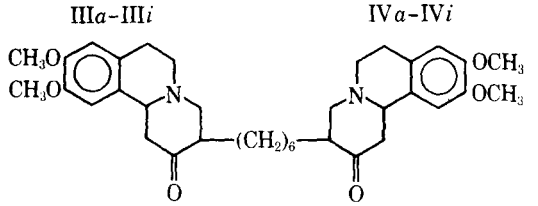
II



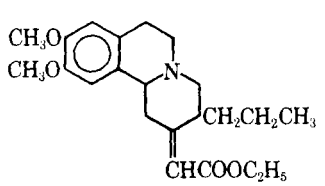
III*a*–III*i*



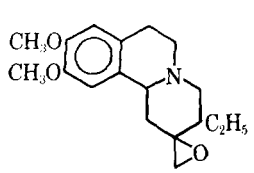
IV*a*–IV*i*



V



VI



VII

Table I—Analogs of II in which the Ethyl Group Has Been Replaced

Compound	R	LE[a] Dose, mg/kg	LE[a] T/C[c], %	PS[b] Dose, mg/kg	PS[b] T/C[c], %
III*a*	H	50	130	12.5	111
III*b*	CH_3	200	127	—	—
III*c* hydrochloride	C_2H_5	400	134	300	128
III*c* methiodide	C_2H_5	—	—	50	106
III*d* hydrochloride	n-C_3H_7	—	—	200	128
III*e*	n-C_4H_9	400	97	—	—
III*e* hydrochloride	n-C_4H_9	100	103	—	—
III*f*	$CH_2CH(CH_3)_2$	400	123	50	103
III*g*	$CH_2CH_2CH{=}CH_2$	—	—	50	113
III*h*	$CH_2C(CH_3){=}CH_2$	—	—	200	131
III*i*	$CH_2C_6H_5$	—	—	50	101
III*i* hydrochloride	$CH_2C_6H_5$	—	—	200	104
V	—	—	—	200	99

[a] L-1210 lymphoid leukemia. [b] P-388 lymphocytic leukemia. [c] Ratio of test (T) evaluation to control (C) evaluation expressed as a percentage.

I possessed activity in the L-1210 or p-388 system, but the results were too scattered to draw any meaningful structure–activity correlations. While some compounds were active, the activity was not sufficient for further investigation.

A number of the compounds also were screened for anticonvulsant activity. A few compounds exhibited activity (Table III), but it was not sufficient for further investigation.

EXPERIMENTAL

Synthesis of III*a*–III*i* and V—These compounds were prepared by the method of Whittaker (1). A solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (0.035 mole) in cold water (30 ml) was just neutralized with concentrated hydrochloric acid, treated with the appropriate Mannich base (0.038 mole), and set aside at room temperature for 3 days. The crystals were triturated under water and filtered.

Compound III*g*, mp 120–122° (methanol), was obtained in a 38% yield.

Anal.—Calc. for $C_{19}H_{23}NO_3$: C, 72.40; H, 7.93. Found: C, 72.59; H, 7.72.

Compound V, mp 207–209° (chloroform–acetone), was obtained in a 52% yield; IR: 1700 cm^{-1}.

Anal.—Calc. for $C_{36}H_{48}N_2O_6$: C, 71.54; H, 7.94; N, 4.63. Found: C, 71.51; H, 7.99; N, 4.67.

Compound II methiodide was formed from II in 85% yield in the usual manner, mp 196–197° (methanol).

Anal.—Calc. for $C_{18}H_{26}INO_3$: N, 3.25. Found: N, 3.24.

Synthesis of VI—A solution of triethylphosphonoacetate (52 ml) in dimethylformamide was added to solid potassium *tert*-butoxide (22.4 g), and III*d* in dimethylformamide (200 ml) was then added at 0°. The solution was allowed to warm to room temperature and stand overnight. It was diluted with water and extracted with ether. The dried ether extracts were evaporated to give a 52% yield of VI, mp 91–93° (ethanol); IR: 1690 and 1630 cm^{-1}.

Anal.—Calc. for $C_{22}H_{31}NO_4$: C, 70.80; H, 8.31; N, 3.75. Found: C, 70.82; H, 8.34; N, 3.81.

Synthesis of IV*g*—A solution of II (0.01 mole) in dimethoxyethane (250 ml), under nitrogen, was treated with potassium *tert*-butoxide (0.1 mole) in butanol (100 ml). A solution of tosylmethyl isocyanide (0.012 mole) in dimethoxyethane (25 ml) was then added over 1 hr. After stirring for 1 hr, the solution was poured into water (500 ml) and extracted with chloroform. The dried chloroform extracts were evaporated to give a 42% yield of IV*g*, mp 140–142° (hexane); IR: 2225 cm^{-1}.

Anal.—Calc. for $C_{18}H_{24}N_2O_2$: C, 72.02; H, 7.99; N, 9.33. Found: C, 71.98; H, 8.03; N, 9.38.

Synthesis of IV*h*—The ester IV*b* (5) (0.02 mole) was dissolved in tetrahydrofuran (100 ml), and lithium aluminum hydride (1 g) was added slowly. After refluxing for 24 hr, calcium hydroxide was added. After filtration, the mixture was concentrated to give a light-yellow oil (IR: 3350 cm^{-1}). The oil was dissolved in benzene (100 ml) and cooled to 0°, and freshly distilled thionyl chloride (10 ml) was added dropwise. The mixture was stirred in the cold for 1 hr and at room temperature for 5 hr. Concentration *in vacuo* gave 89% of the hydrochloride of IV*h*, mp 211–212° (butanol).

Anal.—Calc. for $C_{19}H_{29}Cl_2NO_2$: C, 61.00; H, 7.75; Cl, 18.95; N, 3.74. Found: C, 60.98; H, 7.84; Cl, 18.94; N, 3.77.

Synthesis of IV*i*—To an ice-cold solution of II hydrochloride (0.01 mole) in water (75 ml) was added slowly, with stirring, a solution of sodium cyanide (0.011 mole) in water (15 ml). After stirring for 3 hr at room temperature, the mixture was filtered to give a 51% yield of IV*i*, mp 118–120° (benzene–hexane). This compound can also be prepared by another route (8).

Anal.—Calc. for $C_{18}H_{24}N_2O_3$: C, 68.37; H, 7.59; N, 8.86. Found: C, 68.32; H, 7.57; N, 8.78.

This compound was also converted to its hydrochloride, mp 208–210°.

Anal.—Calc. for $C_{18}H_{25}ClN_2O_3$: C, 61.31; H, 7.09; N, 7.94. Found: C, 61.23; H, 6.95; N, 7.45.

Synthesis of Epoxide VII—This procedure is based on the work of Piccirilli (9). A mixture of sodium hydride (0.035 mole) and trimethylsulfoxonium iodide (0.022 mole) in dimethyl sulfoxide (40 ml) was stirred, under nitrogen, for 15 min; then II (0.02 mole) in dimethyl sulfoxide (50 ml) was added dropwise. After stirring for 1 hr at room temperature and for 1 hr at 50°, the solution was poured onto ice and extracted with chloroform. The dried extracts were evaporated to give a 67% yield of VII, mp 111–112° (ethanol).

Anal.—Calc. for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.30; N, 4.62. Found: C, 71.35; H, 8.32; N, 4.57.

Table II—Analogs of II in which the Carbonyl Group Has Been Replaced

Compound	R_1	R_2	LE[a] Dose, mg/kg	LE[a] T/C[c], %	PS[b] Dose, mg/kg	PS[b] T/C[c], %
IV*a*		$=CHCO_2C_2H_5$	100	96	—	—
IV*b*	H	CH_2CO_2-C_2H_5	—	—	25	114
IV*c* hydrochloride	H	CH_2CO_2H	—	—	50	95
VI	—	—	—	—	50	96
IV*d*		=NOH	—	—	200	112
IV*e*	H	OH	110	200	—	—
IV*f* hydrochloride	H	Cl	—	—	50	101
IV*g*	H	CN	—	—	50	93
IV*h* hydrochloride	H	CH_2CH_2Cl	—	—	50	106
IV*i*	OH	CN	—	—	200	102
VII	—	—	—	—	12.5	114

[a] L-1210 lymphoid leukemia. [b] P-388 lymphocytic leukemia. [c] Ratio of test (T) evaluation to control (C) evaluation expressed as a percentage.

Table III—Anticonvulsant Screening

Compound	MES[a] Dose, mg/kg	MES[a] Protection[c]	MET[b] Dose, mg/kg	MET[b] Protection[c]
III*a*	300	0/1	300	0/1
III*b*	300	0/1	300	0/1
III*c* hydrochloride	300	1/1[d]	300	0/1
III*c*	300	0/1	300	1/1
			100	1/1[e]
III*e*	300	0/1	300	0/1
III*h*	300	0/1	300	1/1
III*i*	300	0/1	300	0/1
V	300	0/1	300	0/1
IV*a*	300	0/1	300	1/1[d]
IV*d*	300	0/1	300	0/1

[a] Maximal electroshock seizure test. [b] Subcutaneous pentylenetetrazol (Metrazol) seizure threshold test. [c] Number of animals protected per number of animals treated. Tests were carried out at 30 min and 4 hr after intraperitoneal administration. [d] Thirty minutes but not 4 hr. [e] Four hours but not 30 min.

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Quantitative Determinations of Two Decongestants and an Antihistamine in Combination Using Paired Ion High-Pressure Liquid Chromatography

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Abstract □ A single method for the quantitative determinations of three active ingredients, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and brompheniramine maleate, and one inactive ingredient (sodium benzoate) in a commercial product for colds is reported. The method is based on paired ion high-pressure liquid chromatography using 1-heptanesulfonic acid as the counterion. It is accurate and precise. The relative standard deviations based on six readings are reported. This method is sensitive; less than 1 μg of each ingredient can be assayed. The peak area of each ingredient is related to its concentration.

Keyphrases □ Phenylephrine hydrochloride—high-pressure liquid chromatographic analysis in dosage forms □ Phenylpropanolamine hydrochloride—high-pressure liquid chromatographic analysis in dosage forms □ Brompheniramine maleate—high-pressure liquid chromatographic analysis in dosage forms □ High-pressure liquid chromatography—analyses, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and brompheniramine maleate in dosage forms □ Adrenergics—phenylephrine hydrochloride and phenylpropanolamine hydrochloride, high-pressure liquid chromatographic analyses in dosage forms □ Antihistaminics—brompheniramine maleate, high-pressure liquid chromatographic analysis in dosage forms

One commercial product[1] for colds contains two decongestants, phenylephrine hydrochloride (I) and phenylpropanolamine hydrochloride (II), and an antihistamine, brompheniramine maleate (III). The dosage forms, sustained-release tablets and elixir, also contain excipients, some of which (especially colors and preservatives in the elixir) may interfere with the analysis of the active ingredients. No single method is available to determine the active ingredients quantitatively.

The USP method (1) for the quantitative determination of I is based on column chromatography. This method is quite tedious and time consuming. A GLC method was reported for the quantitative determination of I (2), but it requires derivatization and is quite lengthy. Other methods available for the analysis of I were reviewed (2). A quantitative colorimetric method for II in pharmaceutical dosage forms was reported (3), but other primary and secondary amines interfered. The only method available for the quantitative analysis of III in combination with other drugs apparently is that of Hudanick (4), which requires reaction with cyanogen bromide, a highly toxic and volatile reagent.

The paired ion extraction technique for the quantitative drug analysis is well documented. The theory and some possible uses of this method were reported (5) and reviewed (6). Numerous applications also were reported for thyroid hormones and sulfa drugs (7), dyes (8), niacin and niacinamide (9), and the simultaneous determinations of hydrocortisone and hydrocortisone phosphate (10).

This paper reports the simultaneous quantitative determinations of I–III in commercial dosage forms. The method is based on paired ion high-pressure liquid chromatography (HPLC), which identifies the compounds. Moreover, inactive ingredients also separate out and may be identified or determined quantitatively without additional work.

EXPERIMENTAL

Chemicals and Reagents—All chemicals and reagents were USP, NF, or ACS grade and were used without further purification. 1-Heptanesulfonic acid sodium salt[2] (IV) was used as received.

Apparatus—A high-pressure liquid chromatograph[3] capable of operating at an inlet pressure up to 6000 psig was used. A multiple wavelength detector[4] was used. For convenience, the wavelength was set at 254 nm (usually found in fixed wavelength detectors) for all ingredients. The detector was attached to a recorder[5] and an integrator[6]. The column[7] (30 cm × 4 mm i.d.) was purchased and used as received.

Chromatographic Solvents—A 13% (v/v) solution of acetonitrile in water containing 1.8% (v/v) acetic acid with or without 0.005 *M* IV was used. The pH of both solvents was 2.6 ± 0.05.

Chromatographic Conditions—The temperature was ambient. The flow rate was 0.6 ml/min (inlet pressure of approximately 300 psig) for the first 12 min and then was 3.6 ml/min (inlet pressure of approximately 3000 psig). The absorbance unit for full-scale deflection was 0.04, and the chart speed was 30.5 cm/hr.

Preparation of Stock Solutions—All stock solutions were prepared in water using a simple solution method. Heating to about 90° for approximately 5 min was required to dissolve III. The concentrations of the

[1] Dimetapp, A. H. Robins, Richmond, Va.

[2] Eastman Kodak Co., Rochester, N.Y.
[3] Waters ALC 202 equipped with a U6K Universal injector, Waters Associates, Milford, Mass.
[4] Spectroflow monitor 770, Schoeffel Instrument Corp., Westwood, N.J.
[5] Omniscribe 5213-12, Houston Instruments, Austin, Tex.
[6] Autolab Minigrator, Spectra-Physics, Santa Clara, Calif.
[7] μBondapak CN, Waters Associates, Milford, Mass.