Synthesis and Anticancer Screening of 2-Indolyl 5-(1,2,3,6-Tetrahydropyridyl) Ketones

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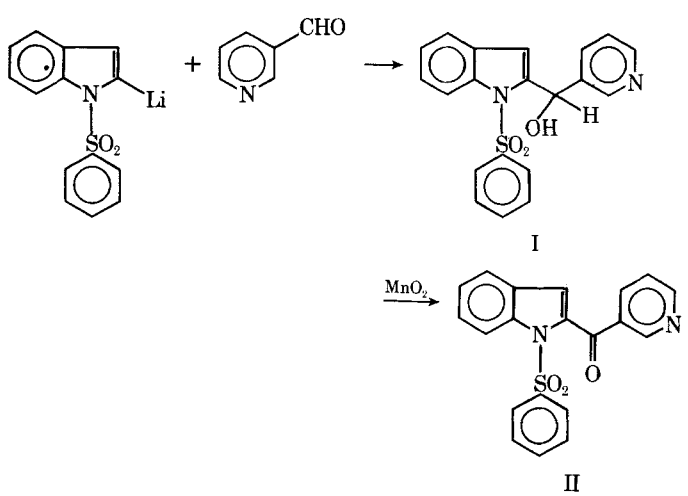
Abstract □ Several derivatives of 2-indolyl 5-(1,2,3,6-tetrahydropyridyl) ketone with various substituents on the pyridine nitrogen and with or without a benzenesulfonyl group on the indole nitrogen were synthesized and characterized by spectroscopic and analytical data. Only one showed erratic but confirmed activity in the P-388 screen. The other derivatives were inactive in the L-1210 leukemia screen.

Keyphrases □ 2-Indolyl 5-pyridyl ketone derivatives—synthesized, screened for cytotoxic activity □ Cytotoxic activity—various 2-indolyl 5-pyridyl ketone derivatives screened □ Structure–activity relationships—various 2-indolyl 5-pyridyl ketone derivatives screened for cytotoxic activity

An intermediate from a program to prepare biologically active indole derivatives submitted for anticancer screening was 1-benzenesulfonyl-2-indolyl 5-[1,2,3,6-tetrahydro-1-(2-oxo-2-ethoxyethyl)pyridyl] ketone (IV*a*). Since this compound showed erratic but confirmed activity in the mouse P-388 leukemia screen, several analogs were prepared.

DISCUSSION

The starting material for each compound was 1-benzenesulfonyl-2-indolyl 5-pyridyl ketone (II), which is obtained efficiently in two steps from 1-benzenesulfonyl-2-lithioindole (1) (Scheme I). Alkylation of II with alkyl bromides followed by catalytic reduction gives analogs of IV with various substituents at the pyridine nitrogen. The partial reduction of 3-acylpyridines is a well-documented procedure that owes its success to the resistance to reduction of the residual vinylogous amide unit (2). Analogs lacking the 1-benzenesulfonyl substituent were prepared by hydrolytic cleavage of the 1-benzenesulfonyl substituent from I prior to alkylation (1). The yields in the alkylation step were good in each case. The yields in the reduction step were lower and are given in Table I.



Scheme I

PMR, UV, and mass spectral data were indicative of the assigned structures. The PMR and UV data are given in Table II. All tetrahydropyridines exhibited a characteristic set of two broadened triplets at δ 2.5 ± 0.2 and 3.2 ± 0.1, attributable to the C-4 and C-2 methylene groups, respectively. The C-3 methylene signal appeared as a broader multiplet at about 2 ppm. There is some uncertainty about the assignment of the vinyl proton at C-6. It probably appears as the signal at 6.2–6.8 ppm observed in each spectrum. An alternative assignment for this peak would be the indole 3-proton, but this proton usually is found in the aromatic multiplet when the indole ring carries a carbonyl substituent as in the present case.

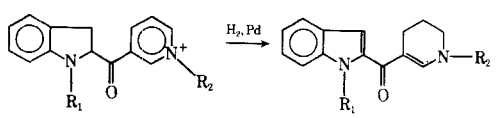
The only chemical complication noted in the preparation of these compounds was in the reduction of III*d*. Concomitant reduction of the ketone group in the *N*-phenacyl substituent occurred, giving the carbinol (IV*e*). The reduction products were usually contaminated with unidentified colored impurities and were best purified by preliminary chromatography on silica gel followed by crystallization. Some products had the troublesome property of forming nonstoichiometric solvates, but satisfactory analyses were obtained by drying at the melting point immediately prior to combustion analysis. The pyridinium salts were also troublesome in this regard and tended to form methanol solvates. Analytical data are given in Table III.

No analog of IV*a* showed significant activity. Compounds I, II, III*h*, IV*c*, and IV*e*–IV*g* were inactive in the L-1210 mouse leukemia screen in the 100–400-mg/kg dose range. Compound IV*b* was inactive in the P-388 leukemia screen, and III*g* and IV*c* showed no cytotoxicity in KB cell culture.

EXPERIMENTAL

Alkylations—The pyridyl ketone and a slight excess (~10%) of the appropriate halide were dissolved in acetonitrile (~2 ml/mmole) and

Table I—Yields and Melting Points of Synthesized 2-Indolyl 5-Pyridyl and 5-(1,2,3,6-Tetrahydropyridyl) Ketones



Compound	R_1	R_2	Yield, %	Melting Point
III*a*	$C_6H_5SO_2$	$-CH_2CO_2C_2H_5$	98	—[a]
IV*a*	$C_6H_5SO_2$	$-CH_2CO_2C_2H_5$	33	157–158°
III*b*	H	$-CH_2CO_2C_2H_5$	90	—[a]
IV*b*	H	$-CH_2CO_2C_2H_5$	29	126–128°
III*c*	H	$C_6H_5C(=O)CH_2-$	95	253–255°
IV*c*	H	$C_6H_5C(=O)CH_2-$	26	194–196.5°
III*d*	$C_6H_5SO_2$	$C_6H_5C(=O)CH_2-$	95	225–227°
IV*e*	$C_6H_5SO_2$	$C_6H_5CHOHCH_2-$	20	158–159°
III*f*	$C_6H_5SO_2$	$-CH_2CH_2CH_2OH$	75	186–187°
IV*f*	$C_6H_5SO_2$	$-CH_2CH_2CH_2OH$	28	164–165°
III*g*	$C_6H_5SO_2$	$CH_3OC_6H_4(C=O)CH_2-$	100	161–162°
IV*g*	$C_6H_5SO_2$	$CH_3OC_6H_4(C=O)CH_2-$	55	107–109°
III*h*	H	$CH_3OC_6H_4(C=O)CH_2-$	91	253–255°

[a] Not extensively purified.

Table II—UV–Visible Absorption and PMR Spectral Data of 2-Indolyl 5-(1,2,3,6-Tetrahydropyridyl) Ketones

Compound	UV–Visible Data[a]	PMR Spectral Data[b]
	1-Benzenesulfonylindoles	
IV*a*	250 (1.51 × 10^4), 320 (2.63 × 10^4)	1.25 (t, 3), 1.95 (2, m), 2.55 (t, 2), 3.20 (t, 2), 3.75 (s, 2), 4.10 (q, 2), 6.55 (s, 1), 7.05–8.30 (m, 10)
IV*e*	265 (1.40 × 10^4), 332 (2.75 × 10^4)	1.8 (m, 2), 2.40 (t, 2), 3.21 (m, 5), 4.70 (m, 1), 6.19 (s, 1), 7.02 (s, 1), 7.0–8.3 (m, 14)
IV*f*	265 (1.23 × 10^4), 329 (2.70 × 10^4)	1.5–2.0 (m, 4), 2.48 (t, 2), 3.15 (m, 4), 3.55 (t, 2), 6.55 (s, 1), 7.0–8.2 (m, 9)
IV*g*	273 (2.38 × 10^4), 329 (2.88 × 10^4)	2.0 (m, 2), 2.58 (t, 2), 3.21 (t, 2), 3.82 (s, 3), 4.46 (s, 2), 6.59, (1, s), 6.87 (d, 2), 7.0–8.3 (m, 12)
	Unsubstituted Indoles	
IV*b*	232 sh (1.07 × 10^4), 260 sh (5.10 × 10^3), 300 (1.29 × 10^4), 355 (2.14 × 10^4)	1.25 (t, 2), 1.7–2.1 (m, 2), 2.61 (t, 2), 3.20 (t, 2), 3.85 (s, 2), 4.17 (q, 2), 6.80 (d, $J \sim 2$ Hz, 1) 7.0–7.7 (m, 4), 10.4 (s, 1)
IV*c*	245 (2.00 × 10^4), 310 sh (1.44 × 10^4), 358 (2.37 × 10^4)	2.02 (m, 2), 2.63 (t, 2), 3.20 (t, 2), 4.53 (s, 2), 6.76 (d, $J \sim$ 2 Hz, 1), 7.0–8.0 (m, 10), 10.0 (s,1)

[a] For absolute ethanol solutions; the wavelengths (in nanometers) of maxima or distinct shoulders (sh) and absorptivities are given. [b] For deuterochloroform solutions~50 mg/ml; chemical shifts are relative to the internal standard, tetramethylsilane, and coupling constants are given in hertz.

heated to reflux overnight under nitrogen. The pyridinium salts precipitated and were isolated by filtration. With III*f*, addition of ether was necessary to effect precipitation. The salts were recrystallized from methanol.

Reductions—The pyridinium salts were suspended or dissolved in ethanol. For the unsubstituted indoles, about 2 mmoles of triethylamine was added per millimole of pyridinium salt. A palladium-on-carbon catalyst was used, and the reductions were carried out at atmospheric pressure, usually overnight. The solutions were filtered and evaporated to dryness. The residue was dissolved in chloroform, and the solution was washed with aqueous sodium bicarbonate solution. The solvent was then evaporated, and the residue was chromatographed on silica gel using chloroform containing 0.5% methanol for elution. Pure fractions were combined and crystallized from chloroform or ethyl acetate.

Table III—Analytical Data

	Calc.			Found		
	C	H	N	C	H	N
IV*a*	63.21	5.35	6.19	63.63	5.43	6.10
IV*b*	69.21	6.45	8.97	69.09	6.50	8.87
III*c*	62.72	4.07	6.65	62.46	4.15	6.62
IV*c*	76.72	5.85	8.13	76.75	5.90	8.13
III*d*	59.90	3.77	4.99	59.85	3.78	5.02
IV*e*	69.12	5.39	5.76	69.00	5.42	5.73
III*f*	55.09	4.22	5.59	54.77	4.34	5.70
IV*f*	65.07	5.70	6.60	65.14	5.76	6.55
III*g*[a]	57.79	4.36	4.49	57.76	4.37	4.56
IV*g*	67.69	5.09	5.44	67.44	5.22	5.07
III*h*	61.20	4.24	6.20	60.97	4.19	6.21

[a] Calculated analysis is for methanol solvate.

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