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Etodolic Acid and Related Compounds. Chemistry and Antiinflammatory Actions of Some Potent Di- and Trisubstituted 1,3,4,9-Tetrahydropyrano[3,4-*b*]indole-1-acetic Acids

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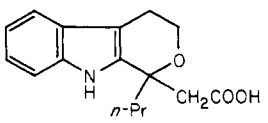
A series of 37 1-ethyl- and 1-*n*-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acids bearing one, or two, substituents on the benzene ring has been synthesized via the acid-catalyzed condensation of a substituted tryptophol with ethyl propionylacetate or ethyl butyrylacetate. Antiinflammatory and ulcerogenic effects were examined and the results show that 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid (etodolic acid, USAN) is a potent agent, particularly active against a chronic rat model of inflammation (ED_{50} 0.7 ± 0.1 mg/kg po in the adjuvant arthritis model) and which has a relatively low acute ulcerogenic potential in the same species.

In a previous publication[1] we have disclosed the antiinflammatory activities of a series of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-alkanoic acids bearing various hydrocarbon substituents on the pyrano ring and on the nitrogen atom. From that series, prodolic acid[2] was selected for further development, and detailed pharmacological studies have appeared.[3] The analog of prodolic acid which has an ethyl group[1] instead of an *n*-propyl group



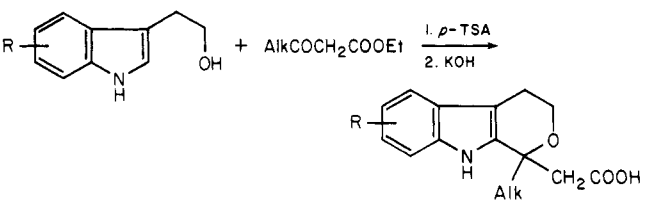
prodolic acid

at position 1 also possessed a high order of activity. In the present report we describe the syntheses and antiinflammatory activities of a series of 1-ethyl- and 1-*n*-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acids which bear one or two substituents on the benzene ring.

Chemistry. The compounds prepared for antiinflammatory testing (Table I) were obtained by the previously described method for the synthesis of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acids.[1] Thus, mono- or disubstituted tryptophols were condensed, in the presence of an acid catalyst, with ethyl propionylacetate or with ethyl butyrylacetate, followed by alkaline hydrolysis, to afford 1-ethyl or 1-*n*-propyl derivatives (Scheme I).

Thirty-one substituted tryptophols were required in this study. Three of them have been previously reported, and 26 others were obtained by the appropriate segment of the pathway illustrated in Scheme II, starting with an aniline,

Scheme I

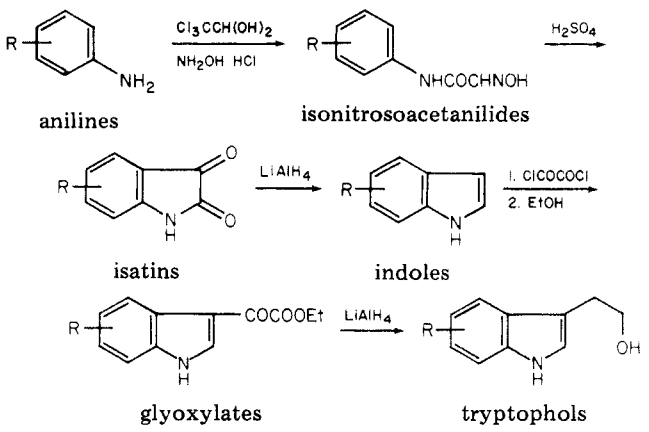


an isatin, or an indole. 7-*tert*-Butyltryptophol was synthesized from 7-*tert*-butylisatin, as shown in Scheme III, by the lithium aluminum hydride reduction of the 3-hydroxy-2-oxoindoline 3-acetate obtained from a Reformatsky reaction on the isatin with ethyl bromoacetate. 7-Cyclopropyltryptophol was prepared in one step from the reaction between 2-cyclopropylphenylhydrazine hydrochloride and 2,3-dihydrofuran using the method developed by Grandberg and Moskvina (Scheme IV).[4] The intermediates encountered in the course of the reactions shown in Schemes I–III were generally used without purification, but in a number of instances intermediates were characterized, principally by NMR spectroscopy (see Experimental Section).

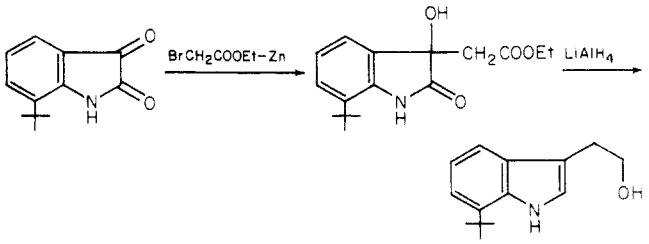
The 37 mono- and disubstituted 1-ethyl- and 1-*n*-propyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acids prepared are collected in Table I along with physical constants and analytical data. In addition, the source of the aniline, isatin, or indole starting material used for each of the compounds is documented in Table I.

Pharmacology. Methods. Compounds were tested orally for antiinflammatory activity in groups of six rats with established adjuvant arthritis ("therapeutic test") as described previously.[1,3,5] Treatment with compounds was

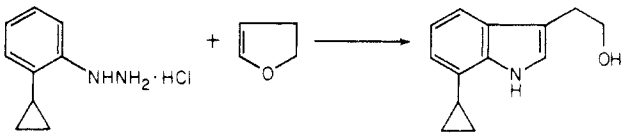
Scheme II



Scheme III



Scheme IV



started 14 days after adjuvant (*Mycobacterium butyricum* in mineral oil) injection in the foot pad of the left hind paw and continued until day 22 (9 po administrations). A decrease of the volume of the injected paw, of 0.5 ml (approximately 50% of the maximum possible decrease) or more, as a result of drug treatment was considered to be a "therapeutic effect". Smaller changes were considered to be negative. Paw volume was measured by mercury displacement. From the number of rats showing a "therapeutic effect", the therapeutic ED_{50} was calculated by probit analysis.[6] Compounds which failed to decrease the injected paw size by 0.5 ml in any of the rats at the arbitrarily chosen maximum screening dose of 100 mg/kg were considered inactive. Selected compounds were also tested orally in rats in the carrageenin paw edema model according to the method of Winter et al.,[7] and for their acute ulcerogenic effect in starved rats. Male Charles River rats (180–200 g), housed in individual cages, were starved for 8 hr prior to oral administration of test compounds. After a further 18 hr of starvation, the animals were sacrificed and their stomachs examined for ulcers. The presence of a lesion was considered an ulcerogenic effect.

Results

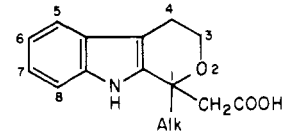
Thirty-seven novel compounds were studied in the therapeutic test and the results are shown in Table I along with those obtained with phenylbutazone (**38**) and indomethacin (**39**). Of the four 5-substituted compounds studied, the 5-methyl-1-*n*-propyl, 5-chloro-1-ethyl, and 5-methyl-1-ethyl derivatives **2–4** had high activity with ED_{50}'s in the range of 7–11 mg/kg while the 5-chloro-1-*n*-propyl analog **1** was inactive at the highest dose tested (25 mg/kg). The introduction of methyl or bromine groups at position 6 (**5, 6**) gave inactive compounds, while the 6-fluoro-1-ethyl analog **7** had substantial activity. The 7-methyl and 7-methoxy derivatives **9** and **10** were inactive while 7-halo and 7-trifluoromethyl compounds (**8, 11–13**) were considerably more potent than phenylbutazone, having ED_{50}'s in the range of 1.2–3.7 mg/kg. The effect of substitution at position 8 was found to be dependent on the nature of the 1-alkyl group. Thus, the methyl, ethyl, and *n*-propyl analogs **14–16**, having a 1-*n*-propyl substituent, had ED_{50}'s in the range of 6.0–11.8 mg/kg. With compounds having a 1-ethyl substituent, however, a dramatic increase in antiinflammatory activity was obtained by the introduction of hydrocarbon groups at position 8. Thus, inspection of the 11 such compounds studied (**18–28**) reveals that six of them (**19, 20, 22–24, 26**) are considerably more active than phenylbutazone (**38**), with activity reaching a maximum for the 1,8-diethyl and the 1-ethyl-8-*n*-propyl analogs, **19** and **20**, having ED_{50}'s of 0.7 and 0.4 mg/kg, respectively. The 8-methoxy derivative **29** was inactive while the 8-chloro analog **17** retained high activity. A number of derivatives, disubstituted in the benzene ring, **30–37**, were also examined, and, with the exception of the 5,8-dimethoxy analog **34**, all exhibited high activity with ED_{50}'s in the range of 0.6–5.5 mg/kg. An analysis of structure–activity relationships in this series of compounds, using substituent constants and regression analyses, is currently being carried out and the results will be reported separately.

The four most active compounds (**19, 20, 35, 36**) were studied further to determine their effects on carrageenin paw edema and to determine their ulcerogenic properties. The results are shown in Table II, in comparison with phenylbutazone and indomethacin. The four novel tetrahydropyrano[3,4-*b*]indole-1-acetic acid derivatives were found to be markedly more potent in the "therapeutic test", a model of chronic inflammation, than in the carrageenin paw edema test, a model of acute inflammation. This type of selective profile has been reported previously for prodolic acid,[3] also a member of this chemical class, and the present results indicate that such a profile is a characteristic of this class of antiinflammatory agents. Investigation of the ulcerogenic effects of the selected compounds shows that compound **19**[8] has a particularly wide spread between the doses that induce ulcers and inhibit chronic adjuvant arthritis. The ratio of these doses for **19** is 85, in comparison to values of 16 for phenylbutazone and 30 for indomethacin.

We have previously reported that 1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid has an ED_{50} of 6.8 ± 1.3 mg/kg in the "therapeutic test",[1] and in the present study we observe that the introduction of an 8-ethyl group, to afford etodolic acid, results in a tenfold increase in potency. The role of the ethyl group in eliciting such a substantial increase in potency is suggested from the results of pharmacokinetic studies conducted in our laboratories. Thus, Robinson et al.[9] have shown that the administration, orally, to rats of equimolar doses of etodolic acid and of analogs lacking an 8-alkyl substituent results in at least fivefold higher serum levels of etodolic acid, and they propose that the ethyl group of etodolic acid interferes with the enzymatic catabolism of the tetrahydropyrano-[3,4-*b*]indole nucleus.

In summary, the studies carried out have identified 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid (**19**, etodolic acid) as a potent antiinflammatory agent which is particularly active against chronic models of inflammation in rats and which has a relatively low acute ulcerogenic potential in the same specie. Etodolic acid,

Table I. Chemical and Antiinflammatory Data on Substituted Tetrahydropyrano[3,4-*b*]indole-1-acetic Acids



No.	Alk	Benzene substituents	Mp, °C	Recrystn solvent[a]	Yield,[b] %	Starting material[c]	Formula[d]	Therapeutic test in arthritic rat, ED_{50}, mg/kg ± SE
1	*n*-Pr	5-Cl	166-169	A, B	65	Indole[e]	$C_{16}H_{18}ClNO_3$	>25[f]
2	*n*-Pr	5-Me	177-178	B, C	28	Indole[g]	$C_{17}H_{21}NO_3$	~10
3	Et	5-Cl	154-157	A, B	72	Indole[e]	$C_{15}H_{16}ClNO_3$	7.0 ± 2.0
4	Et	5-Me	170-172	C, D	37	Indole[g]	$C_{16}H_{19}NO_3$	11.0 ± 4.0
5	*n*-Pr	6-Me	126-129	A, B	45	Indole[h]	$C_{17}H_{21}NO_3$[i]	Inactive[j]
6	Et	6-Br	183-184	B, C	32	Tryptophol[k]	$C_{15}H_{16}BrNO_3$	Inactive[j]
7	Et	6-F	125-126	A, B	41	Indole[l]	$C_{15}H_{16}FNO_3$	~5
8	*n*-Pr	7-Cl	182-183	E	35	Indole[e]	$C_{16}H_{18}ClNO_3$	~3.7
9	*n*-Pr	7-Me	157-158	A	28	Tryptophol[m]	$C_{17}H_{21}NO_3$	Inactive[n]
10	*n*-Pr	7-OMe	164-166	E	13	Tryptophol[o]	$C_{17}H_{21}NO_4$	Inactive[j]
11	Et	7-Cl	182-183	A, E	39	Indole[e]	$C_{15}H_{16}ClNO_3$	3.2 ± 0.8
12	Et	7-F	164-166	A, B	36	Indole[p]	$C_{15}H_{16}FNO_3$[q]	3.0 ± 1.3
13	Et	7-CF_3	185-187	B, F	31	Indole[r]	$C_{16}H_{16}F_3NO_3$	1.2 ± 0.4
14	*n*-Pr	8-Me	127-128	A, B	38	Indole[h]	$C_{17}H_{21}NO_3$	11.8 ± 2.9
15	*n*-Pr	8-Et	103-105	A, D	95	Indole[s]	$C_{18}H_{23}NO_3$	7.4 ± 1.8
16	*n*-Pr	8-*n*-Pr	109	A, B	45	Aniline[t]	$C_{19}H_{25}NO_3$	6.0 ± 1.6
17	Et	8-Cl	168-171	D, G	87	Indole[e]	$C_{15}H_{16}ClNO_3$	2.4 ± 0.7
18	Et	8-Me	160-161	A, B	87	Indole[h]	$C_{16}H_{19}NO_3$	4.3 ± 1.3
19	Et	8-Et	145-148	D, H	93	Indole[s]	$C_{17}H_{21}NO_3$	0.7 ± 0.1
20	Et	8-*n*-Pr	111-114	A, B	40	Aniline[t]	$C_{18}H_{23}NO_3$	0.4 ± 0.1
21	Et	8-*n*-Bu	Oil		38	Aniline[u]	$C_{19}H_{25}NO_3$[v]	Inactive[w]
22	Et	8-(2-Pr)	165-167	D, G	25	Aniline[s]	$C_{18}H_{23}NO_3$	1.6 ± 0.3
23	Et	8-*t*-Bu	169-170	I, J	64	Aniline[x]	$C_{19}H_{25}NO_3$	1.9 ± 0.3
24	Et	8-*sec*-Bu	135-137	A, B	42	Aniline[y]	$C_{19}H_{25}NO_3$	2.6 ± 1.1
25	Et	8-*i*-Bu	Oil		39	Aniline[z]	$C_{19}H_{25}NO_3$[aa]	5.0 ± 2.0
26	Et	8-Cyclopropyl	153-154	G, I	81	Aniline[bb]	$C_{18}H_{21}NO_3$	1.0 ± 0.2
27	Et	8-Cyclopentyl	137-139	A, B	10	Aniline[cc]	$C_{20}H_{25}NO_3$[dd]	>5[f]
28	Et	8-Cyclohexyl	156-159	A, B	35	Aniline[cc]	$C_{21}H_{27}NO_3$	>10[f]
29	Et	8-OMe	132	A, B	51	Indole[h]	$C_{16}H_{19}NO_4$	Inactive[j]
30	Et	5,8-$(Me)_2$	175-176	D, G	56	Indole[ee]	$C_{17}H_{21}NO_3$	3.2 ± 0.4
31	Et	5,8-$(Cl)_2$	168-169	A, B	26	Indole[ff]	$C_{15}H_{15}Cl_2NO_3$	5.5 ± 1.3
32	Et	7,8-$(Cl)_2$	112-117	A, B	37	Isatin[gg]	$C_{15}H_{15}Cl_2NO_3$	1.1 ± 0.3
33	Et	7-Me, 8-Cl	117-120	A, B	58	Aniline[h]	$C_{16}H_{18}ClNO_3$	4.1 ± 1.0
34	Et	5,8-$(OMe)_2$	167-169	A, B	43	Indole[hh]	$C_{17}H_{21}NO_5$	~100
35	Et	7-F, 8-Me	158-160	A	35	Aniline[ii]	$C_{16}H_{18}FNO_3$	0.9 ± 0.1
36	Et	7-Cl, 8-Me	119-123	A, B	67	Isatin[jj]	$C_{16}H_{18}NO_3$	0.6 ± 0.1
37	*n*-Pr	7-Cl, 8-Me	156-158	A, B	31	Isatin[jj]	$C_{17}H_{20}ClNO_3$	3.4 ± 0.6
38	Phenylbutazone							5.4 ± 1.2
39	Indomethacin							0.2 ± 0.05

[a] A = benzene; B = petroleum ether, bp 60-90°; C = acetone; D = hexane; E = acetonitrile; F = ethyl acetate; G = ether; H = chloroform; I = pentane. [b] Yield refers to overall yield of purified acid based on the tryptophol used. [c] This column gives, by footnotes, references to the appropriate substituted aniline, indole, isatin, or tryptophol starting material used to prepare each of the final compounds, as illustrated in Schemes I-IV. [d] All crystalline compounds were analyzed for C, H, and N and gave results within ±0.4% of the calculated values, except for **5**, **12**, and **27**, as indicated below. **21** and **25** were oils for which good analyses could not be obtained. They were characterized by their NMR spectra. [e] H. N. Rydon and J. C. Tweddle, *J. Chem. Soc.*, 3499 (1955). [f] The compound reduced the paw size by 0.5 ml in some rats but the ED_{50} was greater than the dose indicated. [g] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964). [h] Obtained from the Aldrich Chemical Co. [i] C: calcd, 71.05; found, 70.62. [j] Inactive at 25 mg/kg (highest dose tested). [k] B. T. Ho, G. E. Fritchie, M. B. Noel, and W. M. McIsaac, *J. Pharm. Sci.*, **60**, 634 (1971). [l] Obtained from Pfaltz and Bauer. [m] British Patent 778823 (July 10, 1957). [n] Inactive at 50 mg/kg (highest dose tested). [o] R. C. Elderfield and B. A. Fischer, *J. Org. Chem.*, **23**, 332 (1958). [p] M. Bentov, A. Kaluzyner, and Z. Pelchowicz, *J. Chem. Soc.*, 2825 (1962). [q] C: calcd, 64.97; found, 65.42. [r] A. Kalir and Z. Pelah, *Isr. J. Chem.*, **4**, 155 (1966). [s] Obtained from the Ethyl Corp., courtesy of Mr. P. Elsey. [t] G. Baddeley and J. Kenner, *J. Chem. Soc.*, 303 (1935). [u] R. R. Read and D. B. Mullin, *J. Am. Chem. Soc.*, **50**, 1763 (1928). [v] NMR δ 0.9 (6, m, CH_3), 1.7 (6, m, CH_2), 2.8 (4, m, $C{=}CCH_2$), 3.1 (2, s, CH_2COO), 4.1 (2, t, J = 5.5 Hz, CH_2O), 7.2 (3, m, aromatic H's), 8.8 (2, m, NH and COOH). [w] Inactive at 20 mg/kg (highest dose tested). [x] J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 2334 (1928). [y] R. R. Read, C. A. Hewitt, and N. R. Pike, *J. Am. Chem. Soc.*, **54**, 1194 (1932). [z] F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 4127 (1954). [aa] NMR δ 0.9 (9, m, CH_3), 2.05 (3, m, CH and CH_2CH_3), 2.8 (4, m, $C{=}CCH_2$), 3.1 (2, m, CH_2COO), 4.1 (2, t, J = 5.5 Hz, CH_2O), 7.0-7.5 (3, m, aromatic H's). [bb] Yu. S. Shabarov, V. K. Potapov, R. Ya. Levina, *Zh. Obshch. Khim.*, **34**, 3127 (1964); *Chem. Abstr.*, **61**, 14557 (1964). [cc] D. A. Denton, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc.*, 2421 (1964). [dd] C: calcd, 73.36; found, 73.81. [ee] R. B. Carlin, W. O. Hanley, and D. P. Carlson, *J. Am. Chem. Soc.*, **79**, 5712 (1957). [ff] G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958). [gg] F. Buscarons and L. Sanchez Moreno, *Inf. Quim. Anal.*, **21**, 191 (1967). [hh] G. Rodighero, G. Malesani, and U. Fornasiero, *Gazz. Chim. Ital.*, **91**, 742 (1961). [ii] M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961). [jj] B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *ibid.*, **17**, 157 (1952).

Table II. Acute and Chronic Antiinflammatory Activities and Ulcerogenic Properties of Selected Compounds

No.	"Therapeutic" test in arthritic rats, ED_{50}, mg/kg ± SE	Inhibn of carrageenin paw edema, ED_{30}, mg/kg[a]	Ulcerogenic effect, UD_{50}, mg/kg[a]	Ulcerogenic ED_{50} / "therapeutic" UD_{50}
19 (etodolic acid)	0.7 ± 0.1	10.2	60	85
20	0.4 ± 0.1	10.0	20	50
35	0.9 ± 0.1	37.0	26	29
36	0.6 ± 0.1	15.0	25	41
38 (phenylbutazone)	5.4 ± 1.2	11.7	100	16
39 (indomethacin)	0.2 ± 0.05	1.3	6	30

[a] ED_{30}'s and UD_{50}'s were calculated graphically.

as well as prodolic acid, has also been shown by Wolfe et al. to be an inhibitor of prostaglandin synthetase in rat brain homogenates[10] and the results will be reported shortly. The detailed pharmacology of etodolic acid will be reported separately.[11]

Experimental Section

NMR spectra were determined in $CDCl_3$ using a Varian A-60A spectrometer and the chemical shifts (δ) are reported as parts per million downfield from Me_4Si. All compounds were homogeneous by TLC and melting points were taken on a Thomas-Hoover apparatus and need no correction. Microanalyses were done by the Ayerst Analytical Chemistry Section under the direction of Dr. G. Schilling.

(a) Anilines → Isonitrosoacetanilides. 2-(2-Propyl)-α-isonitrosoacetanilide. To a boiling solution of 2-(2-propyl)aniline (27.04 g, 0.2 mol), 1 *N* HCl (200 ml), H_2O (600 ml), hydroxylamine hydrochloride (45.0 g, 0.65 mol), and anhydrous Na_2SO_4 (185 g) was added a hot solution of chloral hydrate (40 g, 0.24 mol) in H_2O (600 ml). The mixture was boiled for 40 min, cooled, and extracted with Et_2O. The Et_2O extracts were dried ($MgSO_4$) and evaporated and the residue was crystallized from Et_2O–hexane to afford the title compound (24.0 g, 59%): mp 104–108°. Anal. ($C_{11}H_{14}N_2O_2$) C, H, N. In a similar manner the following substituted α-isonitrosoacetanilide was prepared and characterized: **7-*tert*-butyl**, mp 151–152° (C_6H_6–Et_2O); NMR δ 1.35 (9, s, CH_3), 7.08–7.50 (3, m, aromatic H's), 11.50 (1, broad, NH).

(b) Isonitrosoacetanilides → Isatins. 7-(2-Propyl)isatin. 2-(2-Propyl)-α-isonitrosoacetanilide (6.2 g, 0.03 mol) was added to a stirred solution of concentrated H_2SO_4 (30 ml) and H_2O (3 ml) during 10 min at 65°. The mixture was then kept at 80° for 10 min and then poured onto cracked ice. After 30 min the product was filtered off and washed with H_2O and dried to afford an orange solid: mp 187–191° (5.4 g, 95%); NMR δ 1.3 (6, d, J = 6.5, CH_3), 3.02 (1, m, CH), 6.85–7.55 (3, m, aromatic H's), 9.90 (1, broad, NH). In a similar manner the following substituted isatins were prepared and characterized: **7-(*n*-propyl)** (mp 128–131°), **7-(*n*-butyl)** [NMR δ 1.0 (3, m, CH_3), 1.5 [4, m, $(CH_2)_2CH_3$], 2.6 (2, m, benzylic CH_2), 7.3 (3, m, aromatic H's), 11.2 (1, s, NH)], **7-(*tert*-butyl)** [mp 227–230° (H_2O); NMR δ 1.35 [9, s, $(CH_3)_3$], 7.08–7.50 (3, m, aromatic H's), 11.50 (1, broad, NH)], **7-(*sec*-butyl)** (mp 130–132°), **7-(isobutyl)** (mp 138–140°), and **6-fluoro-7-methyl** (mp 204–206°).

(c) Isatins → Indoles. 7-(2-Propyl)indole. To a suspension of $LiAlH_4$ (7.6 g, 0.2 mol) in Et_2O (300 ml) was added 7-(2-propyl)isatin (3.78 g, 0.02 mol) and the mixture was stirred at 22° for 18 hr. The reaction was worked up in the conventional manner to afford the crude product. It was purified by elution from a silica gel column with C_6H_6. The pure product (2.0 g, 63%) had mp 52–54° (hexane). Anal. ($C_{11}H_{13}N$) C, H, N. In a similar manner the following substituted indoles were prepared and characterized: **7-isobutyl** [NMR δ 0.95 [6, d, J = 7 Hz, $(CH_3)_2$], 2.05 (1, m, CH), 2.72 (2, d, J = 7 Hz, CH_2), 6.5–7.8 (5, m, aromatic H's), 8.01 (1, s, NH)], **7-cyclopentyl** [NMR δ 1.5–2.5 [8, m, $(CH_2)_4$], 3.2 (1, m, CH), 6.55 (1, m, C=CH), 7.1 (4, m, C=CH and benzene H's), 7.95 (1, s, NH)], **7-cyclohexyl** [NMR δ 2.8 (1, m, CH), 6.6 (1, m, C=CH), 7.0–7.1 (4, m, C=CH and benzene H's), 8.05 (1, s, NH)], **6,7-dichloro** [NMR δ 6.5 (1, m, C=CH), 7.1 (1, m, C=CH), 7.0–7.45 (2, m, benzene H's)], **6-chloro-7-methyl** [mp 119–120° (EtOH–H_2O). Anal. (C_9H_5ClN) C, H, N] and **6-fluoro-7-methyl** [NMR δ 2.33 (3, s, CH_3), 6.45–7.55 (4, m, aromatic H's), 7.9 (1, s, NH)].

(d) Indoles → Glyoxylates. Ethyl 7-(2-Propyl)-3-indolylglyoxylate. Oxalyl chloride (2.98 g, 0.023 mol) in Et_2O (30 ml) was added during 5 min to a solution of 7-(2-propyl)indole (1.7 g, 0.01 mol) in Et_2O (20 ml) at 0°. The mixture was stirred at 22° for 5 hr. The Et_2O was removed by evaporation and absolute EtOH (50 ml) was added. The resulting solution was kept at 22° for 18 hr. Evaporation of EtOH afforded a residue which was crystallized from an Et_2O–hexane mixture to give the product: mp 137–139° (2.2 g, 80%); NMR δ 1.32 (9, m, CH_3), 3.32 (1, m, CH), 4.9 (2, q, J = 7 Hz, CH_2), 7.1–8.6 (4, m, aromatic H's), 10.2 (1, broad, NH).

(e) Glyoxylates → Tryptophols. 7-(2-Propyl)tryptophol. Ethyl 7-(2-propyl)-3-indolylglyoxylate (16.5 g, 0.025 mol) was reduced with $LiAlH_4$ (6.5 g, 0.17 mol) by refluxing in THF (100 ml) for 2 hr. The conventional work-up procedure afforded the crude product which was purified by eluting from a silica gel column with MeOH–$CHCl_3$ (1:10). The product (4.6 g, 90%) was obtained as an oil: NMR δ 1.38 (6, d, J = 7 Hz, CH_3), 1.71 (1, s, OH), 3.0 (2, t, J = 6 Hz, $=CCH_2$), 3.2 (1, m, CH), 3.87 (2, t, J = 6 Hz, CH_2O), 6.9–7.5 (3, m, benzene H's), 8.08 (1, broad, NH). In a similar manner the following tryptophols were prepared and characterized: **4-chloro** [mp 88–92° (C_6H_6–petroleum ether); NMR δ 1.9 (1, s, OH), 3.2 (2, t, J = 6.5 Hz, $=CCH_2$), 3.95 (2, t, J = 6.5 Hz, CH_2O), 6.9–7.3 (4, m, aromatic H's), 8.4 (1, s, NH)], **4-methyl** [NMR δ 2.53 (3, s, CH_3), 6.55 (1, s, C=CH), 7.08 (4, m, C=CH and benzene H's), 7.80 (1, s, NH)], **5-methyl** [NMR δ 1.55 (1, s, OH), 2.46 (3, s, CH_3), 3.0 (2, t, J = 6.5 Hz, $=CCH_2$), 3.9 (2, t, J = 6.5 Hz, CH_2O), 6.9–7.4 (3, m, aromatic H's), 7.9 (1, s, NH)], **6-fluoro** [mp 66–68°; NMR δ 6.55 (1, m, C=CH), 7.1–7.55 (3, m, benzene H's), 8.0 (1, s, NH)], **6-trifluoromethyl** [mp 65–67°; NMR δ 2.95 (2, t, J = 6.5 Hz, $=CCH_2$), 3.85 (2, t, J = 6.5 Hz, CH_2O), 6.8–7.7 (4, m, aromatic H's), 8.4 (1, s, NH)], **7-methyl** [mp 85–86°; NMR δ 1.76 (1, s, OH), 2.44 (3, s, CH_3), 2.93 (2, t, J = 6.5 Hz, $=CCH_2$), 3.93 (2, t, J = 6.5 Hz, CH_2O), 6.90–7.70 (4, m, aromatic H's), 8.13 (1, s, NH)], **7-ethyl** [NMR δ 1.3 (3, t, J = 7 Hz, CH_3), 1.8 (1, s, OH), 2.85 (2, q, J = 7 Hz, CH_2CH_3), 3.0 (2, t, J = 6.5 Hz, $=CCH_2$), 3.9 (2, t, J = 6.5 Hz, CH_2O), 7.3 (4, m, aromatic H's), 8.1 (1, broad s, NH)], **7-*n*-propyl** [NMR δ 0.98 (3, t, J = 7 Hz, CH_3), 1.8 (2, m, CH_2CH_3), 3.0 (2, t, J = 7.0 Hz, $=CCH_2$), 2.8 (2, m, $CH_2CH_2CH_3$), 3.9 (2, t, J = 7.0 Hz, CH_2O), 6.9–7.8 (4, m, aromatic H's), 8.1 (1, s, NH)], **7-chloro** [NMR δ 1.80 (1, s, OH), 3.00 (2, t, J = 6.5 Hz, $=CCH_2$), 3.90 (2, t, J = 6.5 Hz, CH_2O), 6.9–7.70 (4, m, aromatic H's), 8.10 (1, broad, NH)], **7-*n*-butyl** [NMR δ 1.0 (3, m, CH_3), 1.2–2.0 [4, m, $(CH_2)_2CH_3$], 2.8 [2, m, $CH_2(CH_2)_2$], 3.0 (2, t, J = 7 Hz, $=C-CH_2$), 3.9 (2, t, J = 7 Hz, CH_2O), 6.9–7.7 (4, m, aromatic H's), 8.1 (1, s, NH)], **7-cyclopentyl** [NMR δ 1.8 (1, s, OH), 3.0 (2, t, J = 6.25 Hz, $=CCH_2$), 3.3 (1, m, CH), 3.9 (2, t, J = 6.25 Hz, CH_2O), 7.1–7.6 (4, m, aromatic H's), 8.15 (1, s, NH)], **7-cyclohexyl** [NMR δ 3.0 (2, t, J = 6.5 Hz, $=CCH_2$), 3.9 (2, t, J = 6.5 Hz, CH_2O), 7.1–7.6 (4, m, aromatic H's)], **4,7-dimethyl** [mp 80–83° (Et_2O–hexane). Anal. ($C_{12}H_{15}NO$) C, H, N], **4,7-dichloro** [mp 65–67°; NMR δ 1.82 (1, s, OH), 3.2 (2, t, J = 6 Hz, $=CCH_2$), 4.95 (2, t, J = 6 Hz, CH_2O), 7.0 (2, m, benzene H's), 8.6 (1, s, NH)], **7-chloro-6-methyl** [mp 83–84°; NMR δ 1.8 (1, s, OH), 2.47 (3, s, CH_3), 2.95 (2, t, J = 6.5 Hz, $=CCH_2$), 3.9 (2, t, J = 6.5 Hz, CH_2O), 6.9–7.5 (3, m, aromatic H's), 8.3 (1, s, NH)], **6-fluoro-7-methyl** [NMR δ 1.9 (1, s, OH), 2.23 (3, s, CH_3), 2.95 (2, t, J = 6.0 Hz, $=CCH_2$), 3.9 (2, t, J = 6.0 Hz, CH_2O), 6.7–7.5 (3, m, aromatic

H's), 8.2 (1, s, NH)].

Ethyl 3-Hydroxy-7-*tert*-butyl-2-oxoindoline-3-acetate. Ethyl bromoacetate (24.5 ml, 0.22 mol) was added to a stirred suspension of 7-*tert*-butylisatin (15.0 g, 0.074 mol) and granulated zinc (14.0 g, 0.214 g-atom) in C_6H_6 (200 ml). The mixture was heated at reflux for 20 hr and then poured onto cracked ice and 20% aqueous H_2SO_4. The organic phase was washed with H_2O, dried, and evaporated to give a residue which was chromatographed on silica gel. Elution with C_6H_6–EtOAc (7:3) gave the product (15.5 g, 72%) as an oil: NMR δ 1.15 (3, t, J = 7 Hz, CH_2CH_3), 1.35 [9, s, 1.35, $C(CH_3)_3$], 2.93 (2, s, CH_2CO), 4.12 (2, q, J = 7 Hz, CH_2CH_3), 4.65 (1, s, OH), 7.0–7.4 (3, m, aromatic H), 9.4 (1, s, NH).

7-*tert*-Butyltryptophol. Ethyl 3-hydroxy-7-*tert*-butyl-2-oxoindoline-3-acetate (15.5 g) and $LiAlH_4$ (12.0 g) were combined in THF (300 ml) and the mixture was heated at reflux for 2 hr. A conventional work-up procedure afforded the product (11.0 g, 95%) as an oil: NMR δ 1.45 [9, s, $C(CH_3)_3$], 1.95 (1, s, OH), 3.0 (2, t, J = 7.0 Hz, $=CCH_2$), 3.8 (2, t, J = 7.0 Hz, CH_2O), 6.95–7.60 (4, m, aromatic H's), 8.4 (1, s, NH).

2-Cyclopropylphenylhydrazine Hydrochloride. 2-Cyclopropylaniline (26.6 g, 0.2 mol) dissolved in a mixture of concentrated HCl (150 ml) and H_2O (150 ml) was treated at −5° during 40 min with a solution of $NaNO_2$ (14.5 g) in H_2O (28 ml). After 1 hr at 0°, a solution of $SnCl_2 \cdot 2H_2O$ (112.5 g) in concentrated HCl (100 ml) was added during 30 min at −15°. After stirring for 90 min, the resulting precipitate was isolated and stirred with Et_2O and 10% aqueous NaOH. The Et_2O phase was washed with brine, dried, and treated with anhydrous HCl in Et_2O. The precipitate was collected, washed with Et_2O, and dried to give 24.7 g of the product (66.9%): mp 168–169°; NMR δ 0.5–1.1 (4, m, CH_2CH_2), 1.35–1.85 (1, m, CH), 4.13 (3, s, $NHNH_2$), 6.6–7.4 (4, m, aromatic H's).

7-Cyclopropyltryptophol. To a stirred suspension of 2-cyclopropylphenylhydrazine hydrochloride (24.9 g, 0.14 mol) in H_2O (7 ml) and dioxane (110 ml) was added a solution at 2,3-dihydrofuran[12] (16.8 g, 0.28 mol) during 10 min. The mixture was heated at 100° for 6 hr, cooled, and diluted with Et_2O (1.5 l.). The Et_2O phase was decanted from an insoluble residue, dried, and evaporated. The residue was chromatographed on silica gel. Elution with C_6H_6–EtOAc (3.1) gave the product (6.7 g, 24.9%) as an oil: NMR δ 0.8 (4, m, cyclopropane CH_2), 2.0 (1, m, CH), 3.0 (2, t, J = 6.5 Hz, $=CCH_2$), 3.9 (2, t, J = 6.5 Hz, CH_2O), 6.9–7.6 (4, m, aromatic H's), 8.8 (1, broad, NH).

(f) Tryptophols → Tetrahydropyrano[3,4-*b*]indole-1-acetic Acids. 1-Ethyl-8-(2-propyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid (22). A mixture of 7-(2-propyl)tryptophol (1.9 g, 0.0094 mol), ethyl propionylacetate (1.63 g, 0.011 mol), and *p*-toluenesulfonic acid (200 mg) was refluxed in C_6H_6 (50 ml) under a Dean-Stark trap for 5 hr. The C_6H_6 solution was washed with 5% aqueous $NaHCO_3$ and worked up in the conventional manner to give an oil which was eluted from a silica gel column with C_6H_6–Et_2O (4:1) to afford the ethyl ester of the product (1.0 g, 32%). It was dissolved in EtOH (25 ml) and 10% aqueous NaOH (25 ml) was added. The mixture was refluxed for 4 hr and after a conventional work-up procedure the product was obtained as a solid residue. It was crystallized from Et_2O–hexane to give the product **22**. Analytical data and melting points for **22** and other final products prepared by the same method are collected in Table I.

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Adriamycin Analogs. Periodate Oxidation of Adriamycin

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Adriamycin is selectively cleaved in high yield at the C_{13}–C_{14} bond by 1 equiv of sodium metaperiodate to yield carboxylic acid **3**. The corresponding methyl ester **4** is obtained by Fischer esterification. Spectral studies indicate that **3** and **4** bind to calf thymus DNA in a manner similar to adriamycin and daunomycin but T_m measurements suggest that less stable complexes are formed. Ester **4** inhibits DNA and RNA synthesis in cultured L1210 cells at levels comparable to adriamycin but acid **3** is much less effective. Both new compounds are moderately effective as antitumor agents against P388 lymphocytic leukemia in the mouse.

Recent reviews[1,2] have emphasized the importance of adriamycin (**1**) in the treatment of a wide spectrum of human cancers. However, its administration is accompanied by various undesirable side effects,[1] especially cardiomyopathy,[1,3,4] and less toxic analogs would greatly extend its usefulness. Daunomycin (**2**), a closely related antibiotic that appears restricted primarily to use against leukemia,[2] also suffers from similar defects. We are reporting the synthesis and early biological evaluation of two new analogs, carboxylic acid **3** and the corresponding