Synthesis and Pharmacology of Some β-Spiroindolenines and Indolines[1]

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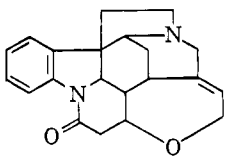
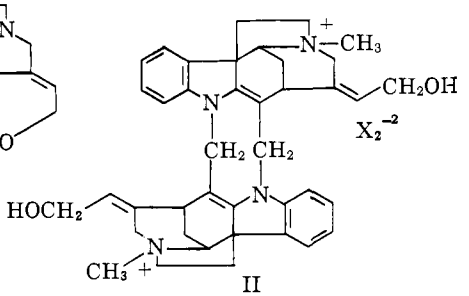
A series of N_b-tosyl-β-spiroindolenines has been prepared. Reduction with sodium borohydride yielded the corresponding tosylindoline. Removal of the tosyl group with concomitant conversion to the indoline was accomplished by two vigorous reductive procedures. Pharmacological studies of these compounds have been performed. The results are described and interpreted.

The β-spiroindoline moiety is a characteristic feature of several classes of naturally occurring alkaloids. Prominent among these are the Strychnos, curare, Aspidosperma, and oxindole types which are exemplified by strychnine (I), toxiferine-I (II), aspidospermine (III), and rhyncophylline (IV, an oxindole), respectively.[3]



I



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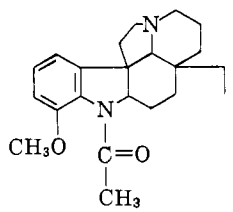
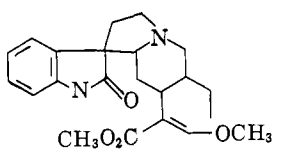


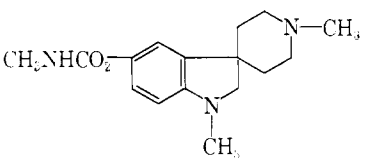
III



IV

Each of these structural variants has provided molecules possessing interesting, and sometimes clinically useful, pharmacological profiles. Thus, once again using compounds I–IV as examples, we find (a) that strychnine is a potent central nervous system stimulant which acts *via* a mechanism of inhibition of inhibitory reflexes[4]; (b) that the toxiferines, obtained from calabash curare, are the most potent curare alkaloids, and act by a highly selective paralysis of motor neuron endplates in skeletal muscle in addition to causing a paralysis of autonomic ganglionic cells[5]; (c) that aspidospermine is a respiratory stimulant and has an atropine-like activity on smooth muscle[6]; and (d) that rhynchophylline, in a recent study of effects upon several species of lower animals,[7] caused activities which included motor paralysis and inhibition of respiration in mice, miosis in frogs, and hypertension in rabbits.

As part of a program designed to evaluate pharmacologically a variety of naturally occurring alkaloids and their transformation products, it was deemed appropriate to examine some synthetic molecules which embodied the common feature of the alkaloid groups just cited. This is the β-spiroindoline moiety (in one case IV is a β-spirooxindole) having a second basic nitrogen incorporated in the five-membered spiro ring. A molecule (V), closely related to this type, was prepared some years ago[8] as an analog of the clinically useful drug, physostigmine. Although V also exhibited cholinesterase-inhibiting properties, the observed activity was of a greatly diminished magnitude.



V

In 1954, Woodward, *et al.*,[9] reported the completion of an elegant synthesis of strychnine. One key reaction in the early phases of the 32-step sequence was the formation of a β-spiroindolinine moiety. The work described below is an application and extension of this reaction for medicinal chemical purposes, rather than for the earlier synthetic goals.

The sequence of reactions used to obtain the primary objective of our study (XI) is illustrated in Scheme I. It was initiated by condensation of a 2-aryltryptamine with an aldehyde to yield the Schiff's base VIII. The latter was not characterized, but instead the crude product was cyclized directly to the tosylindolinine (IX). This compound was reduced to the corresponding tosylindoline (X) with sodium borohydride in methanol. Either IX or X was converted to XI by reductive removal of the tosyl group using lithium aluminum hydride in tetrahydrofuran[10] or sodium in butanol.[11] The former combination was generally applicable, while the latter was useful only in the absence of halogen or where its removal was actually desired. On our hands, either procedure proved superior for tosyl removal to the phosphorus–hydrogen iodide used by Woodward, *et al.*,[9] or to other hydrolytic[12] and oxidative hydrolytic

(1) For purposes of discussion in the first portion of this paper the terms β-spiroindolenine and β-spiroindoline have been used. The official *Chemical Abstracts* names are spiro[3H-indole-3,3′-pyrrolidine] and spiro[indoline-3,3′-pyrrolidine], respectively.

(2) To whom inquiries should be addressed.

(3) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961.

(4) J. C. Eccles, "The Physiology of Nerve Cells," Johns Hopkins Press, Baltimore, Md., 1957.

(5) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1955, p. 576.

(6) J. N. Banerjee and J. J. Lewis, *J. Pharm. Pharmacol.*, **7**, 46 (1955).

(7) K. Usui, *Shinshu Igaku Zasshi.*, **8**, 1458 (1959).

(8) E. Kretz, J. M. Müller, and E. Schlittler, *Helv. Chim. Acta*, **35**, 520 (1952).

(9) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Am. Chem. Soc.*, **76**, 4749 (1954); *Tetrahedron*, **19**, 247 (1963).

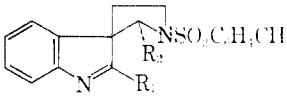
(10) L. Field and F. A. Grunwald, *J. Org. Chem.*, **16**, 946 (1951).

(11) D. Klamann and G. Hofbauer, *Chem. Ber.*, **86**, 1246 (1953).

(12) H. B. Mac Phillamy, R. L. Dźemian, R. A. Lucas, and M. E. Kuehne, *J. Am. Chem. Soc.*, **80**, 2172 (1958).

TABLE I

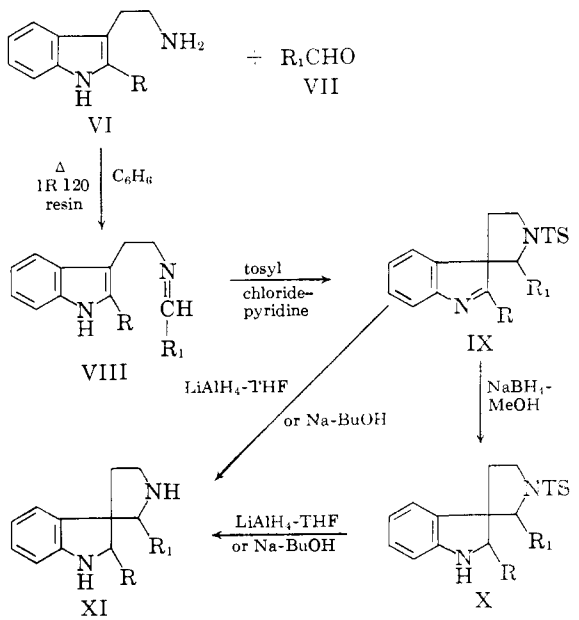
TOSYLSPIRO[3H-INDOLE-3,3'-PYRROLIDINES]



Compd. no.	R_1	R_2	Yield, %	M.p., °C.	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
1	C_6H_5	C_6H_5	61	170–172	$C_{30}H_{26}N_2O_2S$	75.29	5.48	5.85	6.70	74.99	5.84	5.80	6.65
2	C_6H_5	p-ClC_6H_4	49	192–194	$C_{30}H_{25}ClN_2O_2S$	70.23	4.91	5.46	6.25	70.10	5.12	5.44	6.30
3	C_6H_5	m-$CH_3OC_6H_4$	51	171–173	$C_{31}H_{28}N_2O_3S$	73.20	5.55	5.51	6.30	73.09	5.38	5.34	6.59
4	C_6H_5	2-Pyridyl	51	200–202	$C_{25}H_{25}N_3O_2S$	72.63	5.25	8.76	6.69	72.78	5.27	8.64	6.65
5	C_6H_5	m-$NO_2C_6H_4$	27	210–213	$C_{30}H_{25}N_3O_4S$	68.82	4.81	8.03		68.50	4.91	7.98	
6	C_6H_5	$CO_2C_2H_5$	23	184–185	$C_{27}H_{26}N_2O_4S$	68.33	5.52	5.90	6.76	68.35	5.49	5.93	6.74
7	C_6H_5	2-Furanyl	18	154–157	$C_{28}H_{24}N_2O_3S$	71.82	5.15	5.98	6.84	71.92	5.26	5.75	6.94
8	C_6H_5	4-Pyridyl	8	196.5–198	$C_{29}H_{25}N_3O_2S$	72.63	5.25	8.76		72.60	5.27	8.81	
9	p-ClC_6H_4	C_6H_5	62	198–200	$C_{30}H_{25}ClN_2O_2S$	70.23	4.91	5.46	6.25	70.53	5.09	5.31	6.70
10	p-ClC_6H_4	3,4-$CH_2O_2C_6H_3$	49	162–163	$C_{31}H_{25}ClN_2O_4S$	66.84	4.52	5.03	5.76	66.60	4.77	5.40	5.89
11	p-ClC_6H_4	p-ClC_6H_4	64	152–154	$C_{31}H_{28}Cl_2N_2O_3S$[a]	64.24	4.83	4.83	5.52	64.16	4.88	4.67	5.83
12	p-ClC_6H_4	2-Pyridyl	67	200–202	$C_{29}H_{24}ClN_3O_2S$	67.23	4.66	8.11		67.48	4.68	8.22	
13	p-ClC_6H_4	m-$NO_2C_6H_4$	23	211–214	$C_{30}H_{24}ClN_3O_4S$	64.57	4.34	7.53		64.47	4.36	7.71	
14	p-ClC_6H_4	m-$CH_3OC_6H_4$	44	180–181	$C_{31}H_{27}ClN_2O_3S$	68.56	5.01	5.16		68.47	5.01	5.40	

[a] Methanolate.

SCHEME I



reagents.[13] Typical experiments illustrative of each stage of the sequence are found in the Experimental section. Analytical data, etc., are incorporated in Tables I–III.

Pharmacology[14]

The majority of the compounds listed in Tables I–III showed no central nervous system activity when tested in the mouse. The procedure used for determining biological action was essentially subjective, and depended on gross observation following treatment of the animals with the drug. As shown in Table IV, compound **14** produced stimulation and hypersensitivity to sound and touch in 50% of the animals after doses of 100 mg./kg. orally. Compound **19** caused weak central nervous system depression, an increase in pain threshold, bradypnea, and low body posture. Diarrhea and/or increased pain threshold occurred following intraperitoneal doses of 50 or 100 mg./kg., respectively, with **29**. Hypothermia and marked decreased motor activity resulted after intraperitoneal administration of 200 mg./kg. of **30**. Oral administration of 300 mg./kg. of **31** caused bradypnea, slight decreased activity, hypothermia, and moderate ptosis. Compound **33** produced slight stimulation after doses of 50 mg./kg. orally, and moderate decreased activity and excessive defecation and urination after larger doses of 100 mg./kg. orally.

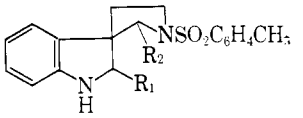
In a modification of the Randall and Selitto test, the measurements of pain, skin temperature, and edema reduction in the rat are taken as presumptive evidence for antiinflammatory action. A specially designed device was used to apply pressure to the plantar surface of the left hind foot of a rat which had been injected with 0.1 ml. of a 20% brewers' yeast suspension. The pain threshold, measured in millimeters of pressure, was determined at the point where the rat would struggle or squeal. Skin temperature was measured with a "banjo" surface probe and a telethermometer. Reduction of edema was determined by gross observation. Phenylbutazone, in this test procedure, has an oral ED_{50} of 27 mg./kg. (15–49 mg./kg.) for elevating pain threshold and an ED_{50} of 29 mg./kg. (17–50 mg./kg.) for antipyresis. It reduced edema in 80% of the animals after oral doses of 100 mg./kg. Several compounds demonstrated activity in one or two of these parameters in the present investigation. Compound **29** was active in all three segments of the test after a dose of 200 mg./kg. orally in the rat. However, tremors were observed at this dose level. Tremors were also observed in the animals receiving oral doses of 50 mg./kg. of **33**. These side effects differed from those observed in the initial dose range or acute toxicity studies which were carried out in mice. However, many compounds have been found to exhibit this sort of species difference. In addition, somewhat different conditions were used for each test. In the dose range

(13) H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, **74**, 2006 (1952); H. R. Snyder and H. C. Geller, *ibid.*, **74**, 4864 (1952).

(14) Descriptions of the test procedures used in this study can be found in J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963); B. Loev, K. M. Snader, and D. T. Walz, *ibid.*, **6**, 506 (1963), ref. 8.

TABLE II

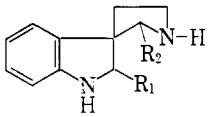
TOSYLSPIRO[INDOLINE-3,3′-PYRROLIDINES]



Compd. no.	R_1	R_2	Yield, %	M.p., °C.	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
15	C_6H_5	C_6H_5	82	210–212.5	$C_{30}H_{28}N_2O_2S$	75.02	5.87	5.82	6.66	75.16	5.94	5.81	6.98
16	C_6H_5	p-ClC_6H_4	97	185–187	$C_{30}H_{27}ClN_2O_2S$	69.96	5.28	5.44	6.23	70.24	5.03	5.39	6.63
17	C_6H_5	m-$CH_3OC_6H_4$	90	195–198	$C_{31}H_{30}N_2O_3S$	72.91	5.92	5.49	6.28	72.93	6.15	5.42	6.52
18	C_6H_5	2-Pyridyl	98	188–190	$C_{29}H_{27}N_3O_2S$	72.23	5.65	8.73	6.66	72.59	5.57	8.58	6.65
19	C_6H_5	m-$NO_2C_6H_4$	92	174–178	$C_{30}H_{27}N_3O_4S$	68.57	5.16	8.00		68.60	5.15	7.93	
20	C_6H_5	$CO_2C_2H_5$	92	206–208	$C_{27}H_{28}N_2O_4S$	68.04	5.92	5.88	6.73	67.88	6.05	5.67	7.21
21	C_6H_5	2-Furanyl	91	196–197	$C_{28}H_{26}N_2O_3S$	71.46	5.57	5.95		71.60	5.46	5.96	
22	C_6H_5	4-Pyridyl	92	228–229	$C_{29}H_{27}N_3O_2S$	72.32	5.65	8.73		72.63	5.47	8.54	
23	p-ClC_6H_4	C_6H_5	97	223–225	$C_{30}H_{27}ClN_2O_2S$	69.96	5.28	5.44	6.22	69.97	5.46	5.34	6.47
24	p-ClC_6H_4	3,4-$CH_2O_2C_6H_3$	98	228–230	$C_{31}H_{27}ClN_2O_4S$	66.60	4.87	5.01		66.76	4.97	5.23	
25	p-ClC_6H_4	p-ClC_6H_4	96	213–215	$C_{30}H_{26}Cl_2N_2O_2S$	65.57	4.77	5.10		65.81	4.84	4.96	
26	p-ClC_6H_4	2-Pyridyl	86	245–249	$C_{29}H_{26}ClN_3O_2S$	67.49	5.08	8.14		67.31	5.11	7.94	
27	p-ClC_6H_4	m-$NO_2C_6H_4$	83	209–213	$C_{30}H_{26}ClN_3O_4S$	64.33	4.68	7.50	5.73	64.32	4.73	7.40	5.91
28	p-ClC_6H_4	m-$CH_3OC_6H_4$	84	195–196	$C_{31}H_{30}ClN_2O_3S$	68.15	5.47	5.12	5.85	68.16	5.32	4.92	5.90

TABLE III

SPIRO[INDOLINE-3,3′-PYRROLIDINES]



Compd. no.	R_1	R_2	Yield, %	M.p., °C.	Formula	Calcd., % C	H	N	Found, % C	H	N
29	C_6H_5	C_6H_5	41[a]	210–212	$C_{23}H_{22}N_2$	84.62	6.79	8.58	84.54	6.74	8.76
30	C_6H_5	p-ClC_6H_4	16[b]	192–194	$C_{23}H_{21}ClN_2$	76.55	5.87	7.76	77.02	5.96	7.78
31	C_6H_5	m-$CH_3OC_6H_4$	38[a]	175–176	$C_{24}H_{24}N_2O$	80.87	6.79	7.86	80.55	7.00	7.88
32	C_6H_5	2-Piperidyl	19[a]	160–162.5	$C_{22}H_{27}N_3$	79.24	8.16	12.60	79.54	8.51	12.77
33	C_6H_5	CH_2OH	35.5[b]	156–158	$C_{18}H_{20}N_2O$	77.11	7.19	9.99	77.24	7.30	9.70
34	p-ClC_6H_4	C_6H_5	19[b]	216–218	$C_{23}H_{21}ClN_2$	76.55	5.87	7.76	76.63	5.84	7.80
35	p-ClC_6H_4	3,4-$CH_2O_2C_6H_3$	7.4[b]	195–197	$C_{24}H_{21}ClN_2O_2$	71.19	5.23	6.92	71.43	5.45	7.04
36	p-ClC_6H_4	p-ClC_6H_4	32[b]	187.5–188.5	$C_{23}H_{20}Cl_2N_2$	69.88	5.10	7.09	69.68	5.10	7.00
37	p-ClC_6H_4	m-$CH_3OC_6H_4$	21.3[b]	195–197	$C_{24}H_{23}ClN_2O$	73.74	5.93	7.17	73.55	5.81	7.12

[a] Na–BuOH reduction. [b] $LiAlH_4$–THF.

or acute toxicity studies, mature, nonfasted mice were utilized, whereas young, fasted rats were used in the antiinflammatory test procedure.

Pleural fluid volume studies, designed to assess antiinflammatory activity, were carried out on compound **25**. However, no reduction of pleural fluid volume was observed at a dose of 100 mg./kg. orally.

The ether–chloralose anesthetized cat was used to measure the effect of drugs on mean arterial blood pressure. Intravenously, **6**, **12**, **18**, **23**, and **31** failed to produce a sustained lowering of mean arterial blood pressure after acute doses ranging from 0.5 to 10 mg./kg. (Table V). Compounds **6** and **18** exhibited weak adrenolytic activity by inhibiting the pressor responses to injected epinephrine. Compound **12** produced parasympatholytic (peripheral) activity by decreasing the fall in blood pressure caused by injecting furfuryltrimethylammonium iodide. Finally, **23** and **31** appeared to be devoid of cardiovascular activity and failed to alter blood pressure or the effects of the autonomic test agents, which were injected prior to and after the drug to be evaluated.

The compounds tested in these series showed little or no hypoglycemic action in the fasted guinea pig following doses of 50 or 100 mg./kg. orally. However, **11**, **20**, **28**, **29**, **30**, **31**, **32**, **36**, and **37** did produce weak or inconsistent hypoglycemic activity, but the degree of lowering of the blood glucose was not considered statistically significant and represented changes in only 20% of the animals tested. Several compounds (**31**, **34**, and **37**) produced tremors in the guinea pig after oral doses, which were correspondingly lower than those causing overt activity in the mouse.

Experimental[15]

2-*p*-Chlorophenylindole.—To a stirred mixture of phenylhydrazine (432.0 g., 4.0 moles) and *p*-chloroacetophenone (618.0 g., 4.0 moles), there was added over 5 min. anhydrous zinc chloride (1091 g., 8.0 moles). The temperature gradually rose to 110° whereupon a spontaneous, vigorous reaction occurred, which rapidly raised the temperature to 220–230°; copious evolution of gaseous products was observed. The reaction mixture was maintained at this temperature for 10 min. and then poured into 10 l. of 2 *N* HCl. The precipitated product was dispersed and the mixture was filtered; the filter cake was washed with water and dried *in vacuo*. Crystallization from benzene yielded an off-white solid, m.p. 202–205° (650.5 g., 71.5%). Recrystal-

(15) Melting points were taken in open glass capillaries using a Thomas–Hoover Uni-Melt apparatus and are corrected. Microanalyses were carried out by the Analytical and Physical Chemistry Section of Smith Kline and French Laboratories.

TABLE IV

SUMMARY OF MOUSE DOSE RANGE

Compd. no.	Dose,[a] mg./kg.	Observations
14	100	Stimulation, hypersensitivity to sound and touch in 50% of animals
19	200[b]	Slight to moderate CNS depression, increased pain threshold, hypothermia, bradypnea, and low posture
29	500	No overt effects
	1000	Hypothermia, increased pain threshold
	2000	As above plus miosis
	10, 25, or 50[b]	Diarrhea in 50% of animals at each dose
	100[b]	Diarrhea, increased pain threshold in 50% of animals
	200[b]	Diarrhea, miosis (50%), hypothermia, moderate depression (50%), slight ptosis (50%), delayed death (50%)
	25[c]	Slight depression
	50[c]	Intention tremors, slight to moderate depression, increased pain threshold (50%), hypothermia (50%), lacrimation
	100[c] or 200[c]	Intention tremors, clonic convulsions, prostration, asphyxial convulsions, vocalization, dyspnea, acute death
30	300	No overt effects
	100[b]	No overt effects
	200[b]	Hypothermia, in tension tremors, slight mydriasis, low posture, marked decreased in spontaneous motor activity, lacrimation (seen in 1/3 of animals)
31	200	No overt effects
	300	Bradypnea, slight decreased activity, salivation, moderate ptosis, intention tremors, hypothermia (seen in 50% of animals)
	200[d] or 300[d]	No overt effects
	50[e]	Low posture, hypothermia, diarrhea, moderate decreased activity
	100[c] or 200[c]	Toxicity (tremors, convulsions)
32	100	No overt effects
	200 or 300	Increased pain threshold (50%)
33	50	Slight stimulation
	100	Slight to moderate decreased motor activity, low body posture, excessive defecation and urination
	200 or 300	Toxicity (tremors, convulsions)

[a] All doses orally in tragacanth suspension except where otherwise noted. [b] Intraperitoneally in tragacanth suspension. [c] Intraperitoneally in acidic suspension, pH 5.0. [d] Orally in acidic suspension, pH 4.0. [e] Intraperitoneally in 1% PEG 400.

lization from benzene produced material, m.p. 203–206° (lit.[16] 205–206°), of sufficient purity for further experimentation.

2-*p*-Chlorophenylindole-3-aldehyde.—Phosphorus oxychloride (470.0 g., 3.1 moles) was added slowly with stirring and cooling to dimethylformamide (1970 g., 25 moles); the temperature was maintained at 10–15°. To the resultant solution there was added in portions, again with cooling and stirring, 2-*p*-chlorophenylindole (636 g., 2.8 moles); the temperature was kept below 60°. The solution was stirred for an additional 45 min. and diluted with water (5.6 l.). Sodium hydroxide (10%, 5.6 l.) was added and the mixture was heated vigorously on the steam bath for 1 hr. The cooled mixture was filtered with suction and dried *in vacuo*

(16) A. F. Crowther, F. G. Mann, and D. Purdie, *J. Chem. Soc.*, 58 (1943).

TABLE V

SUMMARY OF CARDIOVASCULAR ACTIVITY IN ANESTHETIZED CATS

Compd. no.	Minimal hypotensive dose, mg./kg.,[a] i.v.	Responses to standard test agents post drug
6	2.5	EPI[a] and N-EPI,[b] inhibited DMPP,[c] dampened
12	5.0	FTM,[d] inhibited
18	5.0	EPI and N-EPI, dampened
23	...	No changes
31	0.5	No changes

[a] Epinephrine. [b] Nor-epinephrine. [c] Dimethylphenylpiperidinium iodide. [d] Furfuryltrimethylammonium iodide.

at 70°; a crude product (700 g., 98%), pure enough for subsequent reactions, was obtained. Recrystallization from acetone yielded an analytical sample as white platelets, m.p. 263–265°.

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94. Found: C, 70.68; H, 4.15.

β-(2-*p*-Chlorophenylindolideniumethyl) Nitronate.—A mixture of 2-*p*-chlorophenylindole-3-aldehyde (700 g., 2.74 moles), ammonium acetate (700 g., 9.0 moles), and nitromethane (14 l.) were boiled at reflux for 3 hr. The cooled mixture was filtered with suction; the solid was washed with fresh, cold nitromethane and dried *in vacuo*. The crude product was slurried with water (10 l.), filtered, and again dried *in vacuo* to yield a red solid (692 g., 85%) of adequate purity for further reactions. An analytical sample, m.p. 255–256° dec., was obtained by recrystallization from acetone–water.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.64; H, 4.32; N, 9.41.

2-*p*-Chlorophenyltryptamine.—A slurry of β-(2-*p*-chlorophenylindolideniumethyl) nitronate (300 g., 1.0 mole) was added to a stirred slurry of lithium aluminum hydride (304 g., 8.0 moles) in ether (2 l.), under nitrogen, at a rate which maintained a constant reflux. When addition was complete, the mixture was boiled at reflux for 1 hr. and kept at 25° for 1 hr. The mixture was cooled; water (375 ml.) was added dropwise followed by sodium hydroxide (10%, 750 ml.) and again water (250 ml.). Inorganic salts were removed by filtration and washed with ether. The combined ethereal extract was treated with 1.5 l. of 10% HCl, and the resultant precipitate was filtered with suction to yield a crystalline solid (270 g., 88%), m.p. 189–191°. The product was characterized as the corresponding free base which was isolated in the usual manner. An analytical sample, m.p. 104–106°, was obtained by recrystallization from chloroform–petroleum ether.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.59; N, 10.35. Found: C, 70.82; H, 5.44; N, 10.38.

2-Phenyltryptamine.—2-Phenylindole[17] was converted to 2-phenylindole-3-aldehyde as previously described. The crude product was not further purified, but condensed directly with nitromethane as described above to yield the corresponding nitronate salt, m.p. 215.5–217°.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.59; H, 4.63; N, 10.53.

Reduction with lithium aluminum hydride essentially as above yielded 2-phenyltryptamine (83%), m.p. 69–72°. The compound was characterized as the hydrochloride, m.p. 262–264° (from methanol–ethyl acetate).

Anal. Calcd. for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.32; H, 6.49; N, 10.35.

Compound IX (R = R_1 = C_6H_5).—A mixture of 2-phenyltryptamine (10.0 g., 0.042 mole), benzaldehyde (4.9 g., 0.046 mole), benzene (250 ml.), and Amberlite IR 120 (H) sulfonic acid ion-exchange resin (0.20 g.) were boiled at reflux with constant separation of water for 2 hr. The hot mixture was filtered and the solvent removed *in vacuo*. A viscous oil was obtained which was washed with three 50-ml. portions of petroleum ether, after which residual traces of organic solvent were removed *in vacuo*. The viscous residue was dissolved in dry pyridine (100 ml.) and the solution cooled to 0°. *p*-Toluenesulfonyl chloride (10 g., 0.052 mole) was added; the mixture was shaken until solution was effected and left in an ice bath to warm to room temperature over 18 hr. Water (125 ml.) was added dropwise to the stirred

(17) R. L. Shriner, W. C. Ashley, and E. Welsh, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 725.

solution. The crystalline product, which separated, was filtered with suction, washed well with water and cold ether and dried *in vacuo* (12.4 g., 62%). Recrystallization from methanol yielded an analytical sample, m.p. 170–172°.

Compound X (R = R_1 = C_6H_5).—Sodium borohydride (5.0 g., 0.135 mole) was added to a warm mixture of IX (R = R_1 = C_6H_5, 5.07 g., 0.0105 mole) in methanol (125 ml.). The mixture soon became homogeneous and a white crystalline solid separated. After 10 min., water (500 ml.) was added and the product was filtered with suction and dried *in vacuo* (4.11 g., 81%). An analytical sample, m.p. 210–212.5°, was obtained by recrystallization from a methanol–ethanol mixture.

Compound XI (R = R_1 = C_6H_5).—To a warm, stirred solution of IX (R = R_1 = C_6H_5, 5.0 g., 0.0105 mole) in 1-butanol (150 ml.), sodium (15.5 g., 0.67 g.-atom) was added in portions. The mixture was boiled at reflux for 2 hr. Hydrochloric acid (18%, 200 ml.) was added and the mixture was distilled until the distillate was clear and homogeneous. The residue was treated with additional HCl (10%, 200 ml.) and the acidic solution was extracted with three 70-ml. portions of ether. The aqueous layer was made alkaline with ammonia and the resultant white precipitate was filtered, washed with water, and dried *in vacuo* (2.2 g., 65%). Recrystallization from methanol yielded an analytical sample, m.p. 210–212°.

Compound XI (R = C_6H_5; R_1 = CH_2OH).—A mixture of IX (R = C_6H_5, R_1 = $CO_2C_2H_5$; 18.5 g., 0.039 mole), lithium aluminum hydride (25 g., 0.66 mole), and tetrahydrofuran (400 ml.) was stirred and boiled at reflux under a nitrogen atmosphere for 4 days. Ether (1 l.) was added and the stirred mixture was hydrolyzed by dropwise addition of water (200 ml.). Inorganic salts were separated by filtration with Celite. The filter cake was washed with ether, and HCl (18%, 800 ml.) was added to the combined organic layers. The aqueous layer was separated, washed with four 250-ml. portions of ether and made alkaline with concentrated ammonia. The mixture was extracted with chloroform and the organic extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a viscous oil, which crystallized upon trituration with methylene chloride–ether. Recrystallization from the same solvent pair yielded an analytical sample, m.p. 156–158°.

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Steroidal Carbamic Acid γ-Lactones

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The reaction of steroidal 17α-ethynylcarbinols with alkyl isocyanates was used to prepare the 17-carbamoylcarbamate, carbamate, and carbamic acid γ-lactones in the aromatic A-ring, androstenone, and 19-norandrostenone series. The biological testing of these resultant compounds was performed and an interesting gradation in activity in the progestational area was observed.

Substitution of various functional groups at the 17-position of the steroid nucleus produces interesting and useful alterations in the pharmacological activity of the resultant compounds. While the well-documented 17α-alkyl substitution in the 4-androstene molecule increases the androgenic–anabolic activity, the 17α-ethynyl-17β-hydroxy substitution results in progestational activity.[1] The corresponding 17α-ethynyl-17β-hydroxy-19-nor steroids are especially important and useful progestational and anovulatory agents. The spirolactone grouping,[2] on the other hand, transforms these same androstene steroids into clinically useful antimineralocorticoid agents.

Utilizing the results of Easton, *et al.*,[3] of this laboratory, the reaction of various steroidal 17α-ethynyl-17β-carbinols with alkyl isocyanates was examined with the goal of introducing a C-17 spirocarbamic acid γ-lactone group. The reaction of 17α-ethynylestradiol-3-methyl and -ethyl isocyanate gave two products. The more polar product, obtained in the greater amount, was found to be the carbamate (IIA) as evidenced by the analysis and the infrared and n.m.r. spectra. The infrared spectrum showed two peaks at 2.9 and 3.04 μ which corresponded to -NH and acetylenic hydrogen, respectively. The carbonyl region revealed a broad band centered at 5.83 μ. The n.m.r. spectrum[4] supported the structure IIA by demonstrating the presence of a single N-ethyl grouping.

The minor, less polar product assigned structure IA apparently resulted from the reaction of the ethynyl carbinol with 2 molecules of isocyanate. The infrared spectrum indicated no free –NH but a band for weakly hydrogen-bonded –NH at 2.98 and also showed an acetylenic hydrogen at 3.04 μ. The carbonyl region contained an intense band at 5.84 μ for the –OCON– and medium intensity bands at 5.98 and 6.53 μ for –NCONH–. The n.m.r. spectra supported structure IA showing two methyl triplets nearly coincident at δ 1.17 (J = 7.0 c.p.s.) a ≡CH singlet at δ 2.68, an 8-component multiplet at δ 3.30 for NH-CH_2CH_3 in which coupling with NH is 9.0 c.p.s. and with methyl 7.0 c.p.s., a quartet at δ 3.78 for $-CH_2-N(CO)_2$, and a broad signal for hydrogen bonded NH at δ 8.5. These spectra and the analysis favor the assigned structure, IA.

As in the previous work,[3,5a,5b] treatment of the carbamate (IIA) with sodium methoxide yielded a new compound, IIIA, whose infrared spectrum had strong absorption at 5.65 μ in support of the carbamic acid γ-lactone structure. In the n.m.r. the exocyclic methylene gave an AB pattern centered at δ 4.18 for

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(2) J. A. Cella and C. M. Kagawa, *ibid.*, **79**, 4808 (1957).

(3) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962).

(4) The n.m.r. spectra were determined using a HR60 Varian instrument with $CDCl_3$ as solvent and TMS as an internal standard. The δ-values are reported as p.p.m.

(5) (a) R. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962); (b) P. J. Stoffel and A. J. Speziale, *ibid.*, **28**, 2814 (1963).