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A SYNTHESIS OF SOME SPIRO [INDOLINE-3,3′-PYRROLIDINES]

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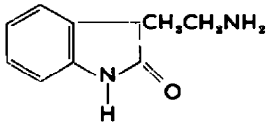
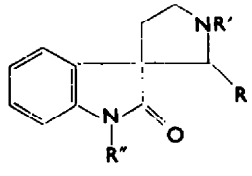
Abstract—A number of 2′-substituted spiro[oxindole-3,3′- pyrrolidines] (II) have been prepared from 2-oxindol-3-ylethylamine and an aldehyde. Reduction of their 1′-acetyl derivatives by LAH gave the corresponding 1′-ethylindolines (III). A more complex reaction occurs with the 1′-tosyl derivatives.

THE paucity of pharmacological data[1] for simple derivatives of the spiro[indoline-3,3′-pyrrolidine] system, e.g. (III), which occurs in strychnine and related alkaloids, prompted us to synthesize members of this class.

Our preferred route consisted of a Pictet-Spengler type condensation of 2-[oxindol-3-yl]ethylamine (I) with an aldehyde to give a spiro[oxindole-3,3′-pyrrolidine], e.g. II, which was then reduced, as a 1′-acyl-derivative, with LAH.



I



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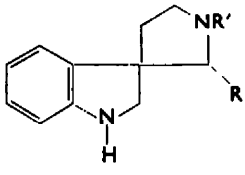

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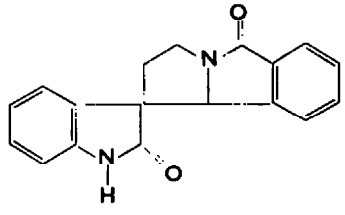

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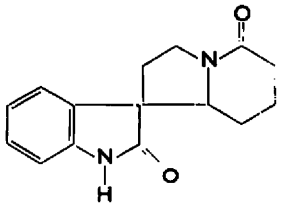

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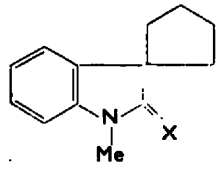

VI

[1] But see now J. A. Weisbach, E. Macko, N. J. De Sanctis, M. P. Cava and B. Douglas, *J. Med. Chem.* 7, 735 (1964).

Table 1. Preparation and properties of oxindoles and indolines

	Compound	Preparation Method	Yield%	M.p.°	Formula	Found/Required% C	H	N	λ max(log ε) mμ
	Oxindoles								
II; R	R′	R″							
H	H	CH_2OH B	77	243–244[a]	$C_{12}H_{14}N_2O_2$	66·0	6·9	12·6	
						66·0	6·9	12·8	
H	Bz	CH_2OBz		337–339(dec.)[b]	$C_{26}H_{22}N_2O_4$	72·6	5·0	6·5	
						73·2	5·2	6·6	
H	Ac	CH_2OAc		313–314(dec.)[b]	$C_{16}H_{18}N_2O_4$	59·4	6·0		
						59·7	6·1		
Et	H	H B		Oil					
Et	p-$MeC_6H_4SO_2$	H		220–220·5[c]	$C_{20}H_{22}N_2O_3S$	65·5	5·9	7·7	233(4·13),
						64·8	6·0	7·6	282(3·20)
						(S, 9·0/8·65)			
Pr^i	H	H A	44	168·5–170[d]	$C_{14}H_{18}N_2O$	72·8	8·05	12·1	
						73·0	7·9	12·2	
Pr^i	$CO{\cdot}CMe_3$	H		198–199·5[e]	$C_{19}H_{26}N_2O_2$	72·6	8·3	8·9	
						72·1	7·95	8·7	
Ph	H	H A		Gum					
Ph	Ac	H		215–217[e]	$C_{19}H_{18}N_2O_2$	73·9	6·1	9·45	
						74·5	5·9	9·2	
3,4-$[OMe]_2$:C_6H_3	H	H A,B		Gum					
3,4-$[OMe]_2$:C_6H_3	Ac	H		236·5–237[e]	$C_{21}H_{22}N_2O_4$	68·3	6·1	7·6	231(4·12),279(3·64),
						68·8	6·05	7·65	283(3·62)
3,4-$[OMe]_2$:C_6H_3	p-$MeC_6H_4SO_2$	H		200–200·5[e]	$C_{26}H_{26}N_2O_6S$	66·2	5·65	5·9	230(4·04),279(3·64),
						66·2	5·9	5·7	
3-OH-4-OMe·C_6H_3	H	H A		Gum					
3-OH-4-OMe·C_6H_3	Ac	H		271·5–272·5[d]	$C_{20}H_{24}N_2O_4$	68·8	5·9	7·8	
						68·2	5·7	7·95	
4-NO_2·C_6H_4	H	H B		Gum					
4-NO_2·C_6H_4	p-$MeC_6H_4SO_2$	H		231–232·5(dec.)[f]	$C_{24}H_{21}N_3O_5S$	62·8	4·9	8·9	229(4·27),262(4·16),
						62·2	4·6	9·1	272(4·11)§
						(S, 6·6/6·9%)			

$PhCH_2$	H	H	B		Gum					
$PhCH_2$	Ac	H			277–278	$C_{20}H_{20}N_2O_2$	75·0	6·3	8·9	
							75·0	6·3	8·7	
$C_6H_4NH{\cdot}CH{:}C$	H	H	B	36	126–127·5†[e]	$C_{19}H_{17}N_3O$	75·55	5·5	13·5	253(3·84),280(3·74),
							75·2	5·65	13·85	282(3·70)
IV			B*	52	275–277(dec.)[c]	$C_{18}H_{14}N_2O_2$	74·4	5·1	9·7	
							74·5	4·9	9·65	
V			B	53	281–282[g]	$C_{15}H_{16}N_2O_2$	70·4	6·3	10·7	251(3·90),281(3·18)
							70·3	6·3	10·9	
	Indolines									
III; R	R′				b.p.°/mm.					
Et	Et			44	95–100‡/5 × 10 [4]	$C_{18}H_{22}N_2$	78·0	9·75	11·7	
							78·2	9·6	12·2	
Pr	Et			56	120–130‡/5 × 10^{-4}	$C_{16}H_{24}N_2$	78·4	9·9	11·5	242(3·80),290(3·43)
							78·6	9·9	11·5	
Ph	Et			66	135–140/0·01	$C_{19}H_{22}N_2$	81·8	7·8	10·3	242(3·81),290(3·38)
							82·0	8·0	10·1	
3,4-$[OMe]_2C_6H_3$	Et				135–140‡/5 × 10^{-4}	$C_{21}H_{26}N_2O_2$	74·75	8·1	9·5	
							74·5	7·7	8·3	
VI, X = H_2				59	74–76‡/0·1	$C_{18}H_{17}N$	83·6	9·0	7·6	249(3·89),295(3·42)
							83·4	9·15	7·5	

* Sodium acetate (2 moles) used in place of sodium hydroxide. † After drying in a high vacuum.
‡ Bath temperature. § inflexion.
Solvent for crystallization: [a] aqueous pyridine, [b] aqueous acetic acid, [c] MeOH, [d] ethyl acetate, [e] aqueous MeOH, [f] EtOH, [g] $CHCl_3$–ether.

An oxindole of the type required (II; R = Ph, R′ = R″ = H) was first prepared by Harley-Mason.[2] Since then, and concurrently with this work, further examples have been reported[3–5] mainly in connection with work on the Mitragyna alkaloids. Following the original method we obtained the expected products (II; R′ = R″ = H, R = Ph, Et, Pr, Pr^i, *p*-$NO_2{\cdot}C_6H_4$, 3-OH-4-MeO·C_6H_3, 3,4-$[MeO]_2C_6H_3$ and $C_6H_4{\cdot}NH{\cdot}CH{:}C$) from the condensation of 2-[oxindol-3-yl]ethylamine with benzaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, *p*-nitrobenzaldehyde, isovanillin, veratraldehyde and 3-formylindole. Only the spiro-oxindoles from isobutyraldehyde and 3-formylindole crystallized; the remainder were oils which could be distilled only with heavy loss of material and were best characterized as 1′-acetyl or 1′-tosyl derivatives.

The compound obtained from formaldehyde was identified as II (R″ = CH_2OH, R = R′ = H) rather than II (R′ = CH_2OH, R = R″ = H) for its acetyl and benzoyl derivatives had absorption bands characteristic of a tertiary amide.

Condensation of 2-[oxindol-3-yl]ethylamine with an aldehyde possessing an acidic or ester function in an appropriate position resulted in spontaneous lactam formation; thus phthalaldehydic acid and methyl glutaraldehydate gave the spirans IV and V respectively.

Several investigators[6–9] have reported the conversion of oxindoles to indolines with LAH but others[6–10] have experienced difficulties. Notably Witkop[10] records that the carbinolamine (VI; X = H, OH) was the only product from the reduction of 1-methylspiro[oxindole-3-cyclopentane] (VI; X = :O) even when an excess of the hydride was employed. Application of our conditions to this oxindole gave the indoline VI (X = H_2) as the only isolable product. Our spiro–oxindoles, however, which had a basic NH-group, formed highly insoluble and hence unreactive aluminium complexes in otherwise suitable reaction media. Hendrickson and Silva[5] overcame this problem by employing the 1′-tosyl derivative of the base II (R = $CH_2{\cdot}C_6H_4$-3,4-$[OMe]_2$, R′ = R″ = H) for the reduction with LAH, but this device did not prove advantageous with our compounds. In general we obtained intractable mixtures; only from the reduction of the sulphonamide II (R = C_6H_3-3,4-$[OMe]_2$, R′ = $SO_2{\cdot}C_6H_4{\cdot}Me$, R″ = H) was a pure product isolated albeit in small yield. This had the composition of the expected indoline III (R = C_6H_3-3,4-$[OMe]_2$, R′ = $SO_2{\cdot}C_6H_4Me$) but its lack of basicity was inconsistent with this structure.

Better success attended the hydride reductions if the pyrrolidine NH-group was acetylated. Thus the 1′-acetyl oxindoles II (R″ = H, R′ = CO·Me, R = Et, Pr, Ph and C_6H_3-3,4-$[OMe]_2$) were smoothly converted to the corresponding 1′-ethylindolines III (R″ = H, R′ = Et, R = Et etc.) which were obtained as distillable liquids. Only traces of non-basic materials were isolated from these reactions.

[2] J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.* 3639 (1958).
[3] Y. Ban and T. Oishi, *Chem. & Ind.* 348 (1960).
[4] Y. Ban and T. Oishi, *Tetrahedron Letters* No. 22, 791 (1961).
[5] J. B. Hendrickson and R. A. Silva, *J. Amer. Chem. Soc.* **84**, 643 (1962).
[6] P. L. Julian and H. C. Printy, *J. Amer. Chem. Soc.* **71**, 3206 (1949).
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[8] B. Belleau, *Chem. & Ind.* 228 (1955).
[9] P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.* **71**, 3207 (1949).
[10] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.* **75**, 2572 (1953).

EXPERIMENTAL

UV determinations were made in EtOH

Spiro(oxindole-3,3′-pyrrolidines)

Method A. A mixture of equimolar amounts of the aldehyde and 2-[oxindol-3-yl] ethylammonium chloride, and a twice molar quantity of $CH_3 \cdot CO_2Na \cdot 3H_2O$ in sufficient 1:1 aqueous EtOH to dissolve the reactants at room temp was heated under reflux for 48 hr in N_2. After removal of the EtOH *in vacuo* the solution was acidified and washed with $CHCl_3$. The aqueous phase was then made alkaline with $NaHCO_3$ and the oxindole isolated with $CHCl_3$.

Method B. An equimolar mixture of the aldehyde and oxindolylethylammonium chloride in sufficient 1:2 aqueous EtOH to dissolve the reactants was brought to pH 8·5 with 10% NaOH and allowed to stand at room temp for a week. After removal of the EtOH *in vacuo* the oxindole was isolated as in Method A.

Acetyl derivatives were prepared with acetic anhydride, either neat at reflux temp for 15 min or in pyridine at room temp for 1 hr. Tosyl derivatives were obtained similarly in pyridine with tosyl chloride.

Details of the individual compounds prepared under this heading and the last one are given in the Table 1.

LAH reduction of 2′-[3,4-dimethoxyphenyl]-1′-tosylspiro[oxindole-3,3′-pyrrolidine]

2′-[3,4-Dimethoxyphenyl]-1′-tosylspiro[oxindole-3,3′-pyrrolidine] (3·21 g, 0·0067 mole) in dry tetrahydrofuran (70 cc) was heated under reflux with LAH (3·0 g) for 24 hr. The cooled reaction mixture was poured into ice-cold 5 N H_2SO_4 (200 cc) and extracted with $CHCl_3$ to give a gum (1·87 g) from which prisms (350 mg), m.p. 185–190°, were obtained on crystallization from MeOH. The analytical sample, obtained after two recrystallizations from aqueous pyridine, had m.p. 215–216°, (Found: C, 67·3; H, 6·0; N, 6·0; S, 6·9. $C_{26}H_{28}N_2O_4S$ requires: C, 67·2; H, 6·1; N, 6·0; S, 6·8%). λ_{max} 287 and 282·5 mμ (log ε 3·76 and 3·75 respectively).

Spiro(indoline-3,3′-pyrrolidines)

The 1′-acetylspiro-[oxindole-3,3′-pyrrolidine] in a 30 fold amount of dry tetrahydrofuran was heated under reflux for 24 hr with an equal weight of LAH. After cooling, the reaction mixture was poured into ice cold 5 N H_2SO_4 and the acid solution extracted with $CHCl_3$. The aqueous solution was made alkaline with solid $NaHCO_3$ and then filtered through a kieselguhr pad. Both the filter pad and the filtrate were repeatedly extracted with $CHCl_3$. Evaporation of the combined extracts left the product as an oil which was purified by distillation.

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