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Studies on the Syntheses of Heterocyclic Compounds. 459.[1] Synthesis of Rescinnamine-Like Compounds as Antihypertensive Agents

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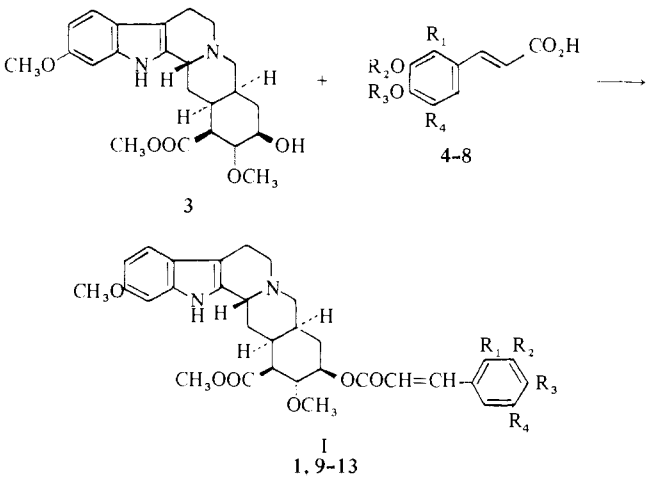
Although rescinnamine (1) and reserpine (2) have essentially equal pharmacological activity the side effects of rescinnamine are weaker than those of reserpine. In hope of finding more pronounced biological activity we have synthesized some new derivatives which have a cinnamoyl substituent[2] at the 18 position of methyl reserpate (3).

Methyl reserpate (3)[3] was esterified with acid chlorides derived from 3,4-dimethoxycinnamic acid (4),[4] 4-ethoxy-3-methoxycinnamic acid (5),[5] 3,4,5-trimethoxy-2-nitrocinnamic acid (6),[6] 3-ethoxycarbonyl-4-methoxycinnamic acid (7),[7] and 4-ethoxycarbonyl-3-methoxycinnamic acid (8)[8] in pyridine-PhH to give rescinnamine-like derivatives 9, 10, 11, 12, and 13, respectively. Treatment of 12 and

Scheme I



13 with 1 equiv of NaOH in a soln of MeOH and THF at room temp gave the phenolic bases 14 and 15.

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Table I. Synthesis (Scheme I) and Antihypertensive Activity of Rescinnamine-Like Compounds

Starting materials							Products								Antihypertensive activity	
Compd	Amt, g	Compd	Amt, g	R_1	R_2	R_3	R_4	Compd	R_1	R_2	R_3	R_4	Yield, %	Mp, °C	Solv used for recrystn	Formula[a]	ED_{20}, mg/kg	Relative activity calcd by ED_{20} (Reserpine = 1.00)
3	1	4[b]	2	H	CH_3	CH_3	H	9	H	OCH_3	OCH_3	H	55 (0.81 g)	180–181	MeOH–$CHCl_3$	$C_{34}H_{40}N_2O_8$	1.0	1.40
3	0.5	5[c]	1.5	H	CH_3	C_2H_5	H	10	H	OCH_3	OC_2H_5	H	75 (0.56 g)	140–141	$CHCl_3$–hexane	$C_{35}H_{42}N_2O_8$	1.6	0.86
3	1.2	6[d]	2	NO_2	CH_3	CH_3	OCH_3	11	NO_2	OCH_3	OCH_3	OCH_3	87 (1.52 g)	Picrate 147–150	MeOH	$C_{41}H_{44}N_6O_{18}$	1.0	1.40
3	1.3	7[e]	2	H	$CO_2C_2H_5$	CH_3	H	12	H	$OCOC_2H_5$	OCH_3	H	75 (1.6 g)	Styphnate 200–201	MeOH	$C_{42}H_{45}N_5O_{18}$	2.5	0.56
3	1.5	8[f]	3	H	CH_3	$CO_2C_2H_5$	H	13	H	OCH_3	$OCOC_2H_5$	H	74 (1.8 g)	Picrate 160–161	MeOH	$C_{42}H_{45}N_5O_{17}$	1.5	0.94
								1 Reserpine (2)	H	OCH_3	OCH_3	OCH_3		238–239 dec			1.4	1.00
														264–265 dec			0.2	7.00

[a] All compds were analyzed for C, H, N. Ir and nmr spectra were as expected. [b] See ref 4. [c] See ref 5. [d] See ref 6. [e] See ref 7. [f] See ref 8.

Table II. Hydrolysis of Ethoxycarbonyl Derivatives

Starting material	I Compd	R_1	R_2	R_3	R_4	Yield, %	Mp, °C	Solv used for recrystn	Formula[a]	ED_{20}, mg/kg	Relative activity calcd by ED_{20} (Reserpine = 1.00)
12 (800 mg)	14	H	OH	OCH_3	H	63 (450 mg)	162–164	$CHCl_3$–hexane	$C_{33}H_{38}N_2O_8 \cdot H_2O$	2.1	0.67
13 (1.5 g)	15	H	OCH_3	OH	H	78 (1.0 g)	259–260	MeOH	$C_{33}H_{38}N_2O_8 \cdot H_2O$	0.8	1.75

[a] See Table I, footnote *a*.

Pharmacology. In general, rescinnamine-like compounds differ from reserpine in hypotensive effect because of its dose dependence and they seem to have a lower adverse effect than that of reserpine. Therefore, the antihypertensive activity of rescinnamine-like compounds was examined by comparison with rescinnamine and reserpine by the canulation method in the unanesthetized, spontaneously hypertensive rat.[9] After iv injection of compounds to groups of 3 rats, the ratio of hypotensive effect for 5 hr was calcd by ED_{20}. The ED_{20} value was calcd by the dose-response regression line. The effect of rescinnamine-like compounds in decreasing the systemic blood pressure depended upon the dose used, and **9** and **15** were the most effective among the 7 compounds shown in Table I.

Experimental Section†

Methyl Reserpate (3). After addn of 0.27 ml of H_2O and 150 ml of THF to a soln of 0.34 g of Na in 300 ml of MeOH, 5 g of reserpine–HCl was added to the resulting soln which was stirred for 24 hr at room temp. The reaction mixt was evapd to give a residue, a soln of which in $CHCl_3$ was washed (satd $NaHCO_3$ and H_2O) and dried (Na_2SO_4). Evapn of the solvent gave a yellowish powder, which was recrystd from MeOH to give 2.87 g (93%) of **3** as colorless needles, mp 233–239°; lit.[2] mp 235–240°.

Esterification of Methyl Reserpate (3). A mixt of 2 g of 3,4-dimethoxycinnamic acid (**4**),[4] 2 ml of $SOCl_2$, and 20 ml of PhH was refluxed for 3 hr. The excess of $SOCl_2$ and PhH was distd off to give the acid chloride as a solid, which was dissolved in PhH. The resulting soln was added to a mixt of 1 g of methyl reserpate and 30 ml of pyridine. The mixt was allowed to stand with occasional shaking at room temp for 24 hr, acidified with dil HCl, and extd ($CHCl_3$). After washing with satd $NaHCO_3$ and H_2O, the $CHCl_3$ layer was distd off to give a brown gum, which was triturated with Et_2O and then recrystd from MeOH–$CHCl_3$ to afford 0.81 g (55%) of **9** as colorless needles, mp 180–181°.

Preparation of the Phenolic Bases. To a mixt of 20 mg of Na, 25 ml of MeOH, and 1 drop of H_2O, a soln of 800 mg of the 3'-ethoxycarbonyl-4'-methoxycinnamate (**12**) in 25 ml of THF was added. After stirring at room temp for 2 hr, followed by addn of 1 drop of AcOH, the reaction mixt was evapd to give a residue, a soln of which in $CHCl_3$ was washed (satd $NaHCO_3$ and H_2O) and dried (Na_2SO_4). Evapn of the solvent gave a brown gum, which was recrystd from $CHCl_3$–hexane to give 450 mg (63%) of **14** as a yellowish powder, mp 162–164°.

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†Melting points were taken with a Yanagimoto Micro apparatus (MP-S_2) and are not corrected. Ir spectra were taken with a type EPI-3 Hitachi recording spectrometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer. Nmr spectra were measured with a Hitachi R-20 instrument in $CDCl_3$ soln (Me_4Si).

Analgetics Based on the Pyrrolidine Ring. 7

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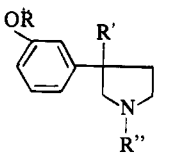
In a previous paper of this series[1] it was shown that whereas profadol (I, R = H; R′ = Pr; R″ = Me) exhibited a high level of analgetic activity, replacement of the *N*-methyl group with *N*-*n*-propyl afforded an analog that was inactive in the rat tail pressure test. There was a similar fall off in



I

analgetic activity in the *O*-methyl analogs on increasing the chain length of R″ from methyl, through ethyl, to *n*-propyl (*i.e.*, I, R = Me; R′ = Pr; R″ = Me, Et, or Pr).

Thus it was surprising to find that on further increasing the chain length of the *N*-alkyl group, analgetic properties were again in evidence and that the *N*-*n*-pentyl analog (I, R = H; R′ = Pr; R″ = $(CH_2)_4Me$) of profadol showed analgetic properties superior to those of codeine in rats. This paper describes the chemistry and pharmacology of compounds that have been prepared to explore this further aspect of the pyrrolidine analgetics.

Chemistry. The *m*-(1-alkyl-3-alkyl-3-pyrrolidinyl)phenols tested as potential analgetics were prepared by standard procedures, the methods used being indicated in the Experimental Section.

An interesting aspect of the physical chemistry of the pyrrolidines was seen in the course of preparing the optical enantiomers of *m*-(3-isobutyl-3-pyrrolidinyl)phenol. When measured in ethanol, the values of $[\alpha]D$ for these optical enantiomers were very close to zero, and it was necessary to