Potential Anticonvulsants. X. (Reissert Compounds Studies. LI.) 1-Methyl-4-(1-isoquinolinyl)piperidin-4-ol and Related Compounds

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The anion of isoquinoline Reissert Compounds has been condensed with 4-piperidones and pyridinecarboxaldehydes to give esters which are easily hydrolyzed to alcohols. The anticonvulsants activity of these alcohols is reported and several are active in the maximal electroshock seizure test.

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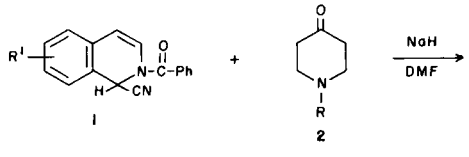
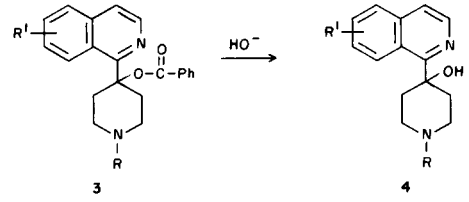
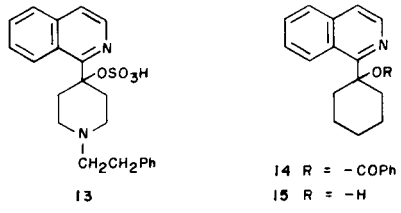
Some time ago, in connection with another study, we reported on the condensation of the anion of the isoquinoline Reissert compounds **1** [1] with 4-piperidones **2** to give **3** which could be hydrolyzed by base to **4** [2]. Routine screening of these previously reported compounds [2] indicated that **4** (R = CH_3, R′ = H; R = CH_3, R′ = 6,7-$(CH_3O)_2$; and R = C_6H_5-CH_2-CH_2, R′ = H) exhibited anticonvulsant activity in the maximal electroshock seizure test (MES) [3].



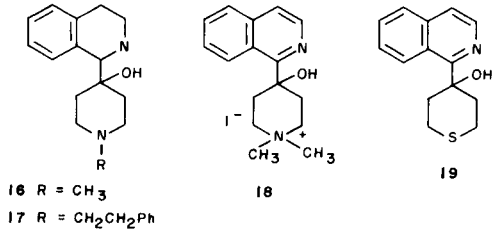




This report describes the results of anticonvulsant screening of the previously reported compounds [2] and the synthesis and screening results on additional analogs.

Reissert compounds were prepared using standard procedures [1]. The anion of the Reissert compounds was generated at room temperature using sodium hydride in dimethylformamide and condensed with various *N*-substituted piperidones. The esters **3** obtained by this procedure are listed in Table 1. None of these esters **3** and none of the esters **3** previously reported [2] exhibited any anticonvulsant activity in either the MES or the pentylenetetrazol seizure threshold test (Met). No product could be conveniently isolated from the reactions of the anions of the Reissert compounds of 5-amino- and 4-nitroisoquinoline with the piperidones. The use of the anions of 3-methylisoquinoline, quinoline, lepidine and phenanthridine Reissert compounds with the piperidones led only to the isolation of the rearrangement products: 1-benzoyl-3-methylisoquinoline, 2-benzoylquinoline, 2-benzoyl-4-methylquinoline, and 6-benzoylphenanthridine respectively. Rearrangement products were also obtained when lepidine and 3-methylisoquinoline Reissert compounds were reacted with the piperidones in the presence of 50% sodium hydroxide and a phase transfer catalyst [4]. Although aldehydes react readily with the Reissert anion, it is well known that in many cases ketones do not successfully undergo this condensation [1].

The esters **3** were hydrolyzed with aqueous-ethanolic potassium hydroxide to the alcohols **4**. The new alcohols obtained are listed in Table 2. The anticonvulsant activity of these alcohols as well as those previously prepared [2], is included in Table 3. It is apparent that a free hydroxyl



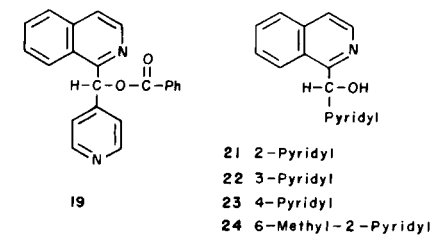
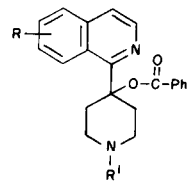


Table 1

Condensation to Form Esters

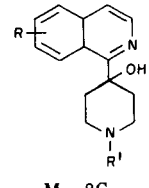


R	R'	Purification Solvent	Mp, °C	Yield (%)	Formula [a]	Analysis % Calcd./Found C	H
H	$COCH_3$	$CHCl_3$-heptane [b]	188-189	80	$C_{23}H_{22}N_2O_3$	73.77	5.92 [c]
						73.87	6.05
H	COC_6H_5	C_6H_6-heptane [b]	128-129	85	$C_{28}H_{24}N_2O_3$	77.04	5.54
						77.20	5.60
H	$CO_2C_2H_5$	C_6H_6-heptane	123-124	75	$C_{24}H_{24}N_2O_4$	71.26	5.98
						71.08	6.03
7-OCH_3	$COCH_3$	95% EtOH	174-175	72	$C_{24}H_{24}N_2O_4$	71.25	5.98
						71.35	5.95
7-OCH_3	COC_6H_5	95% EtOH	161-162	70	$C_{29}H_{26}N_2O_4$	74.65	5.61
						74.33	5.69
7-OCH_3	$CO_2C_2H_5$	*i*-PrOH	166-167	81	$C_{25}H_{26}N_2O_5$	69.21	5.99
						69.11	6.09
7-OCH_3	$CH_2CH_2C_6H_5$	*i*-PrOH	165-166	74	$C_{30}H_{30}N_2O_3$	77.22	6.48
						77.11	6.49
7-OCH_3	$CH_2C_6H_5$	95% EtOH	134-135	47	$C_{29}H_{28}N_2O_3$	76.96	6.24
						76.87	6.23
4-Br	COC_6H_5	*i*-PrOH [b]	205-206	71	$C_{23}H_{21}BrN_2O_3$	60.93	4.66
						60.58	4.81
4-Br	$CH_2CH_2C_6H_5$	95% EtOH	211-212	74	$C_{29}H_{27}BrN_2O_2$	67.57	5.27
						67.65	5.33
4-Br	$CO_2C_2H_5$	*i*-PrOH	205-206	60	$C_{23}H_{23}BrN_2O_4$	59.63	4.79
						59.68	4.79
4-Br	$CH_2C_6H_5$	*i*-PrOH	200-201	65	$C_{28}H_{25}BrN_2O_2$	67.06	5.02
						67.29	4.98
4-Br	COC_6H_5	*i*-PrOH	179-180	71	$C_{28}H_{23}BrN_2O_3$	65.25	4.48
						65.28	4.38
6,7-O-CH_2O	CH_3	95%EtOH	206-207	22	$C_{23}H_{22}N_2O_4$	70.75	5.68
						70.79	5.57

[a] The ir spectra were consistent with structure, all had a C=O absorption at about 1710 cm^{-1}. [b] Chromatographed on silica with chloroform prior to recrystallization. [c] Calcd, N, 7.48. Found, N, 7.43.

Table 2

Hydrolysis to Alcohols

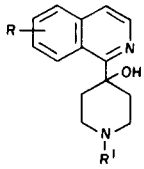


R	R'	Purification Solvent	Mp, °C	Yield (%)	Formula [a]	Analysis % Calcd./Found C	H
H	$COCH_3$ [b]	C_6H_6-petroleum ether	108-109	88	$C_{16}H_{18}N_2O_2$	71.08	6.71
						70.97	6.80
H	$CH_2C_6H_5$ [c]	C_6H_6-hexane	114-115	72	$C_{21}H_{22}N_2O$	79.21	6.96
						79.23	6.92
4-Br	CH_3 [d]	C_6H_6-petroleum ether	161-162	70	$C_{15}H_{17}BrN_2O$	56.08	5.33
						56.22	5.34
4-Br	$CH_2CH_2C_6H_5$	95% EtOH	183-184	65	$C_{22}H_{23}BrN_2O$	64.23	5.63
						64.15	5.58
6,7-OCH_2O	CH_3	95% EtOH	150-151	62	$C_{16}H_{18}N_2O_3$	67.11	6.34
						67.20	6.31

[a] The ir and nmr spectra were consistent with structure shown. [b] See experimental. [c] Ester previously prepared [2]. [d] Crude ester not characterized.

Table 3

Anticonvulsant Screening



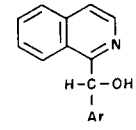
Compound No.	R	R'	MES [a]
5	H	CH_3	30 [b,c]
6	H	$CH_2C_6H_5$	100 [d]
7	H	$COCH_3$	NA [e]
8	H	$CH_2CH_2C_6H_5$	300 [f]
9	4-Br	CH_3	30 [g,j,k]
10	4-Br	$CH_2CH_2C_6H_5$	600
11	6,7-OCH_3	CH_3	100 [d,i,j]
12	6,7-OCH_2O	CH_3	100 [d,l]

[a] MES activity in mg/kg [3]. Unless otherwise noted compounds were inactive in the Met. [b] Toxic at 100 mg/kg. [c] MES ED_{50} 27, TD_{50} 62.5. [d] Some toxicity at this dose. [e] No activity at 600 mg/kg. [f] Met activity at 300 mg/kg. [g] Toxic at 300 mg/kg. [h] MES ED_{50} 30.2, TD_{50} 142.2. [i] Met activity at 100 mg/kg. [j] MES Ed_{50} 28.8, TD_{50} 69.2. [k] Leukemia Screen (3PS31) Inactive 120 mg/kg, Toxic 240 mg/kg. [l] MES ED_{50} 51.9, TD_{50} 102.6.

group is necessary for MES activity for in addition to the lack of activity of the benzoates, the acetates of **5** [2] and **6** [5] and sulfate **13** [5] are all inactive in the MES and Met.

The *N*-methyl compounds **5, 9** and **11** were the most active. The nitrogen is necessary for activity as both **14** [4] and **15** [4] were inactive at 300 mg/kg in the MES and Met. Reduction of the pyridine ring of the isoquinoline also led to loss of activity as both **16** and **17** [5] were inactive. Reaction of **5** with methyl iodide gave a quaternary salt **18** which was also inactive and toxic at 300 mg/kg. The fact that quaternization took place of the piperidine rather than the isoquinoline nitrogen is supported by nmr evidence. The related thio compound **19** was inactive at 300 mg/kg in both screens.

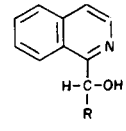
Several related compounds **20-28** were prepared by replacement of the piperidones with pyridinecarboxaldehydes and with other aromatic aldehydes. Again the ester **20** was inactive at 600 mg/kg in both screens. The alcohols derived from the pyridines **21-24** possessed, as shown in Table 4, both activity and toxicity, while those from the other aldehydes **25-28** were inactive.



25 C_6H_5
26 $4\text{-}BrC_6H_4$–
27 $2,3\text{-}(CH_3O)_2C_6H_3$–
28 $2,4,6\text{-}(CH_3O)_3C_6H_2$–

Table 4

Anticonvulsant Screening



R	Mp, °C	Yield %	Formula	Analysis % Calcd./Found C	H	MES [a]	Met [a]	Tox [b]
2-Pyridyl [c]	125-126 [d]	45	$C_{15}H_{12}N_2O$	76.15 76.35	5.08 5.01	100	300	300
3-Pyridyl [e]	81-82 [f]	75	$C_{15}H_{12}N_2O$	76.15 76.17	5.08 5.09	100	300	100 [g]
4-Pyridyl	119-120 [d]	75	$C_{15}H_{12}N_2O$	76.15 76.25	5.08 5.12	300	300	300
6-Methyl-2-pyridyl	110-111 [h]	62	$C_{16}H_{14}N_2O$	76.78 76.71	5.64 5.54	300	NA [i]	—
C_6H_5	108-109 [i]	56	$C_{16}H_{13}NO$ [k]	—	—	NA [i]	[i] NA [i]	—
$4\text{-}BrC_6H_6$	109-110 [h]	68	$C_{16}H_{12}BrNO$ [l]	—	—	NA [i]	NA [i]	—
$2,3\text{-}(CH_3O)_2C_6H_3$	133-135 [h]	48	$C_{18}H_{17}NO_3$ [m]	—	—	NA [i]	NA [i]	—
$2,4,6\text{-}(CH_3O)_3C_6H_2$	143-144 [j]	40	$C_{19}H_{19}NO_4$	70.14 70.05	5.89 6.00	NA [i]	NA [i]	—

[a] Maximal electroshock and antimetrazole activity in mg/kg [3]. [b] Neurotoxicity in mg/kg [3]. [c] MES ED_{50} 75.0 mg/kg; TD_{50} 130.1 mg/kg. [d] Recrystallized from benzene-hexane. [e] MES ED_{50} 76.7 mg/kg, TD_{50} 136.2 mg/kg. [f] Recrystallized from ethyl acetate-petroleum ether. [g] Deaths at 300 mg/kg. [h] Recrystallized from ethanol-water. [i] No activity at 300 mg/kg. [j] Recrystallized from ethanol. [h] Reported [9] mp 108.5-109.5°. [l] Reported [10] mp 111-112°. [m] Reported [10] mp 128-130°.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B spectrometer as potassium bromide pellets. Proton magnetic resonance spectra were determined with a Hitachi Perkin Elmer Model R-24B instrument using tetramethylsilane as an internal standard. Elemental analyses were within 0.4% of the calculated value unless otherwise indicated and were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan. Silica gel (600-200 mesh, J. T. Baker) was used for all column chromatographic separations unless otherwise noted. Thin layer chromatographic comparisons were done on Eastman Kodak silica gel chromatograms with fluorescent indicator No. 13181. Various *N*-substituted piperidones and pyridinecarboxaldehydes were obtained from Aldrich Chemical Company, Milwaukee, Wisconsin and Reissert compounds were prepared by standard procedures [1].

General Procedure for the Condensation Reaction of the Various Reissert Anions with 4-Piperidones.

A solution of 0.01 mole of the Reissert compound and 0.015 mole of the 4-piperidone in dimethylformamide was stirred, under an inert atmosphere of nitrogen or argon, for 5 minutes. To this stirred solution, was added in small portions, 0.02 mole of sodium hydride (50% in oil). The mixture was stirred for an additional 2 hours and poured over ice water. The *p*H of the solution was adjusted to 7. Esters were isolated by filtration, or if no precipitate formed the aqueous layer was extracted with chloroform. Drying and removal of the chloroform *in vacuo* led to the isolation of the product. Esters **3** are shown in Table 1.

Rearrangement of Reissert Anion.

In the following cases the above procedure did not lead to reaction of the Reissert anion with the piperidones. 3-Methylisoquinoline Reissert compound gave (80%) 1-benzoyl-3-methylisoquinoline, mp 101-103°, reported [6] mp 102-103°. Quinoline Reissert compound gave (85%) of 2-benzoylquinoline, compound 107-109°, reported [7] mp 109-110°. Lepidine Reissert compound gave (62%) of 2-benzoyl-4-methylquinoline, mp 107-108° (ethanol); ir (potassium bromide): 2950, 1655, 1600, 1580, 1440, 1340 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}NO$: C, 82.56; H, 5.30; N, 5.76. Found: C, 82.57; H, 5.40; N, 5.70.

The phenanthridine Reissert compound gave (65%) 6-benzoylphenanthridine, mp 151-152°, reported [8] mp 151-152°.

General Procedure for the Hydrolysis of the Benzoate Esters **3** to the Alcohols **4**.

To a suspension of 1.0 g of the ester in 30 ml of 95% ethanol, was added 4 ml of 40% potassium hydroxide solution. The mixture was refluxed for 2-5 hours (monitored by using thin layer chromatography). Ethanol was removed by distillation and the contents were poured over water. The aqueous layer was extracted with chloroform, dried and evaporated to give the alcohol **4**, see Table 2.

Preparation of **19**.

This compound was prepared by the above procedures with tetrahydrothiopyran-4-one replacing the 4-piperidones in the Reissert condensation. The ester mp 139-140° was hydrolyzed directly to give **19** in 50% overall yield, mp 132-133° (methanol).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.54; H, 6.16; N, 5.70. Found: C, 68.73; H, 6.36; N, 5.50.

Preparation of **7**.

To a solution of 1.0 g (0.0026 mole) of **3** (R = $COCH_3$, R′ = H) in 20 ml of methanol was added slowly, in small amounts, 0.30 g of sodium borohydride. After refluxing for 24 hours, the contents were poured onto ice. A white solid was filtered, dried and recrystallized to give 0.62 g (88%) of **7**; ir (potassium bromide): 3380, 2910, 1605, 1580, 1415, 1280, 1110 cm^{-1}, see Table 2.

Preparation of **16**.

A mixture of 2.0 g of **5** (0.008 mole) in 75 ml of glacial acetic acid and 0.05 g of platinum oxide were shaken under a hydrogen pressure of 60 psi for 24 hours. After filtering the catalyst, the acid was removed by distillation. The oil obtained was dissolved in water and the *p*H of the solution was adjusted to 12. The aqueous layer was extracted with ether (3 × 20 ml) and the ether layer was dried (anhydrous magnesium sulfate) and evaporated *in vacuo* to give an oil. On standing this oil solidified to give 1.10 g (84%) of the pure solid, after recrystallizing from benzene/hexane, mp 134-135°; ir (potassium bromide): 3310 (singlet, N-H), 3150, 2920, 2850, 2800, 2750, 1650 cm^{-1}; pmr (deuteriochloroform): δ 7.08 (s, 4H), 3.84 (s, 1H, exchangeable with deuterium oxide), 3.35-2.95 (m, 4H), 2.95-1.30 (m, 12H).

Anal. Calcd. for $C_{15}H_{21}N_2O$: C, 73.43; H, 8.62; N, 11.42. Found: C, 73.08; H, 8.73; N, 11.30.

Preparation of **18**.

A mixture of 0.75 g (0.003 mole) of alcohol **5** and 11.25 g of methyl iodide in 10 ml of methanol were refluxed for 3 hours. The contents were poured onto 100 ml of anhydrous ether. White solid was obtained which was filtered and washed twice with anhydrous ether. Recrystallization from 95% ethanol gave 1.18 g (100%) of **18**, mp 246-248°; ir (potassium bromide): 3280, 3000, 1600, 1580, 1540, 1475, 1320, 1280, 1180 cm^{-1}; pmr (DMSO-d_6): 8.95 (d, 1H, J = 6.0 Hz), 8.25 (d, 1H, J = 6.0 Hz), 8.0-7.5 (m, 4H), 6.10 (s, 1H, exchangeable with deuterium oxide), 3.15 (d, 6H), 2.8-2.2 (m, 8H).

Anal. Calcd. for $C_{16}H_{21}IN_2O$: C, 50.00; H, 5.50. Found: C, 49.76; H, 5.47.

Preparation of **20-28**.

To a solution of 0.01 mole of the isoquinoline Reissert compound in 20 ml of anhydrous dimethylformamide was added 0.02 mole of sodium hydride (50% in oil) at 0° under an argon atmosphere. After stirring for 10 minutes, 0.02 mole of the pyuridine carboxaldehyde was added dropwise with stirring at 0°. After stirring the contents in cold for 1 hour, the mixture was stirred at room temperature for additional 40 minutes. The contents were poured over ice and the *p*H of the solution was adjusted to 7. The solid obtained was filtered and without further characterization (compound **20** from pyridine-4-carboxaldehyde was purified, mp 149-151°, reported [9] mp 149.5-150°) subjected to the general hydrolysis procedure, described above, to give the alcohols **21-28** as shown in Table 4.

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[2] F. D. Popp and R. F. Watts, *J. Heterocyclic Chem.*, **13**, 1129 (1976).

[3] Anticonvulsant screenings were carried out through the Antiepiliptic Drug Development Program of the NINCDS, National Institutes of Health. The standard screening protocol of that group was followed.

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