

1-(2-羟基-3-芳氧基丙基)-4-芳酰基

哌嗪的合成

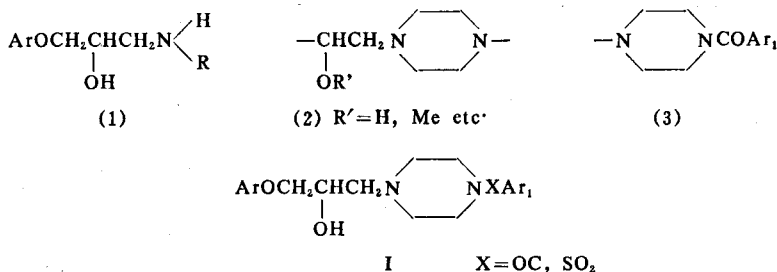
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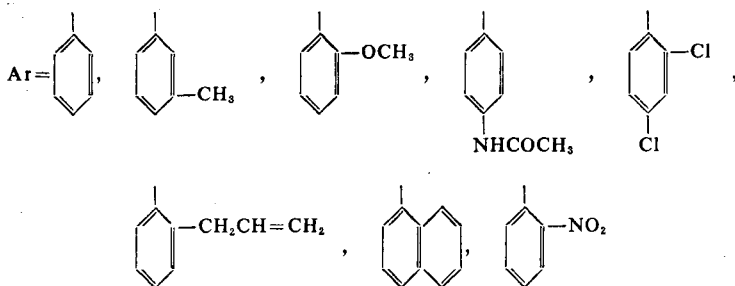
提要 根据拼合原理, 设计并合成了 19 个 1-(2-羟基-3-芳氧基丙基)-4-芳酰基哌嗪类化合物。对其中 8 个化合物 I₁~I₈ 进行了药理试验, 发现它们有明显的降压活性及 α-受体阻滞活性。

关键词 抗高血压; 哌嗪衍生物

根据拼合原理, 将药理作用相同而结构类型不同的化合物拼合起来, 有可能得到活性更佳的化合物^(1~2)。我们从三类有抗高血压活性的化合物中选出各自的共同结构部分: β-受体阻滞剂的基本结构⁽¹⁾; 近年来报道的一些有抗高血压活性化合物^(3~6)的共同结构部分——哌嗪乙氧基结构⁽²⁾; 临床上应用的哌嗪类抗高血压药物的部分结构——芳酰基哌嗪⁽³⁾。综合考虑这三种结构, 设计了一类化合物 I。



由于 β-受体阻滞剂目前仍为一类安全有效的抗高血压药物, 所以 Ar 选用临床上疗效肯定的 β-受体阻滞剂中的一些芳基。例如:



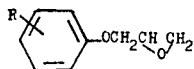
Ar₁ 部分为苯基或取代苯基, 例如邻氯苯基、对甲苯基, 3,4,5-三甲氧基苯基。此外, 根据生物电子等排概念, 用哌嗪中含有的呋喃甲酰基代替苯甲酰基, 用对-甲苯磺酰基代替对-甲苯甲酰基, 设计了一些化合物(见表 3)。


我们采用下列路线合成了 I 类化合物。

本文于 1986 年 3 月 5 日收到。

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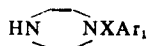
Tab 1. Structures, physical data and yields of 3-aroxy-1,2-epoxypropanes

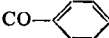
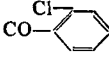

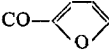
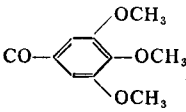



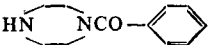


R	Time of reaction (h)	Yield (%)	BP°C or MP°C*
H	12	64.7	93~94/0.533kPa(4 mmHg)
3-CH ₃	24	75.6	104~107/1.20kPa(9 mmHg)
2-OCH ₃	20	71.9	120~125/1.87kPa(14 mmHg)
4-NHCOCH ₃	20	80.8	117~120
2,4-Cl ₂	20	70.8	128~131/2.13kPa(16 mmHg)
2-CH ₂ CH=CH ₂	14	83.7	118~122/2.40kPa(18 mmHg)
Ar = 	13	71.0	169~172/1.87kPa(14 mmHg)
2-NO ₂	25	33.3	49~52

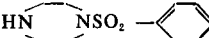
*Pressure and temperature were uncorrected.

Tab 2. Structures, physical data and yields of 1-aroxy-piperazines

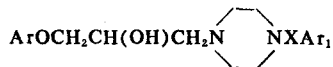



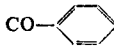
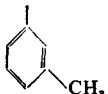
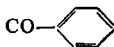
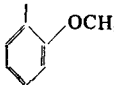
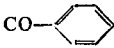
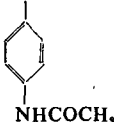
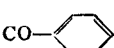
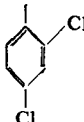
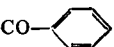
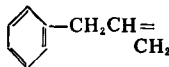
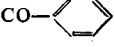

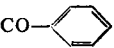
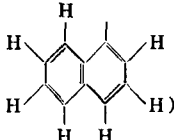
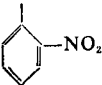
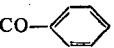
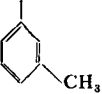
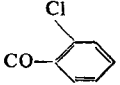
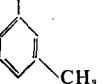

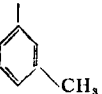
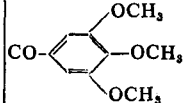
XAr ₁	Base or salt	MP°C (Solvent)	Yield (%)	IR cm ⁻¹
	Free base	65~66	64	3270(NH), 1610(CO), 730, 710
	Hydrochloride	275(d.) (EtOH)	73	3000-2300(N ⁺ H ₂), 1620(CO), 720, 700
	Free base		73.3	
	Hydrochloride	203~205 (EtOH)		2900-2400(N ⁺ H ₂), 1650(CO), 780
	Free base	89~91 (C ₆ H ₆ -Petr ether)	42	
	Hydrochloride	290(d.) (EtOH)	46	2700-2470(N ⁺ H ₂), 1635(CO), 837
	Hydrochloride	201~202 (Ditto)	74	2860-2500(N ⁺ H ₂), 1630(CO), 1290, 1020, 780
	Hydrochloride	221~223 (Ditto)	63	2700-2460(N ⁺ H ₂), 1650(CO), 845, 770
	Free base	108~109 (C ₆ H ₆ -Petr. ether)	34	3300(NH), 1595, 1310-1300, 1180~1150, 810

¹HNMR for  δ ppm 1.69(1H, s, HN<); 2.65~2.85 (4H, m, ); 3.35~3.60(4H, m, -N-CO); 7.33(5H, s, Ar-H,)

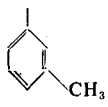
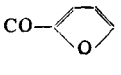
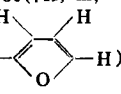
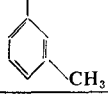



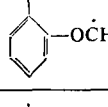
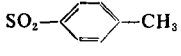



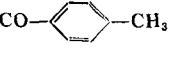
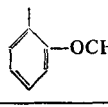
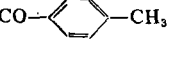
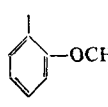
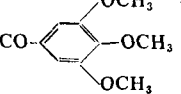
¹HNMR for  1.7(1H, s, HN<); 2.54 (3H, s, -CH₃); 2.95 (8H, s, -N<-N-), 7.30~7.82(4H, q, Ar-H)

Tab 3. Structures, physical properties and spectral data for compounds of I₁~I₁₁.

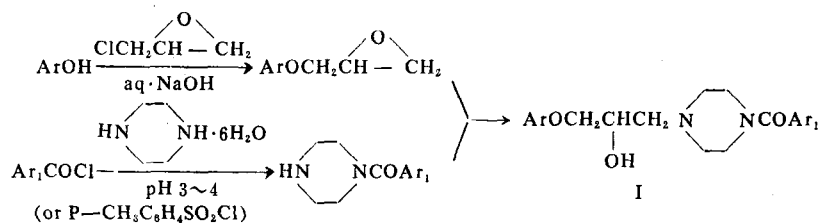


Compd*	Ar	XAr ₁	MP°C (Solvent)	Yield (%)	IR cm ⁻¹	¹ HNMR (CDCl ₃ , TMS) δ ppm**
I ₁			114~115 (EtOH—Me ₂ CO)	79.4	3200(OH), 1615(CO)	2.45~2.70(6H, m, CH ₂ N<CH ₂ > CH ₂), 3.65~4.03(8H, m, — OCH ₂ CH(OH), CH ₂ >N): 6.86~7.20 (5H, m, Ar-H); 7.42(5H, s, Ar ₁ -H)
I ₂			93~94 (Me ₂ CO—Petro.) ether	70.7	3220(OH), 1610(CO)	2.33(3H, s, —CH ₃)
I ₃			169~170 (EtOH)	76.8	3570, 3320(OH), 2700~ 2400(N ⁺ H), 1620(CO)	3.71(3H, s, OCH ₃)
I ₄			148~150 (Ditto)	61.5	3270(OH), 2700 2700~ 2450(N ⁺ H), 1630(CO)	1.97(3H, s, COCH ₃); 6.74~7.09 (5H, m, Ar—H, NHCO)
I ₅			185~186 (EtOH—Et ₂ O)	89.7	3270(OH), 2650~ 2300(N ⁺ H), 1630(CO)	6.77~7.36(3H, m, Ar-H);
I ₆			168~170 Ditto	76.7	3300(OH)	1.97(2H, m, CH ₂ C=C) 5.09~5.11(2H, m, = CH ₂); 5.70~6.30 (1H, m, CH=)
I ₇			224~226(d.) (EtOH—H ₂ O)	90.9	3350(OH), 2700~ 2450(N ⁺ H), 1630(CO)	
I ₈			168~169 (MeOH— i-PrOH)	73.8	3410(OH), 2670~ 2350(N ⁺ H), 1620(CO)	6.94~7.98 (4H, m, Ar—H)
I ₉			181~182 (i-PrOH—Et ₂ O)	68.2	3330(OH), 2650~ 2400(N ⁺ H), 1650(CO)	2.30(3H, s, ArCH ₃)
I ₁₀			103~104 (Me ₂ CO—Et ₂ O)	68.7	3450(OH), 1620(CO)	2.32(3H, s, ArCH ₃)
I ₁₁ ***			155~157 (MeOH—EtOH)	87.3	3300, 3050, 2950, 1700, 1610, 1586, 1500~1420	

Continued

Compd*	Ar	X Ar ₁	MP°C (solvent)	Yield (%)	IR cm ⁻¹	¹ HNMR (CDCl ₃ , TMS) δ (ppm)**
I ₁₂			103~104 (EtOH-Et ₂ O)	69.8	3150(OH), 2950, 2984, 1625(CO)	2.31(3H, s, ArCH ₃); 6.43~7.50(7H, m, Ar-H, )
I ₁₃			119~120 (Ditto)	87.5	3400(OH)	2.32(3H, s, ArCH ₃); 2.46(3H, s, Ar ₁ CH ₃)
I ₁₄			158~159 (EtOH)	91.0	3400(OH)	2.46(3H, s, -CH ₃)
I ₁₅			122~123 (EtOH-Me ₂ CO)	100	3600(OH)	2.46(3H, s, Ar ₁ CH ₃); 3.84(3H, s, ArOCH ₃)
I ₁₆			159~161 (Ditto)	81.7	3320(OH), 1675, 1595	2.06(3H, s, COCH ₃); 2.43(3H, s, -CH ₃)
I ₁₇			108~110 (Me ₂ CO-Et ₂ O)	80.2	3430(OH), 1620(CO)	2.37(3H, s, Ar ₁ CH ₃)
I ₁₈ ***			170~173 (MeOH-i-PrOH)	66.5	3600, 3270(OH), 2670~ 2450(N ⁺ H), 1630(CO)	
I ₁₉ ***			161~163 (Ditto)	78.0	3250(OH), 3040, 2950, 2720~2500 (N ⁺ H) 1710, 1626, 1600~1460	

a: Free base. b: Hydrochloride. c: Maleate.

* Elemental analyses: deviation within ±0.4% (C, H, N), from the calculated value except I₁, I₇, and I₁₇.** Compounds I₃, I₄ and I₇ using D₂O as solvent (Me₂CO, 2.05).*** MS (m/z I₁₁: 444(M⁺), 319, 293, 195; I₁₈: 384(M⁺), 243, 217, 119; I₁₉: 460(M⁺), 319, 305, 293, 279, 195)

Scheme 1. Route of synthesis

酚与环氧氯丙烷在碱性条件下可以顺利地形成 3-芳氧基-1,2-环氧丙烷^(7~10), 有关数据见表 1。

六水哌嗪与芳酰氯在 50% 丙酮水溶液中反应可制得单芳酰基哌嗪^(11~12)。反应过程中需

格控制反应介质的 pH 值,使哌嗪的一个 N 处于成盐状态,而在另一个 N 上发生酰化反应。结果见表 2。

3-芳氧基-1,2-环氧丙烷与 1-芳酰基哌嗪在无水乙醇中回流,就得到 I 类化合物。所合成的 19 个化合物 $I_1 \sim I_{19}$ 均未见文献报道,由元素分析值与光谱数据证明其结构是正确的。

对于化合物 $I_1 \sim I_8$ 进行了大鼠和家兔整体麻醉下血压和心电图变化试验,离体兔动脉条和心房试验以及离体兔空肠试验,发现它们均有明显的降低血压活性,但在低剂量时作用时间较短;此外,这些化合物对兔主动脉条有强的抗 α -受体兴奋作用。进一步的药理试验在进行中。

实 验 部 分

测定熔点的温度计读数未经校正。红外光谱用 WFD-7 G 型红外分光光度计测定, kBr 压片。

3-芳氧基-1,2-环氧丙烷

用市售或自制的酚(0.1 mol)与新配制的 NaOH 水溶液(NaOH 0.12 mol, H₂O 100 ml)搅拌 0.5 h。滴加环氧氯丙烷 0.15 mol,室温搅拌 12~25 h。分出油层、水相用乙醚萃取。合并有机层,用水洗涤。干燥后,蒸去溶剂,残余物经减压蒸馏或用合适的溶剂重结晶,得到 3-芳氧基-1,2-环氧丙烷。

1-芳酰基哌嗪

将六水哌嗪 0.06 mol 溶于水 60 ml,滴加适量甲基橙指示剂,用盐酸(2 mol/L)中和至指示剂刚变色。加入丙酮 60 ml,在搅拌下于 50~60°C 滴加芳酰氯 0.05 mol,同时不断地用醋酸钠水溶液中和反应过程中释放出的酸。水泵减压蒸去丙酮和水,残余物用无水乙醇煮沸,趁热滤去不溶的盐,滤液冷却后即析出 1-芳酰基哌嗪盐酸盐结晶。

蒸去反应后混合物中的丙酮,用 40% NaOH 溶液中和至 pH \approx 10,以氯仿萃取。萃取液干燥后,蒸去氯仿,残余物经减压蒸馏,或用适当溶剂重结晶,得到 1-芳酰基哌嗪。

1-(2-羟基-3-芳氧基丙基)-4-芳酰基哌嗪(I)

将 1-芳酰基哌嗪 0.01 mol 和 3-芳氧基 1,2-环氧丙烷 0.015 mol 溶于 20 ml 乙醇,回流 3.5~5 h,用 TLC 跟踪反应至 1-芳酰基哌嗪色点消失。反应液冷却后析出产物,用适当溶剂重结晶。收率见表 3。

若反应完成后,在混合物中加入含氯化氢的乙醇溶液,或通入干燥 HCl,则制得产物的盐酸盐。

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参 考 文 献

1. 蒋明谦.高等药物化学.北京:科学出版社,1958:127.
2. John JB, et al. Symbiotic approach to drug design antihypertensive β -adrenergic blocking agents. *J Med Chem* 1979; 22:1284.
3. Thieme PC, et al. Phenylpiperazine derivatives. *Ger Offen* 3, 005,287; *CA* 1983; 95:169204 s.
4. Nartin GJ and Clazion GP. 2-Hydroxy-5-(1-hydroxy-2-piperazinyloethyl) benzoic acid derivatives. *Ger Offen* 3,014,813; *CA* 1981; 94:175165 a.
5. Espana SA, et al. Vasoactive N-benzoyl or N-cinnamoylpiperazines. *Span Patent* 422, 189; *CA* 1977; 86:140086 h.
6. Francois AJ, et al. Trimethoxycinnamoylpiperazine, its salts and its application in therapy. *Fr Demande* 2,474,031; *CA* 1982; 96:35305 n.
7. Erhardt PW, et al. Ultra-short acting β -adrenergic receptor blocking agents. I. *J Med Chem* 1982; 25:

1405.

8. Takase and Muneaki, 5-(O-Methoxyphenoxyethyl)-2-oxazolidinone. *Japan Patent* 69 31344; *CA* 1969; 72:90442 j.
9. Kuliev AM, et al. Syntheses of O,O-dipropyl S-(α -alkylphenoxy- β -hydroxypropyl) dithiophosphates. *Uch Zap Azerb Gos Univ, Ser Khim Nauk* 1965(2)9; *CA* 1967; 66:37559.
10. Newman MS, et al. New compounds as plant growth regulators. *J Am Chem Soc* 1947; 69:723.
11. Moore TS, et al. N-Substituted derivatives of piperazine and ethylene diamine. I. Preparation of N-monosubstituted derivatives. *J Chem Soc* 1929:39.
12. Jacobi KR. Monobenzoyl-piperazine. *Ber* 1933; 66:113.

SYNTHESES OF 1-(2-HYDROXY-3-ARYLOXYPROPYL)-4-AROYLPIPERAZINES

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ABSTRACT Nineteen 1-(2-hydroxy-3-aryloxypropyl)-4-arylpiperazines were designed according to synbiotic approach and then synthesized. Eight of them (from I₁ to I₈) were subjected to preliminary pharmacological assay. They were shown to have α -adrenergic blocking and hypotensive activities.

Key words Antihypertensive drug; Piperazine derivatives