·论 文·

N-酰化/磺酰化四氢异喹啉化合物的合成

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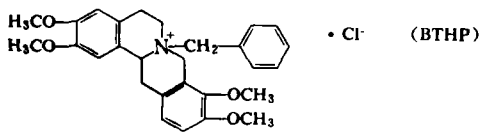
摘 要 为寻找Ⅲ类抗心律失常药物,以钾通道阻滞剂分子中常见的酰胺和磺酰胺结构取代具钾通道阻滞活性和抗心律失常作用的氯化苄基四氢巴马汀(BTHP)分子中的季铵结构,设计合成了25个*N*-酰化或磺酰化的四氢异喹啉化合物(Ⅲ$_{1\sim25}$),其中23个化合物未见文献报道。这些化合物可视为BTHP的开环衍生物,结构均由元素分析、红外、核磁和质谱确证。

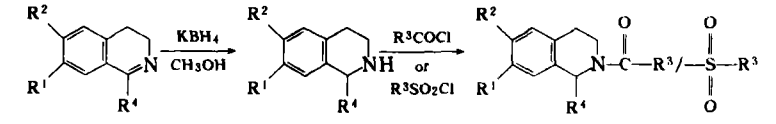
关键词 四氢异喹啉;*N*-酰化衍生物;*N*-磺酰化衍生物;钾通道阻滞剂;抗心律失常药

异喹啉类化合物具有广泛生物活性,在心血管方面的研究十分活跃[1,2]。我室与同济医科大学协作,发现了氯化苄基四氢巴马汀(Benzyltetrahydropalmatine Chloride, BTHP)



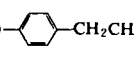
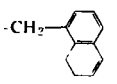
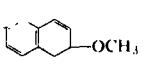
具有心肌钾通道阻滞活性和抗心律失常作用[3]。近年来,抗心律失常药物研究的热点是寻找选择性阻滞心肌钾通道的Ⅲ类抗心律失常药物[4]。从现有钾通道阻滞剂(Potassium Channel Blockers)结构看,除季铵化合物外,其余大多含有酰胺或磺酰胺结构。据此,用多种脂肪、芳香和杂环酰胺或磺酰胺结构取代了BTHP的季铵结构,设计和合成了一系列*N*-酰化的苄基/萘甲基四氢异喹啉化合物。其中,*N*-酰化的苄基四氢异喹啉化合物19个(Ⅲ$_{1\sim13,20\sim25}$,表1),酰化的萘甲基四氢异喹啉化合物6个(Ⅲ$_{14\sim19}$,表2),23个化合物未见文献报道。这两类化合物均可视为BTHP的开环衍生物。期望找到具选择性心肌钾通道阻滞活性的Ⅲ类抗心律失常药物。

我们以Bischler-Napieralski反应制备了3,4-二氢异喹啉化合物(Ⅰ),再在甲醇中以硼氢化钾还原得到了相应的四氢异喹啉化合物(Ⅱ)[6]。以(Ⅱ)为原料,与各种酰氯(或酸酐)或磺酰氯反应,制备目的化合物(Ⅲ)。



(Ⅰ) (Ⅱ) (Ⅲ)

R^1, R^2=-$(OCH_3)_2$, -OCH_2O-

R^4= -$CH(CH_3)$-  -$CH_2CH(CH_3)_2$, -CH_2-  , -$CH(CH_3)$- 

化合物Ⅲ$_4$由Ⅲ$_2$与甲醇钠于无水乙醇中回流反应制得,其余目的化合物均由上述通法制备。

所合成化合物的钾通道阻滞活性和抗心律失常作用正在研究中。

实验部分

熔点在WRS-1型数字熔点仪(上海产)、

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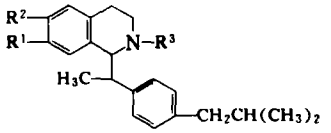
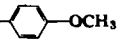
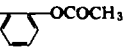
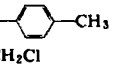
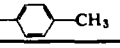
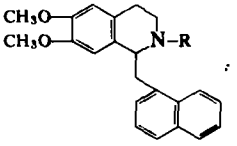
Tab 1. 6,7-Disubstituted-1-substituted benzyl-2-acyl/sulphonyl-1,2,3,4-tetrahydroisoquinolines (Ⅱ)



Compd	R^1	R^2	R^3	Yield, %	mp, ℃	Description
Ⅱ-1	$-OCH_3$	$-OCH_3$	$-COCH_3$	83	105—106	white crystal
Ⅱ-2	$-OCH_3$	$-OCH_3$	$-COCH_2Cl$	72	157—159	white crystal
Ⅱ-3	$-OCH_3$	$-OCH_3$	$-COC_2H_5$	72	99—100	white crystal
Ⅱ-4	$-OCH_3$	$-OCH_3$	$-COCH_2OCH_3$	34	100—102	white crystal
Ⅱ-5	$-OCH_3$	$-OCH_3$	$-COOC_2H_5$	45	69—70	white crystal
Ⅱ-6	$-OCH_3$	$-OCH_3$		51	198—200	white crystal
Ⅱ-7	$-OCH_3$	$-OCH_3$		61	110—112	white powder
Ⅱ-8	$-OCH_3$	$-OCH_3$		32	143—145	pale yellow crystal
Ⅱ-9	$-OCH_3$	$-OCH_3$		19	195—197	pale yellow needle
Ⅱ-10	$-OCH_3$	$-OCH_3$		34	163—165	pale yellow needle
Ⅱ-11	$-OCH_3$	$-OCH_3$	$-SO_2CH_3$	57	118—119	white crystal
Ⅱ-12	$-OCH_3$	$-OCH_3$		35	114—116	white crystal
Ⅱ-13	$-OCH_3$	$-OCH_3$		55	124—125	white crystal
Ⅱ-20	$-OCH_2O-$		$-COCH_2Cl$	69	122—124	pale yellow crystal
Ⅱ-21	$-OCH_2O-$		$-COC_2H_5$	64	125—127	white crystal
Ⅱ-22	$-OCH_2O-$			19	116—118	white crystal
Ⅱ-23	$-OCH_2O-$		$-SO_2CH_3$	54	142—143	white crystal
Ⅱ-24	$-OCH_2O-$			53	152—153	white crystal
Ⅱ-25	$-OCH_2O-$			61	146—147	white crystal

Tab 2. 6,7-Disubstituted-1-substituted naphthylmethyl-2-acyl/sulphonyl-1,2,3,4-tetrahydroisoquinolines (Ⅱ)



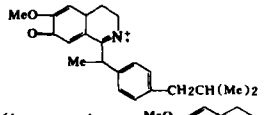
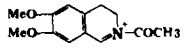
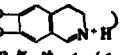
Compd	R	Yield, %	mp, ℃	Description
Ⅱ$_{14}$	$-COCH_3$	43	170—172	white crystal
Ⅱ$_{15}$	$-COCH_2Cl$	70	147—148	pale yellow crystal
Ⅱ$_{16}$		21	244—246(dec.)	pale yellow powder
Ⅱ$_{17}$		59	159—160	pale yellow needle
Ⅱ$_{18}$		13	124—126(dec.)	pale yellow powder
Ⅱ$_{19}$		69	183—184	pale yellow crystal

*Reported compounds[6]

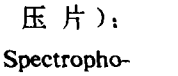
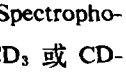
WL-1 型显微熔点仪(厦门产)、电热熔点仪或石腊管熔点仪上测定，温度均未经校正；薄层层析(TLC)板采用硅胶 GF_{254}(青岛海洋化工厂生产)与 CMC-Na 蒸馏水溶液(浓度 0.8%)充分搅匀后铺板，经 100～110℃活化 1～2 h 后置干燥器内保存备用，于紫外灯下(波长 254 nm)观察荧光；元素分析：CARLO ERBA STRUMENTAZIONE ELEMENTAL ANALYZER-MOD. 1106；IR (KBr 压片)：PERKIN-ELMER 983 Infrared Spectrophotometer；^{1}HNMR (溶剂为 CD_3COCD_3 或 $CDCl_3$，TMS 内标)；JEOL FX 90Q Fourier Transform NMR Spectrometer；MS：Nicolet Fourier Transform Mass Spectrometer 2000。

制备通法　(Ⅰ)的游离碱粗品 8.5 mmol 溶于干燥苯 15 ml 中，于激烈搅拌下滴加相应的酰氯(或酸酐)或磺酰氯 17～25.5 mmol 与干燥苯 15 ml 的混合液。滴毕，继续反应 0.5 h，加入粉末状无水碳酸钠 2 g，室温搅拌 6～20 h。减压蒸尽苯，于残物中加入常水或乙醚 30 ml 搅拌(必要时再加入少量稀氢氧化钠溶液使 pH 达 9～10)，析出固体。滤出，水洗至近中性，烘干。粗品经无水乙醇或丙酮-乙醚重结晶(活性炭脱色)，得相应的化合物(Ⅱ)。

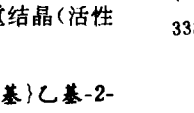
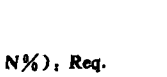
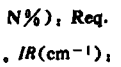
6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-乙酰基-1,2,3,4-四氢异喹啉(Ⅱ-1)

Anal. ($C_{25}H_{33}NO_3$=395.5439；C%，H%，N%)；Req. 75.91，8.41，3.54；Found 76.16，8.59，3.13。*IR*(cm^{-1})：3067，2959，2934(CH)，2843(OCH_3)，1638(C=O)，1609，1515(aromatic)，1257，1120，842，803(CH)。^{1}*HNMR*(δppm)：0.88(d，J=6.3Hz，6H，2×CH_3)，1.28(q，3H，C_α-CH_3)，1.88(m，3H，CH_2CH)，2.43(d，3H，$COCH_3$)，2.78(m，2H，$ArCH_2$)，3.40(m，2H，CH_2NCO)，3.69(s，3H，C_7-OCH_3)，3.76(s，3H，C_8-OCH_3)，4.78(d，1H，C_α-H)，5.61(d，1H，C_1-H)，6.58(s，1H，C_8-H)，6.71(s，1H，C_5-H)，7.10(dd，4H，aromatic)。*MS* (*SCI*；*m*/*z*)：396(M+1，80.64%)，337( ，M$^+$-$COCH_3$-CH_3)，234(base peak， )，192()。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-氯乙酰基-1,2,3,4-四氢异喹啉(Ⅱ-2)

Anal. ($C_{25}H_{32}ClNO_3$=429.9889；C%，H%，N%)；Req. 69.83，7.50，3.26；Found 70.01，7.50，2.90。*IR*(cm^{-1})：3006，2952，2930，2869(CH)，2833(OCH_3)，1638(C=O)，1638，1513(aromatic)，1261，1122，792，869(CH)。^{1}*HNMR* (δppm)：0.88(d，J=7.2Hz，6H，2×CH_3)，1.30(q，3H，C_α-CH_3)，1.85(m，1H，CH)2.43(q，2H，$ArCH_2$)，2.91(m，2H，$ArCH_2$)，3.74(s，3H，C_7-OCH_3)，3.84(s，3H，C_6-OCH_3)，4.07(s，1H，C_α-H)，4.57(s，4H，CH_2Cl，CH_2NCO)，5.54(d，br，1H，C_1-H)，6.63(s，1H，C_8-H)，6.75(s，1H，C_5-H)，6.83-7.22(m，4H，aromatic)。*MS* (*SCI*；*m*/*z*)：430(M+1，26.92%)，337(M$^+$-$COCH_2Cl$-CH_3)，268( ，base peak)，192()。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-丙酰基-1,2,3,4-四氢异喹啉(Ⅱ-3)

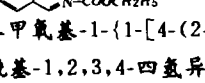
Anal. ($C_{26}H_{35}NO_3$=409.5709；C%，H%，N%)；Req. 76.25，8.61，3.42；Found 76.58，8.74，3.16。*IR*(cm^{-1})：2960，2940，2873(CH)，2840(OCH_3)，1633(C=O)，1610，1515(aromatic)，1259，1119，847，804(CH)。^{1}*HNMR*(δppm)：0.87(m，9H，3×CH_3)，1.28(q，3H，C_α-CH_3)，1.83(m，1H，CH)，2.20(t，2H，$ArCH_2$)，2.45(d，2H，$COCH_2$)，2.80(q，2H，$ArCH_2$)，3.45(m，2H，CH_2NCO)，3.71(s，3H，C_7-OCH_3)，3.77(s，3H，C_8-OCH_3)，3.81(m，1H，C_α-H)，5.63(d，1H，C_1-H)，6.62(s，1H，C_8-H)，6.72(s，1H，C_5-H)，7.12(dd，4H，aromatic)。*MS* (*SCI*；*m*/*z*)：410(M+1，82.07%)，338()，337(338-H)，248( ，base peak)，192()。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-甲氧乙酰基-1,2,3,4-四氢异喹啉(Ⅱ-4)

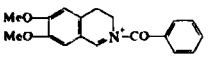
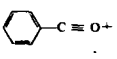
Ⅱ-2　3 g(7 mmol)溶于无水乙醇 60 ml 中，加入 50%甲醇钠-甲醇 1.8 g(含甲醇钠 0.8 g，7.5 mmol)，搅拌，回流反应 10 h。滤除生成的无机盐后的滤液经减压浓缩得油状残物，加入乙醚约 20 ml 并振摇，析出固体。冷却后滤出固体，烘干，得白色粗品 2.5 g(84%)。丙酮 10 ml 和丙酮-无水乙醚(1∶3) 12 ml 分别重结晶一次，得白色晶体 1.0 g (34%)，mp 100～102℃。*Anal.* ($C_{26}H_{35}NO_4$=425.5703；C%，H%，N%)；Req. 73.38，8.29，3.29；Found 74.10，8.60，3.34。*IR*(cm^{-1})：3071，3045，2964，2870(CH)，2844(OCH_3)，1656(C=O)，1608，1517(aromatic)，1115(-O-)，1019，836(CH)。^{1}*HNMR*(δppm)：0.87(d，6H，2×CH_3)，1.25(d，3H，C_α-CH_3)，1.80(m，1H，CH)，2.35(q，2H，$ArCH_2$)，2.80(m，2H，$ArCH_2$)，3.20(m，4H，CH_2NCOCH_2O)，3.45(m，1H，C_α-H)，3.69(s，3H，C_7-OCH_3)，3.75(s，3H，C_6-

OCH_3),3.90(s,3H,OCH_3),5.50(d,br,1H,C_1-H),6.60(s,1H,C_8-H),6.68(s,1H,C_5-H),7.10(m,4H,aromatic)。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-乙氧羰基-1,2,3,4-四氢异喹啉(Ⅱ-5)

Anal. ($C_{26}H_{35}NO_4$=425.5703; C%,H%,N%): Req. 73.38,8.29,3.29; Found 73.70,8.34,3.35。*IR*(cm^{-1}): 3075,3004,2959(CH),2836(OCH_3),1687(C=O),1608,1515(aromatic),1260,1239,847(CH)。^{1}*HNMR*(δppm): 0.88(d,J=7.2Hz,6H,2×CH_3),1.13(t,3H,CH_3),1.30(d,3H,C_α-CH_3),1.85(m,1H,CH),2.44(d,2H,$ArCH_2$),2.75(t,2H,$ArCH_2$),3.25(m,3H,CH_2N,C_α-H),3.72(s,3H,C_7-OCH_3),3.77(s,3H,C_6-OCH_3),3.93(br,2H,$COOCH_2$),5.20(br,1H,C_1-H),6.64(s,1H,C_8-H),6.72(s,1H,C_5-H),7.10(dd,4H,aromatic)。*MS*(*SCI*;*m/z*): 426(M+1,32.35%),380(M+-OC_2H_5),337(M+-$COOC_2H_5$-OCH_3),264( ,base peak),192。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-苯甲酰基-1,2,3,4-四氢异喹啉(Ⅱ-6)

Anal. ($C_{30}H_{35}NO_3$=457.6149; C%,H%,N%): Req. 78.74,7.71,3.06; Found 78.83,7.81,2.80。*IR*(cm^{-1}): 3073,2932,2909,2867(CH),2840(OCH_3),1624(C=O),1577,1515(aromatic),1264,1113,847(CH)。^{1}*HNMR*(δppm): 0.93(d,J=6.3Hz,6H,2×CH_3),1.44(d,3H,C_α-CH_3),1.82(m,1H,CH),2.48(d,2H,$ArCH_2$),2.75(t,2H,$ArCH_2$),3.40(m,3H,CH_2N,C_α-H),3.79(s,3H,C_7-OCH_3),3.84(s,3H,C_6-OCH_3),5.80(d,br,1H,C_1-H),6.71-7.48(m,11H,aromatic)。*MS*(*SCI*;*m/z*): 458(M+1,base peak),337,296(),105()。

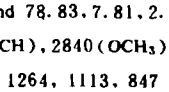
6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-(4-甲氧基)苯甲酰基-1,2,3,4-四氢异喹啉(Ⅱ-7)

Anal. ($C_{31}H_{37}NO_4 \cdot H_2O$=505.6567; C%,H%,N%): Req. 73.63,7.77,2.77; Found 73.44,6.93,2.36。*IR*(cm^{-1}): 3433(br,H_2O),3069,2958,2930(CH),2843(OCH_3),1710(C=O),1607,1509(aromatic),1263,1223,1001,838(CH)。^{1}*HNMR*(δppm): 0.90(d,J=6.3Hz,6H,2×CH_3),1.37(br,3H,C_α-CH_3),1.87(m,1H,CH),2.46(d,2H,$ArCH_2$),2.76(br,2H,$ArCH_2$),3.33(m,3H,CH_2N,C_α-H),3.78(s,3H,C_7-OCH_3),3.82(s,3H,OCH_3),3.93(s,3H,C_6-OCH_3),5.74(br,1H,C_1-H),6.71(s,1H,C_8-H),6.81(s,1H,C_5-H),7.10(dd,4H,aromatic),8.12(dd,4H,aromatic)。

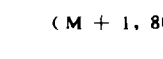
6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-(2-乙酰氧基)苯甲酰基-1,2,3,4-四氢异喹啉(Ⅱ-8)

Anal. ($C_{32}H_{37}NO_6 \cdot H_2O$=533.6671; C%,H%,N%): Req. 72.02,7.37,2.62; Found 71.79,6.96,2.50。*IR*(cm^{-1}): 3447(br,H_2O),3068,2955,2931,2866(CH),2833(OCH_3),1763(ester-C=O),1629(amide-C=O),1607,1515(aromatic),1262,1196,1117,852(CH)。^{1}*HNMR*(δppm): 0.94(d,6H,2×CH_3),1.40(d,3H,C_α-CH_3),1.87(m,1H,CH),2.50(m,3H,$COCH_3$),2.73(br,2H,$ArCH_2$),2.98(m,2H,$ArCH_2$),3.35(br,2H,CH_2N),3.77(s,3H,C_7-OCH_3),3.83(s,3H,C_6-OCH_3),4.19(m,1H,C_α-H),5.78(d,1H,C_1-H),6.28-7.34(m,10H,aromatic)。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-烟酰基-1,2,3,4-四氢异喹啉(Ⅱ-9)

Anal. ($C_{29}H_{34}N_2O_3$=458.6026; C%,H%,N%): Req. 75.95,7.47,6.11; Found 76.03,7.58,5.88。*IR*(cm^{-1}): 3073,2960,2908,2868(CH),2834(OCH_3),1624(C=O),1587,1516(aromatic),1264,1115,1018,848(CH)。^{1}*HNMR*(δppm): 0.90(q,6H,2×CH_3),1.16(d,3H,C_α-CH_3),1.45(m,1H,CH),2.48(d,2H,$ArCH_2$),2.80(s,2H,$ArCH_2$),3.40(m,2H,CH_2N),3.70(m,1H,C_α-H),3.79(s,3H,C_7-OCH_3),3.84(s,3H,C_6-OCH_3),5.80(d,1H,C_1-H),6.72(s,1H,C_8-H),6.96(s,1H,C_5-H),7.25(m,6H,aromatic),8.06(d,1H,aromatic),8.52(q,1H,aromatic)。*MS*(*SCI*;*m/z*): 459(M+1,base peak),458(M+,5.30%),297(),263。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-异烟酰基-1,2,3,4-四氢异喹啉(Ⅱ-10)

Anal. ($C_{29}H_{34}N_2O_3$=458.6026; C%,H%,N%): Req. 75.95,7.47,6.11; Found 75.89,7.16,5.93。*IR*(cm^{-1}): 3019,2952,2866(CH),2835(OCH_3),1635(C=O),1611,1518(aromatic),1265,1113,1017,840(CH)。^{1}*HNMR*(δppm): 0.91(q,6H,2×CH_3),1.15(d,3H,C_α-CH_3),1.45(m,1H,CH),2.48(d,2H,$ArCH_2$),2.76(m,2H,$ArCH_2$),3.34(m,3H,C_α-H,CH_2N),3.78(s,3H,C_7-OCH_3),3.84(s,3H,C_6-OCH_3),5.77(d,1H,C_1-H),6.54-7.36(m,8H,aromatic),8.63(m,2H,aromatic)。*MS*(*SCI*;*m/z*): 459(M+1,80.78%),297( ,base peak)。

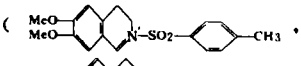
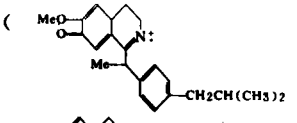
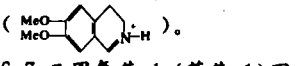
6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-甲磺酰基-1,2,3,4-四氢异喹啉(Ⅱ-11)

Anal. ($C_{24}H_{33}NO_4S$=431.5923; C%,H%,N%): Req. 66.79,7.71,3.25; Found 66.98,7.46,3.28。*IR*(cm^{-1}): 3024,2934,2863(CH),2842(OCH_3),1609,1516(aromatic),1329,1144(N-SO_2),1020,976,838(CH)。^{1}*HNMR*(δppm): 0.88(d,6H,2×CH_3),1.35(d,3H,C_α-CH_3),1.80(m,1H,CH),2.40(t,4H,$ArCH_2$,$ArCH_2$),2.80(m,3H,SO_2CH_3),3.30(m,3H,CH_2N,C_αH),3.78(s,3H,C_7-OCH_3),3.83(s,3H,C_6-OCH_3),4.86(d,1H,C_1-H),6.50(s,1H,C_8-H),6.60(s,1H,C_5-H),7.07(s,4H,aromatic)。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-苯磺酰基-1,2,3,4-四氢异喹啉(Ⅲ-12)

Anal. ($C_{29}H_{35}NO_4S$ = 493.6633; C%, H%, N%); Req. 70.56, 7.15, 2.84; Found 70.80, 7.24, 2.74。*IR* (cm^{-1}): 3067, 2954, 2867(CH), 2834(OCH_3), 1608, 1511(aromatic), 1327, 1164(N-SO_2), 983, 840(CH)。^1HNMR(δppm): 0.85(d,6H,2×CH_3), 1.31(d,3H,C_α-CH_3), 1.82(m,1H,CH), 2.42(d,4H,$ArCH_2$,$ArCH_2$), 3.31(m,3H,CH_2N,C_α-H), 3.68(s,3H,C_7-OCH_3), 3.76(s,3H,C_6-OCH_3), 5.08(d,1H,C_1-H), 6.25(s,1H,C_8-H), 6.85(s,1H,C_5-H), 7.02-7.60(m,9H,aromatic)。

6,7-二甲氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-(4-甲基)苯磺酰基-1,2,3,4-四氢异喹啉(Ⅲ-13)

Anal. ($C_{30}H_{37}NO_4S$=507.6903; C%, H%, N%); Req. 70.97, 7.35, 2.76; Found 70.88, 7.42, 2.75。*IR*(cm^{-1}): 2952, 2865(CH), 2838(OCH_3), 1609, 1515(aromatic), 1330, 1163(N-SO_2), 1091, 973, 836(CH)。^1HNMR(δppm): 0.89(d,J=7.2Hz,6H,2×CH_3), 1.31(d,J=7.2Hz,3H,C_α-CH_3), 1.80(q,1H,CH), 2.29(s,3H,$ArCH_3$), 2.44(q,4H,2×$ArCH_2$), 3.35(m,3H,CH_2N,C_α-H), 3.68(s,6H,2×OCH_3), 5.10(d,1H,C_1-H), 6.45(s,1H,C_8-H), 6.57(s,1H,C_5-H), 7.09-7.51(m,8H,aromatic)。*MS*(*SCI*;*m/z*): 508(M+1, 62.63%), 430, 346 ( , base peak), 337 (), 268, 192 ()。

6,7-二甲氧基-1-(萘基-1)甲基-2-乙酰基-1,2,3,4-四氢异喹啉(Ⅲ-14)

Anal. ($C_{24}H_{25}NO_3$ = 375.4689; C%, H%, N%); Req. 76.77, 6.71, 3.73; Found 76.97, 6.70, 3.71。*IR*(cm^{-1}): 3041, 2955, 2867(CH), 2833(OCH_3), 1634(C=O), 1609, 1513(aromatic), 1266, 1125, 820(CH)。^1HNMR(δppm): 2.12(s,3H,$COCH_3$), 2.75(m,2H,$ArCH_2$), 3.16(m,2H,2×C_α-H), 3.60(m,2H,CH_2N), 3.71(s,3H,C_7-OCH_3), 3.80(s,3H,C_6-OCH_3), 5.55(s,1H,C_8-H), 5.75(q,1H,C_1-H), 6.50(s,1H,C_5-H), 7.0-8.50(m,7H,aromatic)。

6,7-二甲氧基-1-(萘基-1)甲基-2-氯乙酰基-1,2,3,4-四氢异喹啉(Ⅲ-15)

淡黄色晶体,mp147-148℃(文献[5]mp137-138℃)。

6,7-二甲氧基-1-(萘基-1)甲基-2-苯甲酰基-1,2,3,4-四氢异喹啉(Ⅲ-16)

Anal. ($C_{29}H_{27}NO_3 \cdot 3.5H_2O$ = 500.5938; C%, H%, N%); Req. 69.58, 6.85, 2.80; Found 69.64, 6.84, 3.54。*IR*(cm^{-1}): 3443(br,H_2O), 3179, 2931(CH), 2838(OCH_3), 1611(C=O), 1594, 1517(aromatic), 1225, 1123, 812(CH)。^1HNMR(δppm): 3.03(m,2H,$ArCH_2$), 3.70(m,4H,2×C_αH,CH_2N), 4.88(m,br,1H,C_1-H), 5.36(s,1H,C_8-H), 6.58(s,1H,C_5-H), 7.20-8.30(m,12H,aromatic)。

6,7-二甲氧基-1-(萘基-1)甲基-2-苯磺酰基-1,2,3,4-四氢异喹啉(Ⅲ-17)

Anal. ($C_{28}H_{27}NO_4S$ = 473.5883; C%, H%, N%); Req. 71.01, 5.75, 2.96; Found 70.95, 5.87, 2.89。*IR*(cm^{-1}): 3008, 2938, 2849(CH), 2832(OCH_3), 1609, 1510(aromatic), 1335, 1163(N-SO_2), 1119, 1001, 820(CH)。^1HNMR(δppm): 2.70(t,2H,$ArCH_2$), 3.30(m,4H,2×C_α-H,CH_2N), 3.75(s,6H,2×OCH_3), 5.25(q,1H,C_1-H), 5.44(s,1H,C_8-H), 6.45(s,1H,C_5-H), 6.88-8.22(m,12H,aromatic)。

6,7-二甲氧基-1-(萘基-1)甲基-2-(4-甲基)苯磺酰基-1,2,3,4-四氢异喹啉(Ⅲ-18)

Anal. ($C_{29}H_{29}NO_4S \cdot H_2O$ = 505.6307; C%, H%, N%); Req. 68.89, 6.19, 2.77; Found 69.14, 6.69, 3.[illegible]。*IR*(cm^{-1}): 3425(br,H_2O), 2932(CH), 2837(OCH_3), 1609, 1514(aromatic), 1337, 1123(N-SO_2), 1018, 779(CH)。^1HNMR(δppm): 3.08(s,3H,CH_3), 3.20(m,2H,$ArCH_2$), 3.50(m,4H,2×C_α-H,CH_2N), 3.75(s,6H,2×OCH_3), 4.80(br,1H,C_1-H), 5.45(s,1H,C_8-H), 6.62(s,1H,C_5-H), 7.25-8.30(m,11H,aromatic)。

6,7-二甲氧基-1-{1-[(6-甲氧基)萘基-2-]}乙基-2-氯乙酰基-1,2,3,4-四氢异喹啉(Ⅲ-19)

淡黄色晶体,mp 183-184℃(文献[5] mp 176-178℃)。

6,7-次甲二氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-氯乙酰基-1,2,3,4-四氢异喹啉(Ⅲ-20)

Anal. ($C_{24}H_{28}ClNO_3$ = 413.9459; C%, H%, N%); Req. 69.64, 6.82, 3.38; Found 69.71, 6.89, 3.20。*IR*(cm^{-1}): 3047, 2947, 2921(CH), 2873(OCH_2O), 1660(C=O), 1635, 1482(aromatic), 1251, 1039, 855(CH)。^{1}HNMR(δppm): 0.86(d,6H,2×CH_3), 1.30(q,3H,C_α-CH_3), 1.80(m,1H,CH), 2.42(q,2H,$ArCH_2$), 2.83(m,2H,$ArCH_2$), 3.30(m,2H,CH_2N), 3.83(s,2H,CH_2Cl), 4.48(d,1H,C_α-H), 5.58(d,1H,C_1-H), 5.93(s,2H,OCH_2O), 6.55—7.10(m,6H,aromatic)。

6,7-次甲二氧基-1-{1-[4-(2-甲基)丙基]苯基}-2-丙酰基-1,2,3,4-四氢异喹啉(Ⅲ-21)

Anal. ($C_{25}H_{31}NO_3$ = 393.5279; C%, H%, N%); Req. 76.30, 7.94, 3.56; Found 76.26, 8.02, 3.53。*IR*(cm^{-1}): 3047, 2964(CH), 2873(OCH_2O), 1640(C=O), 1610, 1187(aromatic), 1239, 1032, 856(CH)。^1HNMR(δppm): 0.90(m,9H,3×CH_3), 1.30(m,3H,C_α-CH_3), 1.82(m,1H,CH), 2.10(m,2H,$ArCH_2$), 2.42(d,2H,$COCH_2$), 2.80(m,2H,$ArCH_2$), 3.40(m,2H,CH_2N), 4.50(m,1H,C_α-H), 5.62(d,

1H,C_1-H), 5.90 (s, 2H, OCH_2O), 6.58-7.05 (m, 6H, aromatic)。

6,7-次甲二氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-苯甲酰基-1,2,3,4-四氢异喹啉(Ⅱ-22)

Anal. ($C_{29}H_{31}NO_3$=441.5719; C%, H%, N%); Req. 78.88, 7.08, 3.17; Found 78.53, 7.00, 3.10。*IR* (cm^{-1}): 2958(CH), 2872(OCH_2O), 1629(C=O), 1629, 1483(aromatic), 1232, 804(CH)。^{1}*HNMR* (δppm): 0.89(d, 6H, 2×CH_3), 1.50(d, 3H, C_α-CH_3), 1.85(m, 1H, CH), 2.45(d, 2H, $ArCH_2$), 2.65(t, 2H, $ArCH_2$), 3.20(m, 3H, C_α-H, CH_2N), 5.75(s, 1H, C_1-H), 5.90(s, 2H, OCH_2O), 6.55-7.25(m, 11H, aromatic)。

6,7-次甲二氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-甲磺酰基-1,2,3,4-四氢异喹啉(Ⅱ-23)

Anal. ($C_{23}H_{29}NO_4S$=415.5493; C%, H%, N%); Req. 66.48, 7.03, 3.37; Found 66.61, 6.98, 3.36。*IR* (cm^{-1}): 3016, 2950, 2914 (CH), 2866 (OCH_2O), 1619, 1503 (aromatic), 1326, 1155(N-SO_2), 1035, 986, 847, 777(CH)。^{1}*HNMR* (δppm): 0.85(d, 6H, 2×CH_3), 1.31(d, 3H, C_α-CH_3), 1.80(m, 1H, CH), 2.20(s, 2H, $ArCH_2$), 2.42(d, 2H, $ArCH_2$), 2.75(m, 3H, SO_2CH_3), 3.20(m, 2H, CH_2N), 3.50(m, 1H, C_α-H), 4.80(d, 1H, C_1-H), 5.90(s, 2H, OCH_2O), 6.57(d, 2H, C_5-H, C_8-H), 7.08(s, 4H, aromatic)。

6,7-次甲二氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-苯磺酰基-1,2,3,4-四氢异喹啉(Ⅱ-24)

Anal. ($C_{28}H_{31}NO_4S$=477.6203; C%, H%, N%); Req. 70.41, 6.54, 2.93; Found 70.45, 6.47, 3.07。*IR* (cm^{-1}): 2953, 2907 (CH), 2869 (OCH_2O), 1583, 1484 (aromatic), 1333, 1162(N-SO_2), 1034, 860(CH)。^{1}*HNMR* (δppm): 0.86 (d, 6H, 2×CH_3), 1.35(d, 3H, C_α-CH_3), 1.85(m, 1H, CH), 2.38(q, 4H, 2×$ArCH_2$), 3.20(m, 3H, CH_2, C_α-H), 5.03(d, 1H, C_1-H), 5.85(s, 2H, OCH_2O), 6.28(s, 1H, C_8-H), 6.44(s, 1H, C_5-H), 7.00-7.55(m, 9H, aromatic)。

6,7-次甲二氧基-1-{1-[4-(2-甲基)丙基]苯基}乙基-2-(4-甲基)苯磺酰基-1,2,3,4-四氢异喹啉(Ⅱ-25)

Anal. ($C_{29}H_{33}NO_4S$=491.6473; C%, H%, N%); Req. 70.85, 6.77, 2.85; Found 71.10, 6.81, 2.88。*IR* (cm^{-1}): 3014, 2950 (CH), 2869 (OCH_2O), 1598, 1484 (aromatic), 1331, 1151(N-SO_2), 1033, 868(CH)。^{1}*HNMR* (δppm): 0.87 (d, 6H, 2×CH_3), 1.35(d, 3H, C_α-CH_3), 1.85(m, 1H, CH), 2.30(s, 3H, $ArCH_3$), 2.45(m, 4H, 2×$ArCH_2$), 3.25(m, 3H, C_α-H, CH_2N), 5.00(d, 1H, C_1-H), 5.85(s, 2H, OCH_2O), 6.30(s, 1H, C_8-H), 6.40(s, 1H, C_5-H), 7.00-7.45(m, 8H, aromatic)。

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Synthesis of *N*-Acylated/Sulphonylated Tetrahydroisoquinoline Compounds

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In an attempt to search for novel class Ⅲ antiarrhythmic agents, and on the basis of integration of the structural feature of certain potassium channel blockers available, various acyl and sulphonyl groups were introduced to the position 2 of the tetrahydroisoquinoline nucleus in place of the quaternary ammonium group of benzyltetrahydropalmatine chloride (BTHP) which possessed potassium channel blocking activity and antiarrhythmic effect. Thus, 25 *N*-acylated or *N*-sulphonylated tetrahydroisoquinoline compounds (Ⅱ$_{1\sim25}$) were designed and synthesized, 23 of which had not been reported previously in the literature. These compounds were confirmed by elemental analysis, IR, NMR and MS. The effects of the compounds on the potassium channels and their antiarrhythmic activity were under investigation.

Key words Tetrahydroisoquinolines; *N*-Acylated derivatives; *N*-Sulphonylated derivatives; Potassium channel blockers; Antiarrhythmic agents