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论文

5-羟基色胺类似物 Ⅳ.新型抗惊厥药——2-二正丁氨甲基吲(?)的类似化合物

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摘要:

合成了若干2-二烷氨甲基类化合物以及3-二正丁氨甲基吲(口朵)、3-(β-二烷氨乙基)吲(口朵)和2-甲基-3-(β-二正丁氨乙基)-5-甲氧基吲(口朵),这些化合物为前文所述具有抗惊厥作用的2-二正丁氨甲基吲(口朵)的类似化合物,经初步药理评价后,探讨了化学结构与抗惊厥作用间关系,其中以2-二正丁氨甲基-3-甲基吲(口朵)作用为最强。

关键词:

Serotonin Analogues——Ⅳ.Compounds Related to 2-Di-*n*-butylaminomethyl Indole,an Anticonvulsant of a Novel Structural Type

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Abstract:

A novel structural type of anticonvulsants represented by 2-di-n-butylaminomethyl indole (Ia) was previously reported by the authors. In order to investigate further the relationships between structure and activity and to search for more favourable anticonvulsants, in the present work a number of related compounds has been prepared and subjected to pharmacological evaluation. It has been demonstrated that the replacement of the butyl group in Ia by lower or higher alkyls diminishes the anticonvulsant activity. The therapeutic index of Ia can be enhanced and its duration of action prolonged by introducing a methyl group at the 3-position. Substituents on the benzene ring in ;Ⅶ reduce the anticonvulsant activity, but complete loss of activity has been observed only in a few cases. 3-Di-*n*-butylaminomethyl indole, the position isomer of Ia, and its several homologs exhibit almost no anticonvulsant activity. 3-Di-*n*-butylaminomethyl indole was prepared by a Mannich condensation of indole,di-*n*-butylamine, and formaldehyde. 3-*β*-Dialkylaminoethyl indoles were prepared through the interaction of indole-3-glyoxyloyl chloride with dialkylamines followed by the reduction of the resulting amides with lithium aluminium hydride. Ethyl 2-methyl-5-methoxy-indole-3-acetate was converted *via* hydrazide into the corresponding acyl azide, which gave N,N-di-*n*-butyl-2-methyl-5-methoxy-indole-3-acetamide on interaction with di-*n*-butylamine. Reduction of the amide with lithium aluminium hydride afforded 2-methyl-3-*β*-di-*n*-butylaminoethyl indole (Ⅵ). For the syntheses of ring substituted derivatives (Ⅶ), aniline and various substituted anilines were diazotized and subjected to a modified Japp-Klingemann reaction with methyl or ethyl diethyl keto-succinate. The resulting hydrazones were converted into substituted derivatives of ethyl indole-2-carboxylates, which were hydrolyzed to the corresponding acids (Ⅹ). These acids were converted to the acyl chlorides (Ⅺ)and then to the N,N-di-*n*-butyl amides (Ⅻ). Reduction of the compounds Ⅻ led to Ⅶ. 2-Dialkylaminomethyl indoles were prepared similarly from indole-2-carboxylic acid and corresponding dialkylamines.

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