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ANALGETICALLY EFFECTIVE TETRAHYDRONAPHTALENE DERIVATIVES

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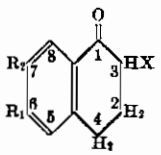
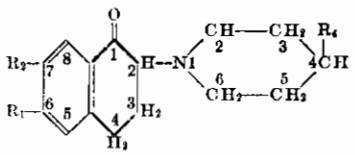
This invention relates to new analgetically effective tetrahydronaphtalene derivatives and to processes for their production.

According to the invention the production of the new compounds takes place in such a manner, that 1-oxo-2-halogen compounds of the tetrahydronaphtalene of the general formula



in which X means one halogen atom are converted in 2-position with a hydrogenated heterocyclic nitrogen base, such as piperidine, tetrahydroisoquinoline or derivatives of these compounds according to known methods to the new compounds which have the general formula



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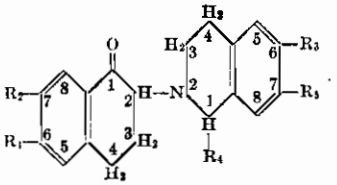

In these formulae mean R_1 and R_2 hydrogen atoms, oxy-, alkyloxy- or alkyl groups and R_3, R_4 and R_5 hydrogen atoms, alkyl- or alkyloxy groups.

The production of the new compounds can take place for instance in that 1-oxo-2-halogen tetrahydronaphtalene is converted in presence of organic solvents with the hydrogenated base, filtered off from the halogen hydrate produced as by-product, and the amino ketone contained in the organic solvent and formed in the conversion is extracted by diluted acids.

For 1 mol of β-halogen-α-tetralon preferably at least 2 mol of nitrogen base are used, as at the conversion 1 mol of halogen hydrogen is formed, which is bound by 1 mol base. The working is carried out preferably with an excess in base, which amounts to about 2.5–3.5 mol.

The solvents which are to be taken into consideration for the conversion of the initial materials are for instance benzene, acetone, ethyl alcohol, propyl alcohol, butyl alcohol, toluene, xylene, dioxane and higher boiling ethers such as propyl ether and butyl ether. It is well to carry out the working at increased temperature, and preferably at such temperatures which correspond to the boiling temperatures of the organic solvents which are used.

Although β-bromide-α-tetralons are generally employed as initial materials, the corresponding chlorine and iodine compounds are also suitable, although these are less easily accessible.

The new compounds may be obtained also in such a manner, that not the hydrogenated heterocyclic nitrogen bases, but the unhydrogenated substances are brought to conversion. Instead of piperidine, for instance pyridine may be used. But in this instance it is necessary to hydrogenate the pyridine ring in the product obtained, which may be carried out for instance with employment of platinum as catalyst.

The amino ketone produced at the conversion is extracted with acids from the actually employed organic solvent. For the extraction diluted mineral acids such as hydrochloric acid, sulphuric acid or organic acids such as tartaric acid, citric acid and lactic acid may be used.

In the following the production of the new compounds will be explained on hand of some examples, without limitation of the invention to the materials, quantity proportions and temperatures employed in the examples being intended.

Example 1—1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene

225 grs of β-bromine-α-tetralon (1.0 mol) are dissolved in 200 ccm benzene and this solution is added into a boiling solution of 260 grs piperidine in 300 ccm benzene. Strong reaction takes place immediately. 154 grs piperidine bromine hydrate=93% of the theory separate out at this occasion. From the benzolic solution the amino ketone is separated out by diluted acids, the acid extract is alkalised and extracted out with benzol. The benzolic solution at the evaporation leaves behind 140 grs 1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene=70% of the theory of the boiling point at 0.3 mm Hg 172°. The colourless chlorine hydrate, which is obtained according to usual methods by conversion with the stoichiometric quantity of hydrochloric acid, shows the melting point 220°.

Example 2—6-methoxy-1-oxo-2-N-piperidyl-1,2,3,4,-tetrahydronaphtalene

382 grs 6-methoxy-2-brom-1-oxo-1,2,3,4-tetrahydronaphtalene (1.5 mol) of the melting point 81° are dissolved in 600 ccm toluene, and this solution is poured into a boiling solution of 400 grs piperidine (4.7 mol) with 750 ccm toluene. After slight reaction piperidine bromine hydrate separates out soon. It is heated for some time on the water bath, then sucked off by the separated out piperidine bromine hydrate (240 grs=96.2% of the theory), and the amino ketone is extracted by diluted acids from the solution in toluene. From the acid solution the amino ketone is separated by diluted alkalis as thick oil taken up by an organic solvent such as benzol or ether, the residue remaining after the expelling of the solvent is distilled or directly worked to chlorine hydrate or to other salts. 325 grs 6-methoxy-1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene (mol weight 259) of the boiling point 0.5 mm 195°=83.8% of the theory are obtained as thick oil, which solidifies to a crystalline mass. The colourless base can be re-crystallised from ether and then melts at 68°. The chlorine hydrate is produced therefrom according to usual methods and shows a melting and decomposition point of 202°.

Example 3—6-oxy-1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene

85 grs 6-acetoxy-1-oxo-2-brom-1,2,3,4-tetrahydronaphtalene (=0.3 mol) are converted in benzol with 100 grs piperidine. After the usual treatment for the obtention of the amino ketone salt (compare example 1), 51 grs 6-oxy-1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene are obtained. The chlorine hydrate has a melting point of 162°. The yield amounts to 60% of the theory.

A similar body is obtained by dealkylisation of 6-methoxy- or 6-ethoxy-1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene, which can be obtained in a similar manner as the compound according to examples 1 and 2, by means of boiling 40–45% hydrobromic acid.

Example 4—6-methoxy-1-oxo-2-N-tetrahydroisoquinolyl-1,2,3,4-tetrahydronaphtalene

180 grs 6-methoxy-1-oxo-2-bromine-1,2,3,4-tetrahydronaphtalene (0.7 mol) are converted with 270 grs tetrahydroisoquinoline into 700 ccm xylene. 172 grs 6-methoxy-1-oxo-2-N-(tetrahydroisoquinolyl) 1,2,3,4-tetrahydronaphtalene are obtained in a yield of 80% of the theory of the melting point 130–132° (from acetone). The chlorine hydrate has a melting point of 215°.

Example 5—6-methoxy-1-oxo-2-N-(6-ethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolyl) 1,2,3,4-tetrahydronaphtalene

77 grs 6-methoxy-1-oxo-2-bromine-1,2,3,4-tetrahydronaphtalene (0.3 mol) are converted boiling with 160 grs 6-ethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline in 400–500 ccm propyl alcohol. 58 grs 6-methoxy-1-oxo-2-N-(6-ethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolyl) 1,2,3,4-tetrahydronaphtalene are obtained in a yield of 55% of the theory of the melting point 130°. The chlorine hydrate has a melting point of 192°.

Example 6—6-methoxy-1-oxo-2-N-piperidyl-1-2-3-4-tetrahydronaphtalene

38 grs 6-methoxy-2-bromine-1-oxo-1,2,3,4-tetrahydronaphtalene (0.15 mol) are dissolved cold with 40 grs piperidine (0.47 mol) in 150 ccm acetone and the temperature of the solution is maintained at 20° by cooling. After some time 23 grs piperidine bromine hydrate=93% of the theory separate out. The acetone solution is worked up to amino ketone according to example 1. 23 grs 6-methoxy-1-oxo-2-N-piperidyl- 1,2,3,4 - tetrahydronaphtalene of the boiling point 172° at 0.2 mm Hg are obtained. The melting point of the substance re-crystallised from ether amounts to 68°. The chlorine hydrate has a melting point of 202°. The yield amounts to 59% of the theory.

Example 7—6-methoxy-1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene

38 grs 6-methoxy-2-bromine-1-oxo-1,2,3,4-tetrahydronaphtalene (0.15 mol) are dissolved warm in 150 ccm alcohol and poured into a boiling solution of 40 grs piperidine (0.47 mol) and 150 ccm alcohol. After boiling for one hour the working is carried out as in example 1. 27 grs 6-methoxy-1-oxo-2 -N-piperidyl - 1,2,3,4 - tetrahydronaphtalene of the boiling point 172° at 0.2 mm Hg are obtained. The melting point amounts to 68°. The chlorine hydrate has a melting point of 202°. The yield amounts to 70% of the theory.

Example 8.—6-methoxy -1- oxo -2- N - piperidyl - 1,2,3,4-tetrahydronaphtalene

20 grs 6 - methoxy - 1 - oxo-1,2,3,4-tetrahydronaphtalene-2-pyridinium bromide (0.06 mol) of the melting point of 250°, produced from molecular quantity 6-methoxy-1-oxo-2-bromine-1,2,3,4-tetrahydronaphtalene and pyridine in xylene, are catalytically hydrogenated in methylalcoholic solution with platinum as catalyst. After a rapid absorption of 0.18 mol hydrogen, the hydrogen absorption comes to standstill. When working up the reaction solution to amino ketone according to example 1, 14.5 grs 6-methoxy-1-oxo-2-N-piperidyl-1,2,3,4-tetrahydronaphtalene of the boiling point 172° at 0.2 mm Hg are obtained. The melting point amounts to 68°. The chlorine hydrate has a melting point of 202°. The yield amounts to 93% of the theory.

Example 9.—6-methoxy -1- oxo-2-N-α-pipecolyl - 1,2,3,4-tetrahydronaphtalene

51 grs 6-methoxy-1-oxo-2-bromine-1,2,3,4-tetrahydronaphtalene (0.2 mol) are converted in a boiling dioxane with 60 grs α-pipecoline (0.6 mol). 35 grs α-pipecoline bromine hydrate (98% of the theory) separate out. When completing the working up of the reaction solution to amino ketone, 33 grs 6-methoxy-1-oxo-2-N-α-pipecolyl-1,2,3,4-tetrahydronaphtalene of the boiling point 192° at 1.6 mm Hg are obtained. The chlorine hydrate has a melting point of 192°. The yield amounts to 60% of the theory.

Example 10.—7 - methyl - 1 - oxo -2- N-(2'4'dimethyl) piperidyl-1,2,3,4-tetrahydronaphtalene

141 grs 7-methyl-1-oxo-2-bromine-1,2,3,4-tetrahydronaphtalene (0.59 mol) are converted with 200 grs 2.4-dimethyl-piperidine (1.77 mol) in 450 ccm n-propyl ether (or n-butyl ether). 168 grs bromine hydrate of the 2.4 dimethylpiperidine (93.5% of the theory) are obtained. Of amino ketone are obtained 80 grs 7-methyl-1-oxo-2-N(2'4'dimethylpiperidyl) - 1,2,3,4 - tetrahydro - naphtalene of the boiling point 165° at 0.25 Hg. The yield amounts to 50% of the theory. The chlorine hydrate has a melting point of 220° under decomposition.

Example 11.—7-methoxy - 1 - oxo -2- N(2'4'dimethyl) piperidyl-1,2,3,4-tetrahydronaphtalene

128 grs 7-methoxy -1- oxo -2- bromine-1,2,3,4-tetrahydronaphtalene (0.5 mol) of the melting point of 84° are converted boiling with 170 grs 2.4-dimethylpiperidine (1.5 mol) in 370 ccm benzol. 93 grs bromine hydrate of the 2.4 dimethyl-piperidine (96% of the theory) are obtained. Of amino ketone are obtained 80 grs 7-methoxy -1- oxo-2-N(2'4'-dimethyl) piperidyl-1,2,3,4-tetrahydronaphtalene of the boiling point 168° at 0.3 mm Hg. The yield amounts to 56% of the theory. The chlorine hydrate has a melting point from 198 to 200° under decomposition.

Example 12.—6-methoxy - 1 - oxo - 2 - N(2'4'dimethyl) piperidyl-1,2,3,4-tetrahydronaphtalene

255 grs 6-methoxy -1- oxo -2- bromine-1,2,3,4-tetrahydronaphtalene (1.0 mol) are converted boiling with 270 grs 2.4-dimethylpiperidine (2.4 mol) in 800 ccm toluene. 97% of the theory are obtained in amino bromine hydrate. By means of tartaric acid solution of amino ketone are isolated 287 grs 6-methoxy -1- oxo -2- N(2'4'dimethyl) piperidyl - 1,2,3,4 - tetrahydronaphtalene (75% of the theory) of the boiling point 180° at 0.36 mm Hg. The chlorine hydrate has a melting point of 203° under decomposition.

Example 13.—1-oxo-2-N(2'4'dimethyl) piperidyl - 1,2,3,4-tetrahydronaphtalene

225 grs β-bromine-α-tetralon (1 mol) are converted with 300 grs 2.4-dimethylpiperidine (2.65 mol) in 1000 ccm xylene at 120°. 186 grs bromine hydrate (96% of the theory) are isolated. The amino ketone is extracted by means of citric acid solution. 103 grs 1-oxo-2-N-(2'4'dimethyl) piperidyl-1,2,3,4-tetrahydronaphtalene (40% of the theory) of the boiling point 158° at 0.2 mm Hg are obtained. The chlorine hydrate has a melting point of 232° under decomposition.

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