

1

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ALPHA-ALKYL-PROPIOPHENONES

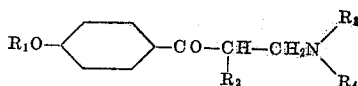
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6 Claims. (Cl. 260—570.5)

The present invention is concerned with compounds having a local anesthetic effect. The compounds according to the invention are basic ketones having the following general formula:



in which R_1 is an alkyl comprising from 2 to 5 and preferably 2–3 carbon atoms, R_2 is an alkyl comprising from 1 to 5 and preferably 1–2 carbon atoms, and R_3 and R_4 are alkyls comprising from 1 to 4 carbon atoms, the number of carbon atoms of R_3 and R_4 together preferably ranging from 2 to 6. Not only the basic ketones themselves but also their salts with e.g. hydrohalic acids have the desired local anesthetic effect and the invention comprises also salts of the basic ketones.

The basic ketones according to the present invention are usually employed in the form of diluted aqueous solutions of their salts with hydrohalic acids. As a rule, about 1% solutions of these salts are used, e.g. for administering local anesthesia by injection or by dropping droplets into the eyes.

In respect of their local anesthetic effect, the new compounds are equivalent to the best known local anesthetics such as for instance xylocaine. An important advantage of the new local anesthetics according to the invention consists in that they have a very low toxicity and, in particular, in that they cause extremely little local irritation.

A further advantage of the local anesthetics according to the invention consists in their being very stable, also when heated in aqueous solution for a longer period of time. It is common practice to sterilize solutions of local anesthetic compounds by heating them to 100° C. in sealed ampoules. Many of the known local anesthetics, especially also certain basic ketones closely related to the compounds according to the present invention, have been found to be chemically unstable when exposed to a longer period of heating. This appears from changes in their absorption spectrum, particularly with respect to the position of the absorption maximum in the ultraviolet range, and also from a decrease in the extinction by a solution of a given concentration. While closely related compounds already after having been heated for 15 minutes show a substantial change, both as regards the position of their absorption maximum in the ultraviolet range and as regards the extinction—and this change is then greatly increased on still further prolonged heating—the compounds according to the present invention have been found to be unaffected by 15 minutes' heating, in respect of their absorption maximum in the ultraviolet range as well as in respect of the extinction. Even after having been heated for 60 minutes the position of their absorption maximum remains completely unchanged, and only a small decrease in extinction can be observed. These desirable properties are found only

2

in the compounds according to the present invention, in which the aliphatic radical attached to the carbonyl group is branched while the alkyl radicals attached to the nitrogen atom do not form a ring together with the nitrogen atom. Basic ketones of this class in which the aliphatic radical attached to the carbonyl group is not branched have been found to be particularly unstable when subjected to heating for a longer period, but also such basic ketones of this class in which the aliphatic radical attached to the carbonyl group is branched but the substituents at the basic nitrogen atom form a cyclic radical together with said nitrogen atom have proved to be far less resistant to prolonged heating than the compounds according to the present invention.

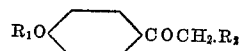
In the above formula, R_2 may be an alkyl radical having from 1 to 5 carbon atoms, but particularly good results are obtained with those of our compounds in which R_2 comprises only 1 or 2 carbon atoms, it having been found that compounds in which R_2 contains from 3 to 5 carbon atoms may still cause a certain degree of local irritation, while this is avoided practically completely with the compounds—in which R_2 comprises only 1 or 2 carbon atoms. When these latter compounds are employed there will be no danger of necrose formations which may otherwise sometimes occur due to the use of local anesthetics causing local irritation.

The below table contains physical data of some of our compounds which have proved to be particularly valuable in practical use.

	Melting Point, ° C.	Halogen	
		Calculated	Found
35 α - methyl - β - dimethyl - amino - p - ethoxypropio-phenone hydrochloride...	150-152	13.0	13.0
α - methyl - β - dipropyl - amino - p - propoxypropio-phenone hydrochloride...	134-135	10.4	10.5
40 α - methyl - β - diethyl - amino - p - propoxypropio-phenone hydrobromide...	106-108	22.3	22.2
α - methyl - β - diethylamino - p - ethoxypropio-phenone hydrochloride...	132-133	11.9	11.9
α - methyl - β - dimethyl - amino - p - propoxypropio-phenone hydrochloride...	146-147	12.4	12.4
45 α - methyl - β - dipropyl - amino - p - ethoxypropio-phenone hydrochloride...	137-138	10.8	10.9

As regards the above-mentioned low toxicity of the compounds according to the present invention, it may be mentioned that when e.g. the second compound in the table is administered to mice by subcutaneous injection the amount of this compound which will cause death of 50% of the mice treated is 35 times greater than the corresponding DL_{50} amount of xylocaine with which said compound of the table is equivalent in its local anesthetic effect. Furthermore, the local irritation caused by this compound is 4 times weaker than that caused by a similar compound in which the substituents at the nitrogen atom form a piperidine ring together with the nitrogen.

The compounds according to the present invention are obtained by reacting, preferably in a solution of hydrohalic acid, a ketone having the formula



in which R_1 and R_2 have the same meanings as above with formaldehyde or a compound generating formaldehyde and with a secondary amine having the formula



3

in which R_3 and R_4 have the same meanings as above. Instead of said amine one may use if desired a salt of said amine with an acid, e.g. a hydrohalic acid.

The preparation of the compounds according to the present invention is further illustrated by the following examples.

Example 1

A mixture of 17.9 gms. of p-ethoxypropio-
phenone, 8.2 gms. of dimethylamino hydrochloride, 5 gms. of para-
formaldehyde, 80 cc. of ethanol and 1 cc. of concen-
trated hydrochloric acid is boiled for 12 hours, 9 gms.
of paraformaldehyde being added in small portions about
every three hours.

When the reaction is complete the mixture is evapo-
rated on a water bath, washed with ether, dissolved in
water, and then adjusted to an alkaline pH. The base
precipitated in this manner is taken up in ether, the ether
layer is washed with water, dried, and then admixed with
alcoholic hydrochloric acid. This results in the precipi-
tation of α -methyl- β -dimethylamino-p-ethoxypropio-
phenone hydrochloride in the form of white crystals melting
at 150–152° C.

Example 2

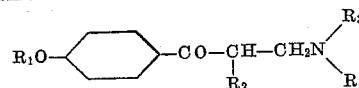
19.2 gms. of p-propoxypropio-
phenone, 18.2 gms. of
dipropylamino hydrobromide, 15 cc. of 40% formalin,
1 cc. of concentrated hydrobromic acid and 50 cc. of eth-
anol are boiled for 15 hours. The solution is evaporated
on a water bath and then treated as in Example 1. On
re-crystallization from a mixture of ethanol and ether,

4

there will be obtained α -methyl- β -dipropylamino-p-pro-
poxypropio-phenone hydrochloride having a melting point
of 134–135° C.

We claim:

1. A member of the group of basic ketones having the
general formula



in which R_1 is an alkyl with 2 to 5 carbon atoms, R_2 is
an alkyl with 1 to 5 carbon atoms, and R_3 and R_4 are
inter se uncombined alkyls with 1 to 4 carbon atoms
and the hydrohalic salts thereof.

2. α -methyl- β -dimethylamino-p-ethoxypropio-
phenone hydrochloride.

3. α -methyl- β -diethylamino-p-propoxypropio-
phenone hydrobromide.

4. α -methyl- β -diethylamino-p-ethoxypropio-
phenone hydrochloride.

5. α -methyl- β -dimethylamino-p-propoxypropio-
phenone hydrochloride.

6. α -methyl- β -dipropylamino-p-ethoxypropio-
phenone hydrochloride.

References Cited in the file of this patent

Mannich et al.: Ber. (Deutsche Chem. Gesell.), vol.
55, p. 3512 (1922).