UNITED STATES PATENT OFFICE

2,686,785

SATURATED DITHIENYL PROPIL AMINES
AND PROCESS OF MAKING

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1. The present invention relates to chemical compounds
of pharmaceutical value and to processes for
making the same.

3-tertiaryamino-1:1-dil-2'-thienylalk-1-enes of the type:

(Th):C=CH.CH=NR1.NR2 (I)

In which Th signifies a 2'-thienyl group, R1
is hydrogen or an alkyl group containing from
1 to 3 carbon atoms and R2 and R2 may be
identical or different and be methyl or ethyl
groups or NR3.R3 may denote the morpholino-
pyrrolidino or piperidino-groups, are already
known, various members of the series being
described for example in co-pending U. S.
application Serial No. 104,810, filed July 14, 1949, now
U. S. Patent 2,561,899. They may be formed by
dehydration of the corresponding carbinols,
which themselves may be formed by a variety of
synthetic routes.

Attempts to reduce the compounds of the type
(I) by many usual hydrogenating processes
either fail altogether or result in attack of the
thienyl groups. We have now found that the
double bond can be reduced by means of metal-
llic sodium without at the same time attacking the
thienyl groups whereby compounds of the general
formula

Th:CH.CH=CH=NR1.NR2 (II)

where Th, R1, R2 and R3 or NR2 may have the
same meanings given above, are produced.
Such compounds are novel and some are found to have
a valuable analgesic and some a spasmyptic
activity. Analgesic activity is most prominent in
those compounds wherein R1=CH3. The com-

pounds are conveniently administered in the form
of their salts such as their hydrochlorides.

The identity of the acid used for preparing the
salt is of no consequence for the physiological
activity, however, providing it is not itself high-
ly toxic. Choice of the acid to be used is gov-
erned by availability or convenience and all salts of the
compounds of this invention with non-
toxic acids are considered equivalent. For
pur-
poses of this application, the base and non-toxic
salts thereof are to be regarded as equivalents.

The compounds of the present invention have
the advantage in presentation, compared with
analogous known dithienyl alkenylamines, that
they are more stable to heat and to exposure to
air which facilitates their sterilisation.

The present invention therefore comprises a
process for the production of compounds of the
general formula (II) as above defined, by
subjecting compounds of the type (I) as above de-


cined to reduce under such conditions that the
thienyl groups are not attacked while the double
bond is reduced, for example by means of meta-
llic sodium in an alcohol (preferably an alcohol
having not more than 6 carbon atoms) with
or without the addition of water or in liquid
ammonia, or by sodium amalgam and acid.

While these variations are equivalent in that
they all suffice to produce the desired reduction,
they are not all equally convenient or efficient.
The reductions in ethanol frequently are incom-
plete and yields are in all cases less than quantita-
tive, usually in the range of 50–70%. When
complete reduction is secured the loss (from the
quantitative yield) is due to de-aminiation which
proceeds concurrently. Such cleavages are rela-
tively prominent when amyl alcohol is used
as the solvent for which reason, and also be-
cause it is harder to get rid of amyl alcohol at
the end of the reduction, it is preferred to use
propanol (either n- or iso), or 80% ethanol.

Completeness of reduction can be determined by
the absorption spectrum of the product. The
parent allylamines possess intense absorption
(λ=14,100) at 290 mμ whereas the saturated
amines have only feeble absorption (λ=800) at
that wave length.

Alternatively, if a sample containing some of
the unsaturated amine is heated to boiling in
concentrated hydrochloric acid an orange color
develops, which, on standing 15–30 minutes be-
comes an intense blue. This test, which is very
sensitive has proved of great utility in deter-
mining the conditions for securing complete re-
action in these reductions.

The invention also provides new pharmaceuti-
cally active compounds, having analgesic and
spasmyptic properties, of the general formula
(II) above defined. Particularly the invention
comprises the compounds herein described or
salts thereof.

The invention is illustrated by the following
examples:

Example 1

Sodium metal (7 g.) was added gradually to
a boiling solution of 3-dimethylamino-1:1-dil-
2'-thienylbut-1-ene (5 g.) in ethanol (70 mI.).
When all had dissolved, the alcohol was evapo-
rated, and the residue dissolved in water and ex-
tracted with ether, yielding 3-dimethylamino-
1:1-dil-2'-thienylbutane (5 g.), the nitrates of
which had a melting point 161°–162° C.

Example 2

A boiling solution of 3-pyrroldino-1:1-dil-2'-
thiénybut-1-ene (5 g.) in ethanol (70 ml.) was added to sodium metal (7 g.) and worked up as above, yielding 3-pyrroldino-1:1-di'-2'-thiénylbutane (3 g.); the hydrochloride of which melted at 154° C.

Example 3

Sodium metal (7 g.) was added to a boiling solution of 3-dimethylamino-1:1-di'-2'-thiénybut-1-ene (6 g.) in anhydrous alcohol (100 ml.) and worked up as above, yielding 3-dimethylamino-1:1-di'-2'-thiénylbutane (2.7 g.).

Example 4

To a solution of 3-dimethylamino-1:1-di'-2'-thiénybut-1-ene (5 g.) in 2 N-hydrochloric acid was added 3% sodium amalgam (250 g.). When the reaction was complete, the aqueous layer was decanted, treated with excess ammonium solution of specific gravity 0.860 and extracted with ether, and dried 3-dimethylamino-1:1-di'-2'-thiénylbutane (1.5 g.).

Example 5

A slight excess of sodium metal was added to 3-dimethylamino-1:1-di'-2'-thiénybut-1-ene (5 g.) in a mixture of equal parts of ether and liquid ammonia. After the addition of excess ammonium chloride, the ammonia was allowed to evaporate and from the ether was obtained 3-dimethylamino-1:1-di'-2'-thiénylbutane (1.4 g.).

Example 6

Seven g. of sodium metal was added to a boiling solution of 5 g. of 3-dimethylamino-1,1-di'-2'-thiénylbutane in 100 cc. of n-propanol. When all the sodium had dissolved, the propanol was evaporated and the residue was dissolved in water and extracted with ether yielding 3.5 g. of 3-dimethylamino-1,1-di'-2'-thiénylbutane, identical with that obtained in Example 1.

Example 7

Sodium metal (40 g.) was added gradually to a solution of 3-dimethylamino-1:1-di'-2'-thiénybut-1-ene hydrochloride (10 g.) in aqueous ethanol (400 ml., 40%) under reflux, and worked up as above, yielding 3-dimethylamino-1:1-di'-2'-thiénylbutane (7 g.).

Similarly, 3-dimethylamino-1:1-di'-2'-thiénybut-1-ene gave 3-dimethylamino-1:1-di'-2'-thiénylbutane (hydrochloride melting at 123°-125° C.). 3-piperidino-1:1-di'-2'-thiénybut-1-ene gave 3-piperidino-1:1-di'-2'-thiénylbutane (55 g.); 3-piperidino-1:1-di'-2'-thiénylbut-1-ene gave 3-piperidino-1:1-di'-2'-thiénylbutane (oxalate, melting at 111°-112° C.).

3-morpholino-1:1-di'-2'-thiénybut-1-ene gave 3-morpholino-1:1-di'-2'-thiénylbutane (hydrochloride, melting at 183°-186° C.).

3-dimethylamino-1:1-di'-2'-thiénylprop-1-ene gave 3-dimethylamino-1:1-di'-2'-thiénylpropene (oxalate, melting at 182°-183° C.).

3-dimethylamino-1:1-di'-2'-thiénylhex-1-ene gave 3-dimethylamino-1:1-di'-2'-thiénylhexane (hydrochloride, melting at 136° C.).

3-ethylmethylamino-1:1-di'-2'-thiénybut-1-ene gave 3-ethylmethylamino-1:1-di'-2'-thiénylbutane (hydrochloride melting at 124°-125° C.).

I claim:

1. Compounds of the class consisting of dimethylamino, diethylamino, methylethylamino, piperidino and pyrroldino, and their non-toxic acid addition salts.
2. As a new compound 3-diethylamino-1:1-di'-2'-thiénylbutane.
3. As a new compound 3-pyrroldino-1:1-di'-2'-thiénylbutane.
4. As a new compound 3-piperidino-1:1-di'-2'-thiénylbutane.
5. As a new compound 3-dimethylamino-1:1-di'-2'-thiénylbutane.
6. As a new compound 3-methylmethylamino-1:1-di'-2'-thiénylbutane.
7. The process of producing bases of the formula

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}_{=\text{N}}\text{CH} = \text{B}
\]

where R is a member selected from the group consisting of lower alkyl groups and hydrogen, N=B is a member of the group lower dialkylamino, piperidino, pyrroldino and morpholino, which consists of reducing the corresponding unsaturated amine

while dissolved in solvent and metal reducing combinations selected from the class consisting of (a) sodium metal and a lower alcohol (b) sodium metal and liquid ammonia and (c) sodium amalgam and a dilute aqueous mineral acid.

8. The process of producing bases of the formula

\[
\text{C}_3\text{H}_7\text{CH}_2\text{CH}_2\text{C}_{=\text{N}}\text{CH} = \text{B}
\]

where R is a member selected from the group consisting of lower alkyl groups and hydrogen, N=B is a member of the group lower dialkylamino, piperidino, pyrroldino and morpholino, which consists of reducing the corresponding unsaturated amine

with metallic sodium while dissolved in n-propanol.

9. The process of producing bases of the formula

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{C}_{=\text{N}}\text{CH} = \text{B}
\]

where R is a member selected from the group consisting of lower alkyl groups and hydrogen, N=B is a member of the group lower dialkylamino, piperidino, pyrroldino and morpholino, which consists of reducing the corresponding unsaturated amine

with metallic sodium while dissolved in isopropanol.

10. The process of producing bases of the formula

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{C}_{=\text{N}}\text{CH} = \text{B}
\]

where R is a member selected from the group consisting of lower alkyl groups and hydrogen, N=B is a member of the group lower dialkylamino, piperidino, pyrroldino and morpholino, which consists of reducing the corresponding unsaturated amine.
where R is a member selected from the group consisting of lower alkyl groups and hydrogen, N=B is a member of the group lower dialkylamino, piperidino, pyrrolidino and morpholino, which consists of reducing the corresponding unsaturated amine

\[
\begin{align*}
\text{C}=\text{CH} \cdot \text{CH} \cdot \text{N} \equiv \text{B} \\
\text{R}
\end{align*}
\]

with metallic sodium while dissolved in 80% aqueous ethanol.

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