United States Patent Office 3,023,146 Patented Feb. 27, 1962



3,023,146

# 2-PROPIONYL-10[γ-(N'-β-HYDROXYETHYL PIPERAZINO)-PROPYL]-PHENOTHIAZINE: PROCESS FOR THE TREATMENT OF WITHDRAWN PSYCHOTIC SUBJECTS

Richard F. Tislow, Philadelphia, William F. Bruce, Havertown, and James A. Page, Berwyn, Pa., assignors to American Home Products Corporation, New York, N.Y., a corporation of Delaware

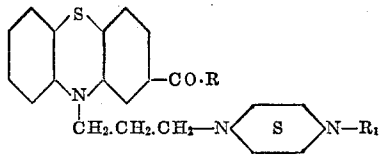
No Drawing. Filed June 6, 1960, Ser. No. 33,894
4 Claims. (Cl. 167—65)

This invention relates to phenothiazine derivatives and more particularly to acylated phenothiazines having useful therapeutic activity.

Phenothiazine compounds have been extensively investigated both pharmacologically and clinically and in general a substantial number have been found to possess a tranquilizing or sedative action, particularly on agitated psychotics. Moreover, a few of these compounds have demonstrated the ability not only to calm the violent patient but to go still further, in the direction of producing a catatonic or cataleptic state. In some circumstances, the latter may be a desirable property.

However, the ability to supress agitation is not invariably desired or useful. It is recognized that there is a large reservoir of mentally ill presons who are not actively violent or agitated. In the case of frank schizophrenia, for example, after a period of time the manifestations are likely to have moved through the agitated stage to a vegetative or catatonic stage. In this latter stage one would not require or seek a tranquilizing or catatonic action in a drug. What is needed is a drug capable of arousing or awakening the patient from the withdrawn or catatonic state.

The present invention involves the discovery of new compounds of the phenothiazine class that have the ability to act on the central nervous system and are specifically useful for the treatment of psychotics. These may be illustrated by the general formula




wherein R represents a lower alkyl, preferably ethyl, while $R_1$ represents a hydroxy substituted lower alkyl radical, and preferably a beta-hydroxyethyl radical. Thus, a compound which has been found to possess an unusual ability to arouse emotionally regressed patients that appear to be in a catatonic state is 2-propionyl-10-[γ-(N'-β-hydroxyethyl piperazino)-propyl]-phenothiazine.

In addition to the basic compounds illustrated by the above formula, the pharmaceutically acceptable acid-addition salts are also contemplated as falling within the scope of the invention. Various acids may be used that will form acceptable non-toxic acid-addition salts at the therapeutic level, as for example, phosphoric, sulfuric, nitric, hydrochloric, hydrobromic, acetic, propionic, sorbic, glutaric, glutamic, adipic, aspartic, fumaric, maleic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, benzoic, benzene sulfonic, phthalic, salicylic, nicotinic or embonic acids.

The preparation of the compounds falling within the above described general formula is not difficult and has already been adequately described in various patents and publications. One procedure that may be used involves the reaction of 2-propionyl phenothiazine with an alkali metal hydride in a suitable solvent, as for example, dimethyl formamide. Thereafter the phenothiazine product is alkylated with an alkylene halide, such as trimethylene chlorobromide. Following the alkylation step, the reaction product is then treated with the N-substituted piperazino compound and the final basic desired compound is isolated. This method is described in the application of Kantor and Tubis, Serial No. 612,881, filed Sept. 28, 1956. To prepare an acid-addition salt, one may use any known procedure, as for example, a simple acid-base reaction carried out in an organic solvent.



The following example more specifically teaches the process of preparation but it is to be understood that the example is merely to be taken as illustrative and not limitative of the invention.

*Example*

In a round-bottomed flask were placed 35 grams of 2-propionyl phenothiazine (0.14 m.), 7 grams of 50% sodium hydride in mineral oil (0.14 m.), and 240 cc. of dimethyl formamide dried over sodium hydride. The resultant solution was stirred at room temperature for 2 hours, and then 88 grams (0.56 m.) of trimethylene chlorobromide was added at once.

The mixture was stirred for 2 hours, heated at 60–70° C. for 1 hour and poured into 2 liters of $H_2O$. The resulting suspension was extracted with ether, the ether layer separated and the ether removed under vacuum. A gummy mass remained which was dissolved in decalin and the solution was partly distilled to remove excess chlorobromide. After removal of most of the decalin under vacuum, the residue was treated with a large excess of N-(β-hydroxyethyl)-piperazine and heated on a steam bath for 2 hours. This material was extracted with dilute aqueous HCl, this acid layer neutralized with aqueous base and the resulting oil extracted into ether. The ether layer was washed with water until the washings were neutral and dried over anhydrous potassium carbonate. On treatment with maleic acid in ether a yellow solid separated which was recrystallized from isopropanol. This yellow solid had M.P. =175–177° C.

$C_{32}H_{39}O_{10}N_3S$ Calc. S=4.9, C=58.4, H=6.0. Found: S=4.7, C=58.6, H=6.6.

The compounds of the invention may be used either orally or parenterally. For parenteral injections a unit dosage range of 5 to 15 mg./cc. is useful, and preferably a unit dosage of not more than about 10 milligrams of active material per cc. The free base may be utilized in suppository compositions but when an oral or injectable composition is contemplated, the active ingredient is utilized in the form of an acid-addition salt. As an oral medicinal, the dosage may range from 10 to 400 mg./day depending on the extent of the disease. Simple dosage units ranging from 10 mg. to 100 mg. are practical. While tablets are preferred, one may also make use of capsules or suspensions. In the latter case, it would be necessary to select a salt that is sparingly water soluble. In the dry form, the active ingredient is incorporated on a carrier which could be the usual well-known excipients. In the case of an aqueous suspension, various well-known suspending agents, as for example, carboxymethyl cellulose should be used.

When considering an injectable preparation, this may be made up in dry form which may be reconstituted for immediate use, or an injectable product may be prepared in the usual way, utilizing an isotonic medium. It should be pointed out that where an acid-addition salt is utilized in an aqueous medium, when the product is not intended to be utilized immediately, it must be buffered and stabilized since phenothiazines are unstable in an aqueous medium. For buffering, one could use, for example, sodium acetate and acetic acid or sodium citrate with citric acid. As stabilizers or antioxidants, useful substances are ascorbic acid or sodium form aldehyde sul-

foxylate or sodium metabisulfite or combinations of these. Preservatives are also utilized in many compositions and illustrative of these may be mentioned the parabens, phenol or sodium benzoate, among the well-known antibacterial and antifungal agents.

This application is a continuation-in-part of our application Serial No. 817,740, filed June 3, 1959.

We claim:

1. The method of treating a chronic psychotic person who exhibits regression predominantly characterized by symptoms of withdrawal and apathy which comprises, administering to such person a therapeutic composition containing a phenothiazine of the group consisting of 2-propionyl-10-[γ-(N'-β-hydroxyethyl piperazino)-propyl]-phenothiazine and pharmaceutically acceptable acid-addition salts thereof, combined with a carrier, said phenothiazine being present in an amount from about 5 to 100 milligrams per dosage unit.



2. The method of treating a chronic psychotic as described in claim 1; wherein the phenothiazine compound is in the form of a non-toxic acid-addition salt and the carrier comprises an aqueous vehicle.

3. The method of treating a chronic psychotic as described in claim 2; wherein the phenothiazine compound is present in an amount from about 5 to 15 mg./cc.

4. The method of treating a chronic psychotic as described in claim 1; wherein the composition comprises a solid excipient carrier.

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