EPHEDRINE SALTS OF FATTY ACIDS AS SOLUBILIZING AGENTS IN MINERAL OIL SYSTEMS.

BY E. E. MOORE.*

It is well known that many alkaloids which are insoluble in mineral oil dissolve in mixtures of mineral and vegetable oils. The importance of the free fatty acids present in the latter has not been fully recognized. A good grade of olive oil will contain about one per cent free fatty acid. Because of its alkaline nature the alkaloid can combine with this free acid to form a salt. The latter is not only much more soluble than the original alkaloid in mineral oil but the resulting solution has much greater solvent power than the original oil. In this work the formation of ephedrine salts of fatty acids and the solvent action of their solutions in mineral oil were studied.

The purpose of this investigation was to prepare a mineral oil solution of ephedrine, a secondary aliphatic amine, and metaphen, an acidic organo mercurial.

Solutions of ephedrine and acidic organo mercurials in vegetable oils may be readily prepared. Investigation indicated that these were not true solutions, but colloidal suspensions. They exhibit the characteristic Tyndall beam, and t e interfacial tension between the oil solution and water is lowered so that emulsions can easily be formed.

These facts suggest that the system may be stabilized by a compound formed between the ephedrine and some substance present in the vegetable oil, presumably the free fatty acid. The system would then consist of oil as the continuous phase, the amine salt of the mercurial as the discontinuous phase, and the amine soap at the interface as the stabilizing agent.

Solubilities were studied in olive oil containing one per cent free fatty acid, neutral olive oil, and neutral methyl and ethyl esters of the fatty acids of olive oil. Ephedrine is soluble in all the above oils, while metaphen and metaphedrin, formed from one mol. each of ephedrine and metaphen, are insoluble.

An excess of ephedrine was added to suspensions of metaphen and of metaphedrin in the different oils. Only in the case of olive oil did solutions result. The rate of solution was much more rapid with the metaphedrin than with the metaphen, which indicates that the amine salt of the organo mercurial must form before the latter can dissolve.

When one per cent of oleic acid was added to the neutralized oils, they behaved like the olive oil. Solutions resulted under the same conditions.

Mineral oil was then tested. When one per cent of oleic acid was added, solutions resulted as readily as with olive oil. Further work showed that the oleic acid content could be reduced. Preparations containing 0.1% oleic acid, 1.0% ephedrine, and 0.04% metaphen show no signs of separation after two years.

Other acidic organo mercurials such as mercurosal, merthiolate and mercurophen were found to behave like metaphen in this respect. Acidic organo metallic compounds other than mercurials were used. Other amines which form oil-soluble soaps, such as the ethanolamines (1) can be used in place of ephedrine. The unsaturated fatty acids of high molecular weight, oleic and erucic, give the most stable systems.

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The rate of solution was estimated by the color development, while completeness of solution and stability were determined by analysis for mercury (2).

The most satisfactory method of preparation consists in first forming the ephedrine salts of the mercurial and of the fatty acid and then stirring these into the oil.

The concentration of mercurial which may be obtained is limited by the requirement that on an average four mols of the ephedrine salt are required for each mol. of the mercurial amine salt. Stable preparations containing 1.0% of the latter have been made.

LITERATURE CITED.

(1) A. L. Wilson, *Ind. Eng. Chem.*, 22 (1930), 143.
(2) Moore and Shelberg, *Ind. Eng. Chem., Analyt. Edit.*, 4 (1933), 224.

A COMPARISON OF THE EFFECT OF PHENYL ETHANOLAMINE AND EPHEDRINE ON NASAL MEMBRANES.*

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Ephedrine solutions are widely used for application to nasal membranes, and Tainter (*J. Pharmacol. Exper. Therap.*, 36 (1929), 52) described the satisfactory behavior of phenyl ethanolamine on nasal membranes. It was, therefore, of interest to prepare phenyl ethanolamine for comparison with ephedrine. The phenyl ethanolamine was prepared by methods described in detail below and was tested as the hydrochloride in 1, 2 and 4% aqueous solution and as the oleate in mineral oil solution using in both cases corresponding ephedrine solutions as controls. The solutions of the oleates were prepared by dissolving 5 Gm. of the base with a chemical equivalent quantity of oleic acid in mineral oil so that the total volume was 100 cc. The tests consisted of applying these solutions to the nasal membranes of both horses and human beings and observing the degree and duration of blanching and recording in the experiments on human beings the relief. As a result of these tests we conclude that there is little difference between the phenyl ethanolamine and ephedrine.

EXPERIMENTAL.

Preparation of ω-Aminoacetophenone.—$C_6H_5.CO.CH_2Cl + (CH_2)_6N_4 \longrightarrow C_6H_5.CO.CH_2.[(CH_2)_6.N_4].Cl.$

$C_6H_5.CO.CH_2[(CH_2)_6.N_4].Cl + 3HCl + 12C_2H_5OH \longrightarrow C_6H_5CO.CH_2.NH_2.HCl + 3NH_4Cl + 6CH_2.(OC_2H_5)_2$

The method of Mannich and Hahn, *Ber.*, 44 (1911), 1542, was used.

23 Gm. of chloracetophenone was dissolved in 140 cc. of chloroform and stirred with 21 Gm. of hexamethylene tetramine until complete solution took place (two hours). After standing over night the addition-reaction was complete; the mass of glistening crystals was filtered off and washed with cold chloroform. Yield 40 Gm. This product was "alcoholyzed" by a mixture of 320 cc. of absolute alcohol and 40 cc. of concentrated hydrochloric acid. After standing 72 hours at room temperature, the precipitated ammonium chloride was filtered off and the alcoholic solution concentrated *in vacuo*. The crude ω-aminoacetophenone hydrochloride which separated

* Section on Practical Pharmacy and Dispensing, Madison meeting, 1933.