The heats of activation for the acid hydrolysis of various unsubstituted acylamides listed in the literature (7) are all in the range 19–21 Kcal./mole. These amides include formamide, acetamide, benzamide, propionamide, and butyramide. However, all of these compounds hydrolyzed at much faster rates; for example, formamide has a half-life at 42° in 0.1 *N* hydrochloric acid of 2.2 hours, at 25° of 7.0 hours (7). Apparently substitution on the nitrogen of the amide markedly slows the rate of hydrolysis.

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Preparation of Microcrystalline Progesterone Using Ultrasound

By JOSEPH R. PRINCIPE† and DONALD M. SKAUEN

Microscopic crystals of progesterone were prepared by insonating saturated solutions of the hormone. Suspensions were made of the crystalline precipitates in 1% tyloxapol solution. Individual crystals were measured by projecting photographs on a calibrated screen.

THE DESIRABILITY of obtaining a chemical compound of uniform microscopic size is considered to be of importance to the pharmaceutical industry, particularly in the preparation of suspensions.

The usual methods of preparing suspensions for injection involve size reduction by milling or crystallization from various solvents to produce crystals of microscopic size and uniformity.

This investigation was undertaken to ascertain the suitability of employing ultrasonic energy in the production of microcrystalline progesterone.

EXPERIMENTAL

Saturated solutions of progesterone in solvent mixtures of varying proportions of ethyl alcohol and ethylene glycol at different temperatures were prepared. This solvent was selected because of good solvent action and because viscosity could be varied without the use of a secondary agent.

One-milliliter samples of the supernatant liquid from the saturated solutions were transferred to small hard-glass test tubes, stoppered, and immediately insonated.[1] The contents of the sound chamber was kept at approximately 20° by means of a cold water coil. The effect of length of time of insonation and the effect of power were explored.

Immediately after insonation, the test tubes containing the resulting precipitates were centrifuged, the supernatant discarded, and the crystals allowed to dry before resuspension in a 1% aqueous tyloxapol solution.

Photomicrographs of the uniformly distributed suspended material were made and examined for particle size by a projection technique.

Table I shows typical data obtained by insonating saturated solutions prepared at 55°.

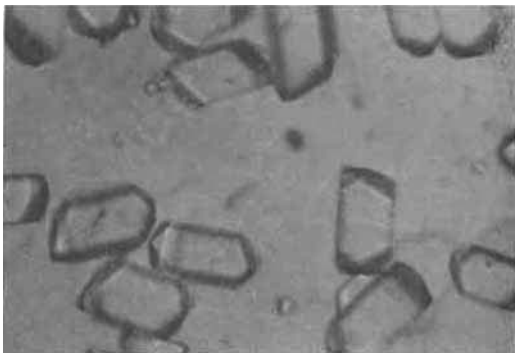

Fig. 1.—Prepared progesterone crystals. Solvent, ethyl alcohol U.S.P., 25 parts, ethylene glycol, 75 parts; insonation time, 5 sec.; arithmetic mean length (μ), 47.3; saturated solution prepared at 55°; plate power, 50 ma.; S.D., 9.4.

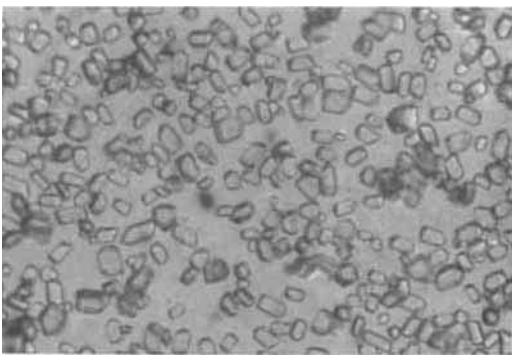

Fig. 2.—Prepared progesterone crystals. Solvent, ethyl alcohol U.S.P., 25 parts, ethylene glycol, 75 parts; insonation time, 5 seconds; arithmetic mean length (μ), 11.0; saturated solution prepared at 55°; plate power, 100 ma.; S.D., 3.3.

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[1] Model G-3, General Electric Ultrasonic Generator.

TABLE I.—PARTICLE SIZE OF PREPARED PROGESTERONE CRYSTALS[a]

Insonation Time / Plate Power, ma.	5 sec. Arithmetic Mean, μ	5 sec. S.D.	15 sec. Arithmetic Mean, μ	15 sec. S.D.	25 sec. Arithmetic Mean, μ	25 sec. S.D.
50	47.3	9.4	23.7	12.2	18.6	9.4
75	16.9	7.5	9.3	4.4	13.5	4.9
100	11.0	3.3	7.8	4.4	8.8	4.1
125	16.9	4.7	9.5	4.5	9.9	4.5
150	14.5	7.1	10.2	8.2	7.3	3.1

[a] Solvent, ethyl alcohol U.S.P., 25 parts, ethylene glycol, 75 parts; insonation time, 5 seconds; saturated solution prepared at 55°.

Figure 1 shows crystals obtained under the conditions specified in Table I, at a plate power of 50 ma. and 5 seconds exposure time. Figure 2 shows crystals exposed for 5 seconds at a plate power of 100 ma.

SUMMARY

1. Microscopic crystals of progesterone were prepared by insonating saturated solutions of the hormone.

2. The results indicated that: (*a*) in general, an increase in plate power from 50 to 100 ma. results in smaller crystals; (*b*) the solvent system 25% ethyl alcohol–75% ethylene glycol appears to favor smaller and more uniform crystal size; (c) the temperature at which the saturated solution is prepared seems to affect crystal size; (*d*) length of time of insonation appears to have minimal influence on crystal size.

3. Crystals prepared under insonation conditions were smaller and more uniform than controls prepared without insonation.

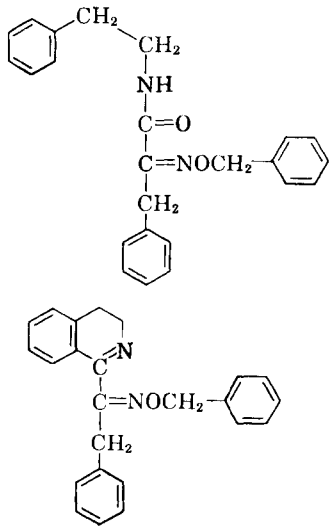
Amides of α-Alkyloximino Acids

By WALTER H. HARTUNG† and DOMINICK A. COVIELLO‡

N-β-Phenethyl amides of α-benzyloximino acids were prepared as intermediates for an attempted cyclization to the corresponding 3,4-dihydroisoquinoline derivatives.

THE ISOQUINOLINE nucleus is found in a large number of medicinally active compounds, both natural and synthetic. With this and the fact that little is known about the biological activity of the alkyloximino group in mind, it was thought that if a substituent containing the alkyloximino group could be introduced into the isoquinoline nucleus a compound of biological interest might result. At the same time, there was also the opportunity to explore further the chemical stability and limitations of the group under various conditions of reaction.

The plan was to prepare N-β-phenethyl amides of α-benzyloximinopropionic acids with the hope that they could be cyclized under the conditions of the Bischler-Napieralski reaction (1) to obtain new 3,4-dihydroisoquinoline derivatives containing the alkyloximino group. These presumably could be dehydrogenated to yield isoquinolines. For example, N-β-phenethyl-β-phenyl-α-benzyloximinopropionamide would yield 1-(1-benzyloximino-2-phenylethyl) 3,4-dihydroisoquinoline.



The amides prepared in this investigation are listed in Table I.

Cyclization was attempted by refluxing the amides

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