A STUDY OF THE ACRYLIC AMIDES AND UREIDES AS HYPNOTICS.*

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It has long been known that the amides and ureides of acids of fairly high molecular weight are more or less hypnotic. The variation in the hypnotic potency is very great and, in the unhalogenated acids, this potency seems to depend upon (1) the molecular weight, (2) the degree of branching of chain (ramification) and (3) the presence or absence of unsaturation.

For those acids which can be viewed as derivatives of acetic acid, the correlation between the above factors and the potency has been rather well worked out. For the derivatives of acrylic acid, $CH_2 = CH - COOH$, this correlation has, however, not previously been worked out. It will be seen that acrylic acid and its derivatives are not derivatives of acetic acid, since there cannot be three separate substituents attached to the alpha carbon.

It was the purpose of the work reported in this paper to evaluate as hypnotics the amides and the ureides of several major types of substituted acrylic acids; and in so far as it is possible over the limited field covered, to set up correlations between physiological activity and molecular weight, type of substituents and configuration.

The acids from which these compounds are derived fall into three major classes from the standpoint of structure, *viz.*:

(1) Aliphatic substituted acrylic acids.
(2) Substituted cinnamic acids.
(3) Furane substituted acrylic acid.

No new synthetic methods have been devised.

ACIDS.

The acids have been prepared by one of five well-known methods:

(A) Oxidation of corresponding aldehyde (1)–(2) by means of silver oxide.

(*a*) α-Ethyl-β-propyl acrylic acid.
(*b*) α-Amyl cinnamic acid.

(B) Condensation of an aldehyde with malonic acid in presence of pyridine (3).

(*a*) Furfuracrylic acid.
(*b*) β-Propyl acrylic acid.
(*c*) β-Propenyl acrylic acid (sorbic acid).

(C) Perkin Synthesis. Condensation of benzaldehyde with the sodium salt of an acid which has no substituents in the alpha position, in the presence of acetic anhydride (4).

(*a*) α-Propyl cinnamic acid.

(D) Claisen Synthesis. Condensation of benzaldehyde with an ester of an acid which has no substituents in the alpha position, by means of sodium.

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(*a*) α-Methyl cinnamic acid.
(*b*) α-Ethyl cinnamic acid.
(*c*) α-Isopropyl cinnamic acid.
(*d*) α-Ethyl *p*-methoxy cinnamic acid.
(*e*) α-Ethyl *o*-chlor cinnamic acid.

(E) Reformatsky Synthesis. Condensation of acetophenone (or a homologue) with bromacetic ester by means of zinc (6).

(*a*) β-Methyl cinnamic acid.

ACID CHLORIDES.

The acid chlorides were all readily prepared by heating the acids with a 100% excess of thionyl chloride under a reflux condenser. When the reaction was complete the excess thionyl chloride was removed in vacuum at room temperature. In most cases the acid chloride was then distilled in vacuum. This was not necessary but facilitated the purification of the end products.

AMIDES.

The amides were prepared by the dropwise addition of the acid chloride to a 28% aqueous solution of ammonia, with mechanical agitation and external cooling. The crude amide separated, usually as a discolored solid mass. The ring-substituted cinnamides tended toward greater discoloration. It was found that recrystallization from anhydrous methyl alcohol was the best means of purification, being facilitated sometimes by treatment with decolorizing carbon. Yields in most cases were not good. Earlier in the work, dilute ethyl alcohol and sometimes 95% alcohol were used as the crystallizing solvent.

The following amides were prepared.

(1) Furfuracrylic amide, melting point—168–169° C.
Previously recorded melting point—168–169° C.

(2) α-Ethyl-β-propyl acrylic amide, melting point—66–67° C.
% N—9.22; calculated for $C_6H_{11}ON$, 9.88.

(3) α-Methyl cinnamic amide, melting point—125.5–126° C.
Previously recorded melting point—128° C.
% N—8.96; calculated for $C_{10}H_{11}ON$, 8.70.

(4) α-Ethyl cinnamic amide, melting point—135–137° C.
Previously recorded melting point—128° C.
% N—7.84; calculated for $C_{11}H_{13}ON$, 8.00.

(5) α-Isopropyl cinnamic amide, high melting isomer. This isomer was obtained by crystallization from dilute alcohol.
Melting point—127–129° C.
% N—7.98; calculated for $C_{12}H_{15}ON$, 7.40.

(6) α-Isopropyl cinnamic amide, low melting isomer. This isomer was obtained by repeated recrystallization from ethyl alcohol.
Melting point—111–111.5° C.
% N—7.48%; calculated for $C_{12}H_{15}ON$, 7.40.

(7) α-Amyl cinnamic amide, high melting isomer. This isomer was obtained by recrystallization, first from dilute alcohol, and finally out of hot water.
Melting point—124–124.5° C.
% N—5.88; calculated for $C_{14}H_{19}ON$, 6.45.

(8) α-Amyl cinnamic amide, low melting isomer. This isomer was obtained by recrystallizing the high melting isomer several times from 95% alcohol.
Melting point—117° C.
% N—6.47; calculated for $C_{14}H_{19}ON$, 6.45.

(9) α-Ethyl *p*-methoxy cinnamic amide.
Melting point—170–170.5° C.
% N—6.95; calculated for $C_{12}H_{15}O_2N$, 6.83.

(10) α-Ethyl *o*-chlor cinnamic amide.
Melting point—93–94° C.
% N—7.16; calculated for $C_{11}H_{12}ONCl$, 6.70.
% Cl—16.50; calculated for $C_{11}H_{12}ONCl$, 16.95.

(11) α-Ethyl cinnamic N-ethyl amide.
Melting point—99.5–100° C.
% N—6.81; calculated for $C_{13}H_{17}ON$, 6.88.

(12) β-Methyl cinnamic amide.
Melting point—115–116° C.
Previously recorded melting point—115–116° C.
% N—9.27; calculated for $C_{10}H_{11}ON$, 8.70%.

UREIDES.

The ureides were in all cases prepared by triturating the acid chloride with three equivalents of dry urea in a mortar, then warming in an oven at 70° C. for 3 hours. Purification was effected by leaching with cold water in order to remove urea, then with dilute sodium bicarbonate solution in order to remove any free acid or unreacted acid chloride. The ureide was recyrstallized repeatedly from dilute alcohol.

The following ureides were prepared.

(1) Furfuracrylic ureide.
Melting point—204–206° C.
% N—15.43; calculated for $C_8H_8O_2N_2$, 15.55.

(2) *n*-Propyl acrylic ureide.
Melting point—181–183° C.
% N—18.11; calculated for $C_7H_{12}O_2N_2$, 17.94.

(3) β-Propenyl acrylic ureide (sorbic ureide).
Melting point—226–228° C.
% N—18.10%; calculated for $C_7H_{10}O_2N_2$, 18.19%.

(4) α-Methyl cinnamic ureide.
Melting point—160–162° C.
% N—14.55; calculated for $C_{11}H_{12}O_2N_2$, 13.72.

(5) α-Ethyl cinnamic ureide.
Melting point—189–190.5° C.
% N—13.70; calculated for $C_{12}H_{14}O_2N_2$, 12.84.

(6) α-Propyl cinnamic ureide.
Melting point—184–186.5° C.
% N—12.41; calculated for $C_{13}H_{16}O_2N_2$, 12.07.

(7) α-Isopropyl cinnamic ureide.
Melting point—190–191° C.
% N—12.55; calculated for $C_{13}H_{16}O_2N_2$, 12.07.

(8) α-Amyl cinnamic ureide.
Melting point—158–159° C.
% N—11.13; calculated for $C_{15}H_{20}O_2N_2$, 10.77.

BIOLOGICAL TESTS, ALBINO RATS.

Minimum sleep inducing doses (M. E. D.), and minimum lethal doses of the several amides were first determined on albino rats. In the cases where the drugs are inactive in very high doses, no attempt was made to determine these values within narrow limits, whereas in the cases of those drugs which were fairly active sufficient data were obtained to gain closer estimates of the true M. E. D. and M. L. D.

Amides (albino rats).

Drug.	M. E. D. Mg./Kilo.	M. L. D. Mg./Kilo.
α-Ethyl-β-propyl acrylic amide	275	525
α-Methyl cinnamic amide	ca. 625	>1500
α-Ethyl cinnamic amide	350	> 400
α-Isopropyl cinnamic amide (high melting)	750–1500	= or >1500
α-Isopropyl cinnamic amide (low melting)	ca. 700	ca. 1350
α-Amyl cinnamic amide (high melting)	>2000	>2000
α-Amyl cinnamic amide (low melting)	>2000	>2000
β-Methyl cinnamic amide	300	> 900
α-Ethyl *o*-chlor cinnamic amide	500–800	1000–1200
α-Ethyl *p*-methoxy cinnamic amide	>3000	>3000
α-Ethyl cinnamic N-ethyl amide	ca. 1750	1750
Furfuracrylic amide	100	< 100
α-Bromo diethyl acetic ureide (Adalin)	350	525
Allyl isopropyl acetic ureide (Sedormide)	350	> 400

Ureides (albino rats).

Drug.	M. E. D. Mg./Kilo.	M. L. D. Mg./Kilo.
β-Propenyl acrylic ureide (sorbic)	>2000	>2000
β-Propyl acrylic ureide	>2000	>2000
α-Ethyl-β-propyl acrylic ureide	>2000	>2000
α-Methyl cinnamic ureide	>2000	>2000
α-Ethyl cinnamic ureide	>2000	>2000
α-Propyl cinnamic ureide	>2000	>2000
α-Isopropyl cinnamic ureide	>2000	>2000
α-Amyl cinnamic ureide	>2000	>2000
Furfuracrylic ureide	ca. 500–600	ca. 500–600
α-Bromodiethyl acetic ureide (Adalin)	350	350
Allyl isopropyl acetic ureide (Sedormide)	350	400

AMIDES AND UREIDES (DOGS).

In the cases of those drugs which were active against rats, further tests were

Drug.	M. E. D. Mg./Kilo.	M. L. D. Mg./Kilo.
α-Bromodiethyl acetic ureide (Adalin)	ca. 75	
Allyl isopropyl acetic ureide (Sedormide)	ca. 40	
α-Ethyl cinnamic amide	>250	>250
α-Ethyl *o*-chlor cinnamic amide	>450	
β-Methyl cinnamic amide	>150	
α-Ethyl-β-propyl acrylic amide	Due to vomiting of all higher doses, results were vitiated.	
Furfuracrylic amide	ca. 25	25 (after 48 hours)

carried out with dogs. Wherever there was no hypnotic activity at 250 mg./Kilo. no attempts were made to obtain a narrower evaluation except in one instance.

All dogs died after three days. Autopsy showed hemorrhagic condition of intestines and moderate congestion of stomach.

Furfuracrylic ureide	>175	<75

Autopsy showed hemorrhagic condition of intestines and congestion of lungs.

NOTE: Retest of both furfuracrylic derivatives on rats were carried out. Rats were in good condition after five days. Autopsies disclosed no intestinal irritation or congestion.

DISCUSSION OF BIOLOGICAL RESULTS.

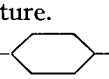
It is to be seen from the biological tests of the amides with rats that (1) the entirely aliphatic α-ethyl-β-propyl acrylic amide is the most active, (2) that in the alpha-alkyl cinnamic amides the activity reaches its peak in the α-ethyl cinnamic amide, and (3) that the β-methyl cinnamic amide is much more active than the α-methyl cinnamic amide. Increasing the molecular weight above that of α-ethyl cinnamic amide seems *per se* to decrease the potency. When this increase of M. W. is due to substituents in which there is inherent tendency toward hypnotic action there is some compensatory action and the decline in potency is less drastic; *i. e.*, α-isopropyl cinnamic amide, and α-ethyl *o*-chlor cinnamic amide. When the increase in molecular weight is through non-hypnotic substituents as in α-ethyl *p*-methoxy cinnamic amide, or is above a certain limit as in α-amyl cinnamic amide this compensatory action is lacking and the hypnotic action is practically obliterated.

The furane ring seems to be very toxic and since there is no sleep produced below the lethal doses with any of its derivatives, it seems to carry no characteristic hypnotic activity. This has also been shown in the case of furoic amide (unreported).

It is to be seen from the biological tests of the ureides with rats that in no case has any characteristic hypnotic action been demonstrated. In the case of the furfuracrylic ureide the sleep produced cannot be ascribed to any characteristic hypnotic action of the drug since it occurred only at lethal doses.

The interpretation of these results is difficult since the resorption and fate of the molecules in the organism have not been studied. Some assumptions are, however, suggested. It seems, for instance, that the ureides are hydrolyzed completely in the intestines of the rat, whereas probably the amides are hydrolyzed much less rapidly. The precipitate drop in activity when the molecular weight is increased beyond that of α-ethyl cinnamic amide and α-isopropyl cinnamic amide suggests that resorption fails due to low solubility.

In the tests with dogs there seems to be evidence that the amides are much more rapidly hydrolyzed in the intestine of the dog than in the intestine of the rat. Other instances of the more rapid destruction of amides and ureides in the higher animals are recorded in the literature.

Structurally, the grouping  seems to contribute little hypnotic activity and deprives the molecule too greatly of its water solubility.

The results with α-ethyl cinnamic N-ethyl amide support the belief that low resorbability is an important factor throughout the series. In this compound it would be expected that both the hypnotic potency and the toxicity should be increased and that the therapeutic ratio potency/toxicity should be decreased. The facts are (1) that the therapeutic ratio decreased greatly so that the hypnotic dose equalled the lethal dose; and (2) that the absolute values of both the potency and toxicity decreased. These facts seem explainable only if it be assumed that only a small part of the dose was resorbed.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

SUMMARY.

1. An extensive series of ureides and amides derived from the substituted acrylic acids were prepared. A large number of these acids were substituted β-phenyl acrylic or cinnamic acids. One example of a β-heterocyclic acrylic acid, *viz.*, furfuracrylic acid, was included.

2. The biological results with rats seem to indicate that the whole series of compounds were characterized by low resorbability and that the ureide series were further characterized by rapid intestinal hydrolysis. This rapid intestinal hydrolysis seems to be shared by the amide series in the intestine of higher animals (dog). The net hypnotic action and toxicities were, therefore, quite low.

3. The furane ring is considerably more toxic than the benzene ring, and contributes no characteristic hypnotic action, so that in practical terms—

is non-hypnotic and toxic, whereas—

is hypnotic and non-toxic.

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THE WATER OF CRYSTALLIZATION OF QUININE SULPHATE.*

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Quinine sulphate crystallized from water has been variously reported as containing 7 and 8 molecules of water. It has also been reported that when exposed

* Scientific Section, A. PH. A., Washington meeting, 1934.

[1] Drug Control, Food and Drug Administration.