resorptions in Group 3 *versus* Control Group 2 equals 0.73, in malformations in Group 4 *versus* Control Group 2 equals 0.39, and in malformations in Group 4 *versus* Group 3 equals 0.39. In any event the incidence of malformations and resorptions is not significant compared to the rate of spontaneous fetal failures in this rabbit colony. It can be concluded from the study that this strain of New Zealand White rabbits is not a suitable animal for further investigation of the teratogenicity of *V. californicum*. This conclusion need be qualified by the report that the toxicity and teratogenic agents in *V. californicum* have shown variation between range areas with regard to activity in the ewe (1).

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New Compounds: Acrylonitrile Derivatives as Potential Antineoplastic Agents

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Abstract □ The synthesis of several heterocyclic acrylonitriles and the corresponding carboxylic acid derivatives is described.

Keyphrases □ Acrylonitriles, heterocyclic—synthesis □ Carboxylic acid derivatives, acrylonitriles—synthesis

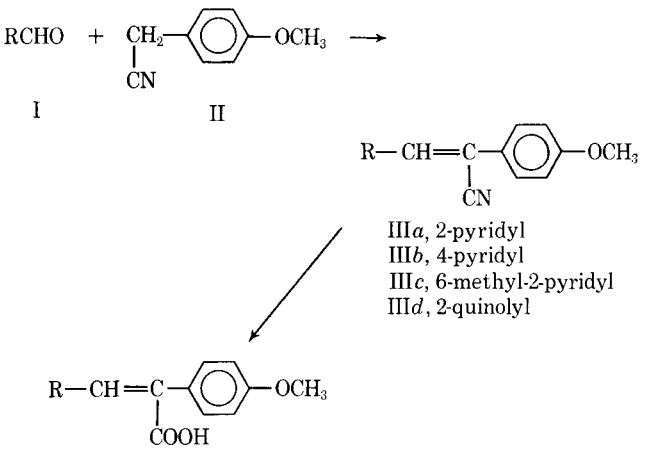
Estrogens have proven to be of clinical value in the treatment of prostatic and breast carcinomas (1). It has been shown that many acrylonitrile derivatives possess excellent estrogenic activity (2). As part of the continuing search for newer and more effective antineoplastic agents, several acrylonitriles and their acid derivatives were prepared for biological evaluation.

The synthesis of 2-(*p*-methoxyphenyl)-3-(4-pyridyl)-acrylonitrile(III*b*) was initially attempted in pyridine but only the corresponding acid, 2-(*p*-methoxyphenyl)-3-(4-pyridyl)acrylic acid (IV*b*), was obtained. Subsequently, it was discovered that III*b*, as well as the other nitriles, could be conveniently prepared by modifying the procedure of Castle and Seese (3). The appropriate heterocyclic aldehyde (I) was allowed to condense with *p*-methoxyphenylacetonitrile (II) under basic conditions (Scheme I).

The other carboxylic acids (IV*a*, *c*, *d*) were prepared by hydrolyzing the nitriles in aqueous sulfuric acid.

EXPERIMENTAL[1]

2-(p-Methoxyphenyl)-3-(2-pyridyl)acrylonitrile (IIIa, Table I)—The procedure described for the preparation of this compound is typical. To a solution of 3.0 g. (0.020 mole of *p*-methoxyphenylacetonitrile and 2.0 g. (0.022 mole) of 2-pyridinealdehyde in 40 ml. of absolute methanol was slowly added an absolute methanol solution of sodium methoxide (0.5 g., 0.022 g.-atom of sodium metal in 10 ml. of absolute methanol). The mixture was heated at 50–60° for 5–10 min., then allowed to stand at room temperature for 30 min., and finally cooled in an ice bath. The solid was removed by filtration, air-dried, and recrystallized from ethanol.

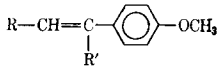


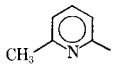
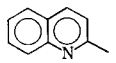
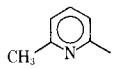
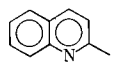
Scheme I

2-(p-Methoxyphenyl)-3-(6-methyl-2-pyridyl)acrylic acid (IVc, Table I)—The preparation of the title compound according to the following procedure may be taken as typical. To 48 ml. of concentrated sulfuric acid in 65 ml. of water was added 6.0 g. (0.027 mole)

[1] Melting points were determined on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Elemental analyses were performed by Dr. Alfred Bernhardt, 433 Mulheim (Ruhr), Hohenweg 17, West Germany. For physical and analytical data see Table I.

Table I—Acrylonitriles and Acid Derivatives



No.[a]	R	R′	Yield, %	M.p., °C.	Formula	Anal., % Calcd.	Anal., % Found
III*a*		CN	98	69.5–70.5	$C_{15}H_{12}N_2O$	C, 76.25 H, 5.12 N, 11.86	C, 76.16 H, 5.32 N, 11.76
III*b*		CN	13	125–127	$C_{15}H_{12}N_2O$	C, 76.25 H, 5.12	C, 76.39 H, 5.14
III*c*		CN	90	84.9–85.1	$C_{16}H_{14}N_2O$	C, 76.77 H, 5.64 N, 11.19	C, 76.78 H, 5.64 N, 11.19
III*d*		CN	41	103.5–107	$C_{19}H_{14}N_2O$	C, 79.70 H, 4.93 N, 9.79	C, 79.46 H, 4.94 N, 9.89
IV*a*		COOH	71	145 dec.[b]	$C_{15}H_{13}NO_3$	C, 70.58 H, 5.14 N, 5.49	C, 70.81 H, 5.25 N, 5.67
IV*b*		COOH	3	210 dec.[b]	$C_{15}H_{13}NO_3$	C, 70.58 H, 5.14	C, 70.98 H, 5.35
IV*c*		COOH	87	96 dec.[b]	$C_{16}H_{15}NO_3$	C, 71.35 H, 5.63 N, 5.20	C, 71.64 H, 5.59 N, 5.12
IV*d*		COOH	84	189 dec.[b]	$C_{19}H_{15}NO_3$	C, 74.74 H, 4.95 N, 4.59	C, 74.57 H, 5.10 N, 4.65

[a] All products were recrystallized from ethanol except IV*b*, which was recrystallized from water. [b] Temperature at which compound was completely melted.

of the nitrile. The reaction mixture was stirred and heated on a steam bath for 3.5 hr. and then was neutralized with 5% aqueous sodium bicarbonate. The solid was collected by filtration and recrystallized from ethanol.

2-(p-Methoxyphenyl)-3-(4-pyridyl)acrylic acid (IVb, Table I)—The following procedure was used in the attempted synthesis of Compound III*b*, Table I, but instead the title compound was obtained as the only isolable product.

A solution consisting of 100 ml. of pyridine, 50.0 g. (0.55 mole) of 4-pyridinealdehyde, 68.0 g. (0.46 mole) of *p*-methoxyphenylacetonitrile was refluxed for 16 hr. The solid which precipitated was collected by filtration and washed with 30 ml. of cold (0°) ethanol. An aqueous solution of this solid was acidic to litmus. The product was recrystallized from water. Attempts to isolate additional material failed.

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