1-Phenyl-2-methyl-3-trifluoromethyl-5-pyrazolone (trifluoroantipyrene) (II). *Method A.* To 8.7 g. (0.068 mole) of 1-phenyl-3-trifluoromethyl-5-pyrazolone was added 30 ml. (40.5 g., 0.32 mole) of methyl sulfate. The flask was immersed in an oil bath and heated at 110–120° for 1.5 hr. After cooling, 100 ml. of ether was added and the solution was chilled. The resulting colorless crystalline precipitate was isolated and suspended in 100 ml. of warm ether. It was then recovered by filtration and washed by suspension in 50 ml. of water which was rendered basic by the addition of 20% sodium hydroxide. Yield 6.6 g. or 72%. After three recrystallizations from methanol it melted at 139.2–140.2°.

Anal. Calcd. for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.34; H, 4.36; N, 11.98.

Method B. In a 50-ml. round bottom flask were placed 5 g. (0.027 mole) of ethyl γ,γ,γ-trifluoroacetoacetate and 3.3 g. (0.027 mole) of *N*-methyl-*N'*-phenylhydrazine.[8] The flask was immersed in an oil bath and was heated at 130–150° for 72 hr. An oil was obtained on cooling which was dissolved in 15 ml. of methanol. After seeding with a crystal of trifluoroantipyrene obtained by method A and allowing to stand in the refrigerator for a week, about 30 mg. of a crystalline material of m.p. 126–136° was obtained. Recrystallization from methanol raised the melting point to 136–138°, which was undepressed on admixture with the product obtained by method A.

Attempted Mannich condensation of trifluoroantipyrene. Four reactions in which 0.004 mole of trifluoroantipyrene and 0.004 mole of piperidine or piperidine hydrochloride were dissolved in 5 ml. of methanol and to which 0.008 mole of formaldehyde was added were refluxed from 5 min. to 3 days. In each case the major portion of the trifluoroantipyrene was recovered unchanged and no other reaction products could be isolated.

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(8) Geigy and Co., German Patent **75,854**; *Frdl.*, **3**, 22; Beilstein, *Handbuch der Organischen Chemie*, Hauptwerk, Vol. XV, 4th Ed. (1932), p. 118.

Synthesis of Some Aromatic Malononitriles[1]

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A series of substituted aromatic malononitriles had been prepared previously by Gal, Fung, and Greenberg,[2] with the purpose of determining the effects in retarding the growth of tumors transplanted in mice. It was shown that substitution on the 2- and 3-positions of the benzene ring had no effect on tumor growth, whereas substitution on the 4-position caused a change which ranged from none to a significant retarding effect.

The purpose of the present work was to synthesize a new series of aromatic malononitriles and to determine their activity in retarding cancer growth in mice. The new compounds prepared here were tested at the National Institutes of Health and none of the compounds showed any significant activity.

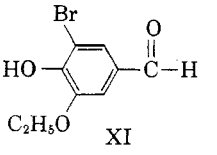
The malononitriles were synthesized by the method of Corson and Stoughton[3] and are listed in Table I.

$$ArCHO + CH_2(CN)_2 \xrightarrow{base} ArCH{=}C(CN)_2 + H_2O$$

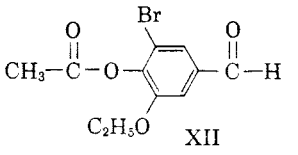
Through a series of interconversions the presence of the acetoxy groups in the aromatic nucleus was verified in compound III, IV, V, VI, VIII, and IX by a procedure described by Rosenmund and Boehm.[4] The general method consists in first forming the acetoxy derivative of the aromatic aldehyde and then treating this with malononitrile. The final product should be identical with that obtained by directly acetylating the phenolic malononitrile derivative.

$$\begin{array}{ccc} HOC_6H_4CHO & \xrightarrow{CH_2(CN)_2} & HOC_6H_4CH{=}C(CN)_2 \\ \downarrow Ac_2O & & \downarrow Ac_2O \\ CH_3COOC_6H_4CHO & \xrightarrow{CH_2(CN)_2} & CH_3COOC_6H_4CH{=}C(CN)_2 \end{array}$$

Two aldehydes, XI and XII, not previously reported, were synthesized as intermediates in the above interconversions.



XI



XII

EXPERIMENTAL[5]

Preparation of benzalmalononitriles. Equivalent quantities of the aromatic aldehyde and malononitrile were dissolved in a suitable solvent and a drop of pyridine or piperidine was added with shaking. The benzalmalononitrile precipitates upon standing.

3-Ethoxy-4-hydroxy-5-bromobenzaldehyde (XI). Twenty-five g. (0.15 mole) of 3-ethoxy-4-hydroxybenzaldehyde (Eastman Kodak Co.) and 15.2 g. of sodium acetate were dissolved in glacial acetic acid. Bromine was added slowly and with shaking until the bromine color persisted. The reaction mixture was poured into 500 ml. of cold water and a white precipitate formed, 25.7 g. (70% yield). The sample was recrystallized from ethanol-water solution, m.p. 143°.

Anal. Calcd. for $C_9H_9BrO_3$: C, 44.08; H, 3.77. Found: C, 44.15; H, 3.88.

3-Ethoxy-4-acetoxy-5-bromobenzaldehyde (XII). This preparation is typical of all acetylation reactions performed in this work. Ten g. of 3-ethoxy-4-hydroxy-5-bromobenzaldehyde were refluxed for 2 hrs. with 30 ml. of acetic anhydride. The mixture was poured into ice water and a white pre-

(1) Abstracted from the M. S. thesis of J. M. Bauer.

(2) (a) E. Gal, E. Fung, and D. Greenberg, *Cancer Research*, **10**, 221 (1950); (b) **12**, 565 (1952); and (c) **13**, 226 (1953).

(3) B. Corson and R. Stoughton, *J. Am. Chem. Soc.*, **50**, 2825 (1928).

(4) K. Rosenmund and T. Boehm, *Ann.* **437**, 125 (1924).

(5) Microanalyses by Micro-Tech Laboratories, Skokie, Ill.

TABLE I

No.	Benzalmalononitrile	Formula	Solvent	Recryst. Solvent	M.P.	Anal. N Calcd.	Anal. N Found
I	3,4-Diethoxy	$C_{14}H_{14}N_2O_2$	None	Ethanol	104–4.5°	11.57	11.40
II	3-Ethoxy-4-hydroxy	$C_{12}H_{10}N_2O_2$	Ethanol	Ethanol	161.5°	13.08	13.04
III	3-Ethoxy-4-acetoxy	$C_{14}H_{12}N_2O_3$	None	Benzene–heptane	84.5°	10.93	10.91
IV	4-Acetoxy	$C_{12}H_8N_2O_2$	None	Benzene-heptane	111.0°	13.20	13.04
V	3-Acetoxy	$C_{12}H_8N_2O_2$	None	Benzene-heptane	71.0°	13.20	12.92
VI	3-Methoxy-4-acetoxy	$C_{13}H_{10}N_2O_3$	None	Benzene-heptane	122.0°	11.57	11.58
VII	3-Ethoxy-4-hydroxy-5-bromo	$C_{12}H_9BrN_2O_2$	Ethanol	Benzene-heptane	175.0°	9.56	9.32
VIII	3-Methoxy-4-acetoxy-5-bromo	$C_{13}H_9BrN_2O_3$	Ethanol	Benzene-heptane	156.5°	8.72	8.56
IX	3-Ethoxy-4-acetoxy-5-bromo	$C_{14}H_{11}BrN_2O_3$	Ethanol	Benzene-heptane	128.0°	8.36	8.43
X	3-Methoxy-4-hydroxy-5-bromo	$C_{11}H_7BrN_2O_2$	Dioxane	Benzene-heptane	176.5°	10.04	9.77

cipitate was formed, 9.4 g. (80% yield). This was recrystallized from a benzene-hexane solvent, m.p. 83.5–84.0°.

Anal. Calcd. for $C_{11}H_{13}BrO_4$: C, 46.00; H, 3.88. Found: C, 46.32; H, 4.12.

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Attempts to Prepare New Progestational Agents: Synthesis and Biological Activity of 11β-Acyloxyprogesterones

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Although 17α-hydroxyprogesterone is essentially devoid of progestational activity, esterification of the hydroxyl group at C-17 produces compounds with long-acting progestational properties both in animals and in man.[1] In an attempt to synthesize new progestational agents, derivatives of 11β-hydroxyprogesterone were prepared and tested. Although 11β-hydroxyprogesterone itself has no activity,[2] it was hoped that esterification of the free hydroxyl group would produce results similar to those obtained with 17α-hydroxyprogesterone.

The compounds prepared for testing were: 11β-formyloxyprogesterone (XIV), 11β-acetoxyprogesterone (XV), 11β,17α-diformyloxyprogesterone (XIX), 11β,17α-diacetoxyprogesterone (XX), 11β-acetoxy-17α-caproyloxyprogesterone (XVII), and 11β-acetoxy-17α-formyloxyprogesterone (XVIII).

Compounds XIV, XIX, and XX were prepared by acylation of the corresponding 4,5-dihydro compound [11β-hydroxypregnane-3,20-dione (IV) or 11β,17α-dihydroxypregnane-3,20-dione (V)], followed by bromination at C-4, and dehydrobromination in the usual fashion. Attempted acetylation of IV gave an oil which could not be crystallized. 11β-Acetoxypregnane-3,20-dione (VII) could be prepared by acetylation of 3α,11β-dihydroxypregnane-20-one to give the diacetate, partial hydrolysis to the 11-monoacetate, followed by oxidation at C-3 to give VII. However, 11β-acetoxyprogesterone (XV) prepared from this could not be obtained crystalline.

The mixed esters (XVII and XVIII) were prepared by direct acylation of 11β-acetoxy-17α-hydroxyprogesterone (XVI).

Bioassays for progestational activity were done according to the method of McPhail.[3] Immature virgin female rabbits were primed with 3.3 micrograms of estradiol benzoate on alternate days for six days, followed by daily injections of the test compound for five days. The compounds were dissolved in sesame oil, and injected subcutaneously.

The animals were killed on the day following the last injection. The uterus was dissected out, trimmed of fat and connective tissue, and weighed. Pieces of both uterine horns were removed and fixed in 10% formalin. Sections were cut at 5 microns and stained with hematoxylin-eosin.

Sections were scored for the degree of endometrial proliferation from 1+ to 4+ by comparison with standard slides of progesterone treated rabbits at high, medium, and low dose. Animals receiving estradiol benzoate alone were used as controls.

Three compounds exhibited progestational ac-

(1) K. Junkmann, *Arch. exp. Pathol. Pharmakol.*, **223**, 244 (1954); M. Davies and G. Wied, *J. Clin. Endocrinol. and Metabolism*, **15**, 923 (1955).

(2) *Cf.* E. Mardones, R. Iglesias, and A. Lipschutz, *Nature*, **174**, 839 (1954).

(3) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).