Trifluoroantipyrene

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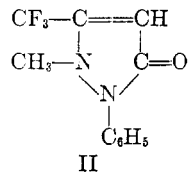
During the study of the Mannich reaction on trifluoroketones, it became of interest to determine if the trifluoro analog of antipyrene(II), prepared by the methylation of 1-phenyl-3-trifluoromethyl-5-pyrazolone(I), would undergo this condensation.

Compound I was first prepared by Swarts[1] by heating the phenylhydrazone obtained from ethyl trifluoroacetoacetate and phenylhydrazine. We were able to prepare this pyrazolone directly by refluxing a methanolic solution of ethyl trifluoroacetoacetate with phenylhydrazine in the presence of hydrochloric acid.

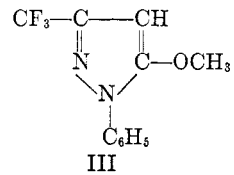
Swarts[1] attempted the preparation of trifluoroantipyrene(II) by treatment of I with methyl iodide. He obtained only three milligrams of product of unreported melting point. In contrast, 1-phenyl-3-methyl-5-pyrazolone is easily methylated by treatment with methyl sulfate and base in refluxing methanol.[2]

Methylation of I could not be achieved using methyl iodide or methyl *p*-toluenesulfonate at elevated temperatures. Trifluoroantipyrene was eventually prepared in a 72% yield by heating I with a large excess of methyl sulfate at 110–120° for 1.5 hr.

It was established that the *N*-methyl ether(II) and not the *O*-methyl ether of I (compound III)



II

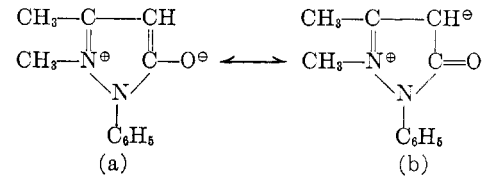


III

was obtained by an independent synthesis of II by the reaction of ethyl trifluoroacetoacetate with *N*-methyl-*N'*-phenylhydrazine and that the infrared spectrum of the trifluoroantipyrene obtained showed a strong absorption band at 1683–1650 cm.$^{-1}$ which is characteristic of a disubstituted amide,[3] and the absence of a band at 1340–1280 cm.$^{-1}$ which is characteristic of the OCH_3 group.[4]

The Mannich condensation of trifluoroantipyrene was attempted using formaldehyde and piperidine, with and without the addition of hydrochloric acid and with dimethylamine hydrochloride. In all attempts 80% or more of the trifluoroantipyrene was recovered. In contrast antipyrene undergoes the Mannich condensation with formaldehyde and amines giving fair to good yields of products.[5]

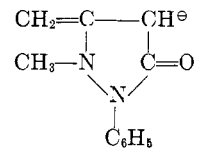
The Mannich reaction of antipyrene may be rationalized as involving the resonance form IVb in which an electron pair is made available at the condensation site for reaction with the carbenium ion $R_2\overset{+}{N}CH_2$.[6] The failure of trifluoroantipyrene to undergo the Mannich reaction is possibly due to the



(a) (b)

IV

presence of the strongly electron-attracting trifluoromethyl group, which might cause a decrease of the electron density around the corresponding carbon atom. Antipyrene may also tautomerize in the following fashion:



and the non-reactivity of trifluoroantipyrene in the Mannich reaction may be explained by the inability of this latter compound to assume such a structure. Alternatively the non-reactivity of trifluoroantipyrene in the Mannich reaction would be explained if a hydrogen on the 3-methyl group of antipyrene is replaced in this reaction rather than a hydrogen on the 4-carbon atom.

In a project now being initiated in this laboratory the requirement of structure in antipyrene to make it undergo the Mannich reaction, as well as the structure of the resulting products, are being studied.

EXPERIMENTAL

1-Phenyl-3-trifluoromethyl-5-pyrazolone (I). To 18.4 g. (0.1 mole) of ethyl γ,γ,γ-trifluoroacetoacetate[7] was added 10.8 g. (0.1 mole) of phenylhydrazine, 20 ml. of methanol, and 2 ml. of concd. hydrochloric acid. The mixture was refluxed for 1 hr., diluted with water while still hot until it became cloudy, and then decolorized with Nuchar. Cooling of the resulting filtrate produced 17 g. (79%) of a colorless crystalline product. The melting point was 193.0–193.5° (literature,[1] m.p. 192.6°).

(1) F. Swarts, *Bull. sci. acad. roy. Belg.*, [5] **12**, 717–720 (1926).

(2) A. I. Vogel, *A Textbook of Practical Organic Chemistry*, 2nd Ed., Longmans, Green and Co., New York, N. Y., 1951, p. 863.

(3) F. A. Miller in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Wiley, New York, 1953, Volume III, p. 147.

(4) Reference 3, p. 148.

(5) (a) C. Mannich and B. Kather, *Arch. Pharm.*, **257**, 18 (1919); *Chem. Abstr.*, **13**, 2511 (1919); (b) R. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1939); *Chem. Abstr.*, **33**, 5855 (1939); (c) K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

(6) H. Hellman and G. Opitz, *Chem. Ber.*, **89**, 81 (1956); H. Hellman and G. Opitz, *Angew. Chem.*, **68**, 265 (1956).

(7) A. L. Henne, M. S. Newman, L. L. Quill, and R. A. Staniforth, *J. Am. Chem. Soc.*, **69**, 1819 (1947).

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.

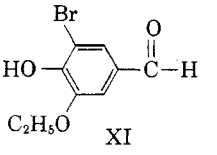
The malononitriles were synthesized by the method of Corson and Stoughton[3] and are listed in Table I.

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

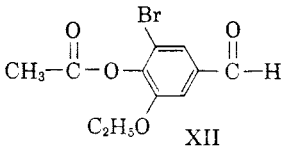
Through a series of interconversions the presence of the acetoxy groups in the aromatic nucleus was verified in compound III, IV, V, VI, VIII, and IX by a procedure described by Rosenmund and Boehm.[4] The general method consists in first forming the acetoxy derivative of the aromatic aldehyde and then 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.