phenyl)glutaric acid[12] VIIb, and 2 ml. of acetic anhydride was heated at reflux temperature for about an hour. The resinous mass obtained upon cooling was crystallized by the addition of ether. Crystallization from dry benzene gave 1.9 g. (72% yield), of brilliantly shining colorless plates (VIIIb), m.p. 104–105°.

o-Carbomethoxy-β-(2-methoxy-4-methylphenyl)glutaraninilic acid (IXb). This compound was prepared by the same procedure as previously described for the preparation of Ia, except that glutaric anhydride (VIIIb) was used instead of glutaconic anhydride. From 2.3 g. (0.01 mole) of VIIIb, 2.6 g. (60% yield) of IXb, m.p. 135–136°, was obtained.

Anal. Calcd. for $C_{21}H_{23}O_6N$: neut. equiv., 385.0. Found: neut. equiv., 389.1.

o-Carboxy-β-(2-methoxy-4-methylphenyl)glutaraninilic acid (Xb). This dicarboxylic acid was prepared by the alkaline hydrolysis of IXb. From 3.9 g. (0.1 mole) of IXb, 2.6 g. (71% yield) of Xb was obtained. Repeated crystallizations from dilute acetic acid and finally from alcohol gave the pure product, m.p. 165–165.5°.

Anal. Calcd. for $C_{20}H_{21}O_6N$: C, 64.69; H, 5.66; neut. equiv., 185.5. Found: C, 64.82; H, 5.51; neut. equiv., 186.5.

β-(2,4-Dimethoxyphenyl)glutaric acid (VIIc). This acid was prepared by the reduction of β-(2,4-dimethoxyphenyl)-glutaconic acid,[13] m.p. 174° (dec.) with sodium amalgum according to the method described by Chitre.[14] From 26.6 g. (0.1 mole) of β-(2,4-dimethoxyphenyl)-glutaconic acid, 21.8 g. (81% yield) of crude reduced acid was obtained, as a white mass. Crystallization from water gave 20.2 g. (76% yield) of VIIc as colorless needles, m.p. 158–159°.

Anal. Calcd. for $C_{13}H_{16}O_6$: neut. equiv., 134.0. Found: neut. equiv., 135.8.

β-(2,4-Dimethoxyphenyl)glutaric anhydride (VIIIc). This compound was prepared from VIIc by heating at reflux temperature with acetic anhydride. The yield was 82% of white crystals, m.p. 122–122.5°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.5; H, 5.8.

o-Carbomethoxy-β-(2,4-dimethoxyphenyl)glutaraninilic acid (IXc). This monobasic acid was prepared from the corresponding glutaric anhydride (VIIIc) by heating it in boiling benzene solution with a molecular quantity of methyl anthranilate. Repeated crystallizations from 50% alcohol gave pure IXc, in 72% yield, m.p. 136–136.5°.

Anal. Calcd. for $C_{20}H_{23}O_7N$: neut. equiv., 401.0. Found: neut. equiv., 398.7.

o-Carboxy-β-(2,4-dimethoxyphenyl)glutaraninilic acid (Xc). This dicarboxylic acid was obtained in 61% yield from IXc by hydrolysis with alcoholic alkali. It was purified by crystallization from acetic acid giving dull crystals, m.p. 128–128.5°.

Anal. Calcd. for $C_{21}H_{21}O_7N$: neut. equiv., 193.5. Found: neut. equiv., 195.2.

BOMBAY, INDIA

(12) D. B. Limaye and R. G. Chitre, *J. Univ. Bombay*, **4**, 101 (1935).

(13) P. R. Bavdekar, M.Sc. thesis, University of Bombay, 1941.

(14) R. G. Chitre, M.Sc. thesis, University of Bombay, 1933.

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Psoralene. II. Certain Reactions of Xanthotoxin[1]

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The behavior of 9-methoxypsoralene under the conditions of oxidation, chlorination, sulfonation, and ether cleavage is described. Chromium trioxide converted 9-methoxypsoralene I into psoralenequinone II. Chlorination with chlorine produced 2,3-dihydro-9-methoxy-2,3,4-trichloropsoralene VII while chlorination with sodium hypochlorite formed 4-chloro-9-methoxypsoralene VIII. Chlorosulfonic acid attacked the 4-position forming both the free sulfonic acid and the acid chloride. The conversion of 9-methoxypsoralene to 9-hydroxypsoralene was accomplished in good yield by heating with anhydrous aluminum chloride.

Xanthotoxin I (9-methoxypsoralene) is a furocoumarin that occurs in a number of plants indigenous to the Eastern Hemisphere. As its name implies xanthotoxin is a fish poison and is, in general, toxic to cold-blooded animals while it is relatively nontoxic to mammals. Current interest in this material stems from its photodynamic activity, which causes the skin to "tan" as opposed to "burn" if the drug is administered orally prior to exposure to the sunlight.

The behavior of 9-methoxypsoralene under the conditions of nitration, bromination, hydrogenation, ozonization, thionation, and various ring-opening procedures has been previously described by this laboratory.[2] This paper is concerned with the oxidation, ether cleavage, chlorination, and sulfonation of this molecule.

Schonberg has reported[3] that oxidation of 4-methoxypsoralene (bergaptene) with sodium dichromate attacked the furan double bond and formed 6-formyl-7-hydroxy-5-methoxycoumarin. His work has been confirmed in this laboratory.

It seemed unusual, therefore, that the isomer of bergaptene, 9-methoxypsoralene, was unaffected by sodium dichromate under identical conditions. Treatment with chromium trioxide in acetic acid,

(1) This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 351, School of Science, Department of Chemistry.

(2) M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958).

(3) A. Schonberg, N. Badran, and N. Starkowsky, *J. Am. Chem. Soc.*, **75**, 1019 (1955).

however, did cause oxidation of 9-methoxypsoralene. Analysis of the product indicated that it might be psoralene quinone, and this was indeed shown to be the case when the product was found to be identical with the psoralene quinone obtained by the previously reported[4] oxidation of 4-amino-9-methoxypsoralene VI. The fact that the oxidation product of 9-methoxypsoralene I was psoralenequinone II was further confirmed by reduction of the quinone with sulfur dioxide to the hydroquinone III and subsequent methylation to yield isopimpinellin IV. The isopimpinellin obtained by these means was identical in melting point and infrared spectrum to the authentic sample (4). This series of reactions is shown in Fig. 1.

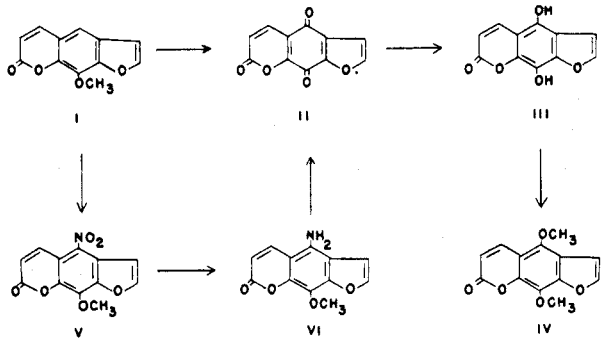


Figure 1

It has been observed that treatment of furocoumarins and chromones with aluminum chloride in benzene resulted in cleavage of the methoxyl groups in addition to the opening of the furan ring.[2,5,6] Studies of this reaction involving the use of an inactive aromatic compound to replace benzene as the solvent were undertaken. It was hoped by this means to cleave the methoxyl and leave the furan ring intact as has been reported for furochromones.[5] In no case, however, was the reaction successful. Nitrobenzene, chlorobenzene, and bromobenzene were tested at various temperatures for different periods, but in each case the product was charred, or the starting material was recovered intact.

Using a procedure of Merchant and Shah[7] for the cleavage of methoxyl groups with aluminum chloride in the absence of a solvent, the conversion of 9-methoxypsoralene to 9-hydroxypsoralene (xanthotoxol) was accomplished in yields of 40–45%. The xanthotoxol obtained by this means had an identical melting point and infrared spectrum with that of an authentic sample (4).

(4) Samples of isopimpinellin and xanthotoxol were kindly supplied by Dr. W. L. Fowlks of the University of Oregon Medical School.

(5) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **15**, 437 (1942).

(6) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **16**, 151 (1942).

(7) J. R. Merchant and R. C. Shah, *J. Org. Chem.*, **22**, 884 (1957).

Direct chlorination of 9-methoxypsoralene with chlorine yielded, in contrast to bromination,[2] only a trichloro-derivative VII. A comparison of the ultraviolet spectrum of this compound with those of other furocoumarins as described elsewhere[2] clearly indicated that the conjugation of the lactone carbonyl to the aromatic nucleus remained intact and that addition of two of the chlorine atoms had occured in the 2,3-position. This conjugation was shown by a peak at 315 mμ.

Chlorination of 9-methoxypsoralene with sodium hypochlorite yielded a monochloro-derivative which melted at 195–196°. 4-Chloro-9-methoxypsoralene VIII has been synthesized from 4-amino-9-methoxypsoralene VI and was reported to melt at 187–188°. A mixed melting point of these two compounds was found to be 187–188°. The infrared spectra were identical between 2000–600 wave numbers with the exception of a peak at 1510 wave numbers in the sample obtained from the amine. It seemed possible that the impurity in this sample might be 4-chloro-2,3-dihydro-9-methoxypsoralene. This compound was prepared but the infrared showed no absorption at 1510 wave numbers. Sublimation of the sample of 4-chloro-9-methoxypsoralene VIII prepared from the amine left behind a small residue which had an infrared spectrum identical with that of 4-nitro-9-methoxypsoralene V and showed a strong absorbance at 1510 wave numbers. It was therefore concluded that the two monochloro-derivatives were identical with the exception that the compound from the Sandmeyer reaction was contaminated with a little of the 4-nitro-derivative.

Direct chlorination of 4-chloro-9-methoxypsoralene VIII with chlorine yielded the same trichloro-derivative VII as was obtained from chlorination of 9-methoxypsoralene. It may therefore be concluded that the three chlorine atoms in this molecule are located in the 2,3,4-positions. The above series of reactions is shown in Fig. 2.

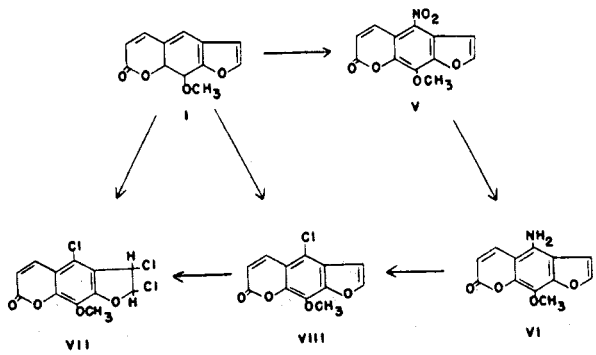


Figure 2

Sulfonation of 9-methoxypsoralene with chlorosulfonic acid yielded either the free sulfonic aid XII or the acid chloride XI; the ratio between these two products being determined by the conditions of the

reaction as described in the experimental section. The acid chloride was readily hydrolyzed to the free acid by boiling water.

That sulfonation occurred in the 4-position was established by bromination and nitration of the sulfonic acid to form the previously described[2] 4-bromo-XIII and 4-nitro-9-methoxypsoralenes V. This type of structural proof finds precedent in the work of Merchant and Shah.[7] These reactions are shown in Fig. 3.

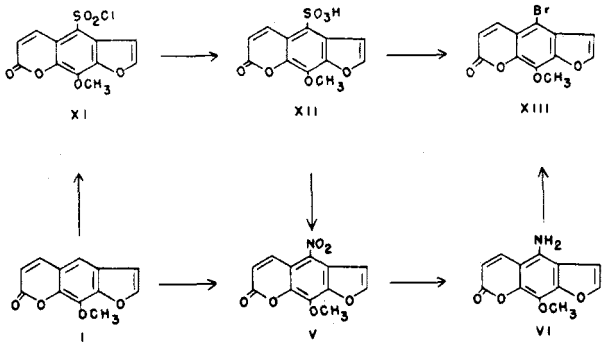


Figure 3

EXPERIMENTAL

Psoralenequinone (II). 9-Methoxypsoralene (1.0 g., 0.0046 mole) was dissolved in 30 ml. glacial acetic acid. To this solution was added 30 ml. of a 15% aqueous chromium trioxide solution. The resulting solution was brought just to boiling on the hot plate and then poured immediately into 250 ml. water and cooled. The product was filtered and crystallized from ethanol; yield 0.16–0.25 gram, 16–25%; m.p. 275–277°, dec.

The infrared spectrum of this compound was identical with that of psoralenequinone which was obtained from the previously described[8] oxidation of 4-amino-9-methoxypsoralene.

4,9-Dihydroxypsoralene (III). Psoralenequinone (0.2 g., 0.00093 mole), obtained by oxidation of 9-methoxypsoralene, was suspended in 50 ml. water and heated on the steam bath. This suspension was saturated with sulfur dioxide by bubbling the gas through the hot liquid for 10 min. At the end of this time, all of the material had dissolved giving the solution a light green color. Upon cooling, green crystals formed; yield, 0.2 g., 99%; m.p. 270° dec. The infrared spectrum of this compound was identical with that of 4,9 dihydroxypsoralene which was obtained by a similar reduction of psoralenequinone prepared from 4-amino-9-methoxypsoralene.

4,9-Dimethoxypsoralene (*isopimpinellin*). (IV). 4,9-Dihydroxypsoralene (0.35 g., 0.0016 mole), obtained by oxidation and subsequent reduction of xanthotoxin, was dissolved in 50 ml. acetone containing 0.5 g. potassium carbonate and 1 ml. (0.011 mole) dimethyl sulfate. This mixture was refluxed 2 hr. At the end of this time, 2 g. more of potassium carbonate were added, and heating was continued for 3 hr. The mixture was cooled, acidified with dilute hydrochloric acid, and diluted with water. The insoluble product was filtered and crystallized from ethanol using activated charcoal as a decolorizing agent; yield 0.10 g., 25%; m.p. 152–153°. A mixed melting point with an authentic sample of isopimpinellin was not depressed. The infrared spectra of the two samples were identical.

9-Hydroxypsoralene (*xanthotoxol*). 9-Methoxypsoralene (1.0 g., 0.0046 mole) was mixed intimately with 4.0 g. anhydrous aluminum chloride. The mixture was placed in a flask, protected with a calcium chloride drying tube, and heated 10 hr. in a bath, at a temperature of 140°. After cooling, the mixture was treated with 100 ml. 6*N* hydrochloric acid. The insoluble product was removed and washed with a small amount of water. The product was crystallized successively from dilute acetic acid and water; yield 0.4 g., 43%; m.p. 238–240°. A mixed melting point with an authentic sample of xanthotoxol (m.p. 242–244°) was found to be 239–240°. The infrared spectra of these two samples were identical.

2,3-Dihydro-9-methoxy-2,3,4-trichloropsoralene (VII). *A.* 9-Methoxypsoralene (1.0 g., 0.0046 mole) was dissolved in 50 ml. of chloroform. Chlorine was passed slowly through this solution for 15 min. at room temperature. The chloroform was then removed by means of a steam bath. At this point, it was possible to isolate the product by repeated crystallizations from ethanol. It was subsequently discovered, however, that the product was stable in the presence of sodium iodide. Furthermore, since treatment with this reagent greatly improved the isolation, the procedure was modified. The residue after evaporation of the chloroform was dissolved in 50 ml. acetone, and 0.5 g. sodium iodide was added with shaking. The resulting solution was kept at room temperature for 3 hr. and then filtered. Water was added to the point of cloudiness, and the solution was cooled in the deep freeze. Upon cooling, 1.0 g., 68%, of product was collected; m.p. 202–203°.

Anal. Calcd. for $C_{12}H_7O_4Cl_3$: C, 44.8; H, 2.17. Found: C, 44.6; H, 2.28. λ_{max} 240, 270, 315 mμ.

B. 4-Chloro-9-methoxypsoralene (0.2 g., 0.0008 mole) was chlorinated under the same conditions as above in 25 ml. chloroform. In this case, a pure product could be easily obtained by crystallization from ethanol; yield 0.1 g., 39%. The melting point and infrared spectrum were identical with those of the product from procedure *A*.

4-Chloro-9-methoxypsoralene (VIII). 9-Methoxypsoralene (0.5 g., 0.0023 mole) was suspended in 25 ml. ethanol and 25 ml. "Chlorox." One ml. 6*N* hydrochloric acid was added, and the mixture was heated gently on the steam bath for 1 hr. The reaction mixture was diluted with water and the insoluble product was collected and recrystallized from ethanol; yield 0.31 g., 54%; m.p. 194–195°.

A mixed melting point determination with 4-chloro-9-methoxypsoralene prepared from the amine,[2] m.p. 187–188°, was found to be 187–188°. The infrared spectra of these two samples were identical with the exception of a peak at 1510 wave numbers in the sample from the Sandmeyer reaction. This peak was shown to be caused by a trace of 9-methoxy-4-nitropsoralene. It was therefore concluded that these materials were identical except for this impurity.

4-Chloro-2,3-dihydro-9-methoxypsoralene (X). 4-Amino-2,3-dihydro-9-methoxypsoralene[2] (0.65 g., 0.0028 mole) was suspended in 20 ml. concentrated hydrochloric acid and cooled in an ice-salt mixture. Sodium nitrite (0.19 g., 0.0028 mole), dissolved in a little water, was added slowly. The mixture was allowed to stand in the cooling bath for 5 min. and was then poured slowly into a boiling solution containing 30 ml. 6*N* hydrochloric acid and 0.75 g. cuprous chloride. The insoluble product was filtered and recrystallized from ethanol; yield 0.36 g., 44%; m.p. 193–194°.

Anal. Calcd. for $C_{12}H_9O_4Cl$: C, 57.0; H, 3.54. Found: C, 56.6; H, 3.44.

9-Methoxypsoralene-4-sulfonyl chloride (XI) *and 9-methoxypsoralene-4-sulfonic acid* (XII). Two procedures were employed for the sulfonation of 9-methoxypsoralene. The first yielded largely the acid chloride; the second yielded predominantly the free sulfonic acid.

A. 9-Methoxypsoralene (0.5 g., 0.0023 mole) was treated slowly at room temperature with 5 ml. chlorosulfonic acid. The resulting solution was allowed to stand for 5 min. and then poured over 75 ml. ice. The insoluble acid chloride was collected and crystallized from a chloroform–petroleum ether mixture; yield 0.58–0.63 g., 80–87%; m.p. 154–155°.

(8) H. Thoms and E. Baetcke, *Ber.*, **45**, 3705 (1911).

Anal. Calcd. for $C_{12}H_7O_6SCl$: C, 46.0; H, 2.23. Found: 46.1; H, 2.43.

The filtrate yielded a trace of the free sulfonic acid upon evaporation before a hot air fan.

B. 9-Methoxypsoralene (1.0 g., 0.0046 mole) was dissolved in 15 ml. chloroform and cooled in an ice bath. Chlorosulfonic acid (3 ml.) was added dropwise with stirring. After standing for 5 min. in the ice bath, the temperature was allowed to rise to 20°. The chloroform solution was then poured over 75 ml. ice. After the ice had melted, more chloroform was added; whereupon the layers separated. The aqueous layer was extracted once more with chloroform. The combined chloroform extracts were taken to dryness and yielded from 0.15 to 0.25 g., 10–16%, 9-methoxypsoralene-4-sulfonyl chloride. This product was identical as judged by mixed melting point with that described in procedure *A*.

The aqueous layer upon evaporation yielded 1.3 g., 89%, of the sulfonic acid. This product was crystallized from acetic acid and dried by an azeotropic distillation of a benzene suspension. The melting point was 205° dec.

Anal. Calcd. for $C_{12}H_8O_7S \cdot H_2O$: C, 46.1; H, 3.18. Found: C, 46.7; H, 3.30.

9-Methoxypsoralene-4-sulfonic acid (XII). 9-Methoxypsoralene-4-sulfonyl chloride (0.2 g.) was suspended in 25 ml. water and refluxed 45 min. The resulting solution was evaporated before a hot air fan yielding 0.17 g., 85%, of product after crystallization from acetic acid. This material was shown by infrared data to be identical with the sulfonic acid obtained by the direct sulfonation described above.

4-Bromo-9-methoxypsoralene (XIII). 9-Methoxypsoralene-4-sulfonic acid (0.25 g., 0.00079 mole) was suspended in 50 ml. chloroform, and 0.09 ml., (0.019 mole) of bromine was added. This mixture was heated on the steam bath with stirring until solution was effected and most of the chloroform had evaporated. Petroleum ether was then added to precipitate the product. The product was dissolved in 50 ml. acetone and treated with 0.5 g. sodium iodide for 4 hr. at room temperature to remove any tribromo-derivative which might have been formed[2]. The acetone solution was filtered and diluted with water. The insoluble product was collected and crystallized from ethanol; yield 0.15 g., 64%. A mixed melting point determination and infrared comparison indicated that this material was identical to 4-bromo-9-methoxypsoralene obtained by direct bromination.[2]

9-Methoxy-4-nitropsoralene (V). 9-Methoxypsoralene-4-sulfonic acid (0.25 g.) was dissolved in 10 ml. glacial acetic acid and 10 ml. concentrated nitric acid. The resulting solution was heated 5 min. on the steam bath. It was then poured onto 50 g. ice, and the insoluble product was collected and crystallized from ethanol; yield 0.15 g., 72%. A mixed melting point determination and a comparison of infrared spectra showed that this product was identical to 9-methoxy-4-nitropsoralene obtained by direct nitration.[2]

Acknowledgment. The authors wish to thank the Paul B. Elder Co. of Bryan, Ohio, whose generous contribution of xanthotoxin made this investigation possible.

CORVALLIS, ORE.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Chemistry of Ethylenimine. VI. Pyrolysis of 7-Acetyl-7-azaspiro[5.2]octane[1]

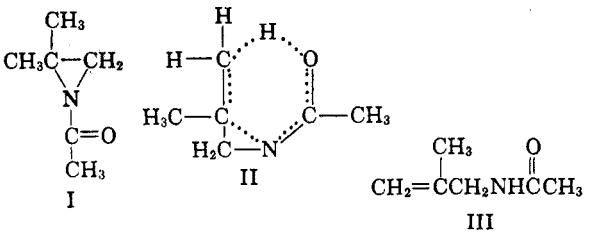
PURNENDU B. TALUKDAR[2] AND PAUL E. FANTA[3]

Received September 16, 1958

7-Acetyl-7-azaspiro[5.2]octane undergoes a pyrolytic rearrangement to give *N*-(1-cyclohexenylmethyl)acetamide. The structure of the latter compound was proven by hydrogenation, followed by hydrolysis to the known cyclohexanemethylamine. Hydrolysis of 7-azaspiro[5.2]octane in dilute sulfuric acid occurs with cleavage of the nitrogen–tertiary carbon bond.

In a previous paper in this series,[4] the pyrolytic rearrangement of 1-acetyl-2,2-dimethylethylenimine (I) to give *N*-(β-methallyl)acetamide (III) was described. Evidence was presented that the rearrangement occurs by an intramolecular mechanism similar to the Chugaev reaction, involving a cyclic transition state (II).

The present research was undertaken with the objective of further elucidating the structural and stereochemical requirements of this novel reaction. For this purpose, the structurally more rigid 7-azaspiro[5.2]octane system was investigated, as summarized in Fig. I.



I II III

7-Azaspiro[5.2]octane (V) was prepared from 1-aminocyclohexanemethanol (VIII) *via* the sulfate ester (IV) according to the conventional Wenker procedure.[5] The imine is a colorless liquid which was further characterized by the preparation of a crystalline *N*-phenylthiocarbamyl derivative.

(1) This research was aided by a grant from the Phillip Armour Foundation Cancer Fund and a grant from the American Cancer Society which provided a postdoctoral stipend for P.B.T.

(2) On study leave from the East India Pharmaceutical Works, Calcutta, India.

(3) To whom inquiries regarding this paper should be sent.

(4) P. E. Fanta and A. S. Deutsch, *J. Org. Chem.*, **23**, 72 (1958).

(5) J. S. Fruton in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 62.