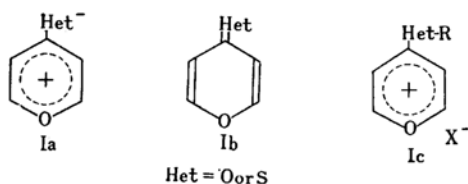


*Non-benzenoid Aromatic Heterocycles. I. Reactions of
4-Pyrone, 4-Thiopyrone, and their Pyrylium
Salts with Active Methylene Compounds*

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It has been widely accepted that the $-O-$ group is equivalent to the $-CH=CH-$ group, thus 4-pyrone and 4-thiopyrone can be regarded as heterocyclic tropone analogues. The physical and chemical properties of these compounds can be more adequately explained in terms of formula Ia than in terms of the conventional formula Ib. In the same sense the pyrylium salts Ic derived from them can be considered as heterocyclic tropylum salt analogues.



In this respect, it is of interest to study some of their reactions. The concept that the carbonyl group of 4-pyrone behaves anomalously and does not react with most carbonyl reagents had long been accepted until Woods' report¹⁾, where he has shown that 2,6-dimethyl-4-pyrone(II) undergoes condensation with malonitrile by refluxing in acetic anhydride. The present authors have tried further the condensation of II and 2,6-dimethyl-4-thiopyrone(III) with active methylene compounds aiming to show, to what extent the carbonyl or thiocarbonyl group of these compounds is active, and to distinguish the difference between these two compounds. 2,6-Dimethyl-4-pyrone(II) reacted with malonitrile, ethyl cyanoacetate, or rhodanine to give the corresponding condensation product IV~VI under the condition reported by Woods, but it failed to react with diethyl malonate, acetylacetone, cyclopentadiene, or nitromethane. Just the same result was obtained when III was treated with the above-cited compounds; this fact indi-

cates essentially the same carbonyl character of these two compounds. The fact that the same condensation products are obtained starting from II or III unequivocally proves the structures of the condensation products. It is noteworthy that the condensation is not effected by the usual catalysts, e.g., sodium ethoxide or *tert.*-butoxide, sodium acetate, or piperidine. This fact suggests anomalous character of pyrone carbonyl group.

Woods reported that IV was hydrolyzed to the corresponding dicarboxylic acid, but in the authors' experiment, the corresponding nitrile-amide VII was the sole product. In this connection, it is worthy of note that malonic acid reacted with II or III by gently warming in acetic anhydride, but the reaction was accompanied by decarboxylation, and the product obtained in each case was black unpurifiable powder.

Recently, Dimroth et al.²⁾ have reported that 2,4,6-trialkylpyrylium borofluorides or perchlorates, when treated with potassium *tert.*-butoxide in nitromethane, give the corresponding nitrobenzene derivatives. As 4-methoxy- or 4-methylmercapto-pyrylium perchlorate, derived from II or III respectively, is structurally similar to trialkylpyrylium salts, the present authors predicted the reaction of the same type. This occurred as expected, and when 4-methoxy-2,6-dimethylpyrylium perchlorate (VIII) was treated with nitromethane and sodium *tert.*-butoxide, 4-methoxy-2,6-dimethylnitrobenzene(IX)* was obtained. This compound IX was converted into 3,5-dimethyl-4-nitrophenol(X)* by refluxing

2) K. Dimroth and D. Bräuniger, *Angew. Chem.*, **68**, 519 (1956); K. Dimroth, G. Bräuniger and G. Neubauer, *Chem. Ber.*, **90**, 1634 (1957); K. Dimroth, G. Neubauer, H. Möllenkamp and G. Oosterloo, *ibid.*, **90**, 1668 (1957).

* Rowe et al.³⁾ prepared X in 2.4% yield by nitrating 3,5-dimethylphenol, and X was converted into IX by dimethyl sulfate.

3) F. M. Rowe, S. H. Bannister, R. R. Seth and R. C. Storey, *J. Soc. Chem. Ind.*, **49**, 469 (1930); *Chem. Abstr.*, **25**, 930 (1931).

1) L. L. Woods, *J. Am. Chem. Soc.*, **80**, 1440 (1958).

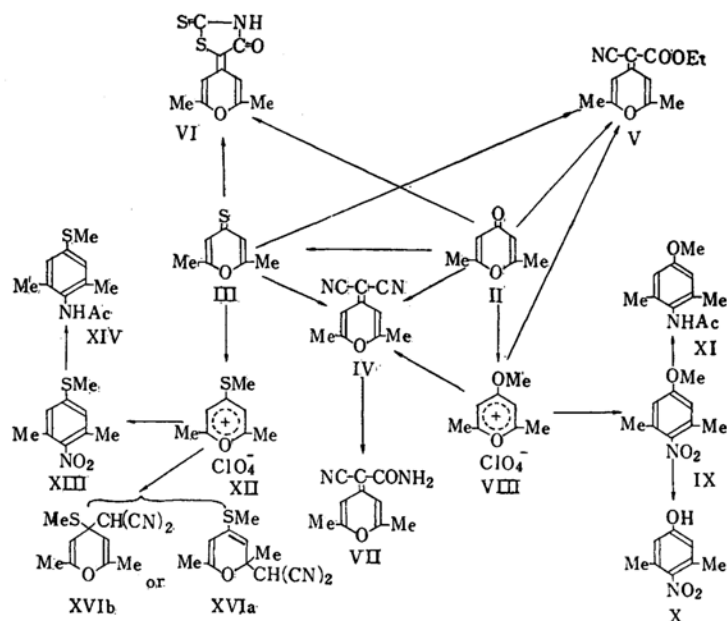
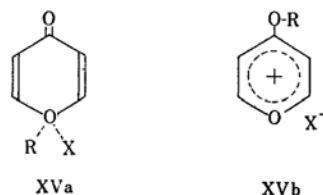


Fig. 1. Reactions of 2,6-dimethyl-4-pyrone and their derivatives with active methylene compounds.

with hydrobromic acid, and to 2,6-dimethyl-*p*-anisidine** by reduction with zinc and hydrochloric acid, which was identified as its acetyl derivative XI. Similarly, 4-methylmercapto-2,6-dimethylpyrylium perchlorate(XII) gave 4-methylmercapto-2,6-dimethylnitrobenzene(XIII) by the reaction with nitromethane and sodium *tert*-butoxide. This compound XIII was reduced, by zinc and hydrochloric acid to the corresponding amine, which was identified as an acetyl derivative(XIV)***. As Dimroth et al. have pointed out, these reactions are of value as a convenient preparatory method of the otherwise unobtainable or not easily accessible compounds. Moreover, the results of these reactions clearly reject the structure XVa which was once proposed for the salts****, and add an unambiguous proof of the widely accepted structure XVb.



Dimroth et al.⁶⁾ have briefly reported that the reaction of 2,4,6-trialkylpyrylium salts with ethyl cyanoacetate leads to benzonitrile derivatives. The present authors have expected the reaction of the same type with VIII, but in this case, the condensation at the position 4 of the salt VIII occurred, and gave exclusively 4-(ethoxycarbonylcyanomethylene)-2,6-dimethyl-4H-pyrane(V). Similarly, when VIII was treated with malonitrile, 4-(dicyanomethylene)-2,6-dimethyl-4H-pyrane(IV) was obtained. In the case of XII, the splitting up of methyl mercaptan did not occur, and the compound of the type XVIa or XVIb was obtained.

These reactions can be interpreted if the reaction mechanism shown in Fig. 2 is taken into account.

In Fig. 2, the key steps which determine the reaction routes are assumed to be steps A, B, C and D. The reactions with nitromethane take place smoothly by way of the steps A and C, but in the reaction with ethyl cyanoacetate, the step

** Bamberger et al.⁴⁾ prepared this compound by treating 2,6-dimethylphenylhydroxylamine with methanol in the presence of sulfuric acid.

4) E. Bamberger, *Ber.*, **36**, 2028 (1903).

*** This compound was prepared by Kloosterziel et al.⁵⁾, starting from 2,6-xyldine via thiocyanate compound followed by reduction with lithium aluminum hydride and methylation.

**** Cf., for example, J. N. Collie and T. Tickle, *J. Chem. Soc.*, 1899, 710; F. Kehrman and A. Duttenhöfer, *Ber.*, **39**, 1299 (1906).

5) H. Kloosterziel and H. J. Backer, *Rec. trav. chim. Pays-Bas*, **72**, 655 (1953).

6) K. Dimroth and G. Neubauer, *Angew. Chem.*, **69**, 95 (1957).

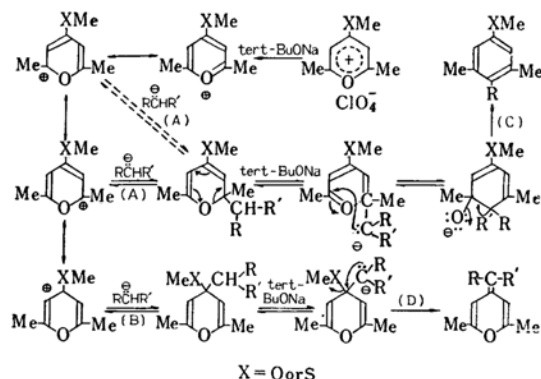


Fig. 2. Mechanism of the condensation reaction.

D (demethoxylation) is more favorable than the step C (decarbomethoxylation), and the reaction leads to the condensation at the position 4. The same reaction mechanism can be assumed to the reaction with malonitrile. In the case of trialkylpyrylium salts, the step D corresponds to dealkylation which is hindered, thus the reaction proceeds thoroughly via the step C to give benzonitrile derivatives, as is observed in Dimroth's report.

As 4-pyrone perchlorate is believed to possess the structure of the pyrylium salt type, the reaction between this compound and malonitrile was tried in hopes of effecting a condensation reaction, but when 2,6-dimethyl-4-pyrone perchlorate was treated with malonitrile and sodium *tert*-butoxide, free 2,6-dimethyl-4-pyrone was obtained.

Experimental

2,6-Dimethyl-4-pyrone (II)⁷.—Dehydroacetic acid (100 g.) was refluxed in concentrated hydrochloric acid (400 ml.) for an hour, and the solution was boiled for two hours to concentrate, and finally concentrated nearly to dryness under reduced pressure. The residue was dissolved in water, and the solution was washed with benzene, saturated with potassium carbonate and extracted with chloroform. The extract, after being dried with potassium carbonate, was evaporated and the residue was collected. Yield, 71 g. (97%); m. p. 130°C. The product was pure enough for use in the subsequent experiments.

2,6-Dimethyl-4-thiopyrone (III).—This compound was prepared by King's method⁸.

Condensation of II or III with Active Methylene Compounds.—2,6-Dimethyl-4-pyrone (II) (1 g.) or -thiopyrone (III) (0.5 g.) and 1 mol.

each of active methyl or methylene compounds were refluxed in acetic anhydride for an hour. Solvent was removed under reduced pressure, and the residue was collected, washed with ether and recrystallized.

The following results were obtained (Yield A refers that from II and Yield B that from III): Malonitrile: pale yellow needles (from ethanol), m. p. 191°C⁹. Yield A, 90%; B, 33%.

Ethyl cyanoacetate: pale yellow needles (from ethanol), m. p. 184°C. Yield A, 31%; B, 44%.

Anal. Found: C, 65.51; H, 6.10; N, 6.67. Calcd. for C₁₂H₁₃O₃N (V): C, 65.74; H, 5.98; N, 6.39%.

Rhodanine: yellow needles (washed with benzene and recrystallized from acetone), m. p. 260°C. Yield A, 32%; B, 59%.

Anal. Found: C, 49.93; H, 4.12; N, 5.17. Calcd. for C₁₀H₉O₂NS₂ (VI): C, 50.21; H, 3.79; N, 5.86%.

The products obtained from III were identified by their melting points, and by the failure of m. p. depressions on admixture with the specimens prepared from II.

These condensations could not be effected by sodium ethoxide or *tert*-butoxide, sodium acetate, or piperidine as catalyst.

In the case of diethyl malonate, acetylacetone, cyclopentadiene, or nitromethane, the reaction occurred neither with II nor with III, and the starting material was recovered unchanged.

When malonic acid (3 g.) was gently warmed in acetic anhydride (15 ml.) with II or III (3 g. each) a marked evolution of gas was observed and black unpurifiable powder (3 g.) was obtained after removal of the solvent. This substance was soluble in aqueous solution of sodium bicarbonate, but insoluble in most solvents.

Hydrolysis of IV.—A suspension of IV (7 g.) in a mixture of concentrated hydrochloric acid (40 ml.) and ethanol (40 ml.) was refluxed for twenty-four hours and then poured into water. The precipitate was collected and recrystallized from ethanol giving pale yellow amorphous powder with green fluorescence. (5 g.) m. p. 252°C (decomp.).

Anal. Found: C, 62.61; H, 5.35; N, 14.42. Calcd. for C₁₀H₁₀O₂N₂ (VII): C, 63.15; H, 5.30; N, 14.73%.

No dicarboxylic acid was obtained when refluxing was prolonged for another thirty hours.

4-Methoxy-2,6-dimethylpyrylium Perchlorate (VIII).—This compound was prepared by Baeyer's method¹⁰.

4-Methylmercapto-2,6-dimethylpyrylium Perchlorate (XII).—This compound was prepared by Arndt's method¹¹.

4-Methoxy-2,6-dimethylnitrobenzene (IX).—A hot solution of sodium *tert*-butoxide (0.47 g. of metallic sodium in 30 ml. of *tert*-butanol) was added into a solution of VIII (2.4 g.) in nitromethane (10 ml.) under stirring and reflux. After refluxing for an hour, the mixture was

7) This is a modification of the procedure reported by Cornubert et al. (*Bull. soc. chim. France*, 1950, 40) and by King et al.⁸

8) L. C. King et al., *J. Am. Chem. Soc.*, 73, 300 (1951).

9) Woods¹¹ reports the m. p. 190–192°C.

10) A. Baeyer, *Ber.*, 43, 2337 (1910).

11) F. Arndt and P. Nachtwey, *ibid.*, 59, 446 (1926).

poured into dilute hydrochloric acid (200 ml. containing 2 ml. of concentrated hydrochloric acid) and the solution was extracted with chloroform. The extract was dried with potassium carbonate, the viscous oily residue which remained after removal of the solvent was distilled under reduced pressure, and the fraction distilling at 129°C/8 mmHg was collected; it soon solidified to pale yellow needles (1 g.), m. p. 50°C¹².

Anal. Found: C, 59.68; H, 6.43; N, 7.67. Calcd. for $C_9H_{11}O_3N$ (IX): C, 56.66; H, 6.12; N, 7.73%.

4-Methylmercapto-2,6-dimethylnitrobenzene (XIII).—A hot solution of sodium *tert*-butoxide (0.32 g. of metallic sodium in 30 ml. of *tert*-butanol) was added to a solution of XII (1.7 g.) in nitromethane (8 ml.), and was treated by essentially the same method as described above. A fraction which was distilled at 148~149°C/8 mmHg was collected, and it solidified to yellow needles (0.6 g.), m. p. 62~63°C.

Anal. Found: N, 7.39. Calcd. for $C_9H_{11}O_2NS$ (XIII): N, 7.10%.

3,5-Dimethyl-4-nitrophenol (X).—A solution of IX (0.5 g.) in a mixture of hydrobromic acid (48%, 10 ml.) and acetic acid (5 ml.) was refluxed for three hours and the reaction mixture was extracted with chloroform. Removal of the solvent left yellow residue, which was recrystallized from ethanol giving yellow plates (0.4 g.), m. p. 107~108°C¹³.

Anal. Found: N, 8.34. Calcd. for $C_8H_9O_3N$ (X): N, 8.38%.

N-Acetyl-2,6-dimethyl-*p*-anisidine (XI).—To a solution of IX (1 g.) in a mixture of hydrochloric acid (10%, 20 ml.) and acetic acid (10 ml.) was added zinc dust (5 g.) portionwise under warming. After two hours, the mixture was extracted with chloroform, and the residue, left after removal of the solvent, was warmed with acetic anhydride. After removal of the solvent, the residue was recrystallized from ethanol giving colorless plates (0.8 g.), m. p. 178°C.

Anal. Found: N, 7.22. Calcd. for $C_{11}H_{15}O_2N$ (XI): N, 7.25%.

N-Acetyl-4-methylmercapto-2,6-dimethylaniline (XIV).—Treatment of XIII (0.4 g.) by the same procedure as described above gave white needles (0.4 g.), m. p. 155~156°C¹⁴.

Anal. Found: N, 6.80. Calcd. for $C_{11}H_{15}ONS$ (XIV): N, 6.69%.

Reaction of VIII with Ethyl Cyanoacetate.—A solution of VIII (2.4 g.) in a mixture of ethyl cyanoacetate (10 ml.) and *tert*-butanol (10 ml.) was treated by the same method as described in the reaction with nitromethane. Distillation gave solid distillate, which on recrystallization from ethanol gave orange leaflets (0.7 g.), m. p. 185°C. (Found: N, 6.35%). No melting point depression occurred when admixed with the authentic specimen V prepared by the condensation of II with ethyl cyanoacetate.

Reaction of VIII with Malonitrile.—A solution of VIII (2.4 g.) in a mixture of malonitrile (3 g.) and *tert*-butanol (15 ml.) was treated as described above. After refluxing for an hour, the mixture was poured into dilute hydrochloric acid and the yellow precipitate which separated out was collected. Yield, 1.7 g., m. p. 189°C. (Found: N, 15.99%). No melting point depression occurred when admixed with the authentic specimen IV¹⁵.

Reaction of XII with Malonitrile.—Into a suspension of XII (2.6 g.) in a mixture of malonitrile (1 g.) and *tert*-butanol (30 ml.) was added a hot solution of sodium *tert*-butoxide (0.47 g. of metallic sodium in 30 ml. of *tert*-butanol) under stirring and reflux. After refluxing for an hour, the mixture was poured into dilute hydrochloric acid and the precipitate which separated out was collected and recrystallized from ethanol giving yellow plates; m. p. 132~133°C.

Anal. Found: C, 60.14, N, 5.54; H, 12.87. Calcd. for $C_{11}H_{12}ON_2S$ (XVI): C, 60.00; H, 5.49; N, 12.72%.

The authors are indebted to Mr. Asaji Kondo for performing the microanalyses.

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12) Rowe et al.³¹ report the m. p. 53°C.

13) Rowe et al.³¹ report the m. p. 107~108°C.

14) Kloosterziel et al.⁵¹ report the m. p. 156.7~157.5°C.