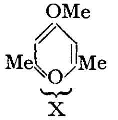
33. *The Reactivity of γ-Pyrone Quaternary Salts.*

By R. M. Anker and A. H. Cook.

2 : 6-Dimethyl-4-pyrone methiodide or methoperchlorate possesses an unexpectedly labile methoxyl group. This grouping is readily exchanged for ethoxyl, and in presence of inorganic or organic tertiary bases it reacts intermolecularly with the formation of a binuclear dyestuff (II). With primary amines the quaternary salts may form 4-methoxy-2 : 6-lutidine quaternary salts but, under other conditions, the methoxyl group also enters into reaction to form substituted aminolutidine quaternary salts. With *sec.*-amines, reaction is limited to the formation of substituted aminopyrylium salts. This reactivity is not confined to amines and reaction with toluenethiol gives 4-benzylthio-2 : 6-dimethylpyrylium salts. The constitutions of these products have been confirmed by their conversion into pyridine derivatives.

The following work forms part of a broad survey of the chemistry of pyrones now in progress and originated in attempts to utilise the reactivity of the methyl groups in 2 : 6-dimethyl-4-pyrone in synthesising dyestuffs of cyanine character. This pyrone is known to condense with benzaldehyde to give 2 : 6-distyryl-4-pyrone (Boon, McKenzie, and Trotter, *Proc.*, 1914, **30**, 206) but preliminary attempts to condense it with *p*-dimethylaminobenzaldehyde, *p*-nitrosodimethylaniline, or 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde were unpromising and attention was turned to quaternary salts of the pyrone.

2 : 6-Dimethyl-4-pyrone methiodide and methoperchlorate have been prepared previously *via* the methosulphate (Kehrmann and Duttenhofer, *Ber.*, 1906, **39**, 1301; Baeyer, *Ber.*, 1910, **43**, 2337; Baeyer and Piccard, *Annalen*, 1915, **407**, 332). In the present investigation, it has not been possible to obtain these quaternary salts without the intermediation of dimethyl sulphate, and direct addition of methyl iodide or toluenesulphonic esters was not observed. Even using dimethyl sulphate, the reaction appeared to be complex and quantities of the pyrone acid sulphate were formed. On heating the pyrone with methyl iodide and a small quantity of dimethyl sulphate a considerable quantity of a red periodide was isolated; it coloured starch blue, gave the iodoform reaction with ethanol and caustic alkali, and was no doubt identical with the periodide, $C_7H_8O_2,HI,I_2$, described by Collie and Steele (*J.*, 1900 **77**, 1114).

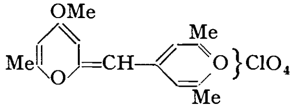


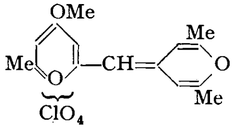
(I.)

The constitution of these quaternary salts has been accepted as (I); the conversion of the perchlorate into 4-methoxy-2 : 6-lutidine (Baeyer, *loc. cit.*) provides convincing chemical evidence and formulation (I) is in agreement with the evidence of absorption spectra (Hantzsch, *Ber.*, 1919, **52**, 1535). The formation of 4-methoxypyridines from pyrone quaternary salts might seem to imply that the methoxyl group in (I) possesses only normal character, but it soon appeared that 2 : 6-dimethyl-4-pyrone methiodide and methoperchlorate contain a methoxy group of hitherto unsuspected lability.

When reaction between (I) and *p*-dimethylaminobenzaldehyde, 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde, or analogous anils (anilinovinyl compounds) was attempted, there was ample visual indication of cyanine-like blue and violet dyes but the products were not homogeneous. These attempted reactions involved the use of bases in the media and part at least of the difficulty was traced to the fact that the pyrone quaternary salts alone underwent self-condensation in presence of inorganic or organic tertiary bases to give an orange–red dyestuff in not inconsiderable amount. Prepared in methanol the *dyestuff perchlorate* was apparently formed from two molecules of the pyrone methoperchlorate by loss of 1 molecule of methanol and 1 molecule of perchloric acid. Structure (II*a*) or a tautomeride thereof (II*b*) seems to be the only one to accommodate these facts and account for the colour. In accordance with this formulation, (II) reacted readily with ammonia to give a colourless base formulated as the *derivative* (III*a* or III*b*).

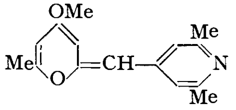
(II*a*.)

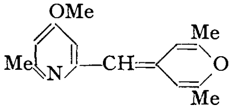




(II*b*.)

(III*a*.)



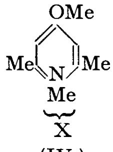


(III*b*.)

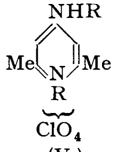
The formation of (II) was doubtless responsible for the observation of Baeyer and Piccard (*loc. cit.*) that the pyrylium salts (I) differ from analogous pyridinium salts in yielding no simple free base on treatment with alkali and in decomposing to give a red solution.

The formation of (II) postulates an unexpected ease of replacement of the methoxyl group in (I), but when this ease was appreciated, one reason for earlier difficulties in the purification of (II) and other products became apparent. Thus when the methoperchlorate (I) was recrystallised from ethanol the corresponding ethoperchlorate was obtained and this reverted to the methoperchlorate when crystallised from methanol; it seemed probable that exchange of radicals was taking place in other attempted condensations before reaction with the solvent and the consequent need for working only in methanol was recognised.

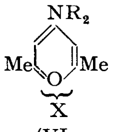
Formation of (II) was not observed with ammonia probably because reaction with the cyclic oxygen atom rapidly converts (I) into 4-methoxy-2 : 6-lutidine in which the methoxyl group no longer possesses any abnormal lability. Similarly reaction with primary amines was also very rapid and in presence, for example, of an approximately equimolecular quantity of aqueous methylamine, 4-methoxy-2 : 6-lutidine methiodide (IV; X = I) (cf. Conrad and Eckhard, *Ber.*, 1889, **22**, 73), and the corresponding *methoperchlorate* was also prepared. Compound (IV) underwent no further reaction with methylamine under the conditions used in these experiments. When, however, (I) was allowed to react with excess of methylamine in methanol the product contained 2 atoms of nitrogen and must be formulated as *4-methylamino-2 : 6-dimethylpyridine methoperchlorate* (V) (R = Me); when aniline was used instead of methylamine, two molecules of base were again introduced to give *4-anilino-2 : 6-dimethylpyridine phenyl perchlorate* (V) (R = Ph).



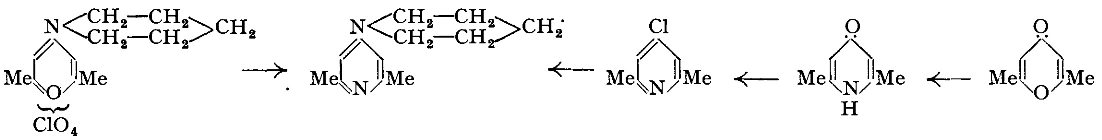
(IV.)



(V.).



(VI.



(VII.) (VIII.)

These reactions can only be interpreted by assuming a ready replaceability of the methoxyl in (I). If conditions are such that reaction of the methoxyl can take precedence over that with the oxonium oxygen, full reaction is completed by the formation of compounds of type (V); if, however, reaction is initiated at the oxonium oxygen, the primary product has no special further reactivity and the product is of type (IV). If this be the case, reaction of (I) with secondary amines presents particular interest in that completion of reaction by formation of pyridine derivatives becomes impossible and reaction should cease with formation of amino-pyrylium salts (VI).

This hypothesis was confirmed by allowing (I) to react with a variety of secondary amines and isolating in good yield 4-N-*piperidyl*-2 : 6-*dimethylpyrylium iodide* and *perchlorate*, 4-*diethylamino*-2 : 6-*dimethyl*- and N-*morpholinyl*-2 : 6-*dimethyl-pyrylium iodide*. Piperazine underwent two-fold reaction with formation of *piperazine*-NN′-*bis*-2 : 6-*dimethylpyrylium perchlorate*. The constitution of these compounds was in no doubt since the piperidyl compound (VII) reacted with ammonia to give 4-N-*piperidyl*-2 : 6-*lutidine* (VIII); the latter was synthesised independently from 2 : 6-dimethyl-4-pyrone *via* 2 : 6-dimethyl-4-pyridone and 4-chloro-2 : 6-lutidine which reacted with piperidine to give (VIII), identical with the material obtained earlier. The difficulty with which even 4-chloro-2 : 6-lutidine reacted with piperidine was in marked contrast with the ease of reaction of (I) with piperidine and emphasised the highly reactive nature of its methoxyl group. Compound (VII) also reacted with methylamine to give 4-N-*piperidyl*-2 : 6-*lutidine methoperchlorate*.

The above transformations suggested that (I) and similar compounds would eliminate alcohols on reaction with more diverse compounds containing " reactive " hydrogen, methin, methylene, or methyl groups. In preliminary experiments (I) was allowed to react in boiling methanol with toluenethiol when 4-*benzylthio*-2 : 6-*dimethylpyrylium perchlorate* was formed. This constitution was confirmed by its giving with ammonia the base, 4-*benzylthio*-2 : 6-*lutidine*; this was also obtained from toluenethiol and 4-chloro-2 : 6-lutidine, the products from the two routes being identified as the *picrate*.

From a theoretical viewpoint this reactivity can be regarded only as a manifestation of the relative reluctance of an oxonium group to contribute to a resonating aromatic system with consequent resemblance of the ring structure in (I) to an olefinic system. Practically, the reactivity of γ-pyrone quaternary salts exemplified above provides routes to many types of compound of general interest and the further examination of these possibilities in the pyrone and chromone fields is in progress.

EXPERIMENTAL.

2 : 6-Dimethyl-4-pyrone (31 g.), dimethyl sulphate (43 g.), and methanol (4 c.c.) were warmed to 55—60° and the homogeneous melt cooled and stirred with sodium iodide (150 g.) in water (100 c.c.). After 2 hours, the solid was collected and washed with acetone. The residue consisted of the pyrone methiodide which decomposed with effervescence at 110°. The acetone washings contained the pyrone hydriodide and turned brown on standing in air. On evaporating the washings crystals of 2 : 6-dimethyl-4-pyrone periodide (Collie and Steele, *loc. cit.*) were deposited; the compound separated from ethyl acetate in stout red needles, m. p. 114° (Found : C, 27·1; H, 2·8; available I, 39·4. Calc. for $C_{14}H_{17}O_4I_3$: C, 26·9; H, 2·7; available I, 40·3%). 2 : 6-Dimethyl-4-pyrone methoperchlorate was prepared according to Baeyer and Piccard (*loc. cit.*), but sodium perchlorate was used instead of perchloric acid; the methoperchlorate could be recrystallised from methanol without serious loss. On crystallising the methoperchlorate from ethanol, the corresponding ethoperchlorate was obtained. It separated in needles, m. p. 124° (the methoperchlorate has m. p. 195°), which were more soluble in chloroform than the methoperchlorate (Found : C, 43·0; H, 4·9. Calc. for $C_9H_{13}O_6Cl$: C, 42·8; H, 5·2%) (Meerwein and Coll, *J. pr. Chem.*, 1937, **147**, 257). The ethoperchlorate dissolved in *n*- or *iso*-propanol on standing for several days but, on evaporating the solutions, perchlorates resulted which could not be obtained pure and which were not reconverted into the methoperchlorate by refluxing in methanol. The methoperchlorate remained apparently unchanged on refluxing in *n*- or *iso*-propanol or fusing at 100° for 30 mins. with phenol.

2 : 6-Dimethyl-4-pyrone methoperchlorate (20 g.), anhyd. sodium acetate (3·5 g.), and methanol (200 c.c.) were refluxed for 15 mins. The solution became deep red almost immediately. On cooling, the solid was collected and recrystallised from methanol; the *dyestuff perchlorate* (II) (10·4 g.) separated in small red-brown prisms which decomposed violently at *ca.* 260° (Found : C, 52·5; H, 4·95. $C_{15}H_{17}O_7Cl$ requires C, 52·2; H, 5·0%). The same material was formed on warming the methoperchlorate (2·5 g.), triethylamine (1·1 g.), and methanol (40 c.c.), removing the unchanged salt which separated on cooling, and evaporating the filtrate and digesting the residue with water. It was also obtained by using diethylaniline in place of triethylamine. It did not appear to condense with *p*-dimethylaminobenzaldehyde. The compound dyed cotton a pale pink, and cotton mordanted with antimony brown, but the dyeings were unstable to hot aqueous sodium carbonate; aqueous solutions of the dye were, however, apparently unaffected by acid or alkali. The dyestuff perchlorate (10·2 g.) was heated in a closed flask with ammonia solution (30 c.c., *d* 0·880) at 70° for 3 hours. On cooling, a base separated in prisms and more was obtained by extracting the mother liquor with chloroform. The *derivative* (III) separated from toluene in prisms, m. p. 186° (Found : C, 74·05; H, 6·8; N, 5·95. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·05; N, 5·75%).

Reactions with primary amines. 2 : 6-Dimethyl-4-pyrone methiodide (4·0 g.) was heated in a sealed tube for 30 mins. at 80° with ethanol (10 c.c.) and methylamine (0·7 g.). On evaporating and recrystallising the product from ethanol, 4-methoxy-2 : 6-lutidine methiodide (0·8 g.) separated in prisms, m. p. 204° (cf. Conrad and Eckhard, *loc. cit.*) (Found : C, 39·3; H, 5·1; N, 4·7. Calc. for $C_9H_{14}ONI$: C, 38·7; H, 5·05; N, 4·4%); it was identical with the product of quaternising 4-methoxy-2 : 6-lutidine with methyl iodide. When the pyrone methoperchlorate (2·4 g.) was added to methylamine carbonate (3 g.) in water (15 c.c.), heat was evolved and after warming and shaking for 20 mins., pptn. commenced and was completed by adding sodium perchlorate. Recrystallisation from methanol gave the corresponding 4-*methoxy*-2 : 6-*lutidine methoperchlorate*, which separated in needles, m. p. 187° (Found : C, 42·9; H, 5·6. $C_9H_{14}O_5NCl$ requires C, 42·9; H, 5·6%). It was identical with the perchlorate obtained by quaternising 4-methoxy-2 : 6-lutidine with methyl iodide and salting out the product from aqueous solution with sodium perchlorate. From the methanolic mother liquors 4-*methylamino*-2 : 6-*lutidine methoperchlorate* separated in octahedra, m. p. 224° (Found : C, 43·2; H, 6·1; N, 10·95. $C_9H_{15}O_4N_2Cl$ requires C, 43·1; H, 6·1; N, 11·2%). The latter was the main product (4 g.) when 2 : 6-dimethyl-4-pyrone methoperchlorate (5 g.) was warmed with methylamine (2 g.) in methanol (50 c.c.) at 70° for 15 mins. 2 : 6-Dimethyl-4-pyrone methoperchlorate (3·0 g.), methanol (20 c.c.), and aniline (1·2 g.) were refluxed for 1 hour and the solution evaporated. The cryst. deposit was recrystallised from ethyl acetate–methanol (5 : 1) and then from methanol when 4-*anilino*-2 : 6-*dimethylpyridine phenyl perchlorate* separated in rhombic plates, m. p. 222° (Found : C, 60·6; H, 5·2; N, 7·9. $C_{19}H_{19}O_4N_2Cl$ requires C, 60·9; H, 5·2; N, 7·5%).

Reactions with secondary amines. 2 : 6-Dimethyl-4-pyrone methiodide (2·7 g.) was refluxed for 15 mins. in ethanol

(30 c.c.) with piperidine (0·9 g.) and the solution allowed to evaporate. The crystals were collected and crystallised from ethanol when 4-N-*piperidyl*-2 : 6-*dimethylpyrylium iodide* separated in prisms, m. p. 188—190° (Found : C, 44·5; H, 5·6; N, 4·4. $C_{12}H_{18}ONI$ requires C, 45·1; H, 5·7; N, 4·4%). When the corresponding pyrone methoperchlorate was treated similarly 4-N-*piperidyl*-2 : 6-*dimethylpyrylium perchlorate* (yield, 65%) was obtained. It separated from ethanol in prisms, m. p. 145° (Found : C, 49·5; H, 6·2. $C_{12}H_{18}O_5NCl$ requires C, 49·4; H, 6·25%). The preceding compound (4 g.), ammonium carbonate (4 g.), 10% aqueous ammonia (30 c.c.), and methanol (20 c.c.) were warmed until solution was complete, water (100 c.c.) added and the base extracted with chloroform. Evaporation and recrystallisation of the residue from ligroin gave 4-N-*piperidyl*-2 : 6-*dimethylpyridine* (2 g.) which separated in octahedra, m. p. 83° (Found : C, 75·5; H, 9·3; N, 14·6. $C_{12}H_{18}N_2$ requires C, 75·7; H, 9·6; N, 14·7%). 2 : 6-Dimethyl-4-pyrone (20 g.) and ammonia solution (30 c.c., *d* 0·880) were heated for 12 hours at 120° and the product evaporated to dryness. The residue was treated with phosphorus oxychloride (30 c.c.) and phosphorus pentachloride (37 g.) and reaction completed by refluxing. Evaporation, addition of excess of sodium hydroxide to the residue and extraction with ether gave 4-chloro-2 : 6-dimethylpyridine (17·2 g.), b. p. 177—178° (cf. Conrad and Epstein, *Ber.*, 1887, **20**, 162). The last compound (2·8 g.) was heated with piperidine (3·6 g.) for 2 hours at 150°, the cold product poured into excess of sodium hydroxide, and the bases extracted with ether. Distillation removed much unchanged chlorolutidine and the solid 4-*N*-piperidyllutidine was recrystallised from ligroin when it separated in octahedra, m. p. 82°, giving no depression in m. p. when mixed with the product prepared earlier. The identity was confirmed by the formation of the same *picrate* which separated from ethanol in prisms, m. p. 149—150° (Found : C, 52·0; H, 4·9; N, 16·5. $C_{18}H_{21}O_7N_5$ requires C, 51·6; H, 5·0; N, 16·7%); it was accompanied by a second picrate which was separated from the first by flotation in ligroin and which formed prisms, m. p. 151°, from benzene, depressing the m. p. of the first compound. 4-*N*-Piperidyl-2 : 6-dimethylpyrylium perchlorate (3·5 g.) was added to 33% methylamine in ethanol (3 g.); the initial reaction was moderated by cooling and completed at 80° (sealed tube) for 20 mins. On evaporation, 4-N-*piperidyl*-2 : 6-*lutidine methoperchlorate* was obtained. It separated from ethanol in prisms (2·2 g.), m. p. 178—179° (Found : C, 51·4; H, 6·6. $C_{13}H_{21}O_4N_2Cl$ requires C, 51·2; H, 6·9%).

The following were prepared by method used for the above piperidylpyrylium salt : 4-*diethylamino*-2 : 6-*dimethylpyrylium iodide*, plates, m. p. 192°, from ethanol (Found : C, 42·85; H, 5·75. $C_{11}H_{18}ONI$ requires C, 43·0; H, 5·9%); 4-N-*morpholinyl*-2 : 6-*dimethylpyrylium iodide*, prisms, m. p. 213°, from ethanol (Found : C, 41·3; H, 5·1. $C_{11}H_{16}O_2NI$ requires C, 41·1; H, 5·05%). Piperazine hydrate (0·8 g.), 2 : 6-dimethyl-4-pyrone methoperchlorate (3·6 g., 2 mols.), and ethanol (60 c.c.) were refluxed for 15 mins. and the solution cooled. The product (2·0 g.) was crystallised from glycol monomethyl ether–ethanol (1 : 1) and then from glycol monomethyl ether alone when *piperazine*-NN′-*bis*-2 : 6-*dimethylpyrylium perchlorate* separated in small prisms which exploded at *ca.* 260° (Found : C, 42·9; H, 4·7. $C_{18}H_{24}O_{10}N_2Cl$ requires C, 43·3; H, 4·8%).

2 : 6-Dimethyl-4-pyrone methoperchlorate (2·4 g.) was refluxed for 90 mins. with methanol (20 c.c.) and toluenethiol (1·3 g.) and the solution cooled to 0°. Unchanged dimethylpyrone methoperchlorate was separated and the mother liquor, on evaporation, gave 4-*benzylthio*-2 : 6-*dimethylpyrylium perchlorate* (0·7 g.) which crystallised from methanol in platelets, m. p. 146° (Found : C, 51·0; H, 4·65. $C_{14}H_{15}O_5ClS$ requires C, 50·85; H, 4·6%). This salt was warmed with ammonium carbonate (2 g.) and aqueous ammonia (10 c.c., 15%) until the solid had become quite oily, the oil extracted with ether and converted into its picrate. It formed needles, m. p. 171—172°, from methyl ethyl ketone–ethanol (1 : 4) giving no depression in m. p. when mixed with the picrate of 4-benzylthio-2 : 6-lutidine prepared as follows. 4-Chloro-2 : 6-lutidine (3 g.) and toluenethiol (2·5 g.) were heated (sealed tube) for 4 hours at 200°, the oil taken up in 2N-hydrochloric acid and the solution extracted with ether. The aqueous layer was basified with sodium carbonate and the liberated base taken up in ether and distilled. 4-*Benzylthio*-2 : 6-*lutidine* (3·5 g.) was obtained as an oil, b. p. 260°/25 mm. (Found : C, 73·3; H, 6·6. $C_{14}H_{15}NS$ requires C, 73·3; H, 6·6%). The *picrate* separated from methyl ethyl ketone–ethanol (1 : 4) in needles, m. p. 171—172°, identical with that described above (Found : C, 52·35; H, 3·85. $C_{20}H_{18}O_7N_4S$ requires C, 52·4; H, 3·95%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7

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