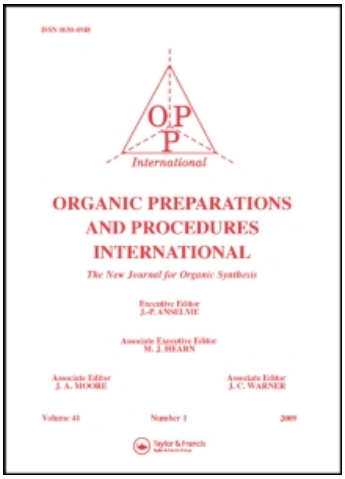

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PREPARATION OF 2,3,4,6-TETRAMETHYLPYRYLIUM PERCHLORATE AND OF 2,3,4,6-TETRAMETHYLPYRIDINE

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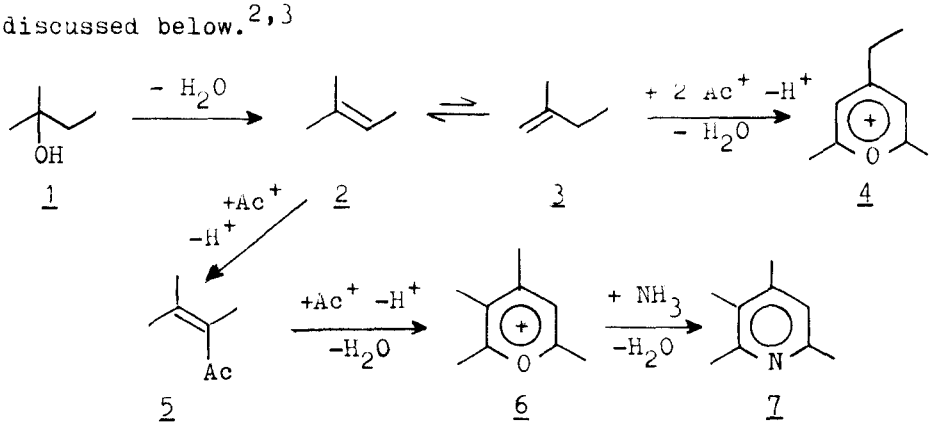
Alkyl substituted pyrylium salts are readily available by diacylation of alkenes,[1-4] and constitute a valuable class of reactive compounds which are converted by nucleophiles into a host of conjugated acyclic compounds and aromatic benzenoid or heterocyclic compounds such as furans,[5] pyridines,[6] etc.[7,8]

The diacetylation of 2-methyl-2-butene (2) and of 2-methyl-1-butene (3), which may be obtained *in situ* by dehydration of t-amyl alcohol (1) or by dehydrochlorination of t-amyl chloride, was shown to yield, according to reaction conditions, 2,6-dimethyl-4-ethylpyrylium salt 4 (with acetyl chloride and aluminium chloride this is essentially the exclusive reaction product) or 2,3,4,6-tetramethylpyrylium salt 6 as will be discussed below.[2,3]



While 4 is easily prepared and purified by recrystallization from water, so far the preparation of 6 and of the corresponding 2,3,4,6-tetramethylpyridine 7 was rather cumbersome because under the usual conditions, e.g., excess acetic anhydride and equimolar amounts of t-amyl alcohol and perchloric acid, a reaction mixture containing 80% of 6 and 20% of 4 is obtained;[2,3] recrystallization of this pyrylium salt mixture from any solvent only enriches it in the less soluble, symmetrical perchlorate 4 because the less symmetrical salt 6 is too soluble (it cannot be conveniently recrystallized from water). The procedure described earlier for obtaining the perchlorate 6 consisted[2] of converting the above mixture of pyrylium perchlorates into chloroferrates, purification of the chloroferrate 6 by fractional crystallization, and reconversion into the 2,3,4,6-tetramethylpyrylium perchlorate 6. When fairly pure, perchlorate 6 can be recrystallized from isopropyl alcohol or from a mixture of ethyl ether and ethanol.

From all electrophilic acetylating agents which were tested, so far only excess acetyl chloride with equimolar amounts of alkene 2 and beryllium chloride gave 6 and practically no 4.[9] The reaction mechanism was checked using ^{14}C-labelling;[10,11] recently, Arnaud, Roussel and Metzger[12] observed that the ratio catalyst/acetylating agent (namely, $AlCl_3$/AcCl in the diacetylation of alkenes 2 and/or 3) had a pronounced influence on the selectivity of the reaction : a low ratio $AlCl_3$/AcCl favours the more substituted pyrylium salt 6.

Having as objective to prepare the monoacetylation product, 3,4-dimethyl-3-penten-2-one (5), we unexpectedly obtained pure 6 as perchlorate, when t-amyl alcohol 1 was treated with

excess acetic anhydride and with less than 0.5 equivalent of 70% perchloric acid per equivalent of 1. Thus, also in this case the low $HClO_4/Ac_2O$ ratio favours the more substituted pyrylium salt 6. The mechanistic implications of this finding will be discussed in a separate paper.

Since pyrylium salts are of increasing interest as nucleophilic conjugated C_5-synthons,[7] and since the Collective Vol. 5 of Organic Syntheses contains no less than four procedures for preparing pyrylium salts,[13] we developed the above observation into a simple and preparatively useful method for obtaining 2,3,4,6-tetramethylpyrylium perchlorate (6) and 2,3,4,6-tetramethylpyridine (7). It should be noted that all pyrylium salts described in Organic Syntheses [13] and the 2,4,6-trimethylpyrylium sulfoacetate [14] are symmetrical ; for regiospecificity studies of nucleophilic attack, non-symmetrical pyrylium salts such as the present one or 2,4-diphenyl-6-methylpyrylium sulfoacetate (readily obtained from acetophenone, acetic anhydride, and sulfoacetic acid),[15] have to be used. Thus Royer and Dreux [16] observed regiospecificity in the attack of Grignard reagents on non-symmetrical pyrylium salts ; also, it was reported earlier [2] that 6 is attacked regioselectively by hydroxyl anions, yielding 2,3,5-trimethylphenol as the major product, with 3,4,5-trimethylphenol as a minor side-product. More detailed studies of the latter reaction, as well as of the reaction of 6 with other nucleophiles such as dialkylamines or cyanide anion, will be published separately.

EXPERIMENTAL

CAUTION ! The perchlorate 6 can be allowed to dry in the atmosphere, but should be stored and handled with care when dry.

All pyrylium perchlorates are explosive, therefore they should be prepared only when needed, in the necessary amount, and used immediately without drying and storing.[13,17] Heating, grinding, rubbing or knocking dry pyrylium perchlorates should be carefully avoided.Another WARNING is at the end of the paper.

2,3,4,6-Tetramethylpyrylium Perchlorate (6).- In a four-necked 1-liter flask equipped with mechanical stirrer, a thermometer reaching into the liquid, a reflux condenser and a dropping funnel, were added 108 ml (88 g., 1 mole) of t-amyl alcohol 1 and 330 ml (357 g., 3.5 moles) of acetic anhydride at room temperature. A good quality of the anhydride is essential for the success of the reaction, since the presence of acetic acid in the anhydride lowers the yield considerably. From the dropping funnel, 43 ml (72 g., 0.5 mole $HClO_4$, also containing by virtue of its concentration 1.2 mole of water) of 70% perchloric acid was then added with vigorous stirring very cautiously, observing the temperature rise of the liquid (the excess acetic anhydride is hydrolyzed exothermally by the water in the presence of the strong acid which acts as catalyst). The first two milliliters of perchloric acid should be added during 2-3 minutes until the temperature in the flask reaches 70°, then the addition rate of the acid can be increased somewhet so that towards the end of the addition the temperature should become stabilized at 90-95° without any external heating or cooling. To prevent overheating and spilling of the hot lachrymatory liquid through the condenser, a cold water bath should be ready at hand, but only for brief correction of any dangerous temperature rise due to a too high addition rate. The whole addition should last 15-20 minutes, during which time the reaction mixture becomes gradually

yellow, then brown, and finally black-brown.

Stirring was continued for 30 minutes, then the mixture was cooled to 25-28°, transferred to a large separatory funnel, and 500 ml of ethyl ether was added. After brief shaking, the lower black layer was immediately separated ; since the mixture is dark-coloured, the viscosity rather than transparency differences of the two layers show when to turn the stopcock of the separatory funnel (another method is to add a small amount of diatomaceous silica, i.e. Super Cel, which goes to the interface of the two layers and is visually detected [18]). The lower layer (collected in a beaker) was scratched with a glass rod (or crystals from a previous run are used for seeding, but most times the lower layer crystallizes spontaneously, therefore its separation should be carried out rapidly at 25-28°) and set for 1 hr. in the freezer. The crystals of 6 (as perchlorate) were collected on a sintered glass filter with suction, washed thoroughly twice with a mixture of acetic acid and ethyl ether (1:2 by volume) interrupting each time the suction and mixing the crystals with the washing liquid using a spatula, then twice with ether. If the washing is done properly, 95-100 g., (81-85 % yield relatively to $HClO_4$) of colorless crystals should result (otherwise the product is brownish and tends to darken on standing), m.p. 98-100°, which can be used directly for most purposes. If desired, the product may be recrystallized from isopropyl alcohol (or by adding ethyl ether into its ethanolic solution) yielding perfectly white crystals with m.p. 100°.

IR (KBr) : strong bands at 954, 1459, 1511, 1548 and 1642 cm^{-1} due to the cation 6 , and at 625 and 1100 cm^{-1} due to the anion

ClO_4^-, as indicated in ref. 19.

^{1}H-NMR (F_3CCO_2H) : 2.42 (s, 3H, 3-Me) ; 2.70 (s, 3H, 4-Me) ; 2.87 (s, 3H, 6-Me) ; 2.92 (s, 3H, 2-Me) ; 7.63 (s, 1H, 5-H). The assignment of most signals is straightforward,[20] but the discrimination between the two α-methyl peaks corresponding to positions 2 and 6 is not ; the present assignment is based on the correspondence with the ^{1}H-NMR spectrum of the 2,3,4,6-tetramethylpyridine with non-deuterated and partly deuterated methyls, on the difference in the rate of deuteration by isotopic exchange in D_2O between the two α-methyl grouos, and on an unambiguous synthesis of 2,3,4-trimethyl-6-(d_3-methyl)-pyrylium and the corresponding pyridine, as will be reported in a separate paper.

The black filtrate remained from the lower layer can be discarded ; it contains about 10 g. of 6 and 2 g. of 4 as perchlorates, in addition to perchloric and acetic acids, as proved by conversion into pyridines and g.l.c. analysis thereof.

The upper original layer was washed in the separatory funnel with one 1 l. and two 0.5 l. portions of water, then with aqueous sodium hydrogen carbonate for removing the acids, dried over anhydrous sodium sulfate or magnesium sulfate, and fractionated under reduced pressure, affording 20-25 g. of ketonic fraction, b.p. 48-55°/15 Torr, which consists mainly of 3,4--dimethyl-3-penten-2-one (5).

2,3,4,6-Tetramethylpyridine (7).-The crude perchlorate 6 (25 g.) was added to a five-fold excess of aqueous ammonia (35 ml of conc. ammonium hydroxide and 50 ml water). In an exothermal reaction, the tetramethylpyridine 7 resulted as an upper yellow layer. Ethyl ether (50 ml) was added to assist in the se-

paration. In order to remove ketonic side-products, the combined organic layers were extracted with 10% hydrochloric acid. Only the pyridine 7 was extracted into the aqueous phase which was separated and re-extracted with ether (the ethereal extracts are discarded). Then 20% sodium hydroxide solution was added to the aqueous phase until all the pyridine 7 separated. After extraction with ether and drying over powdered sodium hydroxide, the ether was evaporated and the pyridine 7 distilled under reduced pressure. Physical constants and melting points of derivatives (picrate, picrolonate, methiodide and chloroplatinate) have already been published;[2] there exist two crystalline modifications of the picrate with distinct melting points. The yield of 7 from 6 was 85-95%.

^{1}H-NMR (CCl_4): 2.07 (s, 3H, 3-Me) ; 2.13 (s, 3H, 4-Me) ; 2.30 (s, 3H, 6-Me) ; 2.37 (s, 3H, 2-Me) ; 6.60 (s, 1H, 5-H) ; the assignment of the two α-methyl peaks is based, in addition to the data quoted above (unambiguous synthesis from CD_3COCl and 5), on lanthanide-induced shifts.[21]

REFERENCES

1. A. T. Balaban and C. D. Nenitzescu, Ann., 625, 74 (1959).
2. A. T. Balaban and C. D. Nenitzescu, J. Chem. Soc., 3553 (1961).
3. P. F. G. Praill and A. L. Whitear, ibid., 3573 (1961).
4. Review on syntheses : A. T. Balaban, W. Schroth and G. Fischer, Adv. Heterocyclic Chem., 10, 241 (1969).
5. A. T. Balaban and C. D. Nenitzescu, Chem. Ber., 93, 599 (1960) ; A. T. Balaban, Org. Prep. Proc., 1, 63 (1969).
6. A. Baeyer and J. Piccard, Ann., 407, 332 (1915) ; 384, 208 (1911).
7. Review on the pyrylium cation as a synthon in organic chemistry : A. T. Balaban, in "Newer Trends in Heterocyclic Chemistry", ed. R. B. Mitra et al. (Monograph 3 in the series "Studies in Organic Chemistry"), Elsevier, Amsterdam, 1979, p. 79.
8. Reviews on reactions of pyrylium salts : K. Dimroth and K. H. Wolf, in "Newer Methods of Preparative Organic Chemistry", ed. W. Foerst, vol. 3, Academic Press, New

York, 1964, p. 357 ; A. T. Balaban, A. Dinculescu, G. N. Dorofeenko, G. W. Fischer, A. V. Koblik, V. V. Mezheritskii and W. Schroth, Adv. Heterocyclic Chem. Supplement 2, Academic Press, New York, in press.
9. A. T. Balaban, E. Barabas and M. Farcasiu, Chem. Ind., 781 (1962).
10. M. Frangopol, A. Genunche, P. T. Frangopol and A. T. Balaban, Tetrahedron, 20, 1881 (1964).
11. D. Farcasiu, A. T. Balaban and M. Gutman, Rev. Roumaine Chim., 9, 727 (1964).
12. M. Arnaud, C. Roussel and J. Metzger, Tetrahedron Lett., 1795 (1979).
13. A. T. Balaban and C. D. Nenitzescu, Org. Synth. Coll. Vol. 5, 1106 (1973) ; K. Hafner and H. Kaiser, ibid., 1119 ; A. T. Balaban and A. J. Boulton, ibid., 1112, 1114 ; K. Dimroth, C. Reichardt and E. Vogel, ibid., 1135.
14. A. Dinculescu and A. T. Balaban, Org. Prep. Proc. Int. (in press).
15. W. Schneider and A. Ross, Ber., 55, 2775 (1922) ; W. Schneider and F. Seebach, ibid., 54, 2285, 2298 (1921).
16. J. Royer and J. Dreux, Bull. Soc. Chim. France, 707 (1972).
17. A. Pelter, Tetrahedron Letters, 22, No. 22, i (1981).
18. Thanks are expressed to a referee for this suggestion : J. P. Hasak, Aldrichimica Acta, 10, 34 (1977).
19. A. T. Balaban, G. D. Mateescu and M. Elian, Tetrahedron, 18, 1083 (1962).
20. A. T. Balaban, G. R. Bedford and A. R. Katritzky, J. Chem. Soc., 1646 (1964).
21. A. T. Balaban, A. Bota, F. Chiraleu, E. Sliam, A. Hanes and C. Draghici, Rev. Roumaine Chim., 22, 1003 (1977).

WARNING. For all pyrylium salts, caution is recommended in handling them in order to avoid contact with skin. They[8] are known to easily undergo, in neutral or alkaline medium, ring-opening to pseudobases (1,5-enediones) which, being related to glutacon-dialdehyde, may cross-link amino groups of polynucleotides. Mutagenic activity of pyrylium salts was reported: Yu. D. Beletskii, A. N. Narkevich, G. N. Dorofeenko and Yu. A. Zhandnov, Zh. Vses. Khim. Obshchestva, 11, 359 (1966) and further papers.

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