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REACTIONS OF PYRYLIUM SALTS WITH NUCLEOPHILES—VI[1]

REACTION WITH AMINO ACIDS

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Abstract—The reaction of 2,4,6-trimethylpyrylium perchlorate (I) with glycine was reinvestigated and was found to yield according to conditions three perchlorates: N-carboxymethylcollidinium perchlorate (II) which can be decarboxylated, a double salt (IV) of the betaine IIIa with perchlorate (II) and a double salt (V) of the betaine IIIa with sodium perchlorate. All three perchlorates are converted into the same picrate, picrolonate and chloroplatinate. The reaction of I with β- and α-alanine, and with glycyl-glycine was also studied, but only with the first could a crystalline perchlorate be isolated. The reaction of I with *o*, *m*, and *p*-aminobenzoic acids affords N-carboxyphenylpyridinium perchlorates (VIII). The IR and NMR spectra and pK$_a$ values of these N-carboxyalkyl- and N-carboxyphenylpyridinium salts are described and discussed.

ALTHOUGH pyridines and pyridinium salts are readily available from pyrylium salts and ammonia or primary amines, the reaction with primary amines possessing functional groups has been little investigated. Only one amino acid has been reported to react with a pyrylium salt. The reaction of 2,4,6-trimethylpyrylium perchlorate (I) with glycine affords[2] the N-carboxymethyl-2,4,6-trimethylpyridinium cation (II), isolated as the picrate. The present paper reports further data on reactions between 2,4,6-trimethylpyrylium perchlorate (I) and amino acids.

Reaction of I *with glycine in neutral medium*

The reaction of one equiv I with two equivs of glycine in water at 100° yields two pyridinium perchlorates which can be separated by recrystallization from ethanol.

The more soluble compound melts at 183–184° and is the perchlorate II ($X = ClO_4$). Its IR spectrum (KBr pellet) presents in the 1500–1800 cm^{-1} range three bands at 1643 vs and 1578 m cm^{-1} due to the 8a and 8b skeletal vibration of the pyridinium ring,[1] and 1744 cm^{-1} (triangular-shaped with the width at half maximum ca. 50 cm^{-1}). Taking into account the presence of broad bands at 3400, 2500 and 2580 cm^{-1} (bonded OH stretching) and of a strong band at 1205 cm^{-1}, we ascribe the band at 1744 cm^{-1} to the carboxyl CO stretching vibration. The elevated frequency is due to the positive nitrogen heteroatom β to the carboxyl group. This assignment is confirmed by the potentiometric titration which shows the presence of one carboxyl with pK$_a$ 2·32 at 30° and by the NMR spectrum. This evidences in liquid SO_2 two methyl groups in the 2 and 6 positions of the pyridinium ring (τ 7·19) and of one methyl in the 4-position (τ 7·41); the N-methylene group appears at τ 4·73 and the protons in the 3 position of the pyridinium ring at τ 2·41, in agreement with previous data.[1]

The less soluble perchlorate melts at 152–153° with decomposition. Its elementary

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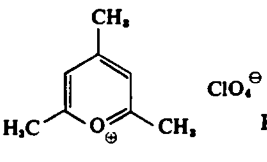
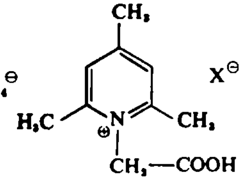
* To whom correspondence should be addressed.

[1] Part V, C. Toma and A. T. Balaban, *Tetrahedron* **22**, Suppl. I, 9 (1966).

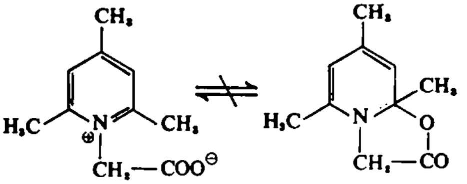
[2] A. T. Balaban and C. D. Nenitzescu, *Liebigs Ann.* **625**, 74 (1959).



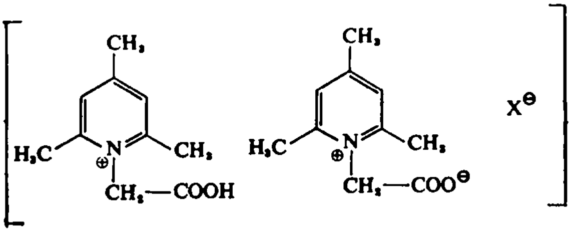
I



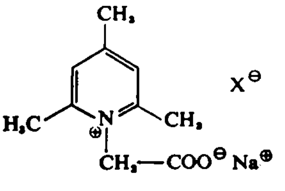
II



IIIa IIIb



IV



V

analysis and potentiometric titration indicates that it has formula IV ($X = ClO_4$) consisting of one mole betaine (IIIa) and of one mole perchlorate (II). The IR spectrum shows in the 1500–1800 cm^{-1} range four bands, all intense at 1574, 1643 (ν8b and ν8a pyridinium), 1738 (νCO carboxyl group) and at 1688 cm^{-1} (asymmetrical stretching of C—O bonds in the carboxylate group). The NMR spectrum in liquid SO_2 has peaks at τ7·29 (2- and 6-methyl groups), 7·45 (4-methyl), 2·45 (3-pyridinium hydrogens) and two N-methylene peaks at τ4·67 and 4·93. By comparison with the NMR spectra of compounds II and V (cf. below), the former is due to a methylene bonded to COOH and the latter to a methylene bonded to COO$^{\ominus}$. A covalent formula IIIb for the betainic moiety of IV is therefore excluded, since the 2- and 6-methyl groups would no longer be identical.

Table 1. IR bands in the 1750–1380 cm^{-1} range of N-

Structure	Anion\Band	νCO	νCO	ν8aPy$^{\oplus}$	ν8Ph	ν8bPy$^{\oplus}$		
II	ClO_4	1744 vs	1708 w	1643 vs		1578 m		1524 vw
II	$FeCl_4$	1740 vs		1645 vs		1578 s		1523 vw
II	$PtCl_6$	1745 vs		1642 vs		1578 s		
IV	ClO_4	1738 s	1688 vs	1643 vs		1574 m		1522 w
V	ClO_4			1643 vs		1583 ms	1533 w	
VIII	ClO_4	1725 vs	1690 w	1643 vs		1578 ms	1538 w	
IX*o*	ClO_4	1730 m	1705 ms	1644 vs	1605 m	1568 ms	1533 vw	1514 vw
IX*o*	$FeCl_4$		1698 vs	1641 vs	1603 m	1565 m		
IX*m*	ClO_4		1705 vs	1643 vs	1590 s	1565 s	1533 vw	1509 w
IX*p*	ClO_4		1695 vs	1643 vs	1612 s	1567 m	1533 w	1512 w

The formation of the double salt IV is not unprecedented; similar behaviour was reported with N-quaternary salts of pyridinecarboxylic acids.[3,4]

Perchloric acid converts IV into II ($X = ClO_4$). Both II and IV yield one and the same tetrachloroferrate, chloroplatinate, picrate and picrolonate; the first two have

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[3] J. Turnau, *Monatsh.* **26**, 530 (1905).

[4] J. A. Gautier and J. Renault, *C.R. Acad. Sci. Paris* **226**, 1736 (1949) and papers cited therein.

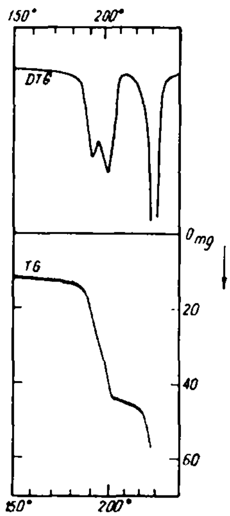


FIG. 1. Thermogravimetric analysis of perchlorate II (200 mg sample).

structure II, X = $FeCl_4$ and $PtCl_6$, respectively, since they have a sharp ν8a pyridinium band at 1645 cm^{-1} and a very strong broad νCO band at 1740 cm^{-1}. The chloroferrate can be converted back into the perchlorate (II) by treatment with $HClO_4$ in ethanol followed by precipitation with ether. An interesting dependence upon the nature of the anion in the IR spectra of II can be observed for the relative intensities and positions of several bands in the 700–1300 cm^{-1} range; such observations have been made previously for the IR spectra of pyrylium salts (also in KBr pellets).[5] In the present case, these modifications are more pronounced. Attempts to isolate the betaine (III) from the reaction of II, (X = $FeCl_4$) with aqueous sodium acetate followed by extraction with ether or methyl ethyl ketone failed.

CARBOXY-METHYL-, -ETHYL-, AND PHENYL-COLLIDINIUM SALTS

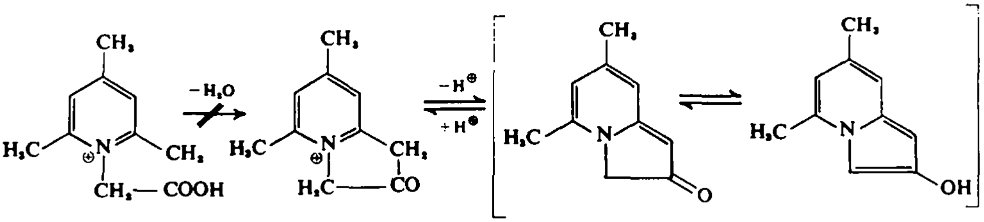
Structure	Anion\Band		$\delta_{as}CH_3$	ν19aPy$^{\oplus}$	ν19bPh	ν19bPy$^{\oplus}$		δ_sCH_3
II	ClO_4	1500 w	1485 s	1455 s		1425 s	1410 ms	1385 ms
II	$FeCl_4$	1508 w	1483 ms	1488 s		1430 m	1418 mw	1388 mw
II	$PtCl_6$	1505 w	1483 s	1455 s		1420 m	1390 s	1378 m
IV	ClO_4	1500 m	1485 s	1455 s		1427 m	1400 w	1385 m
V	ClO_4	1502 m	1490 ms	1460 m		1425 mw		1385 m
VIII	ClO_4	1508 w	1485 s	1455 m		1420 m	1405 w	1385 m
IX*o*	ClO_4	1490 mw	1480 m	1455 mw	1445 mw	1419 mw	1395 w	1380 m
IX*o*	$FeCl_4$	1500 m	1480 m	1455 m	1440 s	1423 s	1410 m	1380 m
IX*m*	ClO_4	1490 mw	1480 ms	1448 mw	1435 s	1420 mw		1383 m
IX*p*	ClO_4		1480 m	1460 w	1435 s	1420 m		1383 m

Thermogravimetric analysis of perchlorate II indicates after melting an endothermal weight loss of 15% between 180° and 205°. The derivative (DTG) curve shows the presence of two consecutive processes (Fig. 1). This weight loss corresponds to decarboxylation (calc. 44/280 = 15·7%). The rapid process above 220° is the explosion of the perchlorate.

[5] A. T. Balaban, G. D. Mateescu and M. Elian, *Tetrahedron* **18**, 1083 (1962).

The decarboxylation is catalysed by bases. Small amounts of pyridine or better ammonia, cause the perchlorate (II) to decompose in the m.p. capillary, with evolution of CO_2 at temperatures ranging from 150 to 180°, then to resolidify and melt again at 200–201° (the pure perchlorate II melts in the capillary at 183–184° without apparent decomposition). By performing the decarboxylation with a larger amount of perchlorate II (with a small amount of ammonia), the product could be isolated and identified with 1,2,4,6-tetramethylpyridinium perchlorate by mixed m.p. (202°). The picrate of the decarboxylation product is also identical with authentical 1,2,4,6-tetramethylpyridinium picrate, by mixed m.p. (128°). Similar decarboxylations of pyridine-N-acetic acids are known; they are accompanied sometimes by cyclization.[6]

Attempts to perform a cyclization of II to VI or VII with sulphuric acid or acetic anhydride have so far been unsuccessful.



II VI VII

Reaction of I *with glycine in alkaline medium*

The reaction of 2,4,6-trimethylpyrylium perchlorate (I) with one equiv glycine and sodium hydroxide in water[1] has been reinvestigated. By acidification of the mixture with perchloric acid, evaporation to dryness, and extraction with ethanol, a mixture of two pyridinium perchlorates could be isolated. These can be separated on the basis of their different solubility in acetone. The soluble portion is IV, identical in all respects with the product obtained in neutral medium. The insoluble portion is V, the sodium salt of perchlorate II ($X = ClO_4$) or the double salt of the betaine III with sodium perchlorate. It melts with decomposition at 198–200°. Its IR spectrum presents a very strong and broad band (half-width ca. 70 cm^{-1}) at 1643 cm^{-1} (superposition of pyridinium 8a vibration and of the asymmetrical vibration of the carboxylate group) with inflexions at 1670 and 1630 cm^{-1}. The symmetrical vibration appears as a very strong band at 1385 cm^{-1}. The pyridinium 8b vibration mode gives a medium-strong band at 1583 cm^{-1}. The NMR spectrum in liquid SO_2 presents a peak due to the two 2- and 6-methyl groups at $\tau 7{\cdot}33$, a peak corresponding to the 4-methyl at $\tau 7{\cdot}47$, a peak due to the protons in the 3 position of the pyridinium ring at $\tau 2{\cdot}48$. The same sodium salt V can be obtained by titration of perchlorate II with sodium hydroxide and evaporation of the water. Also, V can be converted into a chloroferrate and chloroplatinate containing cation II as evidenced by the IR spectrum.

Reaction of I *with α- and β-alanine*

The reaction of I with α-alanine in alkaline solution did not proceed readily and did not afford a crystalline picrate. Neither was it possible to prepare a pure crystalline perchlorate from the reaction in neutral medium, although the reaction takes

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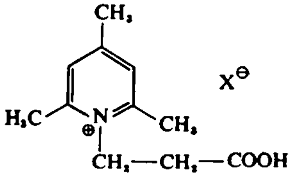
[6] A. Lawson and D. H. Miles, *Chem. & Ind.* 461 (1960).

place. Similar difficulties were encountered in the reaction of I with glycyl–glycine, but the efforts are continued since the reaction could be applied (similarly to the Sanger procedure or to the proposed use of dipropynylketone)[7] for preparing pyridinium salts (possibly coloured) from amino acids or polypeptides.

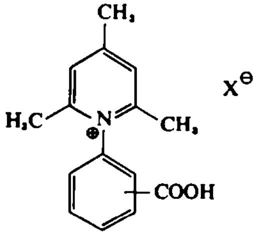
However, the preparation of pure N-2′-carboxyethyl collidinium salts succeeded with β-alanine (perchlorate and picrate). The perchlorate has structure VIII, ($X = ClO_4$), related to II. Its IR spectrum is also similar to that of II, but the νCO stretching vibration appears at 1725 cm^{-1} because the carboxyl group and the nitrogen heteroatom are more distant than in II. The pK_a value of VIII is 3·45 (at 30°); a comparison between pK_a values of chloroacetic and β-chloropropionic acids with those of perchlorates II and VIII, respectively, shows in both cases that the N-collidinium group gives a pK_a value smaller with 0·55 pK_a units. The following sequence of electron-attracting power results from the pK_a values of chloroacetic and cyanoacetic acids compared with II: Cl < CN < N-collidinium.

Reaction of I *with aminobenzenoic acids*

o, *m*, and *p*-Aminobenzoic acids afford with I in water at reflux temperature perchlorates IX ($X = ClO_4$). These were converted into the picrates, picrolonates and chloroplatinates. Analyses and m.p. of all these salts are given in Table 2, together with the pK_a values of the perchlorates at 20°. These pK_a values increase in the order $o < p < m$, in agreement with the mesomeric and inductive effect of the electron-attracting nitrogen heteroatom.



VIII



IX (*o*, *m*, *p*)

By comparing the pK_a data of perchlorates IX (*o*, *m*, *p*) with the pK_a values of substituted benzoic acids, the N-collidinium group appears more electron-attracting than the chlorine atom and slightly less attracting than the cyano and nitro groups; the following sequence of electron-attracting ability can be written: Cl < N-collidinium < CN < NO_2.

The IR absorption spectra of perchlorates IX(*o*, *m*, *p*) present in the 1500–1800 cm^{-1} range four bands (in cm^{-1}) at: 1567 m (ν8b–Py$^{\oplus}$); 1590 m (IX*m*), 1605 m (IX*o*) and 1612 s (IX*p*) (ν8a–Ph); 1643 vs (ν8a–Py$^{\oplus}$); 1695 vs (IX*p*), 1705 vs (IX*o*, *m*) ($\nu C = O$). In addition, IX*o* presents a medium band at 1730 cm^{-1}. The splitting of the $\nu C{=}O$ band in the perchlorate IXa into two bands at 1705 and 1730 cm^{-1}, whose total intensity is equal to that of the $\nu C{=}O$ band of IX*m* and IX*p*, is not observed in the chloroferrate IX*o* which has one very strong band at 1698 cm^{-1}. Bands due to the carboxyl groups also appear in the 2500–2800 cm^{-1} and at 1290 s (IX*p*), 1312 s (IX*m*) and a

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[7] M. Broust-Bournazel, *Ann. Chim.* 5, 1409 (1960).

TABLE 2. N-*o*, *m*, *p*-CARBOXYPHENYL-2,4,6-TRIMETHYLPYRIDINIUM SALTS IX

Structure		Formula	Perchlorate $C_{15}H_{16}ClNO_6$				Picrate $C_{21}H_{18}H_4O_9$			Picrolonate $C_{25}H_{23}N_5O_7$			Chloroplatinate $C_{30}H_{32}Cl_6N_2O_4Pt$					pK_a of the perchlorate
IX		Calc.	C	H	Cl	N	C	H	N	C	H	N	C	H	Cl	N	Pt	
			52·71	4·72	10·38	4·10	53·62	3·85	11·94	59·40	4·95	13·85	40·37	3·61	23·84	3·13	21·88	
o	*ortho*	M.p.	182–183°				175–176°			188–189°			257–258°[a]					2·69
		Found	52·90	5·20	9·38	3·83	53·67	4·08	12·03	59·17	5·03	13·68	40·39	3·84	23·47	2·96	22·00	
m	*meta*	M.p.	202–203°				165–166°			204–205°								3·75
		Found	52·63	5·01	—	4·22	53·25	4·36	11·87	59·50	5·00	13·85						
p	*para*	M.p.	232–233°				192–194°			204–206°			239–240°[a]					3·57
		Found	52·40	4·74	10·03	4·46	53·13	3·92	11·93	60·05	4·67	13·58	40·32	3·97	24·27	3·48	21·83	

[a] Decomposition

medium intensity triplet at 1305, 1290, 1280 cm^{-1} (IX*p*, X = ClO_4 or $FeCl_4$). The NMR spectra of IX*o* and IX*m* (X = ClO_4) in liquid SO_2 present peaks due to the 2- and 6-methyl groups at τ7·69, to the 4-methyl at τ7·36 and the 3-protons at τ2·41. The upfield shift of the 2- and 6-methyl peak is similar to that reported in the preceding part[1] for N-phenylcollidinium perchlorate and is due to the same sterically-conditioned non-coplanarity of the pyridinium and phenyl rings. This configuration of the molecule is probably responsible for the splittings observed in the IR spectra.

EXPERIMENTAL

Reaction of 2,4,6-*trimethylpyrylium perchlorate* (I) *with glycine*

(a) *In neutral solution.* the perchlorate I (22·2 g, 0·1 moles) and glycine (15 g, 0·2 moles) were refluxed in 50 ml water for 1 hr. The solution was evaporated to dryness on the steam bath. The residue was extracted with hot EtOH leaving 5·4 g unreacted glycine, and the solution was heated with ether precipitating 21 g mixture of perchlorates. By recrystallization from EtOH 12 g perchlorate IV m.p. 150–151° (dec) were obtained. (Found: C, 52·51; H, 6·20; N, 6·47. $C_{20}H_{27}ClN_2O_8$ requires: C, 52·35; H, 5·93; N, 6·10%.) The ethanolic filtrate precipitated on treatment with ether 6·5 g perchlorate II, m.p. 180–182°. This product was purified by repeating the dissolution in EtOH and precipitation with ether, m.p. 183–184°. (Found: C, 42·94; H, 5·32; N, 5·39. $C_{10}H_{14}ClNO_6$ requires: C, 42·90; H, 5·04; N, 5·01%.) By treatment of IV with one equiv 70% perchloric acid, dissolution in EtOH and precipitation with ether, IV was converted into II. By decarboxylating IV with one drop conc. ammonia at 150–180° 1,2,4,6-tetramethylpyridinium perchlorate was formed, m.p. 202–204° (from water) identified by mixed m.p. with authentic specimen.

(b) *In alkaline solution.* Glycine (0·2 moles) and NaOH (0·2 moles) were dissolved in 100 ml water. Into this solution, 0·2 moles 2,4,6-trimethylpyrylium perchlorate were gradually introduced with stirring and cooling, then the solution was acidified with perchloric acid, and the filtered solution evaporated to dryness on a steam bath. The residue was dissolved in 150 ml hot EtOH and precipitated with ether (this operation removes soluble tars). The product was extracted with 150 ml hot acetone and washed with hot acetone on the filter. The undissolved perchlorate V (19 g) had m.p. 180–182° (dec) which was raised to 198–200° (dec) by recrystallization from EtOH. (Found: C, 40·08; H, 4·52; N, 4·79; Na, 7·45; $C_{10}H_{13}ClNNaO_6$ requires: C, 39·81; H, 4·35; N, 4·64; Na, 7·62%.) The acetonic extract was evaporated yielding 15 g IV, m.p. 145–146° (from EtOH–ether) identical (analysis, IR spectrum, mixed m.p.) with the IV obtained in neutral solution.

By metathesis of either of these three perchlorates (II, IV and V) with aqueous alcoholic picric or picrolonic acid, or with aqueous chloroplatinic acid, the following salts were prepared:

Picrate II, m.p. 151° from water. (Found: C, 46·82; H, 4·13; N, 13·75. Calc. for $C_{16}H_{16}N_4O_9$: C, 47·06; H, 3·95; N, 13·72%.) It was identical (mixed m.p.) with the previously described[8] picrate with m.p. 151°.

Picrolonate II, m.p. 179° (dec) from dil EtOH. (Found: C, 53·98; H, 5·05; N, 15·65; $C_{20}H_{21}N_5O_7$ requires: C, 54·17; H, 4·77; N, 15·80%.)

Chloroplatinate II, m.p. 212° (dec) from a small amount of dil HCl. (Found: C, 31·48; H, 3·84 N, 3·55; Cl, 27·71; Pt, 25·88. $C_{20}H_{28}Cl_6N_2O_4Pt$ requires: C, 31·26; H, 3·67; N, 3·64; Cl, 27·70; Pt, 25·40%.)

Reaction of I *with β-alanine.* β-Alanine (3·6 g, 40 mmoles) and 4·4 g (20 mmoles) I were refluxed 1 hr in 20 ml water. After filtration on a fluted filter, the solution was evaporated to dryness on the steam bath. The product was extracted with hot abs. EtOH from the unreacted β-alanine; precipitation with ether yielded 5·5 g crude *perchlorate* VII m.p. ca. 135°. It was purified by repeated dissolution in EtOH and fractional precipitation with ether, m.p. 150–152°. (Found: C, 44·76; H, 5·78; N, 5·03. $C_{11}H_{16}ClNO_6$ requires: C, 44·98; H, 5·49; N, 4·77%.) *Picrate* m.p. 220–221° (dec) from water (Found: C, 48·74; H, 4·50; N, 13·19. $C_{17}H_{18}N_4O_9$ requires: C, 48·34; H, 4·31; N, 13·26%.)

Reaction of 2,4,6-*trimethylpyrylium perchlorate* (I) *with* o, m, *and* p-*aminobenzoic acids*

The pyrylium salt (20 mmoles) was refluxed for 0·5 hr with 40 mmoles aminobenzoic acid in 30 ml water, then 3 ml 70% $HClO_4$ was added and the crystals deposited on cooling filtered off and recrystallized from water. The N-*o*-, *m*- and *p*-carboxyphenyl-2,4,6-trimethylpyridinium perchlorates were converted into picrates and picrolonates with picric and picrolonic acids in aqueous EtOH. These were recrystallized from 50% aqueous EtOH. The perchlorates, dissolved in conc. HCl and treated with a solution of FeC_3 in conc. HCl, or the chloroplatinic acid in dil HCl, afforded the chloroferrates or chloroplatinates, respectively, which were washed on the filter with conc. HCl, and recrystallized from dil. HCl aq.

*N-o-carboxyphenyl-*2,4,6-*trimethylpyridinium tetrachloroferrate*, m.p. 178–180°. (Found: C, 41·07; H, 3·64; N, 3·37; Cl, 32·52. $C_{15}H_{16}Cl_4FeNO_2$ requires: C, 40·95; H, 3·66; N, 3·18; Cl, 32·23%.)

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