SOME 5,5′-FREE PYRROKETONES[1]

J. M. OSGERBY[2] AND S. F. MACDONALD
Division of Pure Chemistry, National Research Council, Ottawa, Canada

Received February 23, 1962

ABSTRACT

5,5′-Dicarbethoxypyrromethanes are oxidized to the pyrroketones by lead tetraacetate – lead dioxide in acetic acid. The 5,5′-free pyrroketones obtained by decarboxylating the latter have not yet proved synthetically useful.

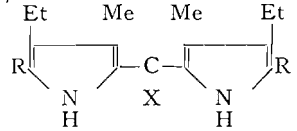
INTRODUCTION

Redistribution reactions may complicate the synthesis and further reactions of pyrromethenes and pyrromethanes. In this respect pyrroketones (2,2′-dipyrrylketones) should be more reliable intermediates in the synthesis of polypyrranes and porphyrins (1), although the behavior of some benzophenones (2) suggests that the difference might be relative rather than absolute. To explore their synthetic possibilities, we prepared some 5,5′-free pyrroketones corresponding to pyrromethanes which had proved synthetically useful (1).

Fischer's only general route to 5,5′-free pyrroketones lay in converting the 5,5′-dimethyl derivatives to dicarboxylic acids with sulphuryl chloride and decarboxylating these (3). 5,5′-Dimethylpyrroketones have been prepared by ring synthesis (4). More generally, they have been obtained by combining 5-methyl-2-free pyrroles with phosgene or with derivatives of 5-methyl-2-carboxypyrroles by the Grignard (5, pp. 361 ff.), Friedel–Crafts (5, pp. 361 ff.), or Vilsmeier (6) methods. It is uncertain whether this general approach could be usefully modified, avoiding both methyl groups for blocking. Both a 5-carbethoxy- (3) and a 5-free pyrrole-carboxylic acid chloride (7) had been used as the acylating component, though there is no general route to the latter. However, the use of a 2,5-free pyrrole as the other component was ambiguous (3), and the less reactive 5-carbethoxy-2-free pyrroles have not been used.

We found that the pyrroketones I*b*, II*b*, III*b*, and IV*b* (5, pp. 361 ff.) are easily obtained from the corresponding pyrromethanes I*a* (1), II*a* (1), III*a* (8), and IV*a* (5, p. 343) by oxidizing with lead tetraacetate in the presence of lead dioxide. Under similar conditions porphyrins have been oxidized to xanthoporphinogens (5, Vol. II/2, pp. 423 ff.). Selenium

I,	A	P	P	A
II,	P	A	A	P
III,	A	P	A	P
IV,	Me	Et	Et	Me
V,	Et	Me	Me	Et



A = $CH_2.COOEt$
P = $CH_2CH_2.COOEt$

a,	X = H_2,	R = COOEt
b,	X = O,	R = COOEt
c,	X = O,	R = H
d,	X = H_2,	R = Me
e,	X = O,	R = Me
f,	X = H_2,	R = CHO

[1]*Issued as N.R.C. No. 6904.*
[2]*National Research Council Postdoctorate Fellow, 1960–62.*

dioxide, manganese dioxide, and permanganate left the pyrromethanes unchanged. The 5,5′-carbethoxy groups may be essential for this oxidation for, although pyrromethenes may reasonably be assumed to be intermediates, our attempts to oxidize 3,3′,5,5′-tetramethyl-4,4′-diethylpyrromethene to its ketone (5, pp. 361 ff.) were unsuccessful. Further, other reagents had oxidized both the 3,3′- and the 4,4′-dicarbethoxytetramethylpyrromethanes to pyrromethenes rather than to pyrroketones (9, 10). Also, 5-positions in pyrromethenes which bear hydrogen or carboxy and other labile groups there (like the methyl group in 2-methylpyrroles (11)) may be hydroxylated by lead tetraacetate (12, 13).

Four 5,5′-free pyrroketones have been previously prepared, the parent dipyrrylketone directly from pyrryl magnesium bromide and phosgene (5, pp. 361 ff.). Representing Fischer's general route, sulphuryl chloride converted the 5,5′-dimethyl pyrroketone V*e* into the 5,5′-dicarboxylic acid corresponding to V*b*, which at 180° *in vacuo* decarboxylated to V*c*; analogous transformations giving IV*b* and IV*c* from IV*e* were carried out but not described (3). Finally, a compound formulated as 3,4-dichlor-3′-methyl-4′-ethyl-5-carbethoxypyrroketone has been decarboxylated in 10% sodium hydroxide at 190° (3), essentially the conditions under which the pyrromethanes I*a*, II*a*, and III*a* lose their 5,5′-carboxyls (1). The free acetic acid groups of pyrrole-acetic acids, unlike their salts, are relatively easily decarboxylated by heat. Consequently we heated the free acids corresponding to I*b*, II*b*, III*b*, and IV*b* with 10% sodium hydroxide at about 160° to obtain acids corresponding to the 5,5′-free pyrroketones I*c*, II*c*, III*c*, and IV*c*.

In general, Fischer's general route and ours will lead to isomeric 5,5′-carboxy- and 5,5′-free pyrroketones from given pyrroles, e.g. to V*b*, V*c* and IV*b*, IV*c* respectively from 2,4-dimethyl-3-ethylpyrrole or its 5-carbethoxy derivative. Although our sequence gives symmetrical ketones more directly, unsymmetrical ones are reached through pyrromethane intermediates whose purity must be scrutinized (8).

The reduction of the ketones was studied both to confirm their structures and as a model for the conversion of derived intermediates into natural products. Xanthoporphinogens had been reduced to porphyrins (5, Vol. II/2, pp. 423 ff.) and the parent dipyrrylketone had been reduced to dipyrrylmethane (5, p. 335). The statements that V*e* was reduced to the pyrromethane are hard to reconcile with the experimental work (14). We reduced the ketone I*b* by Clemmensen's method to the dipyrrylmethane I*a* after catalytic methods had failed.

The carbonyl groups of dipyrrylketones were known to be unusual (5, pp. 361 ff.). In the absence of absorption at normal carbonyl frequencies in the infrared, it is reasonable to assume that exceptionally low frequencies are associated with the carbonyl groups of the ketones: 1627 cm^{-1} in I*b*, 1582 cm^{-1} in I*c*, 1543 cm^{-1} in IV*c*, 1522 cm^{-1} in V*e*.* This last, V*e*, was prepared for comparison from 2,4-dimethyl-3-ethylpyrryl magnesium bromide and phosgene (5, pp. 361 ff.).

The ketone V*e* gives a dibromo derivative (3) and our 5,5′-free pyrroketones all gave Ehrlich's reaction strongly in the cold. However, under conditions which had been successfully applied to the corresponding pyrromethanes (1), they were unreactive or gave no pure products. Attempts to introduce formyl groups into II*c* by the Gattermann–Hoesch method led to recovered starting material, by the Vilsmeier method to intractable tars. Nothing was isolated following attempts to condense II*c* with the methyl ester corresponding to II*f*, with 5,5′-di(bromomethyl)-3,3′-dimethylpyrromethene-4,4′-dipropionic

*NOTE ADDED IN PROOF: *The carbonyl groups in dipyrrylketone and its 4-methoxy derivative absorb at 1597 and 1595 cm^{-1} respectively (H. Rapoport and C. D. Willson. J. Am. Chem. Soc. **84**, 630 (1962)). That of 4,4′-bis(dimethylamino)-benzophenone absorbs, we find, at 1598 cm^{-1}.*

acid, or with formic and hydrobromic acids. Also, heating with formaldehyde in acid solution, which converts rather unreactive pyrroles into pyrromethanes (15), left II*c* unchanged.

There is no pronounced general deactivation peculiar to pyrroketones, for 3,3′,5,5′-tetramethylpyrroketone can be acylated in the 4,4′-positions (5, pp. 361 ff.). Also, we found that the pyrroketones were insoluble in hydrochloric acid and showed no evidence of forming presumably unreactive meso-chloropyrromethenes (5) therein. However, the expected interaction (16) between the 2- and 5- (or 2′- and 5′-) positions may be greater in pyrroketones than in monopyrroles. Thus, in contrast to the 5,5′-free pyrroketones, 2-carbethoxy- and 2-cyano-pyrroles have given 5-aldehydes by the Gatterman–Hoesch (5, pp. 162 ff.) and Vilsmeier (17) methods respectively, and 2,5-diacylpyrroles have been obtained otherwise (5, p. 206). Conversely, nucleophilic attack on 5-bromo-2-carbethoxy-pyrroles is apparently not facilitated (18).

In pyrromethenes there is definitely interaction between the 2- and 5- (or 2′- and 5′-) positions which is incidental to strong interaction between the 5- and 5′-positions. Fischer thus explained the extremely easy acid-catalyzed exchange of halogen for hydroxyl in 5-carbethoxy-5′-bromo- as opposed to 5,5′-dibromo-pyrromethenes (19). Other reactions can be rationalized in the same way. Thus under alkaline conditions the halogen of 5-methyl-5′-bromo- but not of 5-methoxy-5′-bromo-pyrromethenes is exchanged for methoxy (19). Conversely, 5-methoxy-5′-free pyrromethenes condense rapidly with formaldehyde in the presence of acid at room temperature (19) whereas a 5,5′-free pyrromethene condensed slowly at 125° (20).

EXPERIMENTAL

The infrared spectra and their interpretation are by Dr. R. N. Jones and Mr. R. Lauzon, the microanalysis by Mr. H. Séguin. Melting points (block) are corrected.

5,5′-Dicarboxypyrroketone-3,3′-dipropionic acid-4,4′diacetic acid Hexaethyl Ester (Ib)

A solution of 5,5′-dicarboxypyrromethane-3,3′-dipropionic acid-4,4′-diacetic acid hexaethyl ester (1) (2 g) in glacial acetic acid (75 ml) was treated with lead tetraacetate (2.9 g) and stirred at room temperature for 4 days. Lead dioxide (90%, 2.3 g) was then added and stirring continued for 2 days. The mixture was then centrifuged and the supernatant poured into ice water (500 ml). The colorless precipitate was separated, washed with water, and dissolved in ether. The ethereal solution was washed successively with water, 5% aqueous sodium bicarbonate, and water, then dried (sodium sulphate) and concentrated. The crystals which separated (1.27 g, 62%) were recrystallized from ether, affording colorless prisms, m.p. 152.5–153.5°, λ_{max} (log ϵ) in 95% ethanol: 251 mμ (4.35), 303 mμ (4.17), 336 mμ (4.29). Found: C, 58.34; H, 6.34; N, 4.40. Calc. for $C_{33}H_{44}O_{13}N_2$: C, 58.57; H, 6.55; N, 4.14.

Attempted Oxidation of a Pyrromethene

When 1.54 g of 3,5,3′,5′-tetramethyl-4,4′-diethylpyrromethene hydrobromide in 70 ml of acetic acid and 0.45 g of anhydrous sodium acetate was oxidized exactly as above, the product was a black precipitate insoluble in organic solvents.

Reduction of Ib to the Pyrromethane Ia

The ketone I*b* (0.668 g) in 5 ml of ethanol was added to water (1 ml), concentrated hydrochloric acid (1 ml), and amalgamated zinc (0.78 g). The mixture was refluxed for 3 hours, cooled, and filtered. When the filtrate was concentrated and then refrigerated, the pyrromethane I*a* (146 mg, 20%) crystallized; m.p. and mixed m.p. 94° after recrystallization.

5,5′-Dicarboxypyrroketone-3,3′-diacetic acid-4,4′-dipropionic acid Hexaethyl Ester (IIb)

This was prepared from 5,5′-dicarboxypyrromethane-3,3′-diacetic acid-4,4′-dipropionic acid hexaethyl ester (1) (7.91 g), acetic acid (200 ml), lead tetraacetate (11.7 g), and lead dioxide (9.2 g) as described for the isomer I*b* above. The ketone formed colorless prisms (5 g, 62%) after recrystallization from ether (thimble), m.p. 156°, λ_{max} (log ϵ) in 95% ethanol: 250 mμ (4.34), 304 mμ (4.17), 336 mμ (4.29). Found: C, 58.13; H, 6.60; N, 4.39.

5,5′-Dicarboxypyrroketone-3,4′-diacetic acid-4,3′-dipropionic acid Hexaethyl Ester (IIIb)

This was prepared from 5,5′-dicarboxypyrromethane-3,4′-diacetic acid-4,3′-dipropionic acid hexaethyl

ester (8) (1.56 g), lead tetraacetate (2.3 g), and lead dioxide (1.5 g) as described for I*b* above. The crude product (0.694 g, 43.5%) was recrystallized from ether (thimble), affording colorless microneedles, m.p. 149–150°. Found: C, 58.45; H, 6.37; N, 4.12.

4,4′-Dimethyl-3,3′-diethyl-5,5′-dicarbethoxypyrroketone (IVb)

This was prepared from 4,4′-dimethyl-3,3′-diethyl-5,5′-dicarbethoxypyrromethane (5, p. 343) (1.065 g), glacial acetic acid (35 ml), lead tetraacetate (1.45 g), and lead dioxide (1.2 g) as described for I*b*. The product formed colorless rods (300 mg, 27%) from ethanol, m.p. 190–191°. Found: C, 65.04; H, 7.08; N, 7.34. Calc. for $C_{21}H_{28}N_2O_5$: C, 64.92; H, 7.27; N, 7.21.

5,5′-Dicarboxypyrroketone-3,3′-dipropionic acid-4,4′-diacetic acid

Aqueous sodium hydroxide (10%, 3 ml) was added to a solution of the corresponding ester I*b* (400 mg) in ethanol (4 ml) and the mixture heated to dryness on the steam bath in an open flask (about 4 hours). Water (5 ml) was added to the residue. The resulting clear solution was brought to pH 1 with dilute hydrochloric acid, heated to dissolve the colorless precipitate, and allowed to cool. The crystals which separated were washed with water, with ether, then recrystallized from 5 ml of hot water. The product formed colorless needles (170 mg, 56%), m.p. (softening from 159°) 164–168°, Ehrlich's reaction negative in the cold. Found: C, 49.61; H, 4.24; N, 5.41. Calc. for $C_{21}H_{20}N_2O_{13}$: C, 49.61; H, 3.96; N, 5.51.

Pyrroketone-3,3′-dipropionic acid-4,4′-diacetic acid (Compare Ic)

A solution of the ketone I*b* (1.186 g) in ethanol (10 ml) and sodium hydroxide (10%, 5 ml) was hydrolyzed by heating to dryness in an open flask on the steam bath. The residue in water (4 ml) and sodium hydroxide (10%, 4 ml) was heated for 10½ hours at 155–158° in a Teflon-lined closed metal tube. The crude product (0.654 g, 89%) precipitated when the cooled solution was acidified to Congo red with sulphur dioxide. When recrystallized from acetone (thimble) it formed colorless needles, m.p. 203–205°, Ehrlich's reaction positive cold. Found: C, 54.11; H, 5.43; N, 6.51. Calc. for $C_{19}H_{20}N_2O_9$: C, 54.28; H, 4.80; N, 6.66.

Pyrroketone-3,3′-diacetic acid-4,4′-dipropionic acid (Compare IIc)

The ester II*b* (1.14 g) was hydrolyzed and then decarboxylated like the isomer above, giving the crude product (0.583 g, 82%). From aqueous acetone it formed colorless cubes, m.p. 272° (decomp.), Ehrlich's reaction positive cold. Found: C, 54.18; H, 4.94; N, 6.58.

The Tetraethyl Ester (IIc)

The above acid (145 mg) was left at room temperature overnight in 10 ml of 5% ethanolic hydrogen chloride. The solvent was removed *in vacuo* (<50°), leaving a red oil. This was extracted with hot *n*-hexane, from which the product separated as fine colorless plates (60 mg, 33%), m.p. 94–95°, λ_{max} (log ϵ) in 95% ethanol: 297.3 mμ (4.01), 334.5 mμ (4.23). Found: C, 60.64; H, 6.70; N, 5.21. Calc. for $C_{27}H_{36}N_2O_9$: C, 60.89; H, 6.82; N, 5.27.

The same ester (72%) was obtained by treating an ethereal suspension of the acid with freshly distilled ethereal diazoethane.

Pyrroketone-3,4′-diacetic acid-4,3′-dipropionic acid (Compare IIIc)

The ester III*b* (0.873 g) was hydrolyzed and decarboxylated like its isomers. The crude product (255 mg, 47%) was recrystallized from acetone (thimble) as colorless cubes, m.p. 260–262° (decomp.), Ehrlich's reaction positive cold. Found: C, 54.24; H, 4.88; N, 6.51.

4,4′-Dimethyl-3,3′-diethylpyrroketone (IVc)

The ester IV*b* (0.2 g) was heated to dryness with ethanol (25 ml) and sodium hydroxide (10%, 3 ml). The residue was heated in a closed tube for 10 hours at 155–160° with water (4 ml) and sodium hydroxide (10%, 3 ml). The cooled solution was extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid and then with water, dried (sodium sulphate), and evaporated. The residue was dissolved in ether, and *n*-hexane added, precipitating the products as colorless fluffy rods (108 mg, 86%), m.p. 180–180.5° (lit. 166° (3)), Ehrlich's reaction strongly positive cold, λ_{max} (log ϵ) in 95% ethanol: 344 mμ (4.26), 295 mμ (3.96), 207 mμ (3.95). Found: C, 74.02; H, 8.04; N, 11.36. Calc. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47.

3,5,3′,5′-Tetramethyl-4,4′-diethylpyrroketone (Ve)

This was prepared by the method of Fischer and Orth (5, pp. 361 ff.). The crude product (68%) was recrystallized from ethanol, giving slightly yellow needles, m.p. 208.5–210° (lit 207°), λ_{max} (log ϵ): 301 mμ (3.92), 364 mμ (4.44).

Attempted Reactions with IIc

(*a*) It was added to a mixture of phosphorus oxychloride and dimethylformamide, then left at 20° for 18 hours or at 100° for 10 minutes. In both cases working up gave a black tar from which nothing was isolated.

(*b*) It was dissolved in hydrogen cyanide – ether – chloroform, and dry hydrogen chloride passed in at 0°. Evaporation left ether-soluble material, from which the starting ketone (25%) was recovered, but no water-soluble aldimine hydrochloride.

(*c*) It was refluxed for 1 hour in 5% ethanolic hydrogen chloride containing formaldehyde (2 moles). Only the starting ketone (57%) was recovered.

(*d*) Like II*b* it was recovered quantitatively after attempted reduction by hydrogen over palladium black in ethanol or acetic acid.

(*e*) It was recovered (85%) after refluxing with hydroxylamine hydrochloride and sodium acetate in 90% ethanol.

REFERENCES

1. G. P. ARSENAULT, E. BULLOCK, and S. F. MACDONALD. J. Am. Chem. Soc. **82**, 4384 (1960).
2. R. C. FUSON, G. R. BAKKER, and B. VITTIMBERGA. Abstracts of Papers, 135th Meeting of the American Chemical Society. April, 1959. p. 13. M. Wenzing. Ber. **47**, 2152 (1914).
3. H. FISCHER and KLARA GANGL. Hoppe-Seyler's, Z. physiol. Chem. **267**, 188 (1941).
4. A. TREIBS and K. H. MICHL. Ann. **577**, 129 (1952).
5. H. FISCHER and H. ORTH. Chemie des Pyrrols. Vol. I. Leipzig. 1934.
6. A. H. JACKSON. Proc. Chem. Soc. 198 (1961).
7. H. FISCHER and H. ORTH. Ann. **502**, 239 (1933).
8. E. J. TARLTON, S. F. MACDONALD, and E. BALTAZZI. J. Am. Chem. Soc. **82**, 4389 (1960).
9. A. H. CORWIN and K. J. BRUNINGS. J. Am. Chem. Soc. **64**, 2106 (1942).
10. H. FISCHER and H. BELLER. Ann. **444**, 238 (1925).
11. W. SIEDEL and F. WINKLER. Ann. **554**, 162 (1943).
12. W. SIEDEL and H. MÖLLER. Hoppe-Seyler's, Z. physiol. Chem. **259**, 113 (1939).
13. H. v. DOBENECK. Hoppe-Seyler's, Z. physiol. Chem. **269**, 268 (1941).
14. H. FISCHER and H. ORTH. Ann. **489**, 62 (1931).
15. S. F. MACDONALD. J. Chem. Soc. 4176 (1952).
16. A. TREIBS and G. FRITZ. Ann. **611**, 162 (1958).
17. G. P. ARSENAULT and S. F. MACDONALD. Can. J. Chem. **39**, 2043 (1962).
18. W. SIEDEL. Ann. **554**, 144 (1943).
19. H. FISCHER and J. ASCHENBRENNER. Hoppe-Seyler's, Z. Physiol. Chem. **229**, 71 (1934).
20. H. FISCHER and W. LAMATSCH. Ann. **462**, 249 (1928).