Nitroxyls; VI[1]. Synthesis and Reactions of 3-Hydroxymethyl-2,2,5,5-tetramethyl-2,5-dihydropyrrole-1-oxyl and 3-Formyl Derivatives**

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The increasing interest in nitroxyl-type stable free radicals is based on their application in biology and biophysics[2-6]; novel reactive and stable derivatives have been prepared. In our earlier papers, 3-carboxy-2,2,5,5-tetramethyl-2,5-dihydropyrrole-1-oxyl (**1**) and its reactive derivatives (e.g. active esters, carbonyl azide, mixed anhydrides) were used as acylating reagents[1,7,8]. In the present communication, we report the synthesis and reactions of 3-hydroxymethyl-2,2,5,5-tetramethyl-2,5-dihydropyrrole-1-oxyl (**2**) and 3-formyl-2,2,5,5-tetramethyl-2,5-dihydropyrrole-1-oxyl (**3**).

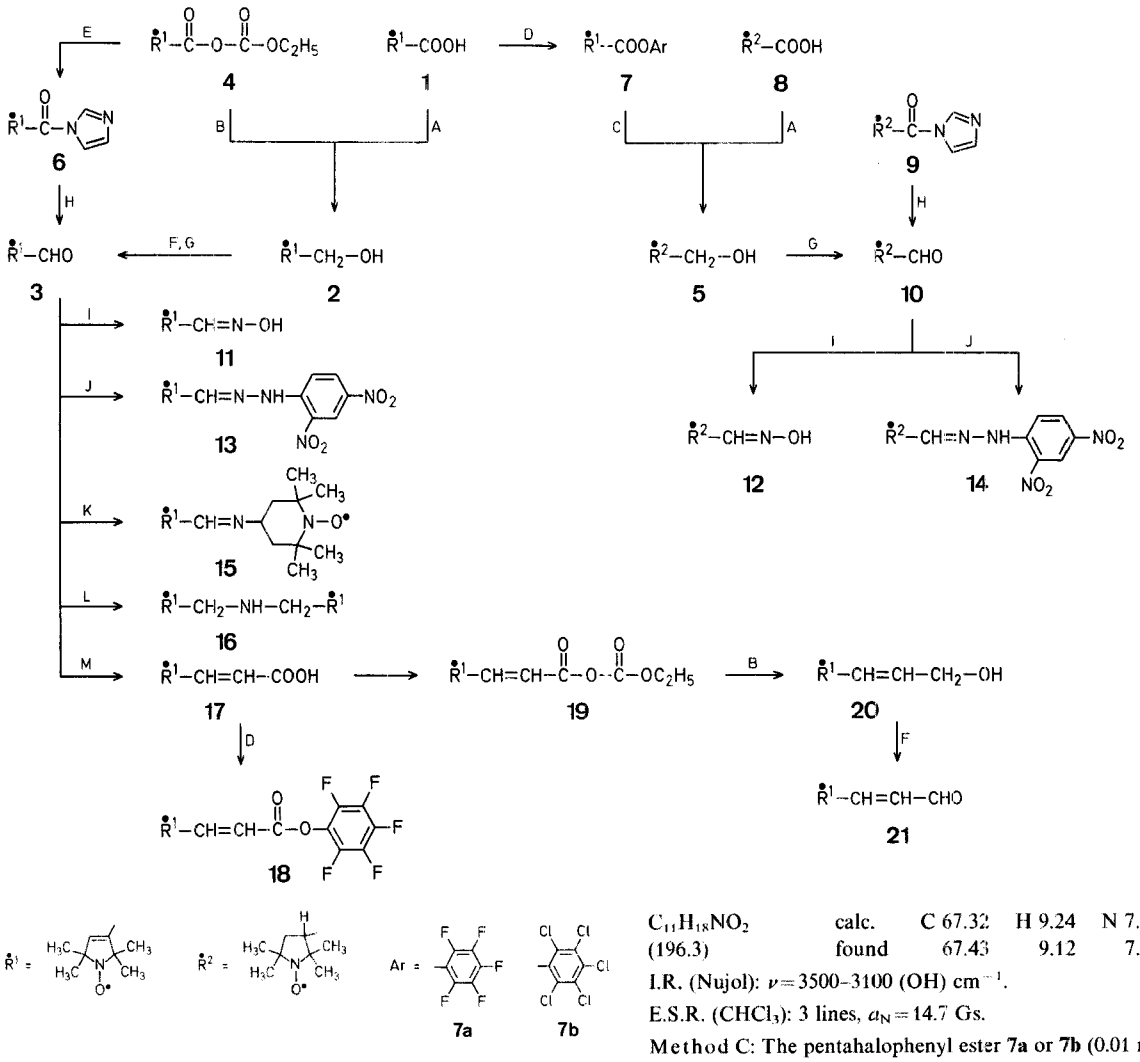
Reduction of the carboxy group of the α,β-unsaturated carboxylic acid **1** by sodium bis[2-methoxyethoxy]-aluminium hydride gives the allylic alcohol **2**. Reduction of the acyl carbonate **4** with sodium borohydride suspension in ethanol also gives the allylic alcohol **2** in high yield. When these reductions are carried out at higher temperature and longer reaction times are used the product mixture contains some 3-hydroxymethyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl (**5**) as an impurity as shown by G.L.C. analysis. It is worth noting that the radical moiety is not reduced under the conditions employed. However, the pentahalophenol esters **7** obtained from pentahalophenols and acid **1** by the DCC method can be reduced to the saturated alcohol **5** with sodium borohydride[18]. In these latter reactions, the vinylogous 1,4-addition of hydride ion has priority over the 1,2-addition. The isolated compounds **2** cannot be reduced to **5** with sodium borohydride.

We have also investigated the synthesis of the unsaturated aldehyde **3**. The reduction of carboxylic acid derivatives to aldehydes with diisobutylaluminium hydride is known and has recently been reviewed[9]. We found that the carbonylimidazole derivatives **6** and **9** can be reduced by this reagent to the corresponding aldehydes (**3, 10**). However, after isolation of the product from the reaction mixture by sublimation the yield is only moderate. We found that the use of active manganese(IV) oxide as oxidizing agent[10] is the most convenient method for preparation of the unsaturated aldehyde **3** from the allylic alcohol **2**. Pyridinium dichromate[11,12] can also be used for the oxidation of **2** to **3**. While the manganese dioxide method does not work in the absence of an allylic double bond the pyridinium dichromate method gives the saturated aldehyde in moderate yield (47%).

The aldehydes **3** and **10** can not only be used for spin-labelling of biomolecules having a primary amino group but also as synthons for further syntheses. A few reactions of the aldehydes were investigated. Oximes (**11, 12**) are formed with hydroxylamine. 2,4-dinitrophenylhydrazones (**13, 14**) with 2,4-dinitrophenylhydrazine. The latter derivatives may be used as haptenes similar to the 2,4-dinitrophenylhydrazone of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl[13]. The mixed biradical Schiff-base **15** is obtained with 2,2,6,6-tetramethyl-4-aminopiperidine-1-oxyl. Compound **3** is converted into a symmetrical secondary amino biradical (**16**) using a large excess of ammonium acetate and sodium cyanoborohydride in methanol. The di-unsaturated carboxylic acid **17** is available from **3** and malonic acid by a Knoevenagel reaction in pyridine in the presence of piperidine as catalyst[18]. The pentafluorophenyl ester **18** and mixed anhydride **19** are obtained by further reaction of the dienoic acid **17**. The mixed anhydride **19** can be reduced to dienol **20** with sodium borohydride; oxidation of **20** with manganese dioxide affords the dienal **21**. These compounds can serve as synthons in further syntheses of spin-labelled compounds.

The starting materials **1**[3], **4**[7], **7b**[7], **8**[3], and **9**[17] were prepared by known methods. Melting points were measured using a Boetius micro m.p.-determining instrument and are not corrected. The I.R. spectra were measured in Nujol suspensions with a Zeiss Specord

0039-7881/80/1132-0911 $ 03.00



71 type instrument. The E.S.R. spectra were obtained from 10^{-3} molar solutions using a Zeiss ER 9 spectrometer.

Hydroxy Compounds 2, 5, 20; General Procedures:

Method A: A solution of sodium bis[2-methoxyethoxy]-aluminum hydride (11 ml, ~70%) is added dropwise to a stirred suspension of acid **1** (1.84 g, 0.01 mol) in dry toluene (10 ml). The solution is refluxed for 2 h. The mixture is then added dropwise to a cooled and stirred 5% aqueous solution (100 ml) of sodium hydroxide. The toluene phase is separated and dried with sodium sulfate. The solvent is evaporated to dryness and the yellow solid residue **(2)** is crystallized from ether/hexane; yield: 1.5 g (88%); m.p. 75–77 °C.

$C_9H_{16}NO_2$	calc.	C 63.50	H 9.47	N 8.23
(170.2)	found	63.58	9.42	8.32

I.R. (Nujol): ν = 3500–3100 (OH) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, a_N = 14.9 Gs.

Reduction of the saturated acid **8** in the same manner affords the saturated alcohol **5**; yield: 85%; m.p. 112 °C (ether/hexane) (Ref.[16], m.p. 112 °C).

Method B: The acyl carbonate **4** (2.56 g, 0.01 mol) is added to a stirred suspension of sodium borohydride (0.5 g) in ethanol (30 ml) at 0 °C. Stirring is continued for 1 h and the mixture then evaporated to dryness. Water (10 ml) is added to the residue, the mixture is extracted with chloroform (30 ml), and worked up as in Method A to give **2**; yield 94%.

The acyl carbonate **19** [prepared from the dienoic acid **17** with ethyl carbonochloridate in the presence of triethylamine in quantitative yield; red oil; I.R. (neat): ν = 1790, 1730, 1620 (C=C–CO–O–CO–O) cm^{-1}] is reduced with sodium borohydride as above to give the dienol **20**; yield: 82%; m.p. 63–64 °C (ether/hexane).

$C_{11}H_{18}NO_2$	calc.	C 67.32	H 9.24	N 7.14
(196.3)	found	67.43	9.12	7.23

I.R. (Nujol): ν = 3500–3100 (OH) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, a_N = 14.7 Gs.

Method C: The pentahalophenyl ester **7a** or **7b** (0.01 mol) is added to a stirred suspension of sodium borohydride (0.5 g) in ethanol (30 ml) at room temperature. Stirring is continued for 6 h and the mixture then worked up as in Method B to give *3-hydroxymethyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl* **(5)**; yield from **7a**: 1.33 g (77%), containing ~10% **2** as an impurity; m.p. 109–111 °C; yield from **7b**: 0.80 g (47%); m.p. 112 °C.

Synthesis of Pentahalophenyl Esters 7a, 7b, 18; General Procedure:

Method D: To a stirred suspension of carboxylic acid **1** or **17** (0.01 mol) and the pentahalophenol (0.01 mol) in dry ethyl acetate (30 ml), a solution of dicyclohexylcarbodiimide (2.06 g, 0.01 mol) in dry ethyl acetate (10 ml) is added at 0 °C. The mixture is stirred 3 h at room temperature. The dicyclohexylurea is filtered off, the filtrate is extracted with 5% sodium hydrogen carbonate solution and with water, dried with sodium sulfate, and evaporated to dryness. The yellow product is crystallized from chloroform/ether; yield for **7b**: 50%; m.p. 193–195 °C (Ref.[7], m.p. 194–195 °C); yield for **7a**: 79%; m.p. 114–115 °C.

$C_{15}H_{13}F_5NO_3$	calc.	C 51.44	H 3.74	N 4.00
(350.3)	found	51.38	3.83	4.11

I.R. (Nujol): ν = 1760 (CO) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, a_N = 14.5 Gs.

Yield of **18**: 62%; m.p. 76–77 °C.

$C_{17}H_{15}F_5NO_3$	calc.	C 54.26	H 4.02	N 3.72
(376.3)	found	54.32	4.00	3.66

I.R. (Nujol): ν = 1750 (CO) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, a_N = 14.6 Gs.

Imidazolide 6:

Method E: A solution of the acyl carbonate **4** (2.56 g, 0.01 mol) and imidazole (0.68 g, 0.01 mol) in dry toluene (10 ml) is refluxed

for 30 min, then evaporated. The residual product is recrystallized from ether/hexane; yield: 1.5 g (64%); m.p. 83–86 °C (Ref.[14], m.p. 82–85 °C; Ref.[15], m.p. 101–102 °C).

The imidazolide compounds **6** and **9** have earlier been synthetized[14,15,17] from the corresponding acids and carbonyldiimidazole by Staab's method.

Aldehydes 3, 10, 21; General Procedures:

Method F, using Active Manganese Dioxide: To a stirred solution of the unsaturated alcohol (**2, 20**; 0.02 mol) in tetrachloromethane (60 ml) is added freshly prepared active manganese dioxide (30 g). The mixture is refluxed for 30 min, then filtered, and the filtrate is evaporated to dryness. The yellow residue is the practically pure aldehyde; yield of **3**: 2.8 g (83%); m.p. 78–79 °C (ether/hexane).

$C_9H_{14}NO_2$	calc.	C 64.26	H 8.39	N 8.33
(168.2)	found	64.11	8.29	8.43

M.S.: $m/e = 168.101354$ (M^+; calc. 168.202447).

I.R. (Nujol): $\nu = 1670$ (CO) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, $a_N = 14.7$ Gs.

Yield of **21**: 75%; m.p. 91–93 °C (hexane).

$C_{11}H_{16}NO_2$	calc.	C 68.01	H 8.30	N 7.22
(194.3)	found	68.11	8.43	7.31

I.R. (Nujol): $\nu = 1660$ (CO) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, $a_N = 14.7$ Gs.

The attempted oxidation of the saturated alcohol **5** to the saturated aldehyde **10** by the above method (even after a reaction time of 40 h) failed.

Method G, using Pyridinium Dichromate: A suspension of **2** or **10** (0.01 mol) and pyridinium dichromate (3.74 g, 0.02 mol) in dry dichloromethane (10 ml) is stirred at 25 °C for 24 h. The mixture is then diluted with ether, filtered, and evaporated; yield of **3**: 1.2 g (71%). The saturated aldehyde **10** is obtained in pure form as a red oil after chromatography on silica gel (chloroform as eluent); yield: 47%.

$C_9H_{16}NO_2$	calc.	C 63.50	H 9.47	N 8.23
(170.2)	found	63.39	9.49	8.11

I.R. (Nujol): $\nu = 1720$ (CO) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, $a_N = 14.5$ Gs.

Method H, using $(i\text{-}C_4H_9)_2AlH$: Diisobutylaluminium hydride (0.011 mol) in hexane (10 ml) is added to a stirred solution of imidazolide **6** or **9** (0.01 mol) in dichloromethane (20 ml) under nitrogen. The mixture is allowed to stand at room temperature for 2 h and is then quenched by the cautious addition of aqueous 2.5 normal sodium hydroxide at 5–10 °C. The organic phase is washed with 1 normal hydrochloric acid and saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness; yield of **3** from **6**: 60%; yield of **10** from **9**: 59%.

Reactions of Aldehydes 3 and 10:

Method I, with Hydroxylamine: To a solution of hydroxylamine hydrochloride (1.39 g, 0.02 mol) and aldehyde **3** or **10** (0.01 mol) in water/methanol (2:1, 9 ml), 40% potassium carbonate solution (4 ml) is added. The oxime precipitates immediately; yield of **11**: 1.65 g (90%); m.p. 193–194 °C.

$C_9H_{15}N_2O_2$	calc.	C 59.00	H 8.25	N 15.29
(183.2)	found	59.11	8.37	15.39

I.R. (Nujol): $\nu = 3400$–2600 (OH); 1700, 1680, 1620 (C=C–C=N) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, $a_N = 14.9$ Gs.

Yield of **12**: 1.6 g (86%); m.p. 154–155 °C (ether/hexane).

$C_9H_{17}N_2O_2$	calc.	C 58.35	H 9.25	N 15.12
(185.3)	found	58.12	9.16	15.23

I.R. (Nujol): $\nu = 3400$–2400 (OH), 1640 (C=N) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, $a_N = 14.7$ Gs.

Method J, with 2,4-Dinitrophenylhydrazine: To a solution of 2,4-dinitrophenylhydrazine (1.98 g, 0.01 mol) in 20% phosphoric acid (50 ml), a solution of the aldehyde **3** or **10** (0.01 mol) in methanol (5 ml) is added. The product is recrystallized from ethyl acetate; yield of **13**: 2.3 g (66%); m.p. 215–216 °C.

$C_{15}H_{18}N_5O_5$	calc.	C 51.72	H 5.21	N 20.10
(348.3)	found	51.82	5.27	20.14

I.R. (Nujol): $\nu = 3200$–2600 (NH), 1600, 1575 (C=C–C=N–) cm^{-1}.

E.S.R. (ethanol): 3 lines, $a_N = 14.6$ Gs.

Yield of **14**: 1.8 g (51%); m.p. 211–212 °C.

$C_{15}H_{20}N_5O_5$	calc.	C 51.43	H 5.75	N 19.99
(350.4)	found	51.58	5.76	20.05

I.R. (Nujol): $\nu = 3300$–3100 (NH), 1600 (C=N) cm^{-1}.

E.S.R. (ethanol): 3 lines, $a_N = 14.6$ Gs.

Method K, with 4-Amino-2,2,6,6-tetramethylpiperidine-1-oxyl: The unsaturated aldehyde **3** (1.68 g, 0.01 mol) and 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (1.71 g, 0.01 mol) are refluxed in toluene (20 ml) for 30 min. The mixture is then evaporated to dryness in vacuo. The red solid biradical **15** is crystallized from ether/hexane; yield: 1.7 g (53%); m.p. 185–186 °C.

$C_{18}H_{31}N_3O_2$	calc.	C 67.25	H 9.73	N 13.07
(321.5)	found	67.31	9.82	13.14

I.R. (Nujol): $\nu = 1630$, 1600 (C=C–C=N–) cm^{-1}.

E.S.R. ($CHCl_3$): 5 lines, $a_N = 15.0$ Gs.

Method L, with Ammonium Acetate/Sodium Cyanoborohydride: To a solution of **3** (1.68 g, 0.01 mol) and ammonium acetate (7.7 g, 0.1 mol) in dry methanol (150 ml), sodium cyanoborohydride (0.43 g, 0.07 mol) is added with stirring. The mixture is kept at room temperature for two days and is then evaporated to dryness. The residue is dissolved in water (20 ml) and extracted with chloroform. The water phase is made alkaline (pH 11) with 10% sodium hydroxide solution and extracted with chloroform. The organic phase is dried and evaporated to dryness to give biradical **16** as a solid product; yield: 2.2 g (68%); m.p. 94–95 °C.

$C_{18}H_{31}N_3O_2$	calc.	C 67.25	H 9.72	N 13.07
(321.5)	found	67.28	9.65	13.06

M.S. (70 eV): m/e (relative intensity) = 321 (M^+, 43%); 322 (M + 1, 12); 323 (M + 2, 9.5); 170 (36); 140 (43); 138 (18); 122 (33.5).

I.R. (Nujol): $\nu = 3440$ (NH) cm^{-1}.

E.S.R. ($CHCl_3$): 5 lines, $a_N = 14.5$ Gs.

Method M, with Malonic Acid: A solution of the unsaturated aldehyde **3** (3.36 g, 0.02 mol) and malonic acid (2.08 g, 0.02 mol) in dry pyridine (30 ml) is heated at 100 °C for 5 h in presence 3 drops of piperidine (as catalyst). The solvent is then removed in vacuo, the dark brown oil is taken up in 5% aqueous sodium hydroxide (20 ml), and extracted with chloroform. The aqueous phase is separated, acidified with 1 normal hydrochloric acid to pH 3 and extracted with chloroform. The chloroform phase is dried with sodium sulfate and evaporated to dryness. The dienoic acid **17** is crystallized from chloroform/hexane; yield: 1.1 g (52%); m.p. 116–117 °C.

$C_{11}H_{16}NO_3$	calc.	C 62.84	H 7.67	N 6.66
(210.3)	found	62.87	7.83	6.75

I.R. (Nujol): $\nu = 1710$ (CO); 1630, 1590 (C=C–C=C) cm^{-1}.

E.S.R. ($CHCl_3$): 3 lines, $a_N = 14.7$ Gs.

This work was supported in part by the Hungarian Academy of Sciences. The authors are indebted to Dr. J. Belágyi for the E.S.R. spectra and to their technicians (Mrs. A. Halász, Miss T. Huszár, Mrs. L. Lovas, and Mrs. M. Ott).

Received: March 17, 1980

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** Presented at the 1st International Symposium on Stable Nitroxide Free Radicals: Synthesis and Applications. May 25, 1979, Pécs, Hungary.

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0039-7881/80/1132-0914 $ 03.00