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FREE IMINOXYL RADICALS IN THE HYDROGENATED PYRROLE SERIES

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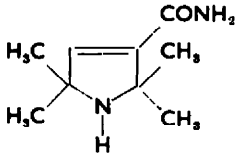
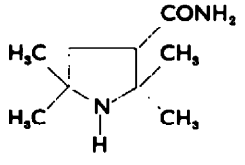
THE structure and reactivity of stable iminoxyl radicals of the piperidine,[1-4] homopiperazinone,[5] carboline[6] and pyrrol[7] series has been reported but no information is available on iminoxyl radicals in the hydrogenated pyrrole series.

In this communication, the synthesis of these radicals and their conversions involving no free valencies is reported.

Carboxamides (I and II) of the hydrogenated pyrroles were the initial compounds used for synthesis of stable free radicals in the new series:[8]

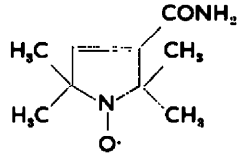


I

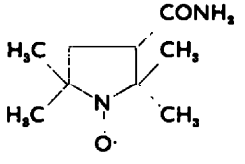


II

Catalytic oxidation of I and II yields the free iminoxyl radicals, 2,2,5,5-tetramethyl-3-carbamidopyrroline-1-oxyl (III) and 2,2,5,5-tetramethyl-3-carbamidopyrrolidine-1-oxyl (IV).



III



IV

These are bright-yellow crystalline compounds exhibiting paramagnetic absorption spectra characteristic of individual iminoxyl radicals (Fig. 1).

The amide-radicals on alkaline hydrolysis, yield acid-radicals (V and VI) which on

[1] E. G. Rozantzev, *Izv. Akad. Nauk SSSR, ser. khim.* 1670 (1963).
[2] E. G. Rozantzev, Y. G. Mamedova, M. B. Neiman, *Izv. Akad. Nauk SSSR, ser. khim.* 2250 (1962).
[3] E. G. Rozantzev, M. B. Neiman, Y. G. Mamedova, *Izv. Akad. Nauk SSSR, ser. khim.* 1510 (1963).
[4] E. G. Rozantzev, M. B. Neiman, *Tetrahedron* **20**, 131 (1964).
[5] E. G. Rozantzev, R. A. Papko, *Izv. Akad. Nauk SSSR, ser. khim.* 2254 (1962).
[6] E. G. Rozantzev, A. B. Shapiro, *Izv. Akad. Nauk SSSR, ser. khim.*, 1123 (1964).
[7] E. G. Rozantzev, A. A. Medgidov, M. B. Neiman, *Izv. Akad. Nauk SSSR, ser. khim.* 1876 (1963).
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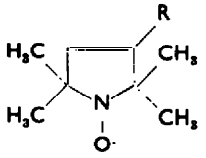
esterification with diazomethane give quantitative yields of the ester-radicals (VII and VIII).

V R = COOH
VII R = COOMe



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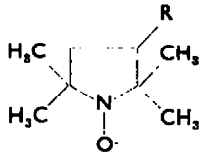
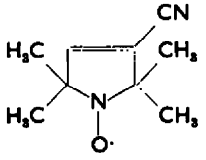


VI R = COOH
VIII R = COOMe

The acid-radicals and their methyl esters may also be obtained concurrently by oxidation of the appropriate secondary amines with hydrogen peroxide. Not all iminoxyls may be synthesized in this manner, as the oxidation of the amine often results in destruction of the molecule skeleton or in simultaneous oxidation of other functional groups. In these cases, the only method of synthesis is the conversion of the iminoxyl radicals involving no free valencies.

In this way, dehydration of amide-radicals with *p*-tosyl chloride in piridine yields nitrile-radicals while (IX and X), 2,2,5,5-tetramethyl-3-oxopyrrolidine-1-oxyl (XI) and

IX



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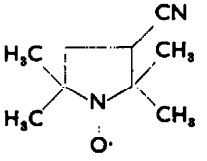
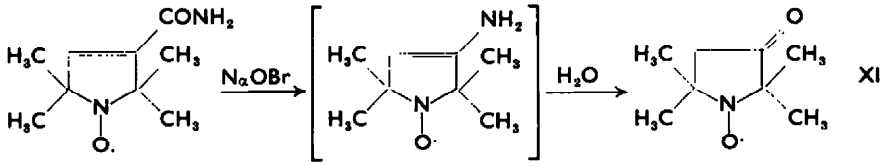
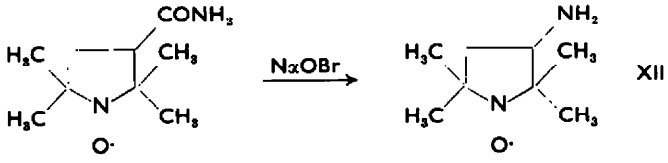


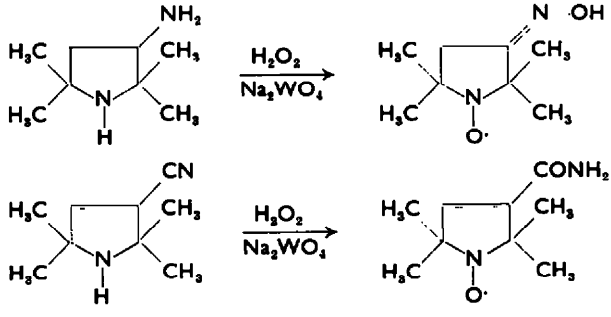
X

2,2,5,5-tetramethyl-3-aminopyrrolidine-1-oxyl (XII) are synthesized by treating the amide-radicals with sodium hypobromite.





However, the action of hydrogen peroxide on 2,2,5,5-tetramethyl-3-aminopyrrolidine and 2,2,5,5-tetramethyl-3-cyanopyrroline results in oxidation of other molecular fragments as well:



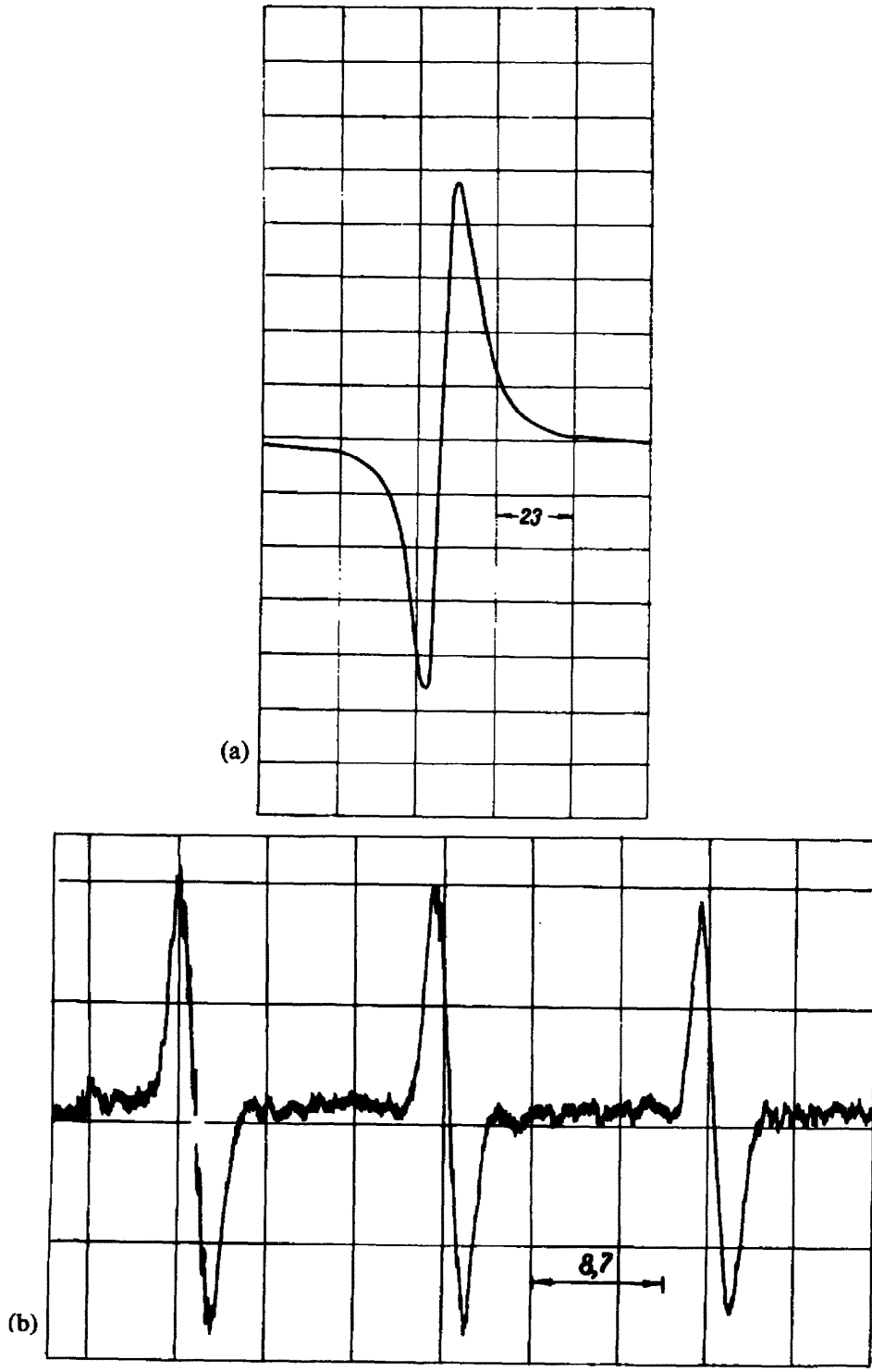


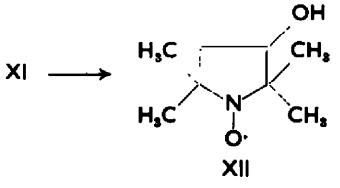
FIG. 1. ESR spectra of free iminoxyl radicals in the hydrogenated pyrrole series: (a) a crystalline sample of 2,2,5,5-tetramethyl-3-carbamidopyrroline-1-oxyl; (b) a benzene solution of a sample in the absence of oxygen.

Catalytic oxidation of 2,2,5,5-tetramethylpyrrolidone-3 results in destruction of the heterocycle, yielding non-radical reaction products. It will be of interest to note that the oxidation of this ketone oxime gives 2,2,5,5-tetramethyl-3-oxopyrrolidine-1-oxyl oxime.

Though certain iminoxyl reactions may be carried out without involving the paramagnetic centre, the iminoxyls are notably very reactive organic radicals sensitive to elevated temperatures, halides, acids, and also oxidizing and reducing agents.

Reduction of the carbonyl group in iminoxyls sometimes involves the iminoxylic function. In catalytic hydrogenation the iminoxyl group is the first to react,[6] being reduced to an amine- or hydroxylamine group. The same is observed during reduction with lithium aluminium hydride.

Selective reduction of 2,2,5,5-tetramethyl-3-oxopyrrolidine-1-oxyl with aluminium isopropylate results in a high yield of paramagnetic 2,2,5,5-tetramethyl-3-hydroxypyrrolidine-1-oxyl (XIII).



XII

This cannot be obtained by catalytic oxidation of 2,2,5,5-tetramethyl-3-hydroxypyrrolidine due to destruction of the heterocycle.

EXPERIMENTAL

2,2,5,5-*Tetramethyl*-3-*carbamidopyrrolidine* (II)

Compound I (30 g) dissolved in 300 ml methanol was hydrogenated with Raney-Ni in a steel autoclave at room temp and initial H_2 press. of 180 atm. After hydrogenation, the solution was filtered, and the methanol removed (red. press.) yielding impure II in quantitative yield, m.p. 126–129°; lit.[8] 129–130° (distilled).

2,2,5,5-*Tetramethyl*-3-*carbamidopyrroline*-1-*oxyl* (III)

A mixture of I (15 g) in 150 ml water with 0·75 g trylon-B, 0·75 g sodium tungstate and 15 ml H_2O_2 (30%) was kept at room temp for 10 days. The bright-yellow crystals obtained (14 g) were separated and dried, HCl aq. added and the filtrate extracted with chloroform. The chloroformic extract was dried (Na_2SO_4) and filtered. The filtrate on evaporation under red. press.; yielded an additional 0·93 g of the total free radical yield amounting to 14·93 g (91·5%), m.p. 203–204° (dec). (Found: C, 59·17; H, 8·28; N, 15·48. $C_9H_{15}N_2O_2$ requires; C, 58·99; H, 8·25; N, 15·30%).

2,2,5,5-*Tetramethyl*-3-*carbamidopyrrolidine*-1-*oxyl* (IV)

This was obtained in a manner similar to that described for III, yield 88%. After recrystallization from a hexane–dioxane and sublimation *in vacuo* (0·2 mm Hg), the m.p. was 174°. (Found: C, 58·08; H, 9·27; N, 15·15. $C_9H_{17}N_2O_2$ requires: C, 58·35; H, 9·25; N, 15·13%).

2,2,5,5-*Tetramethyl*-3-*carboxypyrroline*-1-*oxyl* (V)

(a) The amide (III; 3·6 g) and 10% NaOH aq (40 ml) was heated in a vessel provided with a reflux condenser until no more ammonia was evolved. Hydrochloric acid was added to the reaction mixture after cooling and the precipitated residue filtered off on a porcelain filter. The acid filtrate was extracted with ether and an additional amount of the paramagnetic substance obtained from the ethereal extract. A total 3·57 g (97%) of a bright-yellow crystalline radical acid (V) was obtained; m.p. after recrystallization from benzene 210–211°. Compound V does not replace CO_2 from carbonates. (Found: C, 58·80; H, 7·66; N, 7·71. $C_9H_{14}NO_4$ requires: C, 58·68; H, 7·66; N, 7·60%).

(b) A mixture of 2,2,5,5-tetramethyl-3-carboxypyrroline dihydrate (1·64 g), water (5 ml) and K_2CO_3 (1·5 g) was oxidized using the above technique. The reaction mass was carefully acidified with HCl aq and the radical acid (V) isolated as in section (a), yield 0·84 g (57%), m.p. after recrystallization from water 210·5–211·5° (dec). A mixed m.p. with sample of V obtained by method (a) is 210–211° (dec).

2,2,5,5-*Tetramethyl*-3-*carboxypyrrolidine*-1-*oxyl* (VI)

This was obtained from an the amide-radical (IV) in an 87% yield as bright-yellow crystals. After crystallization from benzene the acid melted at 193° alone or mixed with the substance obtained by direct oxidation of 2,2,5,5-tetramethyl-3-carboxypyrrolidine. (Found: C, 58·05; H, 8.69; N, 7·56. $C_9H_{16}NO_3$ requires: C, 58·05; H, 8·66; N, 7·52%).

2,2,5,5-*Tetramethyl*-3-*carbmethoxypyrroline*-1-*oxyl* (VII)

Excess of an ethereal solution of diazomethane was added dropwise to a solution of acid radicals (V; 1·84 g) in ether (10 ml). The ethereal solution was washed with $NaHCO_3$ aq, then with water and dried (Na_2SO_4). The ether was evaporated and 1·95 g (98·6%) of a yellow crystalline substance with a strong pleasant odour was obtained, m.p. 89·3–89·8° from aqueous methanol. The substance (VII) is readily soluble in organic solvents, slightly soluble in water, and sublimes readily. (Found: C, 60·57; H, 8·18; N, 7·15. $C_{10}H_{18}NO_3$ requires: C, 60·59; H, 8·14; N, 7·07%).

Direct catalytic oxidation of 2,2,5,5-tetramethyl-3-carbmethoxypyrroline obtained in a 10% yield* in the esterification of the appropriate hydrochloride with methanol gives a 90% yield of the ester VII, m.p. 89–89·5°, identical with that described.

2,2,5,5-*Tetramethyl*-3-*carbmethoxypyrrolidine*-1-*oxyl* (VIII)

This was obtained quantitatively by treatment of radical-acid (VI) with an ethereal solution of diazomethane using the above mentioned technique. After additional chromatographic purification on aluminium oxide (benzene as eluent) the following constants were obtained for the ester-radical: b.p. 120° (10·5 mm Hg), n_D^{20} 1·4584; d_4^{20} 1·0357; MR_D found 52·78; MR_D calc. 52·88. The substance is an orange-coloured oil with a pleasant odour, readily soluble in almost all organic solvents. (Found: N, 7·30. $C_{10}H_{18}NO_3$ requires: N, 6·99%).

Direct catalytic oxidation of 2,2,5,5-tetramethyl-3-carbmethoxypyrrolidine obtained in a 9·3% yield by esterification of an appropriate hydrochloride yields the ester-radical (VIII)(n_D^{20} 1·4580) identical after chromatography on aluminium oxide with that described.

2,2,5,5-*Tetramethyl*-3-*cyanopyrroline*-1-*oxil* IX

Tosyl chloride (2·87 g) was added to a solution of 1·53 g of III dissolved in 10 ml dry pyridine and kept at room temp for 48 hr. A solution of KOH (1 g) in water (25 ml) was then added and the mixture heated to 80°. After cooling, the solution was extracted with ether, the extract carefully washed with 10% HCl aq, sat. $NaHCO_3$ aq and water, and dried (Na_2SO_4). After evaporation of the ether, 0·94 g (57%) of IX as a yellow-orange paramagnetic substance was obtained. After purification by chromatography on alumina (benzene as eluent) and subsequent sublimation *in vacuo* it melted at 62·5–63°. The substance (IX) is readily soluble in organic solvents, and slightly soluble in water. (Found: C, 65·13; H, 7·98; N, 16·99. $C_9H_{13}N_2O$ requires: C, 65·43; H, 7·93; N, 16·96%).

2,2,5,5-*Tetramethyl*-3-*cyanopyrroline*

Compound I (5·04 g) was ground in a mortar together with 11·64 g sulphaminic acid. The mixture was then heated to 200° with simultaneous intermixing for 10 min, and then kept for 10 min at 210–220°. After cooling to room temp, the dark mass was treated with 30 ml water, cooled with ice, and 7 g KOH added. The salts were removed by suction, the filtrate extracted with ether and the extract after drying (Na_2SO_4) evaporated under red. press. leaving 2·32 g (51%) of a light-yellow liquid, two-fold distillation *in vacuo* yielded a colourless oil b.p. 80° (10 mm Hg); n_D^{20} 1·4612; d_4^{20} 0·904; MR_D found 45·66; MR_D calc. 44·51. (Found: C, 71·63; H, 9·35; N, 18·99. $C_9H_{14}N_2$ requires: C, 71·96; H, 9·39; N, 18·65%).

The picrate: m.p. 228–230° crystallized from ethyl acetate. (Found: N, 18·45. $C_{15}H_{17}N_5O_7$ requires: 18·47%).

* Esterification with diazomethane gives but traces of methyl ester.

Oxidation of 2,2,5,5,-*tetramethyl*-3-*cyanopyrroline*

2,2,5,5-Tetramethyl-3-cyanopyrroline (0·53 g) were dissolved in a mixture of water (2 ml) and several drops methanol. A catalytic amount of sodium tungstate and trylon-B, and then 30% H_2O_2 (1 ml) were added to the mixture. After 1/2 hr of violent oxidation bright-yellow crystals were formed. These, after filtration, were washed with water and dried (0·44 g). An additional 0·13 g were obtained by extraction of the filtrate with chloroform, total yield 0·57 g (88%). After recrystallization from an ether–alcohol the product melted at 193–194° alone or mixed with 2,2,5,5-tetramethyl-3-carbamidopyrroline-1-oxyl (III).

2,2,5,5-*Tetramethyl*-3-*cyanopyrrolidine*-1-*oxyl* (X)

Compound IV (1·85 g) was dissolved in 5 ml dry pyridine and after addition of tosyl chloride (2·37 g) the procedure was similar to that for preparation of the nitrile IX. After removal of the ether 0·8 g (48%) of a red liquid was obtained. After chromatography on an alumina column (benzene as eluent) the liquid solidified as orange paramagnetic crystals of X, m.p. upon sublimation *in vacuo* 31·5–32·5°, b.p. 99·6–99·8° (2 mm Hg), n_D^{25} 1·4576, d_4^{25} 0·9839, MR_D Found 46·34, MR_D calc. 46·43. (Found: C, 64·70; H, 9·06; N, 16·72. $C_9H_{15}N_2O$ requires: C, 64·66; H, 9·04; N, 16·76%).

2,2,5,5-*Tetramethyl*-3-*oxopyrrolidine*-1-*oxyl* (XI)

The amide (III; 9·15 g) was added at once to a vigorously stirred, ice-cooled solution of NaOBr (prepared from 14 g NaOH, 200 ml water and 10 g Br_2). The mixture was stirred for 2 hr while cooled with ice water, then heated to 70° and set aside at this temp for 1 hr. The mixture was then again cooled with ice water, 100 g NaOH added with continuous stirring, the unreacted amide (III) filtered off (1·8 g) and the filtrate extracted with ether. The ethereal extract was dried overnight (Na_2SO_4) and evaporated under red. press. The red paramagnetic oil obtained (3·13 g; 50%) was chromatographed on alumina (chloroform as eluent) and yielded 2·05 g (33%) of XI as red oil solidifying into orange-red paramagnetic crystals; m.p. 41·5–42·5° (from hexane); readily soluble in water and organic solvents. (Found: C, 61·36; H, 9·04: N 9·19. $C_8H_{14}NO_2$ requires: C, 61·52; H, 9·03; N, 8.97%). Oxime, m.p. 182·5–183·5° (from CCl_4). (Found: C, 55·95; H, 8·75; N, 16·44. $C_8H_{15}N_2O_2$ requires: C, 56·13; H, 8·83; N, 16·37%).

Oxidation of 2,2,5,5-*tetramethyl*-3-*oxopyrrolidine oxime*.

2,2,5,5-Tetramethyl-3-oxopyrrolidine oxime[8] (0·37 g; m.p. 172°) was dissolved in 5 ml water, and catalytic amounts of sodium tungstate, trylon-B and 30% H_2O_2 (1 ml) added. Yellow paramagnetic crystals (0·34 g) were obtained m.p. 183–183·5° (from CCl_4) alone or mixed with oxime of XI.

2,2,5,5-*Tetramethyl*-3-*aminopyrrolidine*-1-*oxyl* (XII).

The amide IV (4.62 g) was added to a cooled solution of NaOBr (prepared from 6 g NaOH, 65 ml water and 5·6 g Br_2). The procedure was similar to that for preparation of the ketone-radical XI. The yield was 2·37 g (61%) of yellow paramagnetic oil solidifying upon distillation *in vacuo*, b.p. 75–80° (1 mm Hg). (Found: N, 17·68. $C_8H_{16}N_2O$ requires: N, 17·82%).

The picrate, m.p. 176–179° with dec. crystallized from acetone–hexane. (Found: C, 43·53; H, 5·33; N, 18·00. $C_{14}H_{20}N_5O_8$ requires: C, 43·50; H, 5·22; N, 18·12%).

Benzoate, m.p. 148° crystallized from acetone–hexane. (Found: 68·74; H, 8·12; N, 10·65. $C_{15}H_{21}N_2O_2$ requires: C, 68·93; H, 8·10; N, 10·72%).

Oxidation of 2,2,5,5-*tetramethyl*-3-*aminopyrrolidine*

This compound[8] (0·48 g) was dissolved in 3·5 ml water, catalytic amounts of sodium tungstate, trylon-B and 30% H_2O_2 (1 ml) were added. After 24 hr, 0·1 g of yellow paramagnetic crystals were precipitated. Extraction of the filtrate with ether gave additional 0·09 g of the substance. The total oxime-radical yield was 0·19 g (33%), m.p. and mixed m.p. 182·5–183° (from CCl_4).

2,2,5,5-*Tetramethyl*-3-*hydroxypyrrolidine*-1-*oxyl* (XIII)

The ketone-radical XI (1·21 g) was dissolved in 30 ml anhydrous isopropyl alcohol, 5 g freshly distilled aluminium isopropylate added, and the mixture heated on an oil bath so as to ensure slow distillation of the isopropyl alcohol. After 3 hr the test for acetone was negative. The reaction

mixture was then cooled and isopropyl alcohol evaporated under red. press. The mixture was treated with 25 ml water and KOH until the salts completely dissolved. The alkaline solution was extracted with ether. After drying (Na_2SO_4), the ether was evaporated under red. press. and 0·98 g (80%) of a solid paramagnetic substance obtained; m.p. 125·5–126° from hexane. (Found: C, 60·63; H, 10·19; N, 8·76. $C_8H_{16}NO_2$ requires: C, 60·73, H, 10·20; N, 8·85%).

Benzoate, m.p. 66·5–67° crystallized from hexane. (Found: C, 68·66; H, 7·75; N, 5·22. $C_{15}H_{20}NO_3$ requires: C, 68·71; H, 7·69; N, 5·34%).

CONCLUSIONS

1. A set of free iminoxyl radical of the hydrogenated pyrrole series have been synthesized for the first time.

2. The reaction involving no free valency has been extended over free iminoxyl radicals of the hydrogenated pyrrole series.