A comparison of the chemical shifts of amino groups in 2,5-APP (Table 1) compels us to conclude that the amino group linked through the benzene ring at position 5 has a high reactivity. Indeed, judging from the PMR spectrum, the intensity of the overall signal of protons 2' and 3' of the acylated R^2 is somewhat greater than the overall intensity of signal 2'-H and 3'-H of the acylated R^1 ring, i.e., the monoamide is formed largely (~60%) due to acylation of the aminophenyl group at position 5, and not at position 2.

The relative reactivities of the amino groups in 2,4-APP can be evaluated only from the difference of the chemical shifts. The proton signal of the amino group of the 2-aminophenyl moiety is upfield. Thus, the aminophenyl group at position 2 is acylated before the one at position 4. The equivalence of positions 4 and 6 is evident, and the stepwise nature of acylation reaction in this case is explained by a small difference in the reactivities of the monoacyl derivative and the diamine. Positions 4 and 5 can be compared by comparing the overall acylation reaction rates of 2,4- and 2,5-APP (Fig. 2) and the chemical shifts of amino group protons at positions 4 and 5 of the aminophenyl groups.

CONCLUSIONS

Using the PMR method, it was shown that the acylation of di(p-aminophenyl)pyrimidine by maleic anhydride occurs in the following order (based on position reactivity): $5 > 2 \geq 4(6)$.

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PREPARATION OF α-HYDROXYAMINOOXIMES OF THE TRIACETONAMINE SERIES AND THEIR REACTIONS WITH CARBONYL COMPOUNDS

L. B. Volodarskii, L. N. Grigor'eva, N. V. Dulepova, and A. Ya. Tikhonov

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Triacetonamines have been used to synthesize biologically active compounds and stable nitroxyl radicals [1, 2]. The 3-halo-2,2,6,6-tetramethyl-4-piperidones (Ia, b) have recently been synthesized [3], together with a number of their derivatives [4]. We have now examined the reactions of the chloroketones (Ia, b) with hydroxylamine in order to obtain α-hydroxyaminooximes (IIa, b) of the triacetonamine series. The use of synthons containing vicinal hydroxyamino and oxime groups should extend the synthetic potential of triacetonamines [5].

Reaction of (Ia, b) with an excess of hydroxylamine gives high yields of the 3-hydroxyamino (IIa) and 1-hydroxy-3-hydroxyamino-2,2,6,6-tetramethyl-4-piperidone oximes (IIb), respectively (see scheme at top of following page).

The most extensively studied reaction of α-hydroxyaminooximes is their reaction with mono- and 1,2-dicarbonyl compounds to give nitrones, and five- and six-membered heterocycles [5, 6]. Heating the α-hydroxyaminooxime (IIa) with benzaldehyde in alcohol in the presence of acetic acid afford the α-phenylnitrone (IIIa). Condensation of the acetate salt of the

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Lenin Komsomol Novosibirsk State University.

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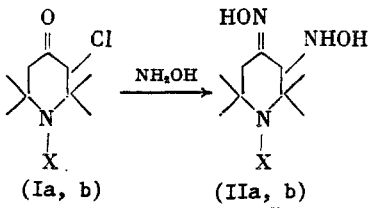
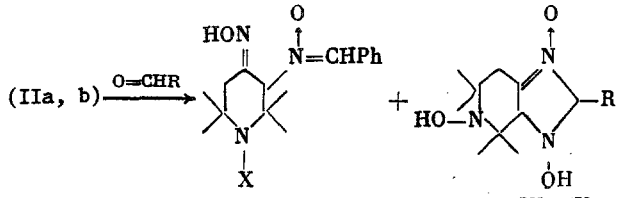


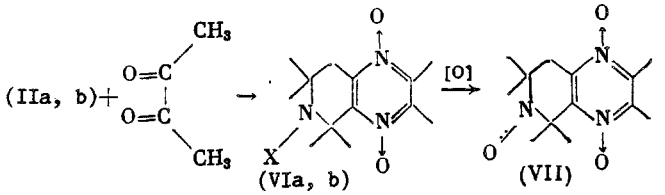
X = H(a), OH(b).

α-hydroxyaminooxime ((IIb)·AcOH) with benzaldehyde at 0°C gives the acetate salt of the α-phenylnitrone ((IIIb)·AcOH), and at ~20°C a mixture of ((IIIb)·AcOH) and the imidazo[5,4-c]pyridine (V):



R = Ph(IV), H(V).

Condensation of (IIa) and ((IIb)·AcOH) with biacetyl in alcohol gives the pyridino[3,4-b]pyrazine 1,4-dioxides (VIa, b):



The reaction of (VIb) with nitrous acid proceeds smoothly to give the stable nitroxyl radical (VII), the IR spectrum of which (in chloroform) shows no absorption for stretching vibrations of the hydroxy group, and the EPR spectrum shows a triplet characteristic of nitroxyl radicals with a hyperfine splitting constant of 16.5 Oe [7].

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in KBr disks, UV spectra on a Specord UV-VIS spectrometer in ethanol, and PMR spectra on Varian A-56/60A (60 MHz) and Bruker WP-200 SY instruments relative to HMDS. The EPR spectrum was recorded on a Sibir EPR-3 instrument in chloroform (C ≈ 10^{-4} M). The properties of the compounds are given in Table 1.

3-Hydroxyamino-2,2,6,6-tetramethyl-4-piperidone Oxime (IIa). To a solution of hydroxylamine, obtained by neutralizing 11.0 g (158 mmoles) of hydroxylamine hydrochloride in 100 ml of methanol with a solution of 8.2 g (152 mmoles) of sodium methoxide in 150 ml of methanol, was added a solution of 5.0 g (26 mmoles) of (Ia) in 40 ml of methanol with stirring over 40 min. The mixture was kept for 4 h at ~20°C, evaporated, the residue dissolved in 40 ml of water, and the solution washed with ethyl acetate. To the aqueous solution was added solid sodium hydroxide until a solid separated. This was filtered off to give 4.5 g (86%) of (IIa). Found, %: C 53.8; H 9.6; N 20.6. $C_9H_{19}N_3O_2$. Calculated, %: C 53.7; H 9.5; N 20.9.

1-Hydroxy-3-hydroxyamino-2,2,6,6-tetramethyl-4-piperidone Oxime Acetate ((IIb)·AcOH) was obtained as for (IIa), from (Ib). The residue was treated with ethyl acetate, washed with water, the extract dried over magnesium sulfate, filtered, acetic acid added, and evaporated. The residue of ((IIb)·AcOH) was treated with ether and filtered, giving a yield of 77%. Found, %: C 47.9; H 8.4; N 14.8. $C_9H_{19}N_3O_3 \cdot C_2H_4O_2$. Calculated, %: C 47.6; H 8.4; N 15.2.

N-(4-Hydroxyimino-2,2,6,6-tetramethylpiperid-3-yl)-α-phenylnitrone (IIIa). A solution of 0.50 g (2.5 mmoles) of (IIa), 0.28 g (2.6 mmoles) of benzaldehyde, and 1 ml of acetic acid in 15 ml of ethanol was boiled for 5 h, evaporated, the residue treated with a mixture of ethyl acetate and ether (7:1), and the solid filtered off to give 0.60 g (82%) of (IIIa). Found, %: C 65.8; H 8.; N 14.7. $C_{16}H_{23}N_3O_2$. Calculated, %: C 66.4; H 8.0; N 14.5.

TABLE 1. Physicochemical Properties of Compounds Obtained

Compound	Mp, °C (solvent	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm †, ‡
(IIa)	192–194 (EtOH)	–	905, 960 1380, 1390	0,96, 1,02, 1,04, 1,09 s (12H, 2,2,6,6-CH_3), 2,21 (1H, H^5). 2,46 (1H, H^5) (AB-system, J_{HH}=13 Hz), 3,04 s (1H, H^3), 5,70, 7,10 br.s (NH, OH), 10,40 s (1H, =NOH)
((IIb)AcOH)	109–111 (EtOAc)	–	915, 970 1390,1420	0,99, 1,03, 1,07 s (12H, 2,2,6,6-CH_3), 1,87 s (3H, CH_3), 2,49 s (2H, H^5) 3,13s (1H, H^3), 5,25 br.s (NH, OH)
(IIIa)	191–192 (EtOAc)	300(4,26)	1130, 1275, 1405, 1570, 1580	1,26, 1,34, 1,41 s (12H, 2,2,6,6-CH_3), 2,70 (1H, H^5), 3.30 (1H, H^5) (AB-system, J_{HH}=15 Hz), 4,29 s (1H, H^3), 7,3–7,5, 8,1–8,3 m (5H, C_6H_5), 7,62 s (1H, =CH)
(IIIb)	175–176 (abs. ether)	299(4,28)	1130, 1455, 1305	1,11, 1,26, 1,37 s (12H, 2,2,6,6-CH_3), 2,73 (1H, H^5), 3,25 (1H, H^5) (AB-system, J_{HH}=15 Hz), 4,46 s (1H, H^3), 7,3–7,6, 8,1–8,3 m (6H, C_6H_5, =CH).
((IIIb)·AcOH)	121–122 (EtOAc)	301(4,23)	1130, 1150, 1300, 1380, 1390, 1430	1,14, 1,26, 1,35, 1,39 s (12H, 2,2,6,6-CH_3), 1,94 s (3H, CH_3), 2,73 (1H, H^5), 3,26 (1H, H^5) (AB system, J_{HH}= 15 Hz), 4,50 s (1H, H^3), 7,3–7,6, 8,1–8,3 m (6H, C_6H_5, =CH)
(IV)	169–170 decomp. (abs. ether)	240(4,11)	1180, 1210, 1370, 1380, 1640	1.12, 1,22, 1,34, 1,43 s (12H, 4,4,6,6-CH_3), 2,33 (1H, H^7), 2,90 (1H, H^7) (AB-system, J_{HH}=16 Hz), 3,99 s (1H, H^{3a}), 5,61 s (1H, H^2), 7,2–7,6 m (5H, C_6H_5)
(V)	203–204 decomp. (DMF)	236(4,09)	1190, 1200, 1375, 1440, 1660	0,83, 0,91, 1,19, 1.26 s (12H, 4,4,6,6-CH_3), 2,18 (1H, H^7), 2,80 (1H, H^7) (AB-system, J_{HH}=14 Hz), 3,85 s (1H, H^{3a}), 4,63 (1H, H^2), 4.86 (1H, H^2) (AB-system, J_{HH}=14,5 Hz), 7,61, 9,51 s (2H, OH)
(VIa)	150–152 (EtOAc)	240(4.53) 310(4,31)	1115, 1325, 1520	1.24 s (6H, 7,7-CH_3), 1.71 s (6H, 5,5-CH_3), 2,51, 2,54 s (6H, 2,3-CH_3), 2,92 s (2H, H^8)
(VIb)	202–204 * (EtOAc)	241(4.51) 310(4,26)	1110, 1320, 1520	1,12 s (6H, 7,7-CH_3), 1.61 s (6H, 5,5-CH_3), 2,37 s (6H, 2,3-CH_3), 2,79 s (2H, H^8)
(VII)	155–156 * (subl.)	242(4,43) 310(4,14)	1120, 1325, 1530	–

*In a sealed capillary.
†The PMR spectra of (IIa), ((IIb)·AcOH), (V), and (VIb) were obtained in $(CD_3)_2SO$, and of (IIIa), (IIIb), ((IIIb)·AcOH), (IV), and (VIa) in CD_3OD.
‡The signal for the methyl group (H^5) in ((IIb)·AcOH) at 2.49 ppm coincided with that of the solvent.

N-(1-Hydroxy-4-hydroxyimino-2,2,6,6-tetramethylpiperid-3-yl)-α-phenylnitrone Acetate ((IIIb)·AcOH). To a solution of 3.0 g (11 mmoles) of ((IIb)·AcOH) in 40 ml of ethanol was added 1.6 g (15 mmoles) of benzaldehyde, and the mixture kept at 0°C for 30 h, evaporated, the residue dissolved in ethyl acetate, two drops of acetic acid added, and the solid filtered off to give 2.9 g (72%) of ((IIIb)·AcOH). Found, %: C 58.7; H 7.2; N 11.1. $C_{16}H_{23}N_3O_3 \cdot C_2H_4O_2$. Calculated, %: C 59.2; H 7.5; N 11.5.

The free base of the α-phenylnitrone (IIIb) was obtained by neutralizing a solution of 2.9 g (79 mmoles) of ((IIIb)·AcOH) in 30 ml of ethanol with a solution of 0.7 g of sodium hydrogen carbonate in 8 ml of water. The precipitate of sodium acetate was filtered off, the filtrate evaporated, and the residue treated with ether and filtered to give 2.13 g (88%) of (IIIb). Found, %: C 62.9; H 7.8; N 13.6. $C_{16}H_{23}N_3O_3$. Calculated, %: C 62.9; H 7.6; N 13.8.

3,5-Dihydroxy-4,4,6,6-tetramethyl-2-phenyl-3,3a,4,5,6,7-hexahydro-2H-imidazo[5,4-c]-pyridine 1-Oxide (IV). A solution of 0.30 g (1.1 mmoles) of ((IIb)·AcOH) and 0.22 g (2.1 mmoles) of benzaldehyde in 10 ml of ethanol was kept at ~20°C for three days, evaporated, and ethyl acetate added to the residue. The solid ((IIIb)·AcOH) was filtered off, yield 0.12 g (30%). Evaporation of the filtrate followed by treatment with ether gave 0.13 g (31%) of ((IV)·H_2O). Found, %: C 59.0; H 7.5; N 13.0. $C_{16}H_{23}N_3O_3 \cdot H_2O$. Calculated, %: C 59.4; H 7.8; N 13.0.

3,5-Dihydroxy-4,4,6,6-tetramethyl-3,3a,4,5,6,7-hexahydro-2H-imidazo[5,4-c]pyridine 1-Oxide (V). To a solution of 3.0 g (11 mmoles) of ((IIb)·AcOH) in 30 ml of ethanol was added 1.2 ml of formalin. After 2 h, 1.82 g (72%) of (V) was filtered off. Found, %: C 52.4; H 8.5; N 18.6. $C_{10}H_{19}N_3O_3$. Calculated, %: C 52.4; H 8.4; N 18.3.

2,3,5,7,7-Hexamethyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazine 1,4-Dioxide (VIa). A solution of 3.0 g (15 mmoles) of (IIa), 1.6 ml (18.6 mmoles) of diacetyl, and 1.0 ml (17 mmoles) of acetic acid in 10 ml of ethanol was kept at ~20°C for one day (followed by TLC), evaporated, and the residue chromatographed on a column of silica gel. Elution with ether followed by acetone gave an acetone fraction which was evaporated, and the residue was treated with ether and filtered to give 1.57 g (42%) of (VIa). Found, %: C 62.1; H 8.0; N 16.8. $C_{13}H_{21}N_3O_2$. Calculated, %: C 62.1; H 8.4; N 16.7.

6-Hydroxy-2,3,5,5,7,7-hexamethyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazine 1,4-Dioxide (VIb). Obtained as for (VIa), from ((IIb)·AcOH). The acetone fraction was evaporated, the residue treated with a mixture of ether and hexane (5:1), and the solid (VIb) filtered off, yield 43%. Found, %: C 58.5; H 7.9; N 15.7. $C_{13}H_{21}N_3O_3$. Calculated, %: C 58.4; H 7.9; N 15.7.

2,3,5,5,7,7-Hexamethyl-6-oxyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazine 1,4-Dioxide (VII). To a suspension of 0.13 g (4.9 mmoles) of (VIb) in 2 ml of water was added all at once a solution of 0.07 g (1 mmole) of sodium nitrite in 1 ml of water, followed by the slow dropwise addition with stirring of 2 ml of 0.5% HCl. After 15 min, the mixture was saturated with potassium carbonate, extracted with ethyl acetate, and the extract dried over magnesium sulfate and evaporated. The residue was treated with a mixture of ether and hexane (3:1), and the solid filtered off to give 0.12 g (92%) of (VII). Found, %: C 58.8; H 7.7; N 15.7. $C_{13}H_{20}N_3O_3$. Calculated, %: C 58.6; H 7.6; N 15.8.

CONCLUSIONS

1. 3-Hydroxyamino- and 1-hydroxy-3-hydroxyamino-2,2,6,6-tetramethyl-4-piperidone oximes have been obtained by reacting chloroketones derived from triacetonamine with hydroxylamine.

2. Condensation of the resulting α-hydroxyaminooximes with benzaldehyde and formaldehyde has given the N-piperidyl-α-phenylnitrones and imidazo[5,4-c]pyridines, and with diacetyl, the pyrido[3,4-b]pyrazine 1,4-dioxides.

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