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3-(4,5-Dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidines and 3-(4,5-Dihydro-1*H*-pyrazol-1-ylmethyl)perhydro-1,3-oxazines

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Abstract—3-(4,5-Dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidines and 3-(4,5-dihydro-1*H*-pyrazol-1-ylmethyl)perhydro-1,3-oxazines were synthesized in 54–85% yield by reactions of α-amino alcohols and 3-aminopropan-1-ol, respectively, with formaldehyde and 4,5-dihydro-1*H*-pyrazoles.

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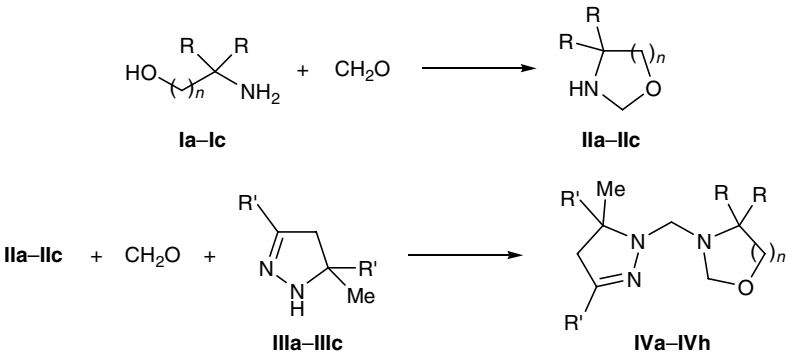
Acetals and their N,O- and N,N-analogs exhibit versatile biological activity and are intermediate products in fine organic synthesis [1]. The same applies to 4,5-dihydropyrazoles [2]. Obviously, compounds containing an N,N- or N,O-acetal moiety and a 4,5-dihydropyrazole fragment in a single molecule attract interest from the viewpoint of studying their biological activity. The present communication reports on the synthesis of such compounds.

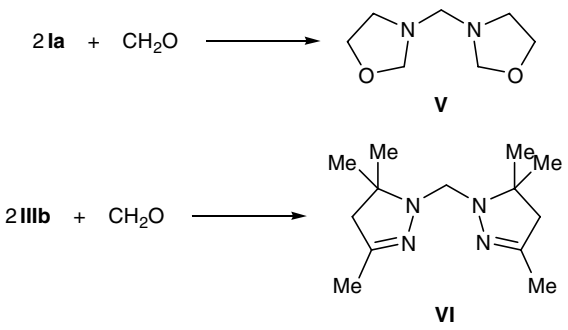
Initially, amino alcohols **Ia**–**Ic** were brought into condensation with formaldehyde to obtain oxazolidines **IIa** and **IIb** and perhydro-1,3-oxazine **IIc** (Scheme 1). The reactions were carried out by heating the reactants in benzene under reflux with simultaneous removal of water as azeotrope. When the reaction was complete (water no longer separated), 4,5-dihydropyrazole **IIIa**–**IIIc** and an additional amount of paraformaldehyde were added, and the mixture was heated again. At an amino alcohol–formaldehyde–dihydropyrazole ratio of 1:2:1, the yields of compounds **IVa**–**IVh** ranged from 54 to 85%. The reactions were accompanied by formation of symmetric aminals as by-products. For exampe, fractional distillation of the reaction mixture obtained from amino alcohol **Ia**, formaldehyde, and dihydropyrazole **IIIb** gave compound **IVb** as the major product and previously described compounds **V** and **VI** [3, 4] in 5 and 7% yield, respectively (Scheme 2). The structure of compounds **IVa–IVh** and **VI** was confirmed by IR and ^{1}H NMR spectroscopy and elemental analysis.

Scheme 1.



I, **II**, n = 1, R = H (**a**), Me (**b**); n = 2, R = H (**c**); **III**, R′ = H (**a**), Me (**b**), Et (**c**); **IV**, n = 1 (**a**–**e**), 2 (**f**–**h**); R = R′ = H (**a**, **f**); R = H, R′ = Me (**b**, **g**); R = H, R′ = Et (**c**, **h**); R = Me, R′ = H (**d**), R = R′ = Me (**e**).

Scheme 2.



EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrophotometer from samples prepared as thin films (neat). The ^{1}H NMR spectra were measured at 26°C on a Bruker DPX-400 instrument (400 MHz) from solutions in $CDCl_3$ using HMDS as internal reference.

3-(4,5-Dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidines IVa–IVe and 3-(4,5-dihydro-1*H*-pyrazol-1-ylmethyl)perhydro-1,3-oxazines IVf–IVh (*general procedure*). A mixture of 0.1 mol of amino alcohol **Ia**–**Ic** and 0.1 mol of paraformaldehyde in 100 ml of benzene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. Dihydropyrazole **IIIa**–**IIIc**, 0.1 mol, and an additional amount of paraformaldehyde, 0.1 mol, were added, and the mixture was again heated under reflux until water no longer separated. The products were isolated by vacuum distillation.

3-(5-Methyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidine (IVa). Yield 65%, bp 131-134°C (25 mm), d_4^{20} = 1.0940, n_D^{20} = 1.5010. IR spectrum, ν, cm^{-1}: 440, 540, 600, 620, 660, 675, 715, 735, 765, 815, 860, 900, 920, 945, 990, 1025, 1045, 1090, 1125, 1140, 1155, 1205, 1245, 1270, 1300, 1350, 1425, 1445, 1645, 2735, 2875, 2930, 2955, 3055. ^{1}H NMR spectrum, δ, ppm: 1.16 d (3H, CH_3, ^3J = 6.4 Hz), 2.17 m (1H, 4′-H), 2.68 m (1H, 4′-H), 2.95–3.26 m (3H, 5′-H, 4-H), 3.72 m (2H, 5-H), 3.81 d (1H, NCH_2N, ^2J = 12.0 Hz), 3.97 d (1H, NCH_2N, ^2J = 12.0 Hz), 3.99 d (1H, 2-H, ^2J = 10.4 Hz), 4.17 d (1H, 2-H, ^2J = 10.4 Hz), 6.54 m (1H, 3′-H). Found, %: C 56.12; H 8.91; N 24.84. $C_8H_{15}N_3O$. Calculated, %: C 56.78; H 8.93; N 24.83.

3-(3,5,5-Trimethyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidine (IVb). Yield 54%, bp 89–93°C (1 mm), d_4^{20} = 1.0446, n_D^{20} = 1.4995. IR spectrum, ν, cm^{-1}: 475, 480, 530, 560, 605, 650, 655, 715, 760, 780, 825, 860, 895, 925, 935, 945, 960, 985, 995, 1025, 1055, 1090, 1130, 1140, 1160, 1200, 1220, 1240, 1300, 1320, 1355, 1375, 1425, 1455, 1615, 2865, 2880, 2910, 2920, 2935, 2955, 2965, 3020. ^{1}H NMR spectrum, δ, ppm: 1.16 s (6H, 5′-CH_3), 1.94 s (3H, 3′-CH_3), 2.43 s (2H, 4′-H), 3.14 t (2H, 4-H, ^3J = 6.9 Hz), 3.61 s (2H, NCH_2N), 3.72 t (2H, 5-H, ^3J = 6.9 Hz), 4.44 s (2H, 2-H). Found, %: C 61.36; H 10.11; N 21.48. $C_{10}H_{19}N_3O$. Calculated, %: C 60.88; H 9.71; N 21.30.

3-(3,5-Diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidine (IVc). Yield 70%, bp 164–169°C (18 mm), d_4^{20} = 1.0274, n_D^{20} = 1.5028. IR spectrum, ν, cm^{-1}: 460, 545, 575, 600, 665, 720, 780, 845, 865, 890, 910, 925, 960, 995, 1050, 1085, 1090, 1130, 1210, 1300, 1360, 1370, 1430, 1455, 1615, 2875, 2930, 2965. ^{1}H NMR spectrum, δ, ppm: 0.89 m (3H, 5′-CH_2CH_3), 1.08 m (6H, 3′-CH_2CH_3, 5′-CH_3), 1.61 m (2H, 5′-CH_2), 1.85–2.54 m (4H, 3′-CH_2, 4′-H), 3.15 m (2H, 4-H), 3.59–3.73 m (4H, 5-H, NCH_2N), 4.39 d (1H, 2-H, ^2J = 6.1 Hz), 4.46 d (1H, 2-H, ^2J = 6.1 Hz). Found, %: C 64.04; H 10.27; N 18.69. $C_{12}H_{23}N_3O$. Calculated, %: C 63.96; H 10.29; N 18.65.

4,4-Dimethyl-3-(5-methyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidine (IVd). Yield 61%, bp 126–129°C (9 mm), d_4^{20} = 1.0208, n_D^{20} = 1.4850. IR spectrum, ν, cm^{-1}: 430, 450, 470, 505, 530, 575, 615, 680, 730, 755, 805, 840, 860, 875, 890, 920, 935, 955, 1005, 1030, 1055, 1090, 1120, 1140, 1155, 1170, 1195, 1240, 1260, 1315, 1330, 1350, 1365, 1400, 1420, 1445, 1490, 1650, 2830, 2860, 2920, 2955, 3045. ^{1}H NMR spectrum, δ, ppm: 1.11–1.28 m (9H, CH_3), 2.29 m (1H, 4′-H), 2.82 m (1H, 4′-H), 3.36–3.52 m (3H, 5′-H, 5-H), 3.93 d (1H, NCH_2N, ^2J = 12.5 Hz), 4.01 d (1H, NCH_2, ^2J = 12.5 Hz), 4.48 m (2H, 2-H), 6.64 m (1H, 3′-H). Found, %: C 60.04; H 10.14; N 21.47. $C_{10}H_{19}N_3O$. Calculated, %: C 60.88; H 9.71; N 21.30.

4,4-Dimethyl-3-(3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)oxazolidine (IVe). Yield 69%, bp 124–127°C (5 mm), d_4^{20} = 0.9845, n_D^{20} = 1.4793. IR spectrum, ν, cm^{-1}: 460, 475, 530, 560, 590, 645, 655, 670, 700, 710, 745, 780, 825, 850, 885, 895, 930, 945, 1020, 1030, 1065, 1100, 1130, 1160, 1205, 1220, 1235, 1255, 1320, 1355, 1365, 1420, 1430, 1460, 1620, 2800, 2810, 2870, 2910, 2930, 2970. ^{1}H NMR spectrum, δ, ppm: 1.12 s and 1.17 s (3H each, 4-CH_3), 1.22 s and 1.24 s (3H each, 5′-CH_3), 1.91 s (3H, 3′-CH_3), 2.43 s (2H, 4′-H), 3.63 s (2H, 5-H), 3.81 s (2H, NCH_2N), 4.61 s (2H, 2-H). Found, %: C 63.41; H 10.18; N 18.29. $C_{12}H_{23}N_3O$. Calculated, %: C 63.96; H 10.29; N 18.65.

3-(5-Methyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)perhydro-1,3-oxazine (IVf). Yield 64%, bp 128–

130°C (12 mm), d_4^{20} = 1.0474, n_D^{20} = 1.4931. IR spectrum, ν, cm^{-1}: 435, 460, 495, 520, 535, 615, 645, 670, 730, 760, 780, 785, 810, 830, 865, 895, 940, 965, 1020, 1040, 1085, 1120, 1150, 1165, 1185, 1230, 1245, 1265, 1315, 1325, 1340, 1350, 1370, 1425, 1440, 1620, 2835, 2840, 2955, 3050. ^{1}H NMR spectrum, δ, ppm: 1.26 d (3H, 5′-CH$_3$, ^3J = 6.1 Hz), 1.65 m (2H, 5-H), 2.28 m (1H, 4′-H), 2.81 m (1H, 4′-H), 2.98–3.07 m (3H, 5′-H, 4-H), 3.35–3.57 m (2H, 6-H), 3.95 d (1H, NCH$_2$N, ^2J = 12.3 Hz), 4.19 d (1H, NCH$_2$N, ^2J = 12.3 Hz), 4.36 d (1H, 2-HO, ^2J = 8.2 Hz), 4.47 d (1H, 2-H, ^2J = 8.2 Hz), 6.66 m (1H, 3′-H). Found, %: C 58.85; H 9.34; N 22.53. $C_9H_{17}N_3O$. Calculated, %: C 58.99; H 9.35; N 22.93.

3-(3,5,5-Trimethyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)perhydro-1,3-oxazine (IVg). Yield 85%, bp 99–102°C (2 mm), d_4^{20} = 1.0200, n_D^{20} = 1.4863. IR spectrum, ν, cm^{-1}: 450, 465, 495, 530, 555, 620, 645, 665, 690, 710, 745, 765, 780, 790, 805, 820, 835, 865, 890, 900, 940, 975, 1030, 1080, 1100, 1130, 1160, 1185, 1205, 1225, 1280, 1295, 1315, 1345, 1370, 1425, 1450, 1615, 2840, 2900, 2930, 2950. ^{1}H NMR spectrum, δ, ppm: 1.19 s (6H, 5′-CH$_3$), 1.64 m (2H, 5-H), 1.92 s (3H, 3′-CH$_3$), 2.43 s (2H, 4′-H), 3.10 m (2H, 4-H), 3.82–3.95 m (4H, 6-H, NCH$_2$N), 4.51 s (2H, 2-H). Found, %: C 62.70; H 10.38; N 19.53. $C_{11}H_{21}N_3O$. Calculated, %: C 62.52; H 10.02; N 19.89.

3-(3,5-Diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-ylmethyl)perhydro-1,3-oxazine (IVh). Yield 76%, bp 138–142°C (5 mm), d_4^{20} = 0.9988, n_D^{20} = 1.4902. IR spectrum, ν, cm^{-1}: 475, 505, 540, 555, 605, 635, 655, 680, 715, 725, 795, 810, 850, 880, 900, 915, 950, 990, 1040, 1045, 1060, 1100, 1110, 1165, 1175, 1200, 1235, 1290, 1310, 1340, 1365, 1380, 1435, 1460, 1620, 2860, 2880, 2945, 2970. ^{1}H NMR spectrum, δ, ppm: 0.89 m (3H, 5′-CH$_2$C**H**$_3$), 1.05 m (6H, 3′-CH$_2$C**H**$_3$, 5′-CH$_3$), 1.61–2.53 m (8H, 5′-CH$_2$, 5-H, 3′-CH$_2$, 4′-H), 3.10 m (2H, 4-H), 3.82–3.94 m (3H, 6-H, NCH$_2$N), 3.95 d (1H, NCH$_2$N, ^2J = 11.3 Hz), 4.46 d (1H, 2-H, ^2J = 10.1 Hz), 4.53 d (1H, 2-H, ^2J = 10.1 Hz). Found, %: C 65.11; H 10.55; N 17.46. $C_{13}H_{25}N_3O$. Calculated, %: C 65.23; H 10.53; N 17.56.

Bis(oxazolidin-3-yl)methane (V) was isolated by vacuum distillation of the reaction mixture in the synthesis of compound **IVb**. Yield 5%, bp 105–107°C (11 mm), d_4^{20} = 1.0731, n_D^{20} = 1.4851; published data [3]: bp 108–110°C (12 mm), n_D^{20} = 1.4890. Found, %: C 53.45; H 8.81; N 17.55. $C_7H_{14}N_2O$. Calculated, %: C 53.15; H 8.92; N 17.71.

Bis(3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)methane (VI) was isolated by vacuum distillation of the reaction mixture in the synthesis of compound **IVb**. Yield 7%, bp 122–124°C (1 mm), d_4^{20} = 0.9651, n_D^{20} = 1.4921 [4]. IR spectrum, ν, cm^{-1}: 470, 530, 555, 630, 640, 675, 705, 740, 770, 815, 850, 890, 910, 915, 940, 975, 1000, 1015, 1085, 1125, 1155, 1210, 1230, 1310, 1345, 1355, 1375, 1420, 1450, 1545, 1610, 2825, 2860, 2875, 2900, 2925, 2955. ^{1}H NMR spectrum, δ, ppm: 1.24 s (12H, 5-CH$_3$), 1.91 s (6H, 3-CH$_3$), 2.43 s (4H, 4-H), 4.18 s (2H, NCH$_2$N). Found, %: C 66.40; H 10.44; N 23.75. $C_{13}H_{24}N_4$. Calculated, %: C 66.06; H 10.23; N 23.70.

REFERENCES

1. Yanovskaya, L.A., Yufit, S.S., and Kucherov, V.F., *Khimiya atsetalei* (Chemistry of Acetals), Moscow: Nauka, 1975; Rakhmankulov, D.L., Zorin, V.V., Latypova, F.N., Zlotskii, S.S., and Karakhanov, R.A., *Khim. Geterotsikl. Soedin*., 1982, p. 435.
2. Kost, A.N. and Ershov, V.V., *Usp. Khim*., 1958, vol. 27, p. 431.
3. Eggensperger, H. and Diehl, K.H., FRG Patent no. 2635389, 1976; *Chem. Abstr*., 1978, vol. 88, no. 170125.
4. Voronkov, M.G., Dmitrieva, Z.T., Shergina, N.I., Atavin, A.S., Mamedova, L.V., and Kukharev, B.F., *Zh. Prikl. Spektrosk*., 1973, vol. 19, p. 449.