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Synthesis and Some Transformations of 4-Aryl-Substituted Amines of the Tetrahydropyran Series

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Abstract—The reaction of 2-isopropyltetrahydropyran-4-one [obtained by isomerization and hydration of 3-isopropylpent-1-en-4-yn-3-ol in the presence of 5% sulfuric acid and mercury(II) sulfate] with ethyl cyanoacetate gave ethyl cyano(2-isopropyltetrahydropyran-4-ylidene)acetate which was treated with 4-tolylmagnesium chloride. The resulting ethyl cyano[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]acetate was subjected to decarbethoxylation to obtain 2-isopropyl-4-(4-tolyl)tetrahydropyran-4-ylacetonitrile. The latter was reduced to the corresponding amine with lithium tetrahydridoaluminate, and the reduction product was brought into condensation with aromatic aldehydes. The Schiff bases thus formed were reduced with sodium tetrahydridoborate, followed by N-acylation with acetyl and propionyl chlorides.

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We previously reported on the synthesis and transformations of 2-[2-isopropyl-4-(*o*-methoxyphenyl)-tetrahydropyran-4-yl]ethanamine [1]. With a view to find a relation between the structure of compounds and their biological activity (antibacterial, anti-inflammatory, anesthetic) in the present work we synthesized analogous derivatives having a 4-methylphenyl substituent. By reaction of 2-isopropyltetrahydropyran-4-one (**I**) with ethyl cyanoacetate we obtained tetrahydropyranylidene-substituted ethyl cyanoacetate **II** which reacted with 4-tolylmagnesium chloride to produce ester **III**. Treatment of **III** with potassium hydroxide resulted in elimination of the ester group with formation of nitrile **IV**. The latter was reduced to primary amine **V** with lithium tetrahydridoaluminate, and condensation of **V** with a series of aromatic aldehydes afforded Schiff bases **VI** which were reduced (without isolation from the reaction mixture) to the corresponding secondary amines **VII**–**XI** with $NaBH_4$. Acylation of amines **VII**–**XI** with acetyl and propionyl chlorides gave amides **XII**–**XXI** (Scheme 1).

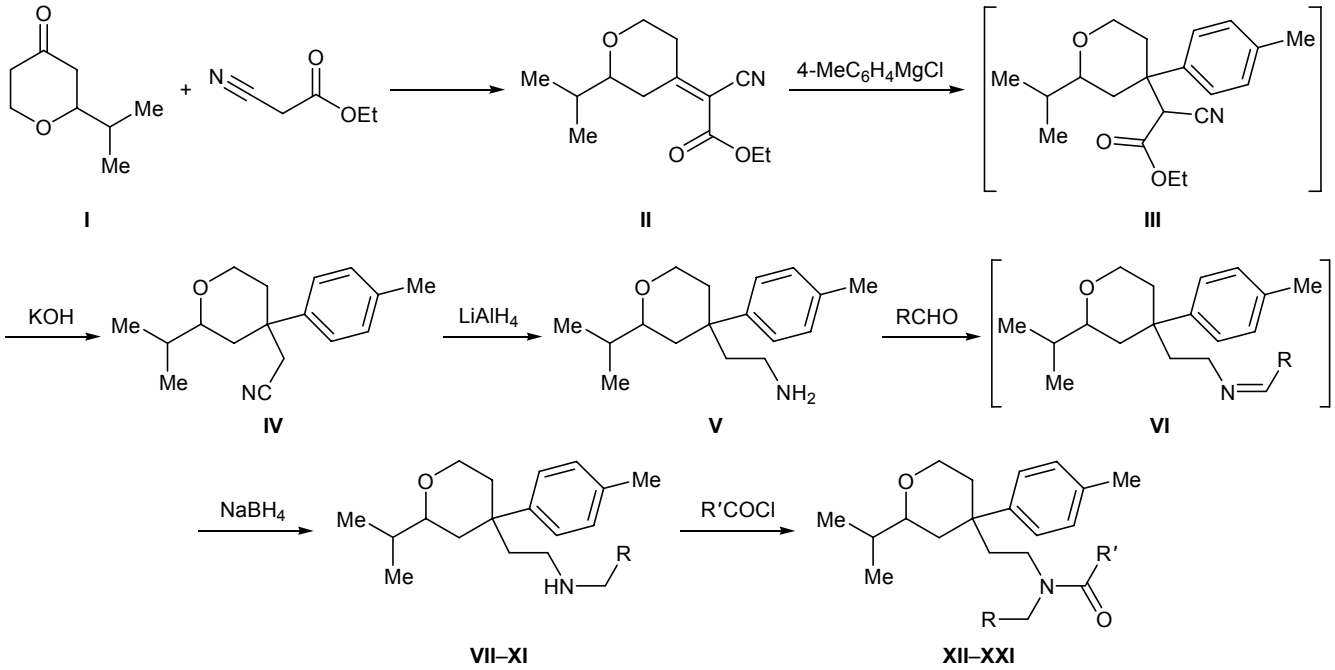
The structure of the newly synthesized compounds was confirmed by their elemental analyses and ^{1}H and ^{13}C NMR spectra.

EXPERIMENTAL

The IR spectra were measured on a Specord 75IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury VX-300 instrument at 300.08 and 75.46 MHz, respectively, using DMSO-d_6–CCl_4 (1:3) as solvent and tetramethylsilane as internal reference.

2-Isopropyltetrahydropyran-4-one (I). A mixture of 400 ml of 20% sulfuric acid, 400 g (3.2 mol) of 3-isopropylpent-1-en-4-yn-3-ol, and 15 g of $HgSO_4$ in 1.1 l of acetone was heated for 20 h at 62°C under vigorous stirring. During this time, additional 30 g of $HgSO_4$ was added in portions. The most part of the solvent was distilled off, and the residue was saturated with potassium carbonate and extracted with diethyl ether. The extract was dried over Na_2SO_4 and evaporated, and the residue was distilled under reduced pressure. Yield 338.3 g (74%), bp 67–69°C (4 mm). ^{1}H NMR spectrum, δ, ppm: 0.92 d (3H, CH_3, J = 6.8 Hz), 0.95 d (3H, CH_3, J = 6.8 Hz), 1.75 sept.d [1H, C**H**$(CH_3)_2$, J = 6.8, 5.9 Hz], 2.18 m (1H, 3-H), 2.22–2.25 m (2H, 3-H, 5-H), 2.51 m (1H, 5-H), 3.26 m (1H, 2-H), 3.57 d.d.d (1H, 6-H, J = 12.4, 11.3, 2.8 Hz),

Scheme 1.



VII, R = Ph; **VIII**, R = 4-$MeOC_6H_4$; **IX**, R = 3,4-$(MeO)_2C_6H_3$; **X**, R = 2-FC_6H_4; **XI**, R = 2-furyl; **XII**, R = Ph, R′ = Me; **XIII**, R = Ph, R′ = Et; **XIV**, R = 4-$MeOC_6H_4$, R′ = Me; **XV**, R = 4-$MeOC_6H_4$, R′ = Et; **XVI**, R = 4-*i*-$PrOC_6H_4$, R′ = Me; **XVII**, R = 4-*i*-$PrOC_6H_4$, R′ = Et; **XVIII**, R = 2-FC_6H_4, R′ = Me; **XIX**, R = 2-FC_6H_4, R′ = Et; **XX**, R = 2-furyl, R′ = Me; **XXI**, R = 2-furyl, R′ = Et.

4.22 d.d.d (1H, 6-H, J = 11.3, 7.4, 1.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.46 and 17.55 (CH_3), 32.45 (**C**HCH_3), 41.53 (C^3), 44.63 (C^5), 65.67 (C^6), 81.83 (C^2), 204.71 (CO). Found, %: C 67.55; H 9.93. $C_8H_{14}O_2$. Calculated, %: C 67.57; H 9.92.

Ethyl cyano(2-isopropyltetrahydropyran-4-ylidene)acetate (II) was synthesized according to the procedure described in [2]. The product was a mixture of *E* and *Z* isomers at a ratio of 1 : 1. Yield 74%, bp 120–124°C (2 mm). IR spectrum, ν, cm^{-1}: 2225 (CN), 1720 (C=O), 1610 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.97 d (1.5H, J = 6.8 Hz), 0.96 d (1.5H, J = 6.8 Hz), 0.97 d (1.5H, J = 6.8 Hz), 0.98 d (1.5H, J = 6.8 Hz) [$CH(CH_3)_2$], 1.36 t (1.5H, CH_3CH_2O, J = 7.1 Hz), 1.36 t (1.5H, CH_3CH_2O, J = 7.1 Hz), 1.79 m [1H, $CH(CH_3)_2$], 2.04 d.d (0.5H, J = 13.8, 10.7 Hz) and 2.29 d.d (0.5H, J = 13.5, 10.7 Hz) (3-H), 2.34 d.d.d (0.5H, J = 14.3, 11.7, 6.3 Hz) and 2.56 d.d.d (0.5H, J = 14.0, 11.7, 6.3 Hz) (3-H), 2.87 m (1H), 3.06 d.d.d (0.5H, J = 10.7, 5.8, 2.1 Hz) and 3.16 d.d.d (0.5H, J = 10.7, 5.8, 2.1 Hz) (2-H), 3.38 t.d (0.5H, J = 11.4, 2.5 Hz), 3.48 t.d (0.5H, J = 11.4, 2.5 Hz), 3.84 d.q (0.5H, J = 14.3, 1.6 Hz), 3.92 d.t (0.5H, J = 13.8, 2.1 Hz), 4.15 d.d.d (0.5H, J = 11.2, 6.3, 1.8 Hz), 4.22 d.d.d (0.5H, J = 11.2, 6.3, 1.8 Hz), 4.26 q (2H, OCH_2CH_3, J = 7.1 Hz). Found, %: C 65.85; H 8.00; N 5.87. $C_{13}H_{19}NO_3$. Calculated, %: C 65.80; H 8.07; N 5.90.

[2-Isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]-acetonitrile (IV) was synthesized according to the procedure described in [2]. Yield 93%, bp 164–166°C (2 mm). IR spectrum: ν 2230 cm^{-1} (CN). Found, %: C 79.36; H 8.99; N 5.41. $C_{17}H_{23}NO$. Calculated, %: C 79.33; H 9.01; N 5.44.

2-[2-Isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]-ethanamine (V). A solution of 12.2 g (0.32 mol) of $LiAlH_4$ in 200 ml of anhydrous diethyl ether was cooled to 0–2°C, a solution of 42 g (0.16 mol) of nitrile **IV** in diethyl ether was added dropwise, the mixture was stirred for 1 h at that temperature and cooled to –10°C (NaCl–ice bath), and 12 ml of water, 12 ml of a 15% solution of sodium hydroxide, and 36 ml of water were added in succession. The mixture was filtered, the inorganic precipitate was washed with diethyl ether, the organic phase of the filtrate was combined with the washings, dried, and evaporated, and the residue was distilled under reduced pressure. Yield 41 g (94%), bp 155–157°C (1.5 mm). IR spectrum: ν 3300 cm^{-1} (NH_2). ^{1}H NMR spectrum, δ, ppm: 0.94 d [6H, $CH(CH_3)_2$, ^3J = 6.8 Hz], 1.23 br (2H, NH_2), 1.35 d.d (1H, 3-H, ^2J = 13.4, ^3J = 11.5 Hz), 1.62 sept.d [1H, $CH(CH_3)_2$, ^3J = 6.8, 5.6 Hz], 1.72 t.d (1H, 5-H,

^2J = 12.3, ^3J = 5.3 Hz), 1.83–1.94 m (2H, 3-H, 5-H), 2.18–2.26 m (4H, C**H**$_2$C**H**$_2$NH$_2$), 2.31 s (3H, C**H**$_3$C$_6$H$_4$), 3.31 d.d.d (1H, 2-H, ^3J = 11.5, 5.6, 1.5 Hz), 3.73 d.d.d (1H, 6-H, ^2J = 12.0, ^3J = 12.3, 1.9 Hz), 3.85 d.d.d (1H, ^2J = 12.0, ^3J = 5.2, 1.3 Hz), 7.06 m (2H) and 7.12 m (2H) (C$_6$H$_4$). Found, %: C 78.00; H 10.51; N 5.27. C$_{17}$H$_{27}$NO·HCl. Calculated, %: C 78.11; H 10.41; N 5.35.

***N*-Arylmethylidene-2-[2-isopropyl-4-(4-tolyl)-tetrahydropyran-4-yl]ethanamines VII–XI (*general procedure*).** A mixture of equimolar amounts (0.01 mol) of amine **II** and aromatic aldehyde in 50 ml of benzene was heated for 4 h under reflux in a flask equipped with a Dean–Stark trap until complete removal of water. The solvent was removed, the residue was dissolved in methanol, and an equivalent amount of NaBH$_4$ was added in portions under stirring and cooling with water, maintaining the temperature below 20°C. The mixture was then stirred for 1 h at room temperature, the solvent was distilled off, and the residue was made alkaline by adding a 20% solution of sodium hydroxide and extracted with benzene. The extract was dried, the solvent was distilled off, and amines **VII**–**XI** were isolated from the residue by distillation.

***N*-Benzyl[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethanamine (VII).** Yield 83%, bp 198–200°C (1 mm). IR spectrum: ν 3320–3310 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 0.91 d (3H, CH$_3$, ^3J = 6.8 Hz), 0.92 d (3H, CH$_3$, ^3J = 6.8 Hz), 1.15 br (1H, NH), 1.35 d.d (1H, 3-H, ^2J = 12.7, ^3J = 11.7 Hz), 1.61 sept.d [1H, C**H**(CH$_3$)$_2$, ^3J = 6.8, 5.8 Hz], 1.70 t.d (1H, 3-H, ^2J = 12.7, ^3J = 5.1 Hz), 1.83–1.93 m (2H, 3-H, 5-H), 1.97 m (2H, C**H**$_2$CH$_2$NH), 2.19 m (2H, CH$_2$C**H**$_2$NH), 2.32 s (3H, C$_6$H$_4$C**H**$_3$), 3.28 d.d.d (1H, 2-H, ^3J = 11.7, 5.8, 1.6 Hz), 3.54 s (2H, PhC**H**$_2$), 3.72 d.d.d (1H, 6-H, ^2J = 11.8, ^3J = 12.6, 1.9 Hz), 3.85 d.d.d (1H, 6-H, ^2J = 11.8, ^3J = 5.2, 1.5 Hz), 7.04–7.23 m (9H, H$_{arom}$). Found, %: C 82.11; H 9.37; N 4.06. C$_{24}$H$_{33}$NO. Calculated, %: C 82.00; H 9.46; N 3.98.

2-[2-Isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]-*N*-(4-methoxybenzyl)ethanamine (VIII). Yield 80%, bp 218–220°C (1 mm). IR spectrum: ν 3330 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 0.92 d (3H, CH$_3$, J = 6.8 Hz), 0.94 d (3H, CH$_3$, J = 6.8 Hz), 1.12 br (1H, NH), 1.36 d.d (1H, CH$_2$, J = 12.8, 11.8 Hz), 1.62 m [1H, C**H**(CH$_3$)$_2$], 1.70 t.d (1H, CH$_2$, J = 12.8, 5.1 Hz), 1.83–2.00 m (6H, CH$_2$), 2.12–2.21 m (2H, CH$_2$), 2.33 s (3H, C$_6$H$_4$C**H**$_3$), 3.29 d.d.d (1H, OCH, J = 11.5, 5.9, 1.2 Hz), 3.47 s (2H, C$_6$H$_4$C**H**$_2$), 3.68–3.89 m (2H, OCH$_2$), 3.75 s (3H, OCH$_3$), 6.73 m (2H) and 7.03–7.14 m (6H) (H$_{arom}$). Found, %: C 78.62; H 9.22; N 3.59. C$_{25}$H$_{35}$NO$_2$. Calculated, %: C 78.70; H 9.25; N 3.67.

***N*-(3,4-Dimethoxybenzyl)-2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethanamine (IX).** Yield 77%, bp 226–230°C (1 mm). IR spectrum: ν 3300 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 0.91 d (3H, CH$_3$, ^3J = 6.8 Hz), 0.92 d (3H, CH$_3$, ^3J = 6.8 Hz), 1.12 br (1H, NH), 1.35 d.d (1H, 3-H, ^2J = 12.7, ^3J = 11.8 Hz), 1.60 sept.d [1H, C**H**(CH$_3$)$_2$, ^3J = 6.8, ^3J = 5.8 Hz], 1.69 t.d (1H, 3-H, ^2J = 13.2, ^3J = 12.8, 5.3 Hz), 1.83–1.94 m (2H, 3-H, 5-H), 1.97 m (2H, C**H**$_2$CH$_2$NH), 2.17 m (2H, CH$_2$C**H**$_2$NH), 2.31 s (3H, C$_6$H$_4$C**H**$_3$), 3.29 d.d.d (1H, 2-H, ^3J = 11.8, 5.8, 1.6 Hz), 3.45 s (2H, C$_6$H$_3$C**H**$_2$), 3.72 m (1H, 6-H), 3.75 s (3H, OCH$_3$), 3.76 s (3H, OCH$_3$), 3.85 d.d.d (1H, 6-H, ^2J = 11.8, ^3J = 5.2, 1.4 Hz), 6.62 d.d (1H, 6′-H, ^3J = 8.1, ^4J = 2.0 Hz), 6.69 d (1H, 5′-H, ^3J = 8.1 Hz), 6.75 d (1H, 2′-H, ^4J = 2.0 Hz), 7.05 m and 7.11 m (2H each, C$_6$H$_4$). Found, %: C 75.76; H = 8.95; N 3.50. C$_{26}$H$_{37}$NO$_3$. Calculated, %: C 75.87; H 9.06; N 3.40.

***N*-(2-Fluorobenzyl)-2-[2-isopropyl-4-(4-tolyl)-tetrahydropyran-4-yl]ethanamine (X).** Yield 85%, bp 200–204°C (1 mm). IR spectrum: ν 3340–3310 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 0.92 d (3H, CH$_3$, ^3J = 6.8 Hz), 0.93 d (3H, CH$_3$, ^3J = 6.8 Hz), 1.28 br (1H, NH), 1.36 d.d (1H, 3-H, ^2J = 13.0, ^3J = 11.7 Hz), 1.62 sept.d [1H, C**H**(CH$_3$)$_2$, ^3J = 6.8, 5.8 Hz], 1.71 t.d (1H, 3-H, ^2J = 12.5, ^3J = 5.1 Hz), 1.83–1.96 m (2H, 3-H, 5-H), 1.99 m (2H, C**H**$_2$CH$_2$NH), 2.20 m (2H, CH$_2$C**H**$_2$NH), 2.32 s (3H, C$_6$H$_4$C**H**$_3$), 3.29 d.d.d (1H, 2-H, ^3J = 11.6, 5.8, 1.5 Hz), 3.60 s (2H, C$_6$H$_4$C**H**$_2$), 3.73 d.d.d (1H, 6-H, ^2J = 11.9, ^3J = 12.5, 2.1 Hz), 3.86 d.d.d (1H, 6-H, ^2J = 11.9, ^3J = 5.3, 1.7 Hz), 6.92–7.25 m (8H, H$_{arom}$). Found, %: C 77.90; H 8.64; N 3.71. C$_{24}$H$_{32}$FNO. Calculated, %: C 78.01; H 8.73; N 3.79.

***N*-(Furan-2-ylmethyl)-2-[2-isopropyl-4-(4-tolyl)-tetrahydropyran-4-yl]ethanamine (XI).** Yield 87%, bp 191–194°C (2 mm). IR spectrum: ν 3320 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 0.91 d (3H, CH$_3$, ^3J = 6.8 Hz), 0.92 d (3H, CH$_3$, ^3J = 6.8 Hz), 1.30 br (1H, NH), 1.34 d.d (1H, 3-H, ^2J = 12.8, ^3J = 11.6 Hz), 1.60 sept.d [1H, C**H**(CH$_3$)$_2$, ^3J = 6.8, 5.8 Hz], 1.69 t.d (1H, 3-H, ^2J = 12.7, ^3J = 5.2 Hz), 1.82–1.92 m (2H, 3-H, 5-H), 1.93 m (2H, C**H**$_2$CH$_2$NH), 2.16 m (2H, CH$_2$C**H**$_2$NH), 2.31 s (3H, C$_6$H$_4$C**H**$_3$), 3.28 d.d.d (1H, 2-H, ^3J = 11.6, 5.8, 1.7 Hz), 3.51 s (2H, C$_4$H$_3$OC**H**$_2$), 3.71 d.d.d (1H, 6-H, ^2J = 11.8, ^3J = 12.7, 1.6 Hz), 3.84 d.d.d (1H, 6-H, ^2J = 11.8, ^3J = 5.2, 1.6 Hz), 5.97 d (1H, 3′-H, ^3J = 3.2 Hz), 6.21 d.d (1H, 4′-H, ^3J = 3.2,

2.0 Hz), 7.05 m and 7.11 m (2H each, C_6H_4), 7.28 d (1H, 5′-H, ^3J = 2.0 Hz). Found, %: C 77.41; H 9.06; N 4.02. $C_{22}H_{31}NO_2$. Calculated, %: C 77.38; H 9.15; N 4.10.

***N*-Benzyl-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}acet(propion)amides XII–XXI (*general procedure*).** Acetyl or propionyl chloride, 0.03 mol, was added to a solution of 0.03 mol of amine **VII–XI** and 3 g (0.032 mol) of triethylamine in 30 ml of anhydrous benzene. The mixture was heated for 4 h under reflux, cooled, washed with water, and extracted with benzene, the solvent was distilled off, and the residue was distilled under reduced pressure to isolate amides **XII–XXI**.

***N*-Benzyl-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}acetamide (XII).** Yield 73% (a mixture of four diastereoisomers), bp 220–225°C (0.5 mm). IR spectrum, ν, cm^{-1}: 3280 (NH), 1640 (amide I), 1520 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.94 m [6H, (C**H**$_3$)$_2$CH, J = 6.9 Hz], 1.26–1.38 m (1H, 3-H), 1.52–1.89 m [4H, (CH$_3$)$_2$C**H**, 5-H), 1.75 s (1.8H) and 1.97 s (1.2H (COCH$_3$), 1.91–2.02 m (2H, C**H**$_2$CH$_2$N), 2.31 s (1.2H) and 2.34 s (1.8H) (C$_6$H$_4$C**H**$_3$), 2.65–2.76 m (1.2H) and 2.77–2.89 m (0.8H) (CH$_2$C**H**$_2$N), 3.17 d.d.d (0.6H, ^3J = 11.6, 5.9, 1.2 Hz) and 3.26 d.d.d (0.4H, ^3J = 11.6, 5.9, 1.2 Hz) (2-H), 3.57–3.73 m and 3.80–3.87 m (1H each, 6-H); 4.22 d (0.4H, ^2J = 12.1 Hz), 4.24 d (0.4H, ^2J = 12.1 Hz), 4.29 d (0.6H, ^2J = 14.5 Hz), and 4.36 d (0.6H, ^2J = 14.5 Hz) (PhC**H**$_2$); 6.94–7.24 m (9H, H$_{arom}$). Found, %: C 79.42; H 9.03; N 4.00. $C_{26}H_{35}NO_2$. Calculated, %: C 79.35; H 8.96; N 3.56.

***N*-Benzyl-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}propionamide (XIII).** Yield 70% (a mixture of four diastereoisomers), bp 230–234°C (1 mm). IR spectrum, ν, cm^{-1}: 3380 (NH), 1637 (amide I), 1510 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.94 m [6H, (C**H**$_3$)$_2$CH, J = 6.9 Hz], 0.97 t (1.8H, ^3J = 7.3 Hz) and 1.03 t (1.2H, ^3J = 7.3 Hz) (C**H**$_3$CH$_2$CO), 1.29–1.38 m (1H, 3-H), 1.52–2.00 m [6H, 5-H, (CH$_3$)$_2$C**H**, C**H**$_2$CH$_2$N], 1.94 q (1.2H, ^3J = 7.3 Hz) and 2.23 q (0.8H, ^3J = 7.3 Hz) (CH$_3$C**H**$_2$CO), 2.31 s (1.2H) and 2.35 s (1.8H) (C$_6$H$_4$C**H**$_3$), 2.62–2.89 m (2H, CH$_2$C**H**$_2$N), 3.17 d.d.d (0.6H, ^3J = 11.5, 5.7, 1.2 Hz) and 3.26 d.d.d (0.4H, ^3J = 11.5, 5.7, 1.2 Hz) (2-H), 3.57–3.74 m and 3.80–3.87 m (1H each, 6-H); 4.23 s (0.8H), 4.29 d (0.6H, ^2J = 14.5 Hz), and 4.37 d (0.6H, ^2J = 14.5 Hz) (PhC**H**$_2$); 6.93–7.26 m (9H, H$_{arom}$). Found, %: C 79.64; H 9.03; N 3.38. $C_{27}H_{37}NO_2$. Calculated, %: C 79.56; H 9.15; N 3.44.

***N*-{2-[2-Isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}-*N*-(4-methoxybenzyl)acetamide (XIV).** Yield 67% (a mixture of four diastereoisomers), bp 240–244°C (1 mm). IR spectrum, ν, cm^{-1}: 3280 (NH), 1650 (amide I). 1520 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.93 m [6H, (C**H**$_3$)$_2$CH, J = 6.9 Hz], 1.28–1.38 m (1H, 3-H), 1.52–1.99 m [6H, 5-H, (CH$_3$)$_2$C**H**, C**H**$_2$CH$_2$N], 1.72 s (1.8H) and 1.97 s (1.2H) (CH$_3$CO), 2.32 s (1.2H) and 2.35 s (1.8H, C$_6$H$_4$C**H**$_3$), 2.59–2.87 m (2H, CH$_2$C**H**$_2$N), 3.18 d.d.d (0.6H, ^3J = 11.8, 5.8, 1.0 Hz) and 3.25 d.d.d (0.4H, ^3J = 11.8, 5.8, 1.0 Hz) (2-H), 3.58–3.73 m and 3.79–3.88 m (1H each, 6-H), 3.75 s (1.8H) and 3.75 s (1.2H) (CH$_3$O); 4.13 d (0.4H, ^2J = 11.7 Hz), 4.16 d (0.4H, ^2J = 11.7 Hz), 4.19 d (0.6H, ^2J = 14.2 Hz), and 4.28 d (0.6H, ^2J = 14.2 Hz) (C$_6$H$_4$C**H**$_2$); 6.68–6.75 m (2H), 6.82–6.89 m (2H), and 7.04–7.14 m (4H) (H$_{arom}$). Found, %: C 76.67; H 8.71; N 3.23. $C_{27}H_{37}NO_3$. Calculated, %: C 76.56; H 8.80; N 3.31.

***N*-{2-[2-Isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}-*N*-(4-methoxybenzyl)propionamide (XV).** Yield 65% (a mixture of two diastereoisomers), bp 243–245°C (0.5 mm). IR spectrum, ν, cm^{-1}: 3275 (NH), 1650 (amide I), 1510 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.93 m [6H, (C**H**$_3$)$_2$CH, J = 6.9 Hz], 0.95 t (1.8H, ^3J = 7.3 Hz) and 1.03 t (1.2H, ^3J = 7.3 Hz) (C**H**$_3$CH$_2$CO), 1.28–1.38 m (1H, 3-H), 1.52–1.97 m [6H, 5-H, (CH$_3$)$_2$C**H**, C**H**$_2$CH$_2$N], 1.91 q (1.2H, ^3J = 7.3 Hz) and 2.24 q (0.8H, ^3J = 7.3 Hz) (CH$_3$C**H**$_2$CO), 2.32 s (1.2H) and 2.35 s (1.8H) (C$_6$H$_4$C**H**$_3$), 2.61–2.87 m (2H, CH$_2$C**H**$_2$N), 3.17 d.d.d (0.6H, ^3J = 11.5, 5.8, 1.2 Hz) and 3.26 d.d.d (0.4H, ^3J = 11.5, 5.8, 1.2 Hz) (2-H), 3.58–3.73 m and 3.78–3.88 m (1H each, 6-H), 3.75 s (3H, CH$_3$O); 4.15 s (0.8H), 4.19 d (0.6H, ^2J = 14.3 Hz), and 4.29 d (0.6H, ^2J = 14.3 Hz) (C$_6$H$_4$C**H**$_2$); 6.67–6.75 m (2H), 6.80–6.88 m (2H), 7.03–7.10 m (1.6H), and 7.11 s (2.4H) (H$_{arom}$). Found, %: C 77.57; H 8.00; N 3.22. $C_{28}H_{39}NO_3$. Calculated, %: C 77.64; H 7.92; N 3.11.

***N*-(4-Isopropoxybenzyl)-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}acetamide (XVI).** Yield 68% (a mixture of two diastereoisomers), bp 242–246°C (0.5 mm). IR spectrum, ν, cm^{-1}: 3280 (NH), 1640 (amide I), 1520 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.93 m [6H, (C**H**$_3$)$_2$CH, J = 6.9 Hz], 1.26–1.39 m (1H, 3-H), 1.30 d [6H, (C**H**$_3$)$_2$CHO, J = 6.1 Hz], 1.50–1.97 m [6H, 5-H, (CH$_3$)$_2$C**H**, C**H**$_2$CH$_2$N], 1.72 s (2H) and 2.00 s (1H) (CH$_3$CO); 2.31 s, 2.32 s, and 2.35 s (3H, C$_6$H$_4$C**H**$_3$); 2.65–2.89 m (2H, CH$_2$C**H**$_2$N), 3.18 (1.3H) and 3.25 d.d.d (0.7H, ^3J = 11.5, 5.9, 1.3 Hz) (2-H), 3.62 t.d

(0.6H) and 3.67 t.d (0.4H, ^2J = 12.0, ^3J = 2.1 Hz) (6-H), 3.79–3.87 m (1H, 6-H); 4.12 d and 4.15 d (0.4H each, ^2J = 12.8 Hz), 4.18 d and 4.28 d (0.6H each, ^2J = 14.3 Hz) ($C_6H_4C\mathbf{H}_2$); 4.50 m (1H, OCH); 6.64–6.73 m (2H), 6.80–6.87 m (2H), and 7.04–7.15 m (4H) (H_{arom}). Found, %: C 77.00; H 9.21; N 3.02. $C_{29}H_{41}NO_3$. Calculated, %: C 77.12; H 9.15; N 3.10.

***N*-(4-Isopropoxybenzyl)-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}propionamide (XVII).** Yield 63%, bp 247–249°C (0.5 mm). IR spectrum, ν, cm^{-1}: 3270 (NH), 1655 (amide I), 1515 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.93 m [6H, $(C\mathbf{H}_3)_2CH$, J = 6.8 Hz], 0.95 t (2H) and 1.03 t (1H) ($C\mathbf{H}_3CH_2CO$, ^3J = 7.3 Hz), 1.26–1.38 m (1H, 3-H), 1.30 d [6H, $(C\mathbf{H}_3)_2CHO$, J = 6.0 Hz], 1.50–1.97 m [6H, 5-H, $(CH_3)_2C\mathbf{H}$, $C\mathbf{H}_2CH_2N$], 1.91 q (1.3H) and 2.24 q (0.7H) ($CH_3C\mathbf{H}_2CO$, ^3J = 7.3 Hz); 2.30 s, 2.32 s, and 2.35 s (3H) ($C_6H_4C\mathbf{H}_3$); 2.64–2.89 m (2H, $CH_2C\mathbf{H}_2N$), 3.17 d.d.d (0.6H) and 3.25 d.d.d (0.4H, ^3J = 11.4, 5.9, 1.2 Hz) (2-H), 3.57–3.73 m and 3.79–3.88 m (1H each, 6-H); 4.14 s (0.6H), 4.18 d (0.6H, ^2J = 14.2 Hz), and 4.29 d (0.6H, ^2J = 14.2 Hz) ($C_6H_4C\mathbf{H}_2$); 4.49 m (1H, OCH); 6.63–6.72 m (2H), 6.78–6.86 m (2H), and 7.04–7.14 m (4H) (H_{arom}). Found, %: C 77.47; H 9.23; N 3.08. $C_{30}H_{43}NO_3$. Calculated, %: C 77.38; H 9.31; N 3.01.

***N*-(2-Fluorobenzyl)-*N*-{2-[2-isopropyl-4-(4-tolyl)-tetrahydropyran-4-yl]ethyl}acetamide (XVIII).** Yield 66%, bp 220–223°C (1.5 mm). IR spectrum, ν, cm^{-1}: 3380 (NH), 1660 (amide I), 1520 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.93 m [6H, $(C\mathbf{H}_3)_2CH$, J = 6.9 Hz], 1.26–1.39 m (1H, 3-H), 1.52–2.04 m [6H, 5-H, $(CH_3)_2C\mathbf{H}$, $C\mathbf{H}_2CH_2N$], 1.68 s (1.8H) and 1.98 s (1.2H) (CH_3CO), 2.31 s (3H, $C_6H_4C\mathbf{H}_3$), 2.68–2.89 m (2H, $CH_2C\mathbf{H}_2N$), 3.20 d.d.d (0.6H) and 3.26 d.d.d (0.4H, ^3J = 11.7, 5.8, 1.4 Hz) (2-H), 3.63 t.d (0.6H) and 3.68 t.d (0.4H, ^2J = 12.0, ^3J = 2.1 Hz) (6-H), 3.80–3.88 m (1H, 6-H), 4.28 s (0.8H) and 4.44 s (1.2H) ($C_6H_4C\mathbf{H}_2$), 6.82–7.29 m (8H, H_{arom}). Found, %: C 75.91; H 8.41; N 3.32. $C_{26}H_{34}FNO_2$. Calculated, %: C 75.88; H 8.33; N 3.40.

***N*-(2-Fluorobenzyl)-*N*-{2-[2-isopropyl-4-(4-tolyl)-tetrahydropyran-4-yl]ethyl}propionamide (XIX).** Yield 64%, bp 223–226°C (1.5 mm). IR spectrum, ν, cm^{-1}: 3280 (NH), 1640 (amide I), 1510 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.90–0.94 m [6H, $(C\mathbf{H}_3)_2CH$, J = 6.7 Hz], 0.93 t (1.8H) and 1.03 t (1.2H) ($C\mathbf{H}_3CH_2CO$, ^3J = 7.3 Hz), 1.27–1.40 m (1H, 3-H), 1.53–1.74 m [2H, $C\mathbf{H}(CH_3)_2$, 3-H], 1.78–2.03 m (4H, 5-H, $C\mathbf{H}_2CH_2N$), 1.86 q (1.2H) and 2.24 q (0.8H) ($CH_3C\mathbf{H}_2CO$, ^3J = 7.3 Hz), 2.31 s (1.2H) and 2.32 s (1.8H ($C_6H_4C\mathbf{H}_3$), 2.69–2.92 m (2H, $CH_2C\mathbf{H}_2N$), 3.20 d.d.d (0.6H) and 3.27 d.d.d (0.4H, ^3J = 11.4, ^3J = 5.8, ^3J = 1.2 Hz) (2-H), 3.64 t.d (0.6H) and 3.69 t.d (0.4H, ^2J = 11.9, ^3J = 2.1 Hz) (6-H), 3.80–3.88 m (1H, 6-H), 4.29 s (0.8H) and 4.46 s (1.2H ($C_6H_4C\mathbf{H}_2$), 6.82–7.28 m (8H, H_{arom}). Found, %: C 76.11; H 8.60; N 3.36. $C_{27}H_{36}FNO_2$. Calculated, %: C 76.20; H 8.53; N 3.29.

***N*-(Furan-2-ylmethyl)-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}acetamide (XX).** Yield 70% (a mixture of two diastereoisomers), bp 210–213°C (1 mm). IR spectrum, ν, cm^{-1}: 3300 (NH), 1635 (amide I), 1520 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.91 d (3.2H) and 0.92 d (2.8H) [$(C\mathbf{H}_3)_2CH$, ^3J = 6.7 Hz], 1.28–1.39 m (1H, 3-H), 1.54–1.74 m [2H, $C\mathbf{H}(CH_3)_2$, 3-H], 1.64 s (1.6H) and 2.04 s (1.4H) (CH_3CO), 1.78–1.95 m (4H, 5-H, $C\mathbf{H}_2CH_2N$), 2.33 s (3H, $C_6H_4C\mathbf{H}_3$), 2.73–2.86 m (2H, $CH_2C\mathbf{H}_2N$), 3.24 m (1H, 2-H), 3.67 m and 3.84 m (1H each, 6-H); 4.15 s (~1H), 4.34 d (0.5H), and 4.36 d (0.5H, ^2J = 15.2 Hz) ($C_4H_3OC\mathbf{H}_2$); 5.91 d and 6.04 d (0.5H each, 3′-H, ^3J = 3.3 Hz), 6.25 m (1H, 4′-H), 7.06–7.15 m (4H, H_{arom}), 7.33 d and 7.36 d (0.5H each, 5′-H, ^3J = 1.7 Hz). Found, %: C 75.10; H 8.58; N 3.58. $C_{24}H_{33}NO_3$. Calculated, %: C 75.16; H 8.67; N 3.65.

***N*-(Furan-2-ylmethyl)-*N*-{2-[2-isopropyl-4-(4-tolyl)tetrahydropyran-4-yl]ethyl}propionamide (XXI).** Yield 78%, bp 220–222°C (1 mm). IR spectrum, ν, cm^{-1}: 3380 (NH), 1650 (amide I), 1520 (amide II). ^{1}H NMR spectrum, δ, ppm: 0.89–0.94 m [$(C\mathbf{H}_3)_2CH$, ^3J = 6.8 Hz], 0.95 t (2H) and 1.03 t (1H) ($C\mathbf{H}_3CH_2CO$, ^3J = 7.3 Hz), 1.26–1.38 m (1H, 3-H), 1.31 d (6H, CH_3, ^3J = 6.1 Hz), 1.50–1.97 m [6H, $C\mathbf{H}(CH_3)_2$, 5-H, $C\mathbf{H}_2CH_2N$], 1.91 q (1.3H) and 2.24 q (0.7H) ($CH_3C\mathbf{H}_2CO$, ^3J = 7.3 Hz); 2.30 s, 2.32 s, and 2.35 s (3H, $C_6H_4C\mathbf{H}_3$), 2.64–2.89 m (2H, $CH_2C\mathbf{H}_2N$), 3.17 d.d.d (0.6H) and 3.25 d.d.d (0.4H, ^3J = 11.4, 5.9, 1.2 Hz) (2-H), 5.91 d and 6.04 d (0.5H each, 3-H, ^3J = 3.3 Hz), 6.25 m (1H, 4′-H), 7.06–7.15 m (4H, H_{arom}), 7.33 d and 7.36 d (0.5H each, 5′-H, ^3J = 1.7 Hz). Found, %: C 75.42; H 8.79; N 3.63. $C_{25}H_{35}NO_3$. Calculated, %: C 75.53; H 8.87; N 3.52.

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