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# Synthesis of Water-Soluble Lithium, Sodium, Potassium, and Cesium Salts of (*E*)-2-[4-Methoxy(3,4-dimethoxy)-benzylideneamino]-2-alkyl(aralkyl)acetic Acids

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**Abstract**—A convenient method of preparative synthesis of water-soluble lithium, sodium, potassium, and cesium salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl(aralkyl)acetic acids via reaction of anisic or veratric aldehyde with natural amino acids (glycine, L-valine, L-leucine, L-isoleucine or L-tryptophan) in the presence of lithium hydride or carbonates of sodium, potassium, or cesium in boiling methanol was developed.

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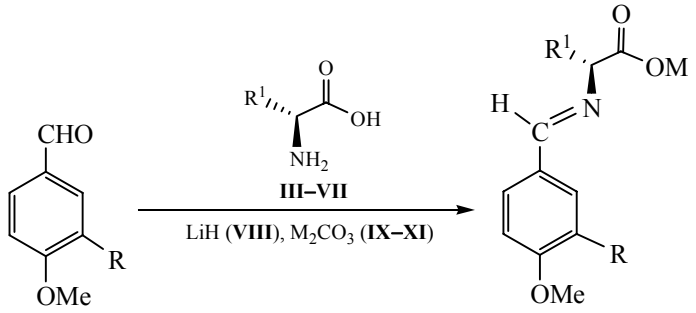
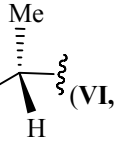
Derivatives of natural amino acids possess high biological activity [1–3], which encourages the research on the elaboration of convenient methods for their preparation [4, 5]. The synthesis of water-soluble derivatives is of great interest due to prospects of their use for bio-testing and creating of drugs [6, 7].

This work presents a convenient preparative method for the synthesis of stable water-soluble lithium, sodium, potassium, and cesium salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl-(aralkyl)acetic acids by reacting equimolar amounts of anisic **I** or veratric **II** aldehydes with natural amino

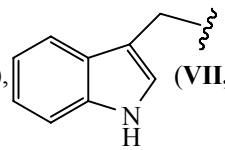



**I, II** **XII–LI**

R = H (**I, XII–XXXI**), OMe (**II, XXXII–LI**); M = Li (**XXII, XVI, XX, XXIV, XXVIII, XXXII, XXXVI, XL, XLIV**, **XLVIII**), Na (**IX, XIII, XVII, XXI, XXV, XXIX, XXIII, XXVII, XLI, XLV, XLIX**), K (**X, XIV, XVIII, XXII, XXVI, XXX, XXXIV, XXXVIII, XLII, XLVI, L**), Cs (**XI, XV, XIX, XXIII, XXVII, XXXI, XXXV, XXXIX, XLIII, XLVII, LI**); $R^1$ = H (**III, XII–XV, XXXII–XXXV**), $Me_2CH$ (**IV, XVI–XIX, XXXVI–XXXIX**), $Me_2CHCH_2$ (**V, XX–XXIII, XL–XLIII**),




(**VI, XXIV–XXVII, XLIV–XLVII**),




(**VII, XXVIII–XXXI, XLVIII–LI**).

acids like glycine **III**, L-valine **IV**, L-leucine **V**, L-isoleucine **VI**, or L-tryptophan **VII** in the presence of lithium hydride **VIII** or carbonates of sodium **IX**, potassium **X**, or cesium **XI** in boiling anhydrous methanol. After removal of methanol in vacuo, lithium, sodium, potassium, and cesium salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl-(aralkyl)acetic acids **XII–LI** were obtained in quantitative yields with a purity of 99%. These results can be obtained when the purity of initial components **I–XI** is sufficient and the weighing of the reagents is precise.

Synthesized salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl(aralkyl)acetic acids **XII–LI** are colorless crystalline substances, which are very well soluble in methanol, ethanol, DMSO, and water. Potassium and cesium salts are also soluble in diethyl ether, benzene, and chloroform. Furthermore, cesium salts are more soluble than potassium. Unlike lithium and sodium salts, potassium and cesium salts are hygroscopic, they can easily be obtained in dry form removing water by azeotropic distillation with benzene.

The composition and structure of the obtained salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl(aralkyl)acetic acids were confirmed by elemental analysis data, IR and $^1$H NMR spectroscopy. The melting points and elemental analysis data for the salts **XII–LI** are given in the table. According to $^1$H NMR spectroscopy, the purity of salts **XII–LI** is of 99.5±0.4%. Similar to related (*E*)-azomethines, vanillin derivatives [4, 5], compounds **XII–LI** also possess the *E*-configuration, which is confirmed by the $^1$H NMR data [6]. Salts **XVI–XXXI, XXXVI–LI** derived from L-valine **IV**, L-leucine **V**, L-isoleucine **VI**, and L-tryptophan **VII** are chiral compounds and do not suffer racemization during their preparation [4, 5].

The IR spectra of the salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl(aralkyl)acetic

Melting points and elemental analysis data of salts **XII–LI**

| Comp. no. | mp, °C | Found, % | | | | Formula | Calculated, % | | | | *M* calculated |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | M | N | | C | H | M | N | |
| **XII** | 130–131 | 60.07 | 4.90 | 3.12 | 6.58 | $C_{10}H_{10}LiNO_3$ | 60.32 | 5.06 | 3.49 | 7.03 | 199.13 |
| **XIII** | 215–216 | 56.12 | 4.35 | 10.25 | 6.32 | $C_{10}H_{10}NaNO_3$ | 55.82 | 4.68 | 10.68 | 6.51 | 215.18 |
| **XIV** | 198–199 | 52.09 | 4.22 | 16.71 | 5.84 | $C_{10}H_{10}KNO_3$ | 51.93 | 4.36 | 16.90 | 6.06 | 231.29 |
| **XV** | 132–133 | 37.12 | 2.99 | 40.36 | 4.05 | $C_{10}H_{10}CsNO_3$ | 36.95 | 3.10 | 40.88 | 4.31 | 325.97 |
| **XVI** | 277–278 | 64.51 | 6.62 | 3.03 | 5.57 | $C_{13}H_{16}LiNO_3$ | 64.73 | 6.69 | 2.88 | 5.81 | 241.13 |
| **XVII** | 192–193 | 60.53 | 6.04 | 8.72 | 5.18 | $C_{13}H_{16}NaNO_3$ | 60.69 | 6.27 | 8.94 | 5.44 | 257.26 |
| **XVIII** | 238–239 | 57.36 | 6.10 | 14.01 | 4.84 | $C_{13}H_{13}KNO_3$ | 57.12 | 5.90 | 14.30 | 5.12 | 273.37 |
| **XIX** | 208–209 | 42.88 | 4.16 | 35.82 | 3.56 | $C_{13}H_{16}CsNO_3$ | 42.52 | 4.39 | 36.20 | 3.81 | 367.02 |
| **XX** | 269–270 | 65.72 | 7.30 | 3.03 | 5.10 | $C_{14}H_{18}LiNO_3$ | 65.88 | 7.11 | 2.72 | 5.49 | 255.24 |
| **XXI** | 194–195 | 62.19 | 6.45 | 8.13 | 4.88 | $C_{14}H_{18}NaNO_3$ | 61.98 | 6.69 | 8.47 | 5.16 | 271.29 |
| **XXII** | 196–197 | 58.31 | 6.14 | 13.25 | 4.50 | $C_{14}H_{18}KNO_3$ | 58.51 | 6.31 | 13.60 | 4.87 | 287.40 |
| **XXIII** | 173–174 | 44.52 | 4.90 | 34.40 | 3.25 | $C_{14}H_{18}CsNO_3$ | 44.11 | 4.76 | 34.86 | 3.67 | 381.20 |
| **XXIV** | 212–213 | 65.52 | 7.21 | 2.45 | 5.19 | $C_{14}H_{18}LiNO_3$ | 65.88 | 7.11 | 2.72 | 5.49 | 255.24 |
| **XXV** | 155–156 | 62.07 | 6.83 | 8.61 | 4.96 | $C_{14}H_{18}NaNO_3$ | 61.98 | 6.69 | 8.47 | 5.16 | 271.29 |
| **XXVI** | 256–257 | 58.35 | 6.39 | 13.60 | 4.98 | $C_{14}H_{18}KNO_3$ | 58.51 | 6.31 | 13.60 | 4.87 | 287.40 |
| **XXVII** | 195–196 | 43.92 | 4.82 | 34.66 | 3.56 | $C_{14}H_{18}CsNO_3$ | 44.11 | 4.76 | 34.86 | 3.67 | 381.20 |
| **XXVIII** | 166–167 | 69.78 | 5.37 | 1.90 | 8.22 | $C_{19}H_{17}LiN_2O_3$ | 69.51 | 5.22 | 2.11 | 8.53 | 328.29 |

**Table** (Contd.)

| Comp. no. | mp, °C | Found, % | | | | Formula | Calculated, % | | | | *M* calculated |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | M | N | | C | H | M | N | |
| **XXIX** | 142–143 | 66.56 | 5.18 | 6.30 | 7.78 | $C_{19}H_{17}NaN_2O_3$ | 66.27 | 4.98 | 6.68 | 8.14 | 344.34 |
| **XXX** | 115–116 | 63.70 | 4.32 | 11.00 | 7.19 | $C_{19}H_{17}KN_2O_3$ | 63.31 | 4.75 | 10.85 | 7.77 | 360.45 |
| **XXXI** | 67–68 | 50.08 | 3.91 | 28.98 | 6.29 | $C_{19}H_{17}CsN_2O_3$ | 50.24 | 3.77 | 29.26 | 6.17 | 454.26 |
| **XXXII** | 137–138 | 57.23 | 5.45 | 2.84 | 5.95 | $C_{11}H_{12}LiNO_4$ | 57.65 | 5.28 | 3.03 | 6.11 | 229.16 |
| **XXXIII** | 56–57 | 53.45 | 5.08 | 9.24 | 5.34 | $C_{11}H_{12}NaNO_4$ | 53.88 | 4.93 | 9.38 | 5.71 | 245.21 |
| **XXXIV** | 110–111 | 50.02 | 4.75 | 15.08 | 4.90 | $C_{11}H_{12}KNO_4$ | 50.56 | 4.63 | 14.96 | 5.36 | 261.32 |
| **XXXV** | 124–125 | 37.50 | 3.44 | 37.09 | 3.57 | $C_{11}H_{12}CsNO_4$ | 37.20 | 3.41 | 37.43 | 3.94 | 355.12 |
| **XXXVI** | 248–249 | 62.26 | 6.35 | 2.19 | 4.78 | $C_{14}H_{18}LiNO_4$ | 61.99 | 6.69 | 2.56 | 5.16 | 271.24 |
| **XXXVII** | 154–155 | 58.84 | 6.07 | 7.78 | 4.51 | $C_{14}H_{18}NaNO_4$ | 58.53 | 6.32 | 8.00 | 4.88 | 287.29 |
| **XXXVIII** | 148–149 | 55.12 | 6.04 | 12.65 | 4.20 | $C_{14}H_{18}KNO_4$ | 55.42 | 5.98 | 12.89 | 4.62 | 303.40 |
| **XXXIX** | 39–40 | 42.50 | 4.32 | 33.35 | 3.08 | $C_{14}H_{18}CsNO_4$ | 42.33 | 4.57 | 33.46 | 3.53 | 397.20 |
| **XL** | 243–244 | 62.88 | 7.20 | 2.08 | 4.99 | $C_{15}H_{20}LiNO_4$ | 63.16 | 7.07 | 2.43 | 4.91 | 285.26 |
| **XLI** | 138–139 | 60.02 | 6.46 | 7.34 | 4.66 | $C_{15}H_{20}NaNO_4$ | 59.79 | 6.69 | 7.63 | 4.65 | 301.31 |
| **XLII** | 62–63 | 57.00 | 6.21 | 12.11 | 4.52 | $C_{15}H_{20}KNO_4$ | 56.76 | 6.35 | 12.32 | 4.41 | 317.42 |
| **XLIII** | 52–53 | 44.12 | 5.12 | 32.05 | 3.07 | $C_{15}H_{20}CsNO_4$ | 43.81 | 4.90 | 32.32 | 3.41 | 411.23 |
| **XLIV** | 257–258 | 63.63 | 7.24 | 2.03 | 4.57 | $C_{15}H_{20}LiNO_4$ | 63.16 | 7.07 | 2.43 | 4.91 | 285.26 |
| **LV** | 222–223 | 59.50 | 6.96 | 7.25 | 4.60 | $C_{15}H_{20}NaNO_4$ | 59.79 | 6.69 | 7.63 | 4.65 | 301.31 |
| **XLVI** | 76–77 | 56.51 | 6.44 | 12.48 | 4.10 | $C_{15}H_{20}KNO_4$ | 56.76 | 6.35 | 12.32 | 4.41 | 317.42 |
| **XLVII** | 47–48 | 44.05 | 4.69 | 31.98 | 3.15 | $C_{15}H_{20}CsNO_4$ | 43.81 | 4.90 | 32.32 | 3.41 | 411.23 |
| **XLVIII** | 171–172 | 67.43 | 5.52 | 2.07 | 7.53 | $C_{20}H_{19}LiN_2O_4$ | 67.04 | 5.34 | 1.94 | 7.82 | 358.32 |
| **XLIX** | 143–144 | 64.32 | 5.28 | 5.87 | 7.16 | $C_{20}H_{19}NaN_2O_4$ | 64.17 | 5.12 | 6.14 | 7.48 | 374.37 |
| **L** | 128–129 | 61.88 | 5.06 | 9.67 | 6.78 | $C_{20}H_{19}KN_2O_4$ | 61.52 | 4.90 | 10.01 | 7.17 | 390.47 |
| **LI** | 103–104 | 49.47 | 4.04 | 27.10 | 5.43 | $C_{20}H_{19}CsN_2O_4$ | 49.60 | 3.95 | 27.44 | 5.78 | 484.28 |

acids **XII–LI** contain the following characteristic absorption bands (ν, $cm^{-1}$): 3100–3005, 860–640 ($CH_{arom}$), 2980–2830 ($CH_{aliphatic}$), 1610–1580, 1415–1405 ($CO_2^-$), 1648–1634 (C=N), 1605–1595, 1515–1505 ($C{=}C_{arom}$), 1260–1240, 1175–1160, 1030–1015 (C–O), and there are no absorption bands at 1700–1680 $cm^{-1}$ ($C{=}O_{aldehyde}$), which are typical of initial benzaldehydes **I, II**.

$^1$H NMR spectra of the salts of (*E*)-2-[4-methoxy-(3,4-dimethoxy)benzylideneamino]-2-alkyl(aralkyl)-acetic acids **XII–LI** contain singlet signals of MeO and HC=N groups in the ranges of 3.79–3.90 and 8.05–8.20 ppm, respectively, indicating the (*E*)-configuration of the obtained compounds [8].

The IR and $^1$H NMR spectra of salts **XII–LI** contain also the absorption bands and proton signals confirming the presence of appropriate structural fragments of amino acids **III–VII**.

The compounds obtained showed a high fungicidal activity against fungal strains *Alternnaria alternata,*

*Aspergillus niger, Botritis cinerea, Fusarium oxysporum, Monilia sp., Mucor sp., Penicillum lividum* and moderate activity at $c \sim 200$ μg $mL^{-1}$ against strains of *Escherichia coli B, Pseudomonas aeruginosa PA01, Pseudomonas putida M, Serratia marcescens, Pantoea herbicola EH103, Salmonella typhimurium TA100, Staphylococcus aureus, Bacillus subtilis 494, Sarcina lutea, Mycobacterium smegmatis* [9, 10]. These compounds may be of interest for developing drugs to treat fungal infections of domestic and farm animals [11].

## EXPERIMENTAL

IR spectra were recorded on a Nicolet Protege-460 FTIR spectrophotometer from KBr pellets. $^1$H NMR spectra were registered on a Tesla BS-587A (100 MHz) spectrometer in $CDCl_3$ or DMSO-$d_6$, internal refeence TMS.

Anisic and veratric aldehydes, glycine, L-valine, L-leucine, L-isoleucine, L-tryptophan, lithium hydride, carbonates of sodium, potassium and cesium used were of the content of the main substance ~ 99.5±3%. Methanol was distilled twice through a Vigreux column before use.

**Salts of (*E*)-2-[4-methoxy(3,4-dimethoxy)benzylideneamino]-2-alkyl(aralkyl)acetic acids (XII–LI).** A mixture of 0.01 mol of aldehyde **I** or **II**, 0.01 mol of amino acid **III–VII**, 0.01 mol of lithium hydride **VIII** or 0.005 mol of an alkali metal carbonate **IX–XI** in 50 mL of anhydrous methanol was refluxed for 3–4 h until complete dissolution of the reagents. The solvent was removed in vacuo. Yields of the salts **XII–LI** were ~ 100%.

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