# Synthesis of some 2-(*N*-Protected or Free Aminoacyl or *N*-Tosyltripeptide)-aminophenazines, aminonaphthophenazines and 4-(*N*-Protected or Free Aminoacyl or *N*-Tosyltripeptide)aminophenazone Derivatives



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The syntheses of different 2-(*N*-tosyl- or *N*-phthalyl- or free aminoacyl or *N*-tosyltripeptide)-aminophenazines, and the corresponding derivatives of 2-aminonaphthophenazines and some derivatives of 4-aminophenazones (IV-XXXIII) are described. Compounds XI-XIII, XX-XXIII, XXX-XXXII, XXXIV-XXXIX and XL-XLV were found to be active against a number of microorganisms.

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In previous communications (1-10) we reported the synthesis of some coumarins, furocoumarins, chromones, aminopyridines, aminothiazoles, thiophene and furan, as well as other heterocyclic compounds incorporating amino acid and peptide moieties. Some of these compounds were found to display antimicrobial properties (1-10). The importance of 2-aminophenazine, 2-aminonaphthophenazine and 4-aminophenazone (4-aminoantipyrine) from the point of view of pharmaceutical chemistry attracted the authors to synthesize several amino acid and peptide derivatives (IV-XLV) which may enhance the activity of these compounds or verify their biological action.

For the preparation of 2-(*N*-phthalyl- or *N*-tosylaminoacyl)aminophenazine or -aminonaphthophenazine or the corresponding 4-aminophenazone derivatives (IV-XXXIII), the appropriate *N*-phthalyl- or *N*-tosylamino acid was reacted with 2-aminophenazine, 2-aminonaphthophenazine or 4-aminophenazone (I-III) in a dioxan-DMF-triethylamine medium using the dicyclohexylcarbodiimide (DCC) procedure.

Hydrazinolysis of 2-(*N*-phthalyl-L-Val)aminophenazine (VI) with 0.5*M* hydrazine hydrate in ethanol under mild reflux afforded 2-(*N*-L-Val)aminophenazine (XXXIV). Chromatographic and electrophoretic studies on XXXIV revealed its homogeneity (positive ninhydrin reaction, E = 10 cm, E start = zero), and its structure was convincingly supported by the ir and uv spectral data. This structure was further confirmed by its complete acid hydrolysis (6*N* hydrochloric acid, 24 hours) affording valine. Similarly, compounds XXXV-XXXIX were obtained.

Synthesis of the tripeptide derivatives (XL-XLV) was achieved starting from the hydrazide tosyl-L-Ala-Gly-hydrazide, which was converted into the corresponding azide. The azide on coupling with the free amino-compounds (XXXIV-XXXIX) furnished the tripeptides (XL-XLV), which were isolated and purified in the usual manner (11,12). The tripeptides (XL-XLV) gave deep violet complexes with copper(II), $\lambda$ max 570-580 nm.

Compounds IV-XLV were prepared and characterized for the first time. All of the compounds which were synthesized (IV-XLV) gave ir, uv and nmr spectra consistent with their assigned structures.

Biological Screening Results.

The antimicrobial activity of the compounds which were synthesized were tested using the hole plate and filter paper disc methods (13-16). The results were compared with the activity of the parent amino compounds (I-III). Some *N*-tosylaminoacyl derivatives such as 2-(*N*-tosylaminoacyl)aminophenazines (XI-XIII), 2-(*N*-tosylaminoacyl)aminonaphthophenazines (XX-XXIII) and 4-(*N*-tosylaminoacyl)aminophenazones (XXX-XXXII) were found to be active against *Bacillus subtilis*, *Bacillus cereus*, *Bacillus mycoids*, *Salmonella typhosa* and *Escherichia coli*, but inactive against *Penicillum chrysogenum*.

4-(*N*-tosyl-DL-Ser)aminophenazone (XXXIII) was found to be highly active only against *Penicillum chrysogenum*. All of the synthesized *N*-phthalylaminoacyl derivatives (IV-VIII, XIV-XVIII and XXIV-XXVIII) were found to be biologically inactive towards the tested microorganisms. On the other hand, hydrazinolysis of the phthalyl group gave the free amino compounds (XXXIV-XXXIX) of high biological activities. All of the unprotected amino compounds (XXXIV-XXXIX) were found to possess high antimicrobial activities against *Bacillus subtilis*, *Bacillus cereus*, *Bacillus mycoids*, *Salmonella typhosa*, *Escherichia coli* and *Penicillum chrysogenum*.

The *N*-tosyl- or *N*-phthalyl-glycine and $\beta$-alanine derivatives possess very low antimicrobial activity. All *N*-tosyl-tripeptide derivatives (XL-XLV) gave promising results against *Bacillus subtilis* and *Escherichia coli*.

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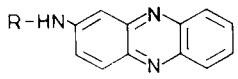
Table I

2-(*N*-Phthalyl-, *N*-Tosyl-, Free Aminoacyl or *N*-Tosyl-Tripeptide)aminophenazines, -Aminonaphthophenazines and 4-Aminophenazone Derivatives (IV-XLV) (a)

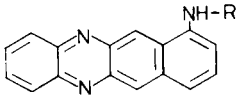
| Compound No. (Type) | R | Yield % | M.p., °C | $R_f$ | $[\alpha]_D^{20}$ DMF | Molecular Formula | Elemental Analysis, % Calculated C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IV (A) | Pht-Gly | 65 | 265-267 | 0.62 | – – | $C_{22}H_{14}N_4O_3$ | 69.10 | 3.66 | 14.65 | 69.30 | 3.69 | 14.59 |
| V (A) | Pht-β-Ala | 60 | 272-274 | 0.70 | – – | $C_{23}H_{16}N_4O_3$ | 69.69 | 4.04 | 14.14 | 70.10 | 4.10 | 14.59 |
| VI (A) | Pht-L-Val | 70 | 261-263 | 0.68 | -14 (c, 5.5) | $C_{25}H_{20}N_4O_3$ | 70.75 | 4.71 | 13.20 | 70.95 | 4.90 | 13.50 |
| VII (A) | Pht-L-Leu | 70 | 242-244 | 0.76 | -33 (c, 3.5) | $C_{26}H_{22}N_4O_3$ | 71.30 | 5.02 | 12.78 | 71.38 | 5.10 | 13.00 |
| VIII (A) | Pht-DL-Phe | 75 | 228-230 | 0.68 | – – | $C_{29}H_{20}N_4O_3$ | 73.72 | 4.23 | 11.86 | 73.76 | 4.30 | 11.69 |
| IX (A) | Tos-Gly | 78 | 278-280 | 0.80 | – – | $C_{21}H_{18}N_4O_3S$ | 62.06 | 4.43 | 13.79 | 62.16 | 4.42 | 13.80 |
| X (A) | Tos-L-Ala | 60 | 214-216 | 0.77 | -8.5 (c, 4) | $C_{22}H_{20}N_4O_3S$ | 62.85 | 4.76 | 13.33 | 62.87 | 4.80 | 13.53 |
| XI (A) | Tos-L-Val | 63 | 270-272 | 0.84 | -9.5 (c, 5) | $C_{24}H_{24}N_4O_3S$ | 64.28 | 5.35 | 12.50 | 64.38 | 5.40 | 12.70 |
| XII (A) | Tos-L-Leu | 72 | 236-238 | 0.88 | +6.5 (c, 4.3) | $C_{25}H_{26}N_4O_3S$ | 64.93 | 5.62 | 12.12 | 65.12 | 5.64 | 12.18 |
| XIII (A) | Tos-DL-Ser | 70 | 281-283 | 0.73 | – – | $C_{22}H_{20}N_4O_4S$ | 60.55 | 4.58 | 12.84 | 60.90 | 4.70 | 12.89 |
| XIV (B) | Pht-Gly | 75 | 235-237 | 0.77 | – – | $C_{26}H_{16}N_4O_3$ | 72.22 | 3.70 | 12.96 | 72.50 | 3.80 | 13.00 |
| XV (B) | Pht-β-Ala | 60 | 252-254 | 0.70 | – – | $C_{27}H_{18}N_4O_3$ | 72.64 | 4.03 | 12.55 | 72.85 | 4.20 | 12.70 |
| XVI (B) | Pht-L-Val | 62 | 240-242 | 0.69 | -11 (c, 4.7) | $C_{29}H_{22}N_4O_3$ | 73.41 | 4.64 | 11.80 | 73.46 | 4.70 | 12.00 |
| XVII (B) | Pht-L-Leu | 68 | 277-279 | 0.82 | -26.5 (c, 3) | $C_{30}H_{24}N_4O_3$ | 73.77 | 4.91 | 11.47 | 74.01 | 5.02 | 11.53 |
| XVIII (B) | Pht-DL-Phe | 55 | 259-261 | 0.84 | – – | $C_{33}H_{22}N_4O_3$ | 76.44 | 3.47 | 10.81 | 76.48 | 3.49 | 10.79 |
| XIX (B) | Tos-Gly | 60 | 233-235 | 0.58 | – – | $C_{25}H_{20}N_4O_3S$ | 65.78 | 4.38 | 12.28 | 65.97 | 4.41 | 12.30 |
| XX (B) | Tos-L-Ala | 65 | 241-243 | 0.75 | -6.5 (c, 3.5) | $C_{26}H_{22}N_4O_3S$ | 66.38 | 4.25 | 11.90 | 66.80 | 4.30 | 12.10 |
| XXI (B) | Tos-L-Val | 72 | 220-222 | 0.89 | -8.6 (c, 4.3) | $C_{28}H_{26}N_4O_3S$ | 67.46 | 5.22 | 11.24 | 67.50 | 5.23 | 11.50 |
| XXII (B) | Tos-L-Leu | 59 | 266-268 | 0.68 | +7.5 (c, 4.5) | $C_{29}H_{28}N_4O_3S$ | 67.96 | 5.46 | 10.90 | 68.13 | 5.50 | 11.20 |
| XXIII (B) | Tos-DL-Ser | 63 | 248-250 | 0.83 | – – | $C_{26}H_{22}N_4O_4S$ | 64.48 | 4.48 | 11.42 | 64.53 | 4.50 | 11.47 |
| XXIV (C) | Pht-Gly | 68 | 196-198 | 0.62 | – – | $C_{21}H_{18}N_4O_4$ | 64.61 | 4.61 | 14.35 | 64.70 | 4.73 | 14.48 |
| XXV (C) | Pht-β-Ala | 70 | 185-187 | 0.85 | – – | $C_{22}H_{20}N_4O_4$ | 65.34 | 4.95 | 13.86 | 65.60 | 5.01 | 13.87 |
| XXVI (C) | Pht-L-Val | 64 | 215-217 | 0.75 | -12.5 (c, 3.7) | $C_{24}H_{24}N_4O_4$ | 66.60 | 5.50 | 12.96 | 66.85 | 5.61 | 13.10 |
| XXVII (C) | Pht-L-Leu | 75 | 180-182 | 0.75 | -22 (c, 3) | $C_{25}H_{26}N_4O_4$ | 67.26 | 5.82 | 12.55 | 67.36 | 5.81 | 12.80 |
| XXVIII (C) | Pht-DL-Phe | 62 | 205-206 | 0.80 | – – | $C_{28}H_{24}N_4O_4$ | 70.02 | 5.01 | 11.66 | 70.12 | 5.10 | 11.83 |
| XXIX (C) | Tos-Gly | 70 | 175-177 | 0.58 | – – | $C_{20}H_{22}N_4O_4S$ | 57.97 | 5.31 | 13.50 | 58.17 | 5.53 | 13.52 |
| XXX (C) | Tos-L-Ala | 72 | 190-192 | 0.78 | -8.1 (c, 4) | $C_{21}H_{24}N_4O_4S$ | 58.80 | 5.60 | 13.08 | 58.98 | 5.71 | 13.09 |
| XXXI (C) | Tos-L-Val | 65 | 226-228 | 0.38 | -10.5 (c, 4.8) | $C_{23}H_{28}N_4O_4S$ | 60.50 | 6.14 | 12.28 | 60.61 | 6.19 | 12.30 |
| XXXII (C) | Tos-L-Leu | 64 | 205-207 | 0.77 | +5.2 (c, 4) | $C_{24}H_{30}N_4O_4S$ | 61.27 | 6.38 | 11.90 | 61.30 | 6.50 | 11.79 |
| XXXIII (C) | Tos-DL-Ser | 72 | 183-185 | 0.70 | – – | $C_{21}H_{24}N_4O_5S$ | 56.75 | 5.40 | 12.60 | 56.80 | 5.48 | 12.77 |
| XXXIV (A) | L-Val | 58 | 244-246 | 0.73 | -9 (c, 3.5) | $C_{17}H_{18}N_4O$ | 69.38 | 6.12 | 19.04 | 69.50 | 6.20 | 19.12 |
| XXXV (A) | L-Leu | 73 | 126-128 | 0.87 | -17 (c, 2.5) | $C_{18}H_{20}N_4O$ | 70.12 | 6.49 | 18.18 | 70.40 | 6.50 | 18.25 |
| XXXVI (B) | L-Val | 56 | 218-220 | 0.80 | -11 (c, 4) | $C_{21}H_{20}N_4O$ | 73.25 | 5.80 | 16.27 | 73.50 | 5.90 | 16.18 |
| XXXVII (B) | L-Leu | 71 | 235-237 | 0.89 | -15 (c, 2.1) | $C_{22}H_{22}N_4O$ | 73.74 | 6.14 | 15.60 | 73.80 | 6.20 | 15.80 |
| XXXVIII (C) | L-Val | 60 | 207-209 | 0.84 | -9.3 (c, 3.5) | $C_{16}H_{22}N_4O_2$ | 63.50 | 7.28 | 18.50 | 63.61 | 7.40 | 18.54 |
| XXXIX (C) | L-Leu | 65 | 145-147 | 0.86 | -19 (c, 3.1) | $C_{17}H_{24}N_4O_2$ | 64.50 | 7.59 | 17.70 | 64.80 | 7.71 | 17.69 |
| XL (A) | Tos-L-Ala-Gly-L-Val | 55 | 270-272 | 0.96 | -15.5 (c, 4) | $C_{29}H_{32}N_6O_5S$ | 61.37 | 5.64 | 14.81 | 61.41 | 5.70 | 14.90 |
| XLI (A) | Tos-L-Ala-Gly-L-Leu | 56 | 216-218 | 0.79 | -3.5 (c, 2.5) | $C_{30}H_{34}N_6O_5S$ | 61.96 | 5.84 | 14.45 | 62.20 | 5.90 | 14.52 |
| XLII (B) | Tos-L-Ala-Gly-L-Val | 50 | 260-262 | 0.75 | -13 (c, 3.7) | $C_{33}H_{34}N_6O_5S$ | 63.25 | 5.43 | 13.40 | 63.50 | 5.46 | 13.61 |
| XLIII (B) | Tos-L-Ala-Gly-L-Leu | 59 | 252-254 | 0.74 | -4.9 (c, 3.5) | $C_{34}H_{36}N_6O_5S$ | 63.75 | 5.62 | 13.12 | 63.80 | 5.70 | 13.32 |
| XLIV (C) | Tos-L-Ala-Gly-L-Val | 62 | 241-243 | 0.70 | -17.5 (c, 5) | $C_{28}H_{36}N_6O_6S$ | 57.53 | 6.16 | 14.38 | 57.60 | 6.20 | 14.42 |
| XLV (C) | Tos-L-Ala-Gly-L-Leu | 60 | 228-230 | 0.65 | -9.8 (c, 3) | $C_{29}H_{38}N_6O_6S$ | 58.19 | 6.35 | 14.04 | 58.22 | 6.41 | 14.06 |

(a) Electrophoretic mobility (E) for compounds XXXIV = 10 cm, XXXV = 12 cm, XXXVI = 11 cm, XXXVII = 13.5 cm, XXXVIII = 10.5 cm, XXXIX = 13 cm and for all the remaining compounds E = zero.

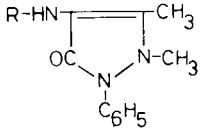
Other pharmacological activities of the compounds reported in this paper are in progress.



(Compounds Type A )



(Compounds Type B )



(Compounds Type C )

## EXPERIMENTAL

All melting points are uncorrected. All thin-layer chromatograms ($R_f$ value) were made on Silica Gel G using benzene-ethyl acetate (1:1) as the solvent system and an iodine-potassium iodide solution (20%) as the detection reagent. Benzidine, ninhydrin and silver nitrate reactions were used for detection of the amino acid derivatives on paper chromatograms (spot reactions) (11). The electrophoretic mobilities (E), were measured with 1000 V, 2 hours in pyridine-acetate buffer (*p*H 5.6). The uv spectra were measured in ethanol with a Unicam SP 8000, ir spectra were measured with a Unicam SP 1200 in potassium bromide and nmr data were determined on Varian T-60 A spectrometer in DMSO-$d_6$ and shifts are reported in ppm ($\delta$) relative to internal TMS. Optical activities $[\alpha]_D^{20}$ were taken in a Zeiss polarimeter 1 dm tube in DMF.

2-Aminophenazine (I), 2-Aminonaphthophenazine (II) and 4-Aminophenazone (III).

The title compounds were prepared according to the procedures described earlier (17-21).

General Procedure for the Synthesis of 2-(*N*-Tosyl- or *N*-Phthalylaminoacyl)aminophenazines (IV-XIII), 2-(*N*-Tosyl- or *N*-Phthalylaminoacyl)aminonaphthophenazines (XIV-XXIII) and 4-(*N*-Tosyl- or *N*-Phthalylaminoacyl)aminophenazones (XXIV-XXXIII).

*N*-Phthalyl- or *N*-tosylamino acid (0.002 mole) and 2-aminophenazine or 2-aminonaphthophenazine or 4-aminophenazone (I-III) (0.002 mole) were dissolved in a mixture of dioxane (35 ml.) and dimethylformamide (5 ml.). The mixture was cooled to 0° and dicyclohexylcarbodiimide (0.42 g.) was added. The mixture was then stirred for 3 hours at 0°, left for 24 hours at 0° and for another 24 hours at room temperature. The dicyclohexylurea was filtered off, and the filtrate was evaporated *in vacuo*. The residual solid was recrystallized from methanol, ethanol, water or their mixtures. The products (IV-XXXIII) were soluble in alcohols, DMF, dioxane and nitromethane, and insoluble in water, ether and petroleum ether. The materials were chromatographically homogeneous when developed with iodine or benzidine.

2-(*N*-Phthalyl-DL-Phe)aminophenazine (VIII).

This compound had ir: 1760 (>C=O), 3300, 3020 (NH and N), 1650, 1570, 1340 $cm^{-1}$ (amide I, II and III); uv: $\lambda$ max 312 nm (log $\epsilon$ 2.61), 315 (2.63); nmr: $\delta$ 3.20 (s, 1H, >CH-), 3.46 (s, 2H, $-CH_2-$), 7.80 (s, 1H, NH), 6.82, 7.30, 7.86 (aromatic protons).

2-(*N*-Tosyl-L-Leu)aminonaphthophenazine (XXII).

This compound had ir: 3300, 3080 (NH and N), 1670, 1560, 1340 (amide I, II and III), 1700, 1440, 1270, 1090 ($SO_2NH$), 2920, 2840 ($CH_3$), 1780 $cm^{-1}$ (>C=O); uv: $\lambda$ max 310 nm (log $\epsilon$ 2.60), 298 (2.59); nmr: $\delta$ 3.25 (s, 1H, >CH-), 3.46 (s, 2H, $-CH_2-$), 1.52 (s, gemdimethyl, 6H), 7.84 (s, 1H, Ar-NH), 7.86, 7.30, 6.82 (s, aromatic protons).

4-(*N*-Phthalyl-$\beta$-Ala)aminophenazone (XXV).

This compound had ir: 3310, 3240 (NH and N), 2920, 2840 ($CH_3$), 1760 (>C=O), 1660, 1570, 1360 $cm^{-1}$ (amide I, II and III); uv: $\lambda$ max 289 nm (log $\epsilon$ 2.81), 295 (2.85); nmr: $\delta$ 3.42 (s, 2H, $-CH_2-$), 7.85 (s, 1H, NH), 6.84, 7.39, 7.81 (s, aromatic protons).

General Procedure for the Synthesis of 2-(L-Val- or L-Leu-)aminophenazines (XXXIV-XXXV), 2-(L-Val- or L-Leu-)aminonaphthophenazines (XXXVI-XXXVII) and 4-(L-Val- or L-Leu-)aminophenazones (XXXVIII-XXXIX).

2-(*N*-Phthalylaminoacyl)aminophenazine or the corresponding aminonaphthophenazine or 4-(*N*-phthalylaminoacyl)aminophenazone derivatives (0.002 mole) was dissolved in ethanol (20 ml.) and treated with 0.5*M* hydrazine hydrate in ethanol (8 ml.). The reaction mixture was refluxed for 2 hours and left for 24 hours at room temperature. The residue obtained after evaporation of the solvent was treated with 2*N* hydrochloric acid (25 ml.) for 10 minutes at 40°. The reaction mixture was cooled and the insoluble phthalyl hydrazide was filtered. The filtrate was evaporated in vacuum and the residual hydrochloride was dissolved in ethyl acetate (30 ml.) and triethylamine (3 ml.) was added. The reaction mixture was stirred for 20 minutes at room temperature and then cooled to 0°. The precipitated triethylamine hydrochloride was filtered off. The filtrate was evaporated in vacuum and the residual material was recrystallized from methanol or ethanol. The products (XXXIV-XXXIX) gave a positive ninhydrin reaction.

2-(L-Val-)aminophenazine (XXXIV).

This compound had ir: 3440, 3360, 3300 ($NH_2$, NH and N); 2920, 2840 ($CH_3$), 1760 (>C=O), 1650, 1570, 1280 $cm^{-1}$ (amide I, II and III); uv: $\lambda$ max 312 nm (log $\epsilon$ 2.82), 315 (2.95); nmr: $\delta$ 3.22 (s, 1H, >CH-), 1.49 (s, gemdimethyl, 6H), 1.36 (s, C-$CH_3$, 3H), 7.96 (s, 2H, $NH_2$), 6.94, 7.35, 7.89 (s, aromatic protons).

General Procedure for the Synthesis of 2-(*N*-Tosyltripeptide)-aminophenazines (XL-XLI), 2-(*N*-Tosyltripeptide)aminonaphthophenazines (XLII-XLIII) and 4-(*N*-Tosyltripeptide)aminophenazones (XLIV-XLV).

Tosyl-L-Ala-Gly-hydrazide (0.314 g., 0.001 mole) was dissolved in a mixture of acetic acid (2 ml.), 5*N* hydrochloric acid (1 ml.) and water (15 ml.), and cooled to -5°. Sodium nitrite (0.27 g.) in water (3 ml.) was cooled and the mixture was stirred for 5 minutes at -5°. The azide was extracted with ethyl acetate (50 ml.) and the extract was washed successively with water, sodium bicarbonate (3%), and water, and dried (sodium sulfate). Compounds XL-XLV were prepared by the addition of a cold dry ethyl acetate solution of the azide to a cooled (-5°) solution of 2-(L-Val-)aminophenazine (XXXIV) (0.294 g., 0.001 mole) or any other amino derivative (XXXV-XXXIX, 0.001 mole) in ethyl acetate (25 ml.) and keeping the reaction mixture for 24 hours at

0° and for another 24 hours at room temperature. It was washed successively with hydrochloric acid (0.5*N*), water, sodium hydrogen carbonate (3%) and water, and dried (sodium sulfate). The solvent was removed and the residual material was recrystallized from ethanol, methanol, water or their mixtures. All tripeptides (XL-XLV) were found to be homogeneous (tlc gave a single spot with iodine solution) and showed negative ninhydrin and silver nitrate reactions. Complete acid hydrolysis of XL (6*N* hydrochloric acid, 24 hours) afforded glycine, alanine and valine.

2-(*N*-Tosyl-L-Ala-Gly-L-Leu)aminophenazine (XLI).

This compound had ir: 3450, 3050 (NH, $SO_2NH$, N), 2950, 2840 ($CH_3$), 1650, 1550, 1260 (amide I, II and III), 1780 $cm^{-1}$ (>C=O); uv: λ max 312 nm (log ε 2.86), 315 (2.98); nmr: δ 2.19 (s, 3H, *p*-$CH_3$-Ar), 3.22 (s, 1H, >CH–), 1.54 (s, gemdimethyl), 7.10-7.67, 7.80-7.84 (s, aromatic protons), 8.94 (s, 1H, NH).

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