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Epoxymethylation of 2-Acyl-Substituted NH Heterocycles and Transformations of the Epoxymethylation Products

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Abstract—A new procedure has been proposed for the synthesis of previously unknown pyrrolo- and indolo-1,4-epoxy[1,4]oxazepines by epoxymethylation of 2-benzoyl-1*H*-pyrrole and 2-benzoyl-1*H*-indoles with epichlorohydrin. Some transformations of the epoxymethylation products have been studied.

Keywords: epoxymethylation, 1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]benzimidazole, 7,8,9-trimethyl-1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxypyrrolo[2,1-*c*][1,4]oxazepine, phenyl[3,4,5-trimethyl-1-(oxiran-2-ylmethyl)-1*H*-pyrrol-2-yl]methanone, 11-methyl-1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]indole, 6-methyl-9-(oxiran-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, 9-[2-hydroxy-3-(piperidin-1-yl)propyl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one

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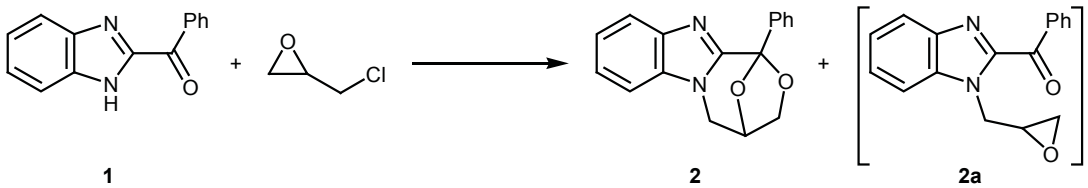
1-Phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]benzimidazole (**2**) is known as the drug oxapadol [1] exhibiting diuretic, sedative, antiulcer, analgesic, anti-inflammatory, cardiac, and analeptic properties. It was synthesized [1] in 50% yield by reaction of 2-benzoyl-1*H*-benzimidazole (**1**) sodium salt with an equimolar amount of epichlorohydrin [2-(chloromethyl)oxirane] in anhydrous ethanol (Scheme 1). It can be anticipated that epoxymethylation of 2-acyl-substituted NH-heterocycles such as pyrrole and indole will produce structurally related compounds of pharmacological interest.

The present work was aimed at improving the procedure for the synthesis of oxapadol (**2**) and utilize it in the preparation of epoxy-1,4-oxazepines fused to pyrrole and indole. Benzimidazole **1** was found to react with 10 equiv of epichlorohydrin in the presence of 2 equiv of potassium hydroxide and a catalytic amount of 18-crown-6 at 40°C (1 h) to give 63% of **2**. Epoxymethylation of 2-benzoyl-3,4,5-trimethyl-1*H*-pyrrole (**3**) according to the same procedure led to the formation of two products (Scheme 2), 7,8,9-trimethyl-1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxypyrrolo[2,1-*c*]-[1,4]oxazepine (**4**) and phenyl[3,4,5-trimethyl-1-(oxiran-2-ylmethyl)-1*H*-pyrrol-2-yl]methanone (**5**).

Compounds **4** and **5** had very similar ^{1}H NMR spectra with the difference that the aromatic proton signals of **4** resonated as two multiplets at δ 7.33–7.40 (3H) and 7.55–7.62 ppm (2H) and the OCH signal was located at δ 4.95–5.02 ppm (m), whereas the OCH signal of **5** was observed at δ 3.61–3.7 ppm (m). The ^{13}C NMR spectrum of **4** lacked carbonyl carbon signal (δ_C 186.1 ppm in the spectrum of **5**), but there was a signal at δ_C 103.9 ppm which was assigned to the acetal carbon atom (C^1).

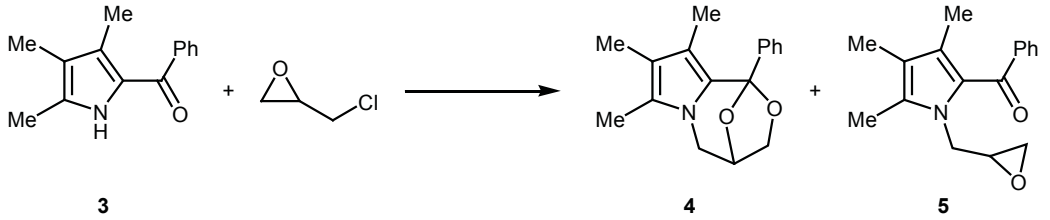
Scheme 3 shows the results of epoxymethylation of three substituted indoles **6a**–**6c**. The reaction of (3-methyl-1*H*-indol-2-yl)(phenyl)methanone (**6a**) with

Scheme 1.



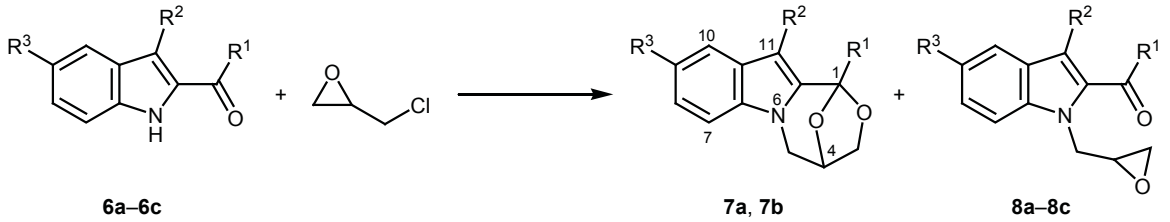
1 **2** **2a**

Scheme 2.



3 **4** **5**

Scheme 3.



6a–6c **7a**, **7b** **8a–8c**

R^1 = Ph, R^2 = Me, R^3 = H (**a**); R^1 = Ph, R^2 = $CH_2C(O)OEt$, R^3 = H (**b**); R^1R^2 = $(CH_2)_3$, R^3 = Me (**c**).

epichlorohydrin gave 11-methyl-1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]indole (**7a**) which was isolated as colorless crystals in 49% yield. The residue obtained after isolation of **7a** was a yellow non-crystallizable resin containing [3-methyl-1-(oxiran-2-ylmethyl)-1*H*-indol-2-yl](phenyl)methanone (**8a**) which was not isolated in pure form. The structure of **7a** was confirmed by two-dimensional homonuclear COSY and NOESY experiments. The COSY spectrum of **7a** showed cross-peaks with similar intensities between the C^4H proton and protons of the C^3H_2 and C^5H_2 groups, as well as cross-peaks between the *ortho* protons and *meta* and *para* protons of the phenyl ring and between 7-H, 8-H, 9-H, and 10-H (indole fragment). The NOESY spectrum of **7a** showed cross-peaks C^5H_2/C^7H, C^4H/C^3H_2, C^4H/C^5H_2, and 11-CH_3/1-C_6H_5.

Ethyl 2-(2-benzoyl-1*H*-indol-3-yl)acetate (**6b**) reacted with epichlorohydrin to give ethyl 2-(1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]-indol-11-yl)acetate (**7b**) and ethyl 2-[2-benzoyl-1-(oxiran-2-ylmethyl)-1*H*-indol-3-yl]acetate (**8b**) at a ratio of ~1:1 with an overall yield of 82%. The epoxymethylation of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**6c**) afforded 6-methyl-9-(oxyran-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**8c**) as the only product (yield 86%). In this case, no expected 1,4-epoxy[1,4]oxazepine derivative was obtained, presumably because of rigid structure of the carbonyl-containing fragment.

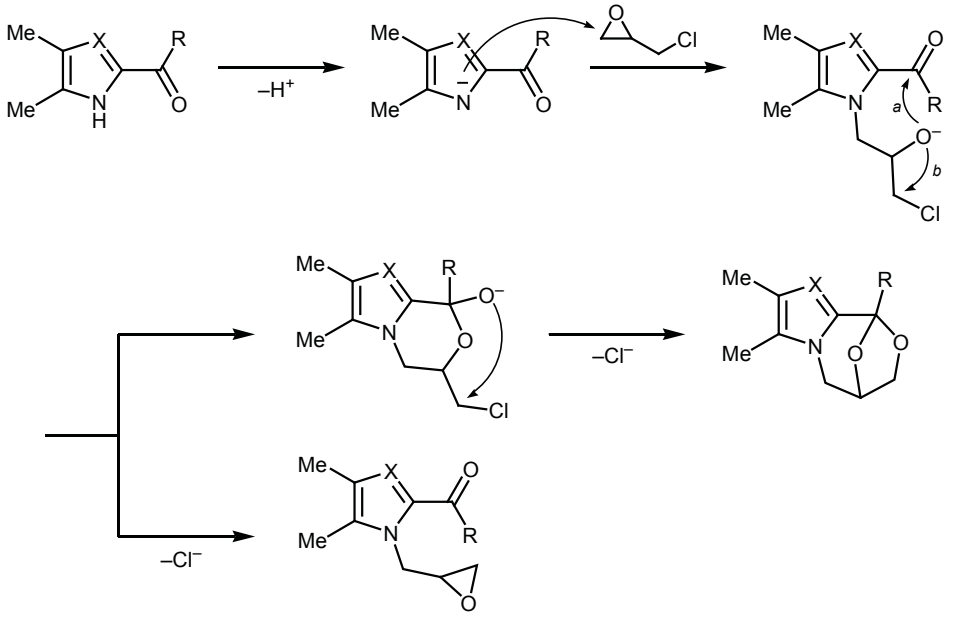
Scheme 4 shows a plausible mechanism of the epoxymethylation of compounds **1**, **3**, **6a**, **6b**, and **6c**. A similar mechanism was proposed previously [2] for the cyclization of glycidyl phenyl ether with acetylacetone.

The yields of oxazepines **2**, **7a**, and **7b** were almost equal to those of glycidyl derivatives **2a**, **8a**, and **8b**, which suggests equal probabilities of the attack of alkoxide ion on the carbonyl and C–Cl carbon atoms. Exceptions were carbazolone **6c** and pyrrole **3**. The yield of epoxyoxazepine **4** from pyrrole **3** was quite low, which may be rationalized by weak polarization of the C=O bond in **4** and hence reduced probability of nucleophilic attack on the carbonyl carbon atom. In the ^1H NMR spectrum of **3**, the *ortho* protons of the benzoyl group resonated as a doublet at δ 7.56 ppm located near the *meta*- and *para*-proton signals, whereas the signal of the *ortho* protons of the benzoyl group of benzimidazole **1** and indoles **6a** and **6b** appeared as a doublet in the region δ 8.0–8.2 ppm. These findings cannot be regarded as an unambiguous proof that benzoyl rather than phenyl substituent is present in molecule **3**. On the other hand, the ^{13}C NMR spectrum **3** contained a signal at δ_C 185.9 ppm, which unambiguously corresponds to carbonyl carbon atom. These data also confirm weak polarization of the carbonyl group in **3**.

The overall yields of oxazepines and oxiranes in the above epoxymethylation reactions were fairly high but not quantitative. This may be related to side reaction of the oxirane with the azolate anion present in the reaction mixture, which leads to the formation of dimeric product according to Scheme 5.

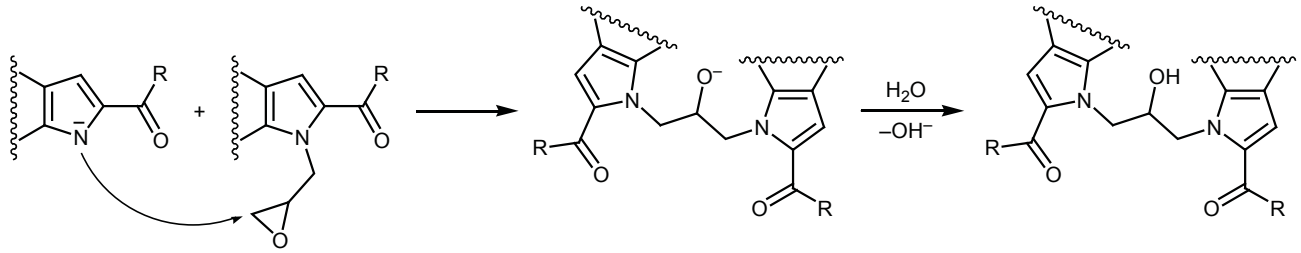
Getautis et al. [3] studied epoxymethylation of salicylaldehyde with excess epichlorohydrin in the presence of benzyl(triethyl)ammonium chloride

Scheme 4.

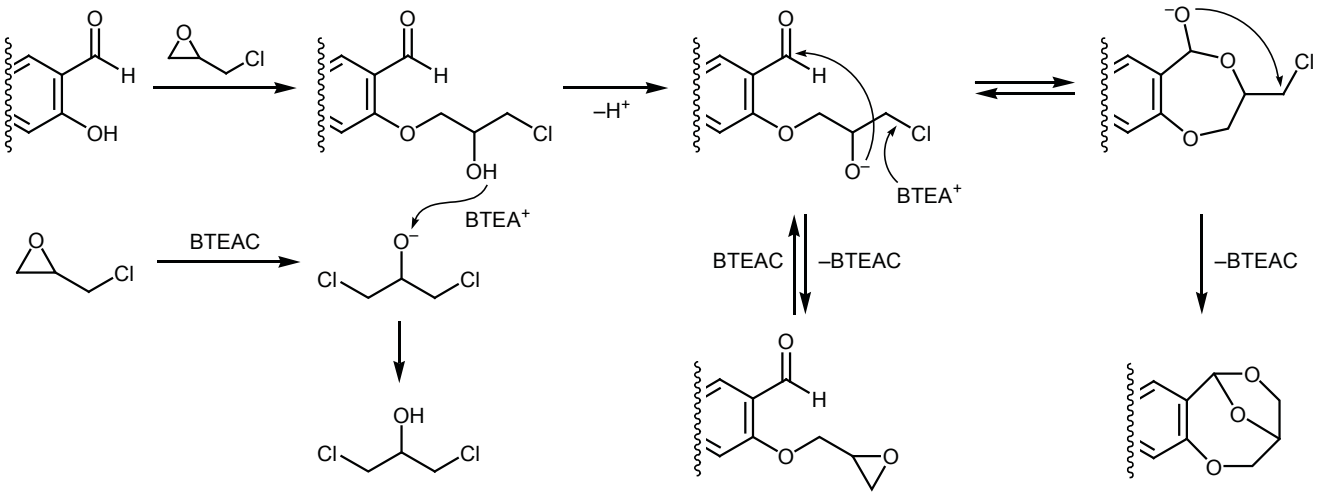


(BTEAC). It was found that the reaction was complete in 10 min with quantitative yield. When the reaction mixture was further heated for 60 h, the glycidyl derivative was quantitatively converted to 3,4-dihydro-2*H*,6*H*-3,6-epoxy-1,5-benzodioxocine. In this reaction, an interesting role is played by BTEAC as catalyst. We believe that the benzodioxocine derivative is formed according to the mechanism outlined in Scheme 6.

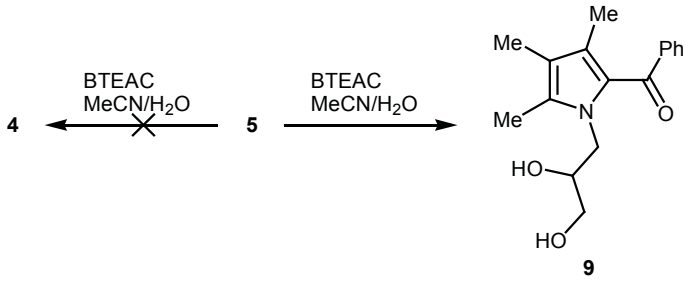
Scheme 5.



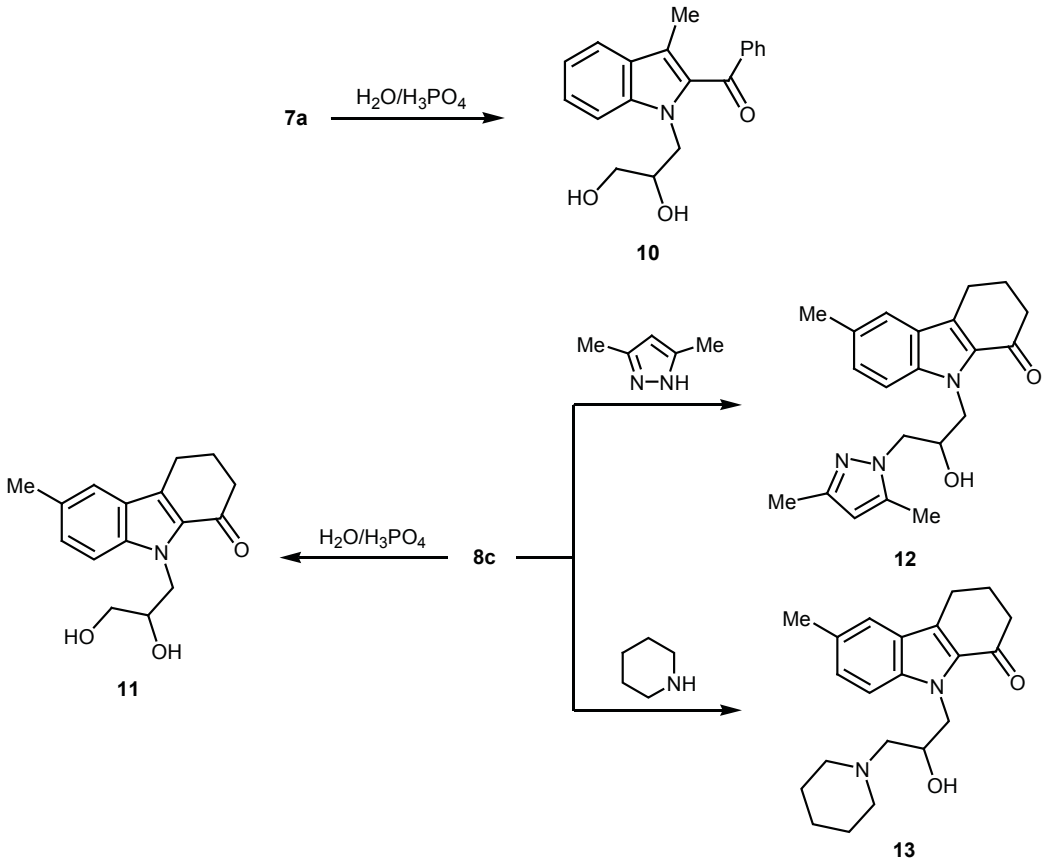
Scheme 6.



Scheme 7.



Scheme 8.



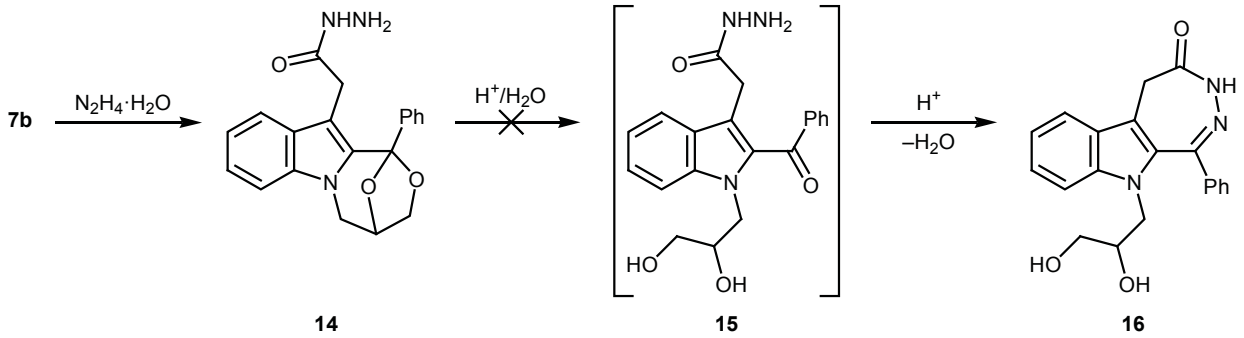
We tried to obtain oxazepine **4** from oxirane **5** in a similar way. When oxirane **5** was heated in acetonitrile in the presence of BTEAC for 10 h, we isolated [1-(2,3-dihydroxypropyl)-3,4,5-trimethyl-1*H*-pyrrol-2-yl](phenyl)methanone (**9**) (Scheme 7); i.e., the reaction involved common hydrolysis of the oxirane ring with water remaining in acetonitrile after standard purification. In an attempt to synthesize pyrrole **9** via addition of water to oxirane **5** in the presence of H_3PO_4 as catalyst, the reaction was accompanied by debenzoylation of **5**.

Thus, epoxymethylation of 2-acyl-saubstituted NH-heterocycles provides a convenient method of synthesis of epoxy-1,4-oxazepine derivatives fused to both benzimidazole and pyrrole or indole fragments. Exceptions are derivatives of carbazolone.

The other reaction products, *N*-glycidyl derivatives, are equally interesting. Oxiranes are known to react with water, phenols, primary and secondary amines, alcohols, and NH-heterocycles. Biological screening of such compounds revealed their CNS activity [4]. Scheme 8 shows some reactions of compounds **7a** and **8c** involving the oxirane ring.

By heating oxirane **8c** with 3,5-dimethyl-1*H*-pyrazole or piperidine in 2-ethoxyethanol (Strukov reaction) we obtained 9-[3-(3,5-dimethyl-1*H*-pyrazol-1-

Scheme 9.



yl)-2-hydroxypropyl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**12**) and 9-[2-hydroxy-3-(piperidin-1-yl)propyl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**13**). Acid hydrolysis of **8c** in dioxane in the presence of phosphoric acid gave 9-(2,3-dihydropropyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**11**) as a result of opening of the oxirane ring. [1-(2,3-Dihydropropyl)-3-methyl-1*H*-indol-2-yl](phenyl)methanone (**10**) was synthesized in a similar way from compound **7a**. Thus, oxazepine **7a** can be regarded as a latent form of oxirane **8a**. However, oxazepines **2**, **4**, **7a**, and **7b** failed to react with phenols, primary and secondary amines, alcohols, and NH-heterocycles, in contrast to oxiranes **2a**, **5**, and **8a**–**8c**. The reaction of oxazepine **7b** with hydrazine hydrate under reflux involved the ester group rather than oxazepine ring, and the product was 2-(1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]-indol-11-yl)acetoxyhydrazide (**14**) (Scheme 9). It should be noted that no reaction occurred when compound **7b** was heated with excess hydrazine hydrate in methanol.

Compound **14** in acidic aqueous medium was presumed to undergo oxazepine ring opening to give indole **15**. The latter can be regarded as a 1,5-dicarbonyl compound which, by analogy with the data of [5], could be converted to diazepinone derivative, 10-(2,3-dihydroxypropyl)-1-phenyl-5,10-dihydro[1,2]-diazepino[4,5-*b*]indol-4(3*H*)-one (**16**). However, from the reaction mixture we isolated a yellow non-crystallizable resin whose ^{1}H NMR spectrum did not correspond to structure **16**. Presumably, it was a dimerization product.

Thus, the epoxymethylation reaction considered in this work is an important tool for the synthesis of not only epoxy-1,4-oxazepine derivatives but also N-glycidyl-substituted nitrogen heterocycles which can be used as starting materials in the synthesis of potentially biologically active compounds.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The melting points were measured on a Boetius hot stage and are uncorrected.

Oxazepines 2, 4, 7a, and 7b (*general procedure***).** A mixture of 25 mmol of benzoyl derivative **1**, **3**, **6a**, **6b**, or **6c**, 250 mmol of epichlorohydrin, 2.8 g of potassium carbonate, 50 mmol of potassium hydroxide, and 5 mol % of 18-crown-6 was vigorously stirred at 40°C for 2 (with compound **1**), 6 (**3**), or 4 h (**6a**–**6c**). The inorganic precipitate was filtered off and washed with 10 mL of epichlorohydrin, and epichlorohydrin was removed from the filtrate under reduced pressure (first, using a water-jet pump and then under high vacuum) to leave a crude product.

1-Phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]-oxazepino[4,3-*a*]benzimidazole (2). The crude product was recrystallized from propan-2-ol. Yield 63%, colorless crystals, mp 149–150°C. ^{1}H NMR spectrum, δ, ppm: 4.12 d.d (1H, CH_2O, J = 8.0, 1.6 Hz), 4.28 t (1H, CH_2O, J = 6.4 Hz), 4.33 d (1H, CH_2N, J = 12.0 Hz), 4.53 d.d (1H, CH_2N, J = 12.0, 3.2 Hz), 5.33–5.41 m (1H, CH), 7.20 t (1H, H_{arom}, J = 7.2 Hz), 7.27 t (1H, H_{arom}, J = 7.2 Hz), 7.41–7.51 m (4H, H_{arom}), 7.55 d (1H, H_{arom}, J = 8.0 Hz), 7.71–7.81 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 47.5 (CH_2), 67.9 (CH_2), 71.7 (CH), 103.4, 109.6 (CH), 119.6 (CH), 121.7 (CH), 122.6 (CH), 126.9 (2C, CH), 127.3 (2C, CH), 128.8 (CH), 133.8, 134.6, 141.7, 150.1. Found, %: C 73.36; H 5.10; N 10.05; O 11.49. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.37; H 5.07; N 10.07; O 11.50. M 278.31.

7,8,9-Trimethyl-1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxypyrrolo[2,1-*c*][1,4]oxazepine (4). The crude

product was mixed with 70 mL of heptane, the solution was heated to the boiling point, 6 g of silica gel was added, and the mixture was refluxed for 10 min with stirring and transferred while hot to a Soxhlet extractor. After 30-min extraction, the solvent was removed by half, the flask was cooled to room temperature, and the precipitate was filtered off and washed with heptane. Yield 10%, colorless crystals, mp 131–132°C. ^{1}H NMR spectrum, δ, ppm: 1.04 s (3H, CH_3), 1.76 s (3H, CH_3), 2.07 s (3H, CH_3), 3.78 d (1H, CH_2, J = 12.0 Hz), 3.87 d.d (1H, CH_2, J = 7.6, 1.2 Hz), 4.04–4.16 m (2H, CH_2), 4.94–5.03 m (1H, CH), 7.31–7.41 m (3H, H_{arom}), 7.55–7.65 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 8.7 (CH_3), 8.8 (CH_3), 8.9 (CH_3), 47.2 (CH_2), 66.7 (CH_2), 71.1 (CH), 103.9, 111.7, 112.6, 122.1, 126.3 (CH), 128.2 (2C, CH), 128.6 (2C, CH), 129.3, 137.6. Found, %: C 75.79; H 7.15; N 5.18; O 11.88. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20; O 11.88. *M* 269.35.

Phenyl[3,4,5-trimethyl-1-(oxiran-2-ylmethyl)-1*H*-pyrrol-2-yl]methanone (5). After extraction of **4**, the Soxhlet thimble content was dried from heptane and extracted with methanol. The solvent was removed almost completely, and the residue was left overnight. A small amount of cold (0°C) methanol was added to the solidified material, and the precipitate was quickly filtered off and washed with a small amount of cold methanol. Yield 52%, brownish crystals, mp 115–117°C. ^{1}H NMR spectrum, δ, ppm: 1.56 s (3H, CH_3), 1.89 s (3H, CH_3), 2.26 s (3H, CH_3), 3.29–3.37 m (2H, CH_2O), 3.61–3.70 m (1H, CH), 4.05 d.d (1H, CH_2N, J = 14.4, 8.4 Hz), 4.29 d.d (1H, CH_2N, J = 14.4, 3.6 Hz), 7.43 t (2H, H_{arom}, J = 7.2 Hz), 7.51 t (1H, H_{arom}, J = 7.2 Hz), 7.60 d (2H, H_{arom}, J = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 9.0 (CH_3), 10.3 (CH_3), 12.0 (CH_3), 47.5 (CH_2), 69.8 (CH_2), 72.0 (CH), 115.5, 127.0, 127.6, 127.8 (2C, CH), 128.6 (2C, CH), 130.8 (CH), 135.0, 141.3, 186.1 (C=O). Found, %: C 75.78; H 7.14; N 5.18; O 11.90. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20; O 11.88. *M* 269.35.

11-Methyl-1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]oxazepino[4,3-*a*]indole (7a). The crude product was treated with 10 mL of propan-2-ol, the mixture was heated to the boiling point and left overnight, and the crystalline solid was filtered off and washed with propan-2-ol. Yield 49%, colorless crystals, mp 150–151°C. ^{1}H NMR spectrum, δ, ppm: 1.42 s (3H, CH_3), 4.03 d.d (1H, CH_2O, J = 7.6, 1.6 Hz), 4.19 d (1H, CH_2N, J = 11.6 Hz), 4.23 d (1H, CH_2O, J = 6.8 Hz), 4.37 d.d (1H, CH_2N, J = 11.6, 3.6 Hz), 5.19–5.23 m (1H, CH), 7.00 t (1H, H_{arom}, J = 7.2 Hz), 7.15 t (1H, H_{arom}, J = 7.6 Hz), 7.28 d (1H, H_{arom}, J = 8.4 Hz), 7.36 d (1H, J = 7.6 Hz), 7.40–7.48 m (3H, H_{arom}), 7.63–7.71 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 8.1 (CH_3), 47.0 (CH_2), 67.3 (CH_2), 71.4 (CH), 103.9, 105.0, 108.5 (CH), 118.6 (CH), 118.8 (CH), 121.8 (CH), 127.7 (4C, CH), 128.0, 128.7 (CH), 132.2, 134.8, 137.0. Found, %: C 78.30; H 5.92; N 4.80; O 10.98. $C_{19}H_{17}NO_2$. Calculated, %: C 78.33; H 5.88; N 4.81; O 10.98. *M* 291.35.

Ethyl 2-(1-phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy-[1,4]oxazepino[4,3-*a*]indol-11-yl)acetate (7b). The crude product was treated with 100 mL of heptane, the mixture was heated to the boiling point with stirring, and 6 g of silica gel was added. The mixture was refluxed with stirring for 10 min and transferred while hot to a Soxhlet extractor. After 3-h extraction, the solvent was completely removed. The residue (a mixture of **7b** and **8b**; overall yield 82%) was treated with 30 mL of methanol, the mixture was heated to the boiling point and left to stand for crystallization, and the precipitate was filtered off and washed with methanol. Yield 43%, colorless crystals, mp 141–142°C. ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, CH_3, J = 6.8 Hz), 2.67 d (1H, CH_2C=O, J = 17.2 Hz), 2.98 d (1H, CH_2C=O, J = 17.2 Hz), 3.86–3.95 m (2H, CH_2O), 4.09 d.d (1H, CH_2N, J = 7.6, 1.2 Hz), 4.18–4.30 m (2H, CH_2), 4.42 d.d (1H, CH_2N, J = 11.6, 3.2 Hz), 5.21–5.28 m (1H, CH), 7.02 t (1H, H_{arom}, J = 8.0 Hz), 7.19 t (1H, H_{arom}, J = 7.2 Hz), 7.34 d (2H, H_{arom}, J = 8.0 Hz), 7.39–7.49 m (3H, H_{arom}), 7.56–7.73 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.9 (CH_3), 28.6 (CH_2), 47.1 (CH_2), 59.4 (CH_2), 67.5 (CH_2), 71.4 (CH), 102.6, 103.5, 108.8 (CH), 118.8 (CH), 119.2 (CH), 122.0 (CH), 127.5, 127.7 (2C, CH), 128.8 (CH), 133.8, 134.8, 136.4, 169.9 (C=O). Found, %: C 72.70; H 5.84; N 3.84; O 17.62. $C_{22}H_{21}NO_4$. Calculated, %: C 72.71; H 5.82; N 3.85; O 17.62 *M* 363.42.

Ethyl 2-[2-benzoyl-1-(oxiran-2-ylmethyl)-1*H*-indol-3-yl]acetat (8b). The mother liquor obtained after separation of **7b** was evaporated, and the residue was left to stand for several days in an open vessel. The resinous material gradually crystallized. The product contained ~20% of **7b**, and we failed to find an appropriate solvent to purify compound **8b** from **7b**. The NMR spectra of **8b** were obtained by subtracting signals of **7b** from the spectrum of their mixture. ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, CH_3, J = 6.8 Hz), 2.30 t (1H, CH_2O, J = 2.4 Hz), 2.65 t (1H, CH_2O, J = 4.0), 3.22–3.29 m (1H, CH), 3.47 s (2H, CH_2), 3.95 q (2H, CH_2, J = 6.8 Hz), 4.38 d.d (1H, CH_2N, J = 15.2, 4.8 Hz), 4.77 d.d (1H, CH_2N, J =

15.6, 2.8 Hz), 7.14 t (1H, H_{arom}, J = 7.6 Hz), 7.35 t (1H, H_{arom}, J = 7.6 Hz), 7.51 t (2H, H_{arom}, J = 7.6 Hz), 7.55–7.66 m (3H, H_{arom}), 7.78 d (2H, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.8 (CH_3), 30.5 (CH_2), 44.4 (CH_2), 44.9 (CH_2), 50.7 (CH), 60.0 (CH_2), 110.8 (CH), 113.8, 120.2 (CH), 124.9 (CH), 126.3 (CH), 127.7, 127.3 (2C, CH), 128.4, 129.1 (2C, CH), 132.6 (CH), 138.0, 138.9, 169.6 (C=O), 188.9 (C=O).

6-Methyl-9-(oxiran-2-ylmethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (8c). The crude product was treated with 10 mL of methanol, the mixture was heated to the boiling point with stirring and left overnight, and the crystalline solid was filtered off and washed with methanol. Yield 86%, colorless needles, mp 77–78°C. ^{1}H NMR spectrum, δ, ppm: 2.18 quint (2H, CH_2, J = 6.4 Hz), 2.43 s (3H, CH_3), 2.51–2.60 m (3H, CH_2), 2.68 t (1H, CH_2, J = 6.0 Hz), 2.96 t (2H, CH_2, J = 6.0 Hz), 3.16–3.24 m (1H, CH), 4.42 d.d (1H, CH_2N, J = 14.8, 5.2 Hz), 4.88 d.d (1H, CH_2N, J = 14.8, 3.6 Hz), 7.16 d.d (1H, H_{arom}, J = 8.4, 1.2 Hz), 7.36 d (1H, H_{arom}, J = 8.4 Hz), 7.38 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.0 (CH_3), 21.2 (CH_2), 24.2 (CH_2), 39.2 (CH_2), 44.5 (CH_2), 45.7 (CH_2), 50.7 (CH), 110.7 (CH), 120.0 (CH), 1214.5, 128.2 (CH), 128.3, 128.7, 129.3, 137.8, 190 (C=O). Found, %: C 75.30; H 6.73; N 5.52; O 12.45. $C_{16}H_{17}NO_2$. Calculated, %: C 75.27; H 6.71; N 5.49; O 12.53 *M* 255.32.

[1-(2,3-Dihydroxypropyl)-3,4,5-trimethyl-1*H*-pyrrol-2-yl](phenyl)methanone (9). A mixture of 150 mg (0.56 mmol) of compound **5** and 100 mg of BTEAC in 8 mL of undried acetonitrile was refluxed for 10 h. The solvent was distilled off, the residue was treated with 5 mL of water, and the oily material rapidly solidified. The precipitate was filtered off and washed with water. The product required no further purification. Yield 0.147 g (92%), fine colorless crystals, mp 113–114°C. ^{1}H NMR spectrum, δ, ppm: 1.55 s (3H, CH_3), 1.89 s (3H, CH_3), 2.25 s (3H, CH_3), 3.26–3.34 m (2H, C**H**$_2$OH), 3.63 sept (1H, CH, J = 4.4 Hz), 4.03 d.d (1H, CH_2N, J = 14.0, 8.4 Hz), 4.28 d.d (1H, CH_2N, J = 14.0, 3.6 Hz), 4.37 t (1H, OH, J = 5.6 Hz), 4.73 d (1H, OH, J = 6.0 Hz), 7.43 t (2H, H_{arom}, J = 7.2 Hz), 7.51 t (1H, H_{arom}, J = 7.2 Hz), 7.59 t (2H, H_{arom}, J = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 9.0 (CH_3), 10.3 (CH_3), 12.0 (CH_3), 47.4 (CH_2), 63.7 (CH_2), 71.7 (CH), 115.5, 126.9, 127.5, 127.8 (2C, CH), 128.6 (2C, CH), 130.8 (CH), 135.0, 141.3, 186.1 (C=O). Found, %: C 71.01; H 7.42; N 4.82; O 16.75. $C_{17}H_{21}NO_3$. Calculated, %: C 71.06; H 7.37; N 4.87; O 16.70. *M* 287.36.

[1-(2,3-Dihydroxypropyl)-3-methyl-1*H*-indol-2-yl](phenyl)methanone (10). A mixture of 0.3 g (1.01 mmol) of compound **7a**, 10 mL of water, and 2 mL of 85% H_3PO_4 was refluxed for 4 h with stirring. The mixture was cooled to room temperature and neutralized to pH ~7 with aqueous ammonia. The aqueous phase was separated by decanting from the yellow viscous oil, and the oil was washed with water and dried at 110°C. Yield 0.30 g (94%), yellow viscous oily material. ^{1}H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 3.27–3.36 m (2H, CH_2O), 3.65–3.75 m (1H, CH), 4.32 d.d (1H, CH_2N, J = 14.8, 8.0 Hz), 4.48 d.d (1H, CH_2N, J = 14.4, 3.6 Hz), 7.10 t (1H, H_{arom}, J = 7.2 Hz), 7.31 t (1H, H_{arom}, J = 7.2 Hz), 7.48–7.59 m (4H, H_{arom}), 7.62 t (1H, H_{arom}, J = 7.2 Hz), 7.83 d (2H, H_{arom}, J = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 10.6 (CH_3), 46.4 (CH_2), 63.6 (CH_2), 70.9 (CH), 110.9 (CH), 116.5, 119.3 (CH), 119.9 (CH), 124.4 (CH), 127.0, 128.2 (2C, CH), 129.4 (2C, CH), 132.3 (CH), 133.8, 139.5, 189.7 (C=O). Found, %: C 73.81; H 6.21; N 4.50; O 15.48. $C_{19}H_{19}NO_3$. Calculated, %: C 73.77; H 6.19; N 4.53; O 15.51. *M* 309.37.

9-(2,3-Dihydroxypropyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (11). A mixture of 1 g (3.9 mmol) of compound **8c**, 5 mL of 1,4-dioxane, 0.2 mL of water, and 0.2 mL of H_3PO_4 was refluxed for 2 h. The mixture was cooled to room temperature, 15 mL of water was added, and a mobile oily material separated and crystallized on grinding. The precipitate was filtered off and washed with water. Yield 1 g (94%), colorless flocculent crystals, mp 117–118°C. The product required no further purification. ^{1}H NMR spectrum, δ, ppm: 2.18 quint (2H, CH_2, J = 5.6 Hz), 2.42 s (3H, CH_3), 2.56 t (2H, CH_2, J = 6.0 Hz), 2.96 t (2H, CH_2, J = 5.6 Hz), 3.28–3.40 m (2H, CH_2O), 3.72–3.83 m (1H, CH), 4.35 d.d (1H. CH_2N, J = 14.0, 6.8 Hz), 4.53 d.d (1H, CH_2N, J = 14.0, 5.2 Hz), 7.14 d (1H_{arom}, J = 8.8 Hz), 7.36 s (1H_{arom}), 7.43 d (1H_{arom}, J = 8.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.0 (CH_3), 21.3 (CH_2), 39.4 (CH_2), 47.1 (CH_2), 63.5 (CH_2), 71.4 (CH), 111.2 (CH), 119.7 (CH), 124.3, 127.9 (CH), 128.0, 128.2, 129.7, 138.0, 190.4 (C=O). Found, %: C 70.34; H 7.04; N 5.09; O 17.53. $C_{16}H_{19}NO_3$. Calculated, %: C 70.31; H 7.01; N 5.12; O 17.56. *M* 273.33.

9-[3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-hydroxypropyl]-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (12) and 9-(2-hydroxy-3-piperidin-1-ylpropyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (13) (*general procedure*). A mixture of 1 mmol of compound **8c** and 1.5 mmol of 3,5-dimethyl-1*H*-pyrazole or piperidine in 2 mL of 2-ethoxyethanol was refluxed for 6 h. The mixture was treated with 8 mL of water, an oily material separated and was ground until complete crystal-

lization, and the solid product was filtered off, washed with water, dried, and recrystallized from methanol.

Compound **12**. Yield 91%, colorless crystals, mp 139–140°C. ^{1}H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 2.19 t (2H, CH_2, J = 6.0 Hz), 2.21 s (3H, CH_3), 2.43 s (3H, CH_3), 2.57 t (2H, CH_2, J = 5.6 Hz), 2.97 t (2H, CH_2, J = 6.0 Hz), 3.84 d.d (1H, C**H**$_2$NN, J = 14.0, 4.0 Hz), 3.92 d.d (1H, C**H**$_2$NN, J = 14.0, 7.6 Hz), 4.08–4.21 m (1H, CH), 4.37 d.d (1H, CH_2N, J = 14.0, 7.2 Hz), 4.59 d.d (1H, CH_2N, J = 14.0, 5.6 Hz), 4.96 br.s (1H, OH), 5.68 s (1H, CH), 7.15 d.d (1H, H_{arom}, J = 8.8, 1.2 Hz), 7.35 d (1H, H_{arom}, J = 8.4 Hz), 7.37 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 10.8 (CH_3), 13.2 (CH_3), 21.0 (CH_3), 21.3 (CH_2), 24.3 (CH_2), 39.4 (CH_2), 48.1 (CH_2), 51.7 (CH_2), 70.0 (CH), 104.1 (CH), 111.0 (CH), 119.9 (CH), 124.4, 128.1 (CH), 128.2, 128.4, 129.5, 137.9, 139.1, 145.5, 190.4 (C=O). Found, %: C 71.79; H 7.20; N 12.00; O 9.01. $C_{21}H_{25}N_3O_2$. Calculated, %: C 71.77; H 7.17; N 11.96; O 9.10. *M* 351.45.

Compound **13**. Yield 88%, colorless crystals, mp 109–110°C. ^{1}H NMR spectrum, δ, ppm: 1.40 quint (2H, CH_2, J = 5.2 Hz), 1.53 quint (4H, CH_2, J = 5.2 Hz), 2.18 quint (2H, CH_2, J = 6.0 Hz), 2.29 d (2H, CH_2, J = 6.0 Hz), 2.35–2.45 m (4H, CH_2), 2.42 s (3H, CH_3), 2.55 t (2H, CH_2, J = 6.0 Hz), 2.96 t (2H, CH_2, J = 5.6 Hz), 3.86–3.98 m (1H, CH), 4.23 d.d (1H, CH_2, J = 14.0, 7.6 Hz), 4.62 d.d (1H, CH_2, J = 14.0, 4.4 Hz), 7.12 d.d (1H, H_{arom}, J = 8.8, 1.2 Hz), 7.35 s (1H, H_{arom}), 7.41 d (1H, H_{arom}, J = 8.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.0 (CH_3), 21.3 (CH_2), 23.9 (CH_2), 24.3 (CH_2), 25.5 (2C, CH_2), 48.9 (CH_2), 54.5 (2C, CH_2), 62.6 (CH_2), 67.5 (CH), 111.3 (CH), 119.7 (CH), 127.7 (CH), 127.8, 128.1, 129.7, 138.2, 190.3 (C=O). Found, %: C 74.05; H 8.31; N 8.26; O 9.38. $C_{21}H_{28}N_2O_2$. Calculated, %: C 74.08; H 8.29; N 8.23; O 9.40. *M* 340.47.

2-(1-Phenyl-4,5-dihydro-1*H*,3*H*-1,4-epoxy[1,4]-oxazepino[4,3-*a*]indol-11-yl)acetohydrazide (14). A mixture of 2 g (5.49 mmol) of compound **7b** and 8 mL (160 mmol) of hydrazine hydrate was refluxed for 1 h with stirring. The suspension was cooled to room temperature and diluted with 15 mL of water, and the precipitate was filtered off, washed with water, and recrystallized from 7 mL of methanol. Yield 1.7 g (88%), colorless crystals, mp 118–119°C. ^{1}H NMR spectrum, δ, ppm: 2.42 d and 2.77 d [1H each, CH_2C(O), J = 16.4 Hz], 4.04–4.15 m (1H, CH_2), 4.16–4.29 m (2H, CH_2), 4.34–4.48 m (1H, CH_2), 5.15–5.30 m (1H, CH_2), 7.02 t (1H, H_{arom}, J = 7.2 Hz), 7.18 t (1H, H_{arom}, J = 7.2 Hz), 7.32 d (1H, H_{arom}, J = 8.0 Hz), 7.38 d (1H, H_{arom}, J = 7.6 Hz), 7.40–7.51 m (3H, H_{arom}), 7.55–7.83 m (2H, H_{arom}), 8.04 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 28.9 (CH_2), 47.0 (CH_2), 67.5 (CH_2), 71.4 (CH), 103.4, 103.7, 108.7 (CH), 119.1 (2C, CH), 122.0 (CH), 126.6, 127.5, 127.6 (2C, CH), 128.9 (CH), 133.9, 134.9, 136.3, 169.0 (C=O). Found, %: C 68.72; H 5.51; N 12.06; O 13.71. $C_{20}H_{19}N_3O_3$. Calculated, %: C 68.75; H 5.48; N 12.03; O 13.74. *M* 349.39.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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