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Synthesis of Indole 2,3-Epoxypropyl Derivatives and Their Reactions with Amines

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Abstract—Indole derivatives with a 2,3-epoxypropyl substituent attached to nitrogen were synthesized. In reactions with primary and secondary amines these compounds afforded the corresponding 1,2-aminoalcohols.

2,3-Epoxypropyl derivatives of various heterocycles are interesting objects for preparation of pharmacologically active 1,2-aminoalcohols [1, 2]. Besides the epoxides of the heterocyclic series proper are known to exhibit antitumor activity [3]. Inasmuch as the indole ring is present in numerous pharmaceuticals and alkaloids we studied the possibility to synthesize N-epoxypropyl derivatives of indole. Moreover, the indole containing in position *3* a 1,2-aminoalcohol moiety is known to by administered in the therapy of heart diseases [4].

The goal of this study was preparation of indole N-epoxypropyl derivatives and investigation of their reactions with amines.

Reactions of highly basic azoles with epichlorohydrin in the presence of alkali were described in [5], and the reaction mechanism was discussed. It was suggested that the process might start as a direct interaction of the reagents not involving the alkali. This reaction path is impossible for indole derivatives of low basicity, therefore we first have generated the N-indolyl anion by treatment with sodium hydride in DMSO. The subsequent reaction apparently occurred as N-alkylation. To accelerate the process we used epibromohydrin instead of epichlorohydrin (Scheme 1). The initial 5-methyl-4-[(1*H*-indol-3-yl)methylene]-2-phenyl-2,4-dihydropyrazol-3-one (**I**) was obtained from indole-3-carbaldehyde and the corresponding pyrazolone by Knoevenagel condensation.

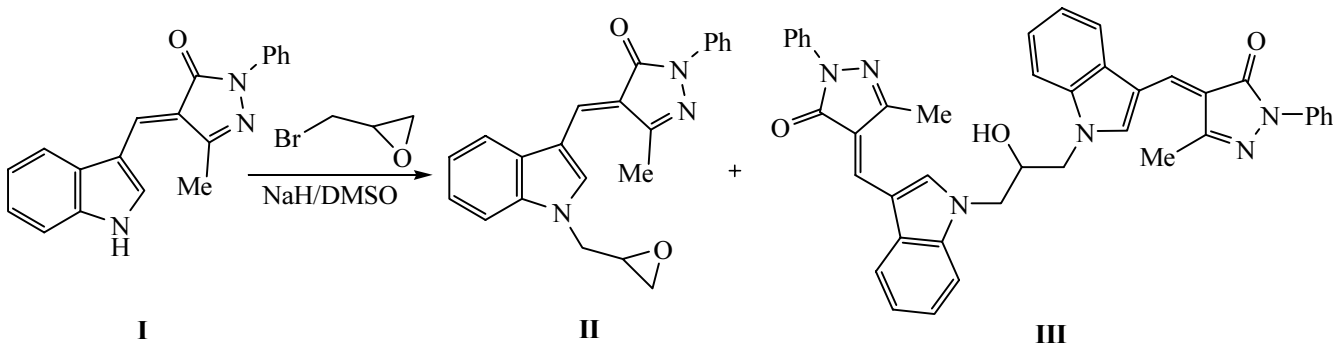
Alongside compound **II** product **III** formed also in a low yield by reaction of one epibromohydrin molecule with two molecules of compound **I**. Compound **III** formation occurred presumably through the opening of the epoxy ring in compound **II** by indole **I** N-anion. A similar compound was isolated from the products of reaction between carbazole derivatives and epichlorohydrin [6].

Epoxy derivatives **Va, Vb** were obtained under similar conditions from indole-containing chalcones **IVa, IVb** and epibromohydrine (Scheme 2).

In this case no compound like **III** was obtained.

Reactions of epoxides **II** and **Va, Vb** with amines were investigated. Despite the presence in the initial reagents of reactive keto groups and double bonds the

Scheme 1.



I **II** **III**

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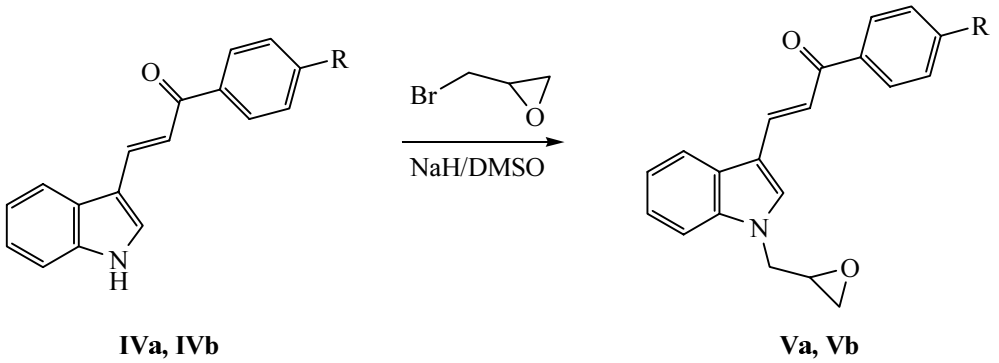
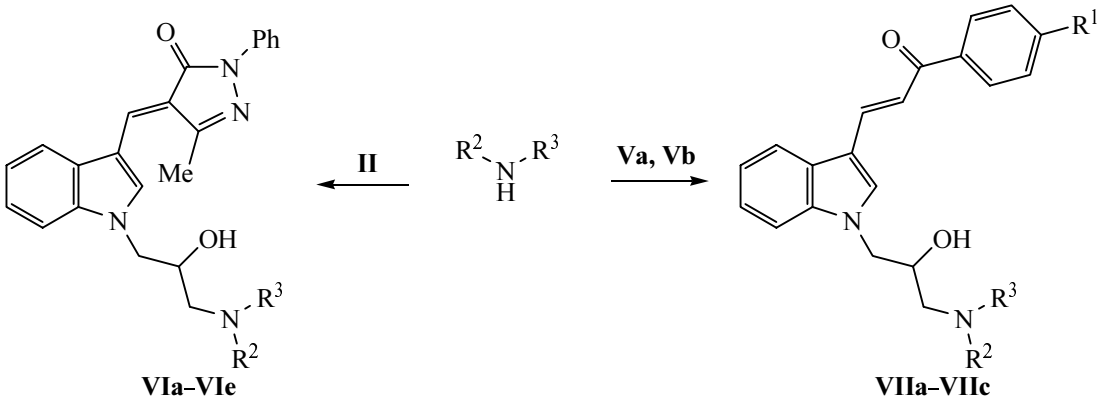
Scheme 2.



IVa, IVb **Va, Vb**

IV, V, R = Me (**a**), OMe (**b**).

Scheme 3.



VIa–VIe **VIIa–VIIc**

VI, NR^2R^3 = N O (**a**), N NMe (**b**), NBu_2 (**c**), N(*i*-Bu)$_2$ **d**), N O (**e**);

HN

VII, R^1 = Me, NR^2R^3 = N O (**a**), R^1 = OMe, NR^2R^3 = N O (**b**), R^1 = OMe, NR^2R^3 = HN Me (**c**).

amines attack the epoxy ring affording 1,2-aminoalcohols **VIa–VIe** and **VIIa–VIIc** (Scheme 3).

The structure of compounds obtained was confirmed by spectral data.

Thus we developed a synthetic method for 3-substituted indoles containing a 1,2-aminoalcohol moiety at the indole nitrogen atom.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian Unity-300 (300 MHz), IR spectra were recorded on Specord 75IR instrument from mulls in mineral oil. The elemental analyses (C, H, N) of compounds synthesized (**I, II, III, Va, Vb, VIa–VIe, VIIa–VIIc**) correspond to those calculated within the limits of common errors. The yields are given with respect to the quantity of recrystallized substances.

Initial indole chalchones **IVa, IVb** were obtained by procedure [7].

5-Methyl-4-[(1*H*-indol-3-yl)methylene]-2-phenyl-2,4-dihydropyrazol-3-one (I). A mixture of 1.45 g (0.01 mol) of indole-3-carbaldehyde, 1.74 g (0.01 mol) of 3-methyl-1-phenyl-2-pyrazolin-5-one, and 0.17 g (23 mol%) of piperidine was heated at reflux in 10 ml of butanol for 1 h. On cooling the precipitate was filtered off. Yield 2.72 g (90%), bright orange crystals, mp 138–140°C. IR spectrum, ν, cm^{-1}: 1587–1607 (C=C, C–C_{arom}), 1653 (C=O), 3223 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.45 s (3H, CH_3), 7.20–8.09 m (10H, H_{arom}), 10.10 d (1H, CH=), 10.27 br.s (1H, NH). Found,

%: C 75.9; H 4.9; N 14.1. *M* 301. $C_{19}H_{15}N_3O$. Calculated, %: C 75.7; H 5.0; N 14.0. *M* 301.36.

5-Methyl-4-{[1-(2,3-epoxyprop-1-yl)-1*H*-indol-3-yl]methylene}-2-phenyl-2,4-dihydropyrazol-3-one (II) and 1,3-di[3-(5-oxo-3-methyl-1-phenyl-1,5-dihydropyrazol-4-ylidenemethyl)indole-1-yl]propan-2-ol (III). To 0.75 g (0.019 mol) of 60% suspension of sodium hydride in mineral oil mixed with 10 ml of anhydrous DMSO was added at stirring 5 g (0.017 mol) of compound **I**. As soon as the hydrogen evolution stopped (approximately in 30 min) 4.98 g (0.036 mol) of epibromohydrin and 2 ml of DMSO was added. The mixture was stirred for 3 h at room temperature, the separated precipitate of compound **III** was filtered off and washed with 2-propanol. Yield 0.25 g (4%) , orange powder, mp 280°C (from DMF). IR spectrum, ν, cm^{-1}: 1600 (C–C_{arom}), 1660, 1673 (C=O), 3366 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.40 s (6H, $2CH_3$), 4.30–4.40 m (3H, CH_2, CH), 4.83 d (2H, CH_2), 5.62 d (1H, OH), 7.10–8.22 m (20H, H_{arom}), 9.90 s (2H, 2–CH=). Found, %: C 74.5; H 5.3; N 12.7. *M* 659. $C_{41}H_{34}N_6O_3$. Calculated, %: C 74.7; H 5.2; N 12.8. *M* 658.9.

The mother liquor in DMSO left after the first filtration was diluted with water and extracted with chloroform (3×30 ml). The extract was twice washed with water, dried over anhydrous Na_2SO_4, and the solvent was distilled off. To the residue 5–7 ml of butanol was added, and crystallization was provoked by grinding. The separated precipitate of red-orange color was filtered off, washed with petroleum ether (bp 40–70°C), and recrystallized from butanol. Yield of compound **II** 3.82 g (63%), mp 163°C. IR spectrum, ν, cm^{-1}: 1607 (C=C, C–C_{arom}), 1667 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.42 s (3H, CH_3), 2.52–2.62 m, 2.82–2.92 m (1H, 1H, OCH_2), 3.30–3.40 m (1H, CH), 4.30 d.d, 4.60 d.d (1H, 1H, NCH_2), 7.15–8.00 (10H, H_{arom}), 9.90 s (1H, CH=). Found, %: C 77.3; H 5.3; N 12.3. *M* 341. $C_{22}H_{19}N_3O$. Calculated, %: C 77.4; H 5.6; N 12.3. *M* 341.4.

1-(4-Methylphenyl)-3-[1-(2,3-epoxyprop-1-yl)-1*H*-indol-3-yl]prop-2-en-1-one (Va). To 0.24 g (6 mmol) of 60% suspension of sodium hydride in mineral oil mixed with 5 ml of anhydrous DMSO was added at stirring 1.32 g (5 mmol) of chalcone **IVa** (product of indole-3-carbaldehyde reaction with acetophenone). In 30 min, when the hydrogen evolution finished, 2.08 g (15 mmol) of epibromohydrine was added. Within 1 h the solvent changed color from dark red to dark yellow. The mixture was left overnight, an then 0.5 ml of water was added dropwise. The separated precipitate was filtered off, washed with methanol, recrystallized ftom 7 ml of 2-propanol. Yield 0.88 g (55%), lemon-yellow needle crystals, mp 121–122°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 1590, 1607 (C–C_{arom}, C=C), 1646 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.40 s (3H, CH_3), 2.47–2.53 m, 2.80–2.90 m (1H, 1H, OCH_2), 3.08–3.15 m (1H, CH), 4.18 d.d, 4.52 d.d (1H, 1H, NCH_2), 7.15–8.10 m (11H, H_{arom}, CH=CH). Found, %: C 79.7; H 6.1; N 4.2. *M* 340. $C_{21}H_{19}NO_2$. Calculated, %: C 79.5; H 6.0; N 4.4. *M* 340.2.

1-(4-Methoxyphenyl)-3-[1-(2,3-epoxyprop-1-yl)-1*H*-indol-3-yl]prop-2-en-1-one (Vb) was obtained like epoxide **Va** from chalcone **IVb**. Yield 61%, lemon-yellow needle crystals, mp 125–126°C. IR spectrum, ν, cm^{-1}: 1587, 1603 (C–C_{arom}, C=C), 1640 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.43–2.53 m, 2.80–2.88 m (1H, 1H, OCH_2), 3.27–3.35 m (1H, CH), 3.90 s (3H, OCH_3), 4.17 d.d, 4.52 d.d (1H, 1H, NCH_2), 6.90–8.13 m (11H, H_{arom}, CH=CH).

4-{[1-(3-Amino-2-hydroxypropyl)-1*H*-indol-3-yl]methylene}-5-methyl-2-phenyl-2,4-dihydro-

Table 1. Reaction conditions for preparation of 1,2-aminoalcohols

Compd. no.	Initial compounds		Solvent, ml	Time, h	Yield, g (%)	mp, °C (solvent for recrystallization)
	Epoxide quantity, mg (mol)	Amine quantity, g (mol)				
VIa	357 (1)	0.2 (2)	3	2.5	0.38 (86)	168–170 (*i*-PrOH)
VIb	357 (1)	0.2 (2)	3	2	0.1 (22)	145 (*i*-PrOH)
VIc	300 (0.8)	0.23 (1.7)	3	4	0.1 (26)	127 (*i*-PrOH)
VId	720 (2)	0.52 (4)	5	5	0.13 (27)	132 (MeOH)
VIe	710 (2)	0.52 (4)	5	2	0.2 (21)	168–170 (PhMe)
VIIa	317 (1)	0.2 (2.3)	3	6	0.32 (79)	132 (*i*-PrOH)
VIIb	333 (1)	0.2 (2.3)	3	6	0.36 (86)	131–132 (*i*-PrOH)
VIIc	333 (1)	0.16 (1.5)	3	7	0.36 (81)	168–170 (*i*-PrOH)

Table 2. Spectral characteristics of 1,2-aminoalcohols

Compd. no.	^{1}H NMR spectrum, δ, ppm, solvent for **VIa–VId**, **VIIa–VIIc** $CDCl_3$, for **VIe** – DMSO-d_6	IR spectrum, ν, cm^{-1}
Ia	2.30–2.50 m (7H, CH_2NCH_2, CH_3), 2.56–2.65 m (2H, $CH_2N_{morph.}$), 3.51 d (1H, OH), 3.60–3.74 m (4H, CH_2OCH_2), 4.10–4.20 m (1H, CH), 4.24–4.38 m (2H, CH_2N_{indole}), 7.11–8.00 m (10H, H_{arom}), 9.89 (1H, –CH=)	1593, 1607 (C=C), 1647, 1673 (C=O), 3387 (OH)
VIb	2.23 s (3H, C–CH_3), 2.30–2.67 m [10H, $(CH_2)_5$], 2.40 s (3H, NCH_3), 3.67 s (1H, OH), 4.11–4.20 m (1H, CH), 4.20–4.41 m (2H, CH_2), 7.10–8.00 m (10H, H_{arom}), 9.88 s (1H, –CH=)	1600 (C=C), 1660 (C=O), 3293 (OH)
VIc	0.90 t [6H, $(CH_3)_2$], 1.10–1.50 m [8H, $(CH_2)_4$], 2.25–2.60 m [6H, $(CH_2)_3$], 2.40 s (3H, CH_3), 3.90–4.10 m (2H, CHOH), 4.28 d (2H, CH_2), 7.10–8.07 m (10H, H_{arom}), 9.92 s (1H, –CH=)	1590 (C=C), 1675 (C=O), 3430 (OH)
VId	0.88 d.d [12H, $(CH_3)_4$], 1.60–1.80 m [2H, $(CH)_2$], 2.06–2.27 m [4H, $(CH_2)_2$], 2.30–2.75 m [4H, $(CH_2)_2$], 2.41 s (3H, CH_3), 3.75 s (1H, OH), 3.96–4.15 m (1H, CH), 4.29 d (2H, CH_2), 7.10–8.08 m (10H, H_{arom}), 9.88 s (1H, –CH=)	1587 (C=C), 1673 (C=O), 3433 (OH)
VIe	2.30–2.52 m [10H, $N(CH_2)_2N$, NCH_2, CH_3, NH], 2.51–2.71 m (4H, CH_2NCH_2), 3.50–3.61 m (4H, CH_2OCH_2), 3.90–4.07 m (1H, CH), 4.28 d.d, 4.50 d.d (1H, 1H, CH_2N_{indole}), 5.10 br.s (1H, OH), 7.05–8.09 m (10H, H_{arom}), 9.85 s (1H, –CH=)	1593 (C=C), 1673 (C=O), 3107 (NH)
VIIa	2.20–2.40 m (4H, CH_2NCH_2), 2.42 s (3H, CH_3), 2.53–2.68 m (2H, $CH_2N_{morph.}$), 3.48 br.s (1H, OH), 3.60–3.75 m (4H, CH_2OCH_2), 4.03–4.33 m (3H, CH, CH_2N_{indole}), 7.20–8.15 m (11H, H_{arom}, –CH=CH–)	1580, 1590 (C=C), 1640 (C=O), 3395 (OH)
VIIb	2.20–2.43 m (4H,CH_2NCH_2), 2.52–2.69 m (2H, $CH_2N_{morph.}$), 3.48 br.s (1H, OH), 3.59–3.78 m (4H, CH_2OCH_2), 3.88 s (3H, OCH_3), 4.05–4.35 m (3H, CH, CH_2N_{indole}), 7.20–8.12 m (11H, H_{arom}, –CH=CH–) 2.22 s (3H, CH_3), 2.52 br.s (1H, NH), 3.12 d.d, 3.32 d.d (1H, 1H,	1580, 1600 (C=C), 1640 (C=O), 3393 (OH)
VIIc	$CH_2N_{toluene}$), 3.70–3.90 br.s (1H, OH), 3.87 s (3H, OCH_3), 4.15–4.40 m (3H, CH_2N_{indole}, CH), 6.51–8.10 m (15H, H_{arom}, –CH=CH–)	1596, 1600 (C=C), 1636 (C=O), 3340 (NH, OH)

Table 3. Elemental analyses of 1,2-aminoalcohols

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
VIa	70.4	6.4	12.4	$C_{26}H_{28}N_4O_3$	70.3	6.3	12.6
VIb	70.7	6.8	15.1	$C_{27}H_{31}N_5O_2$	70.9	6.8–7.9	15.3
VIc	74.1	7.8	11.4	$C_{30}H_{38}N_4O_2$	74.0	7.9	11.5
VId	74.2	7.8	11.4	$C_{30}H_{38}N_4O_2$	74.0	7.9	11.5
VIe	69.1	6.9	14.2	$C_{28}H_{33}N_5O_3$	69.0	6.8	14.4
VIIa	74.1	7.1	6.9	$C_{25}H_{28}N_3O_3$	74.2	7.0	6.9
VIIb	71.4	6.9	6.5	$C_{25}H_{28}N_2O_4$	71.4	6.7	6.7
VIIc	75.6	6.4	6.7	$C_{27}H_{28}N_2O_3$	75.7	6.5	6.5

pyrazol-3-ones (VIa–VIe) and 3-[1-(3-amino-2-hydroxypropyl)-1H-indol-3yl]-1-phenylprop-2-en-1-ones (VIIa–VIIc). Compounds **III** and **Va, Vb** were boiled with amines in toluene. The reaction conditions are given in Table 1. An individual procedure was developed for isolation of every compound. Compounds **VIa, VId, VIe** precipitated from the reaction mixture on cooling. Compounds **VIb** and **VIIa–VIIc** were precipitated by adding petroleum ether (bp. 40–70°C) to the cooled reaction mixture. Compound **VIc** was isolated after distilling off the solvent by adding 2-propanol to the residue. Spectral characteristics of compounds are given in Table 2, and elemental analyses, in Table 3.

REFERENCES

1. Gella, I.M., *Azotistye geterotsikly i alkaloidy* (Nitrogen-containing Heterocycles and Alkaloids), Kartsev, V.G. and Tolstikov, G.A., Moscow: Iridium-Press, 2001, vol. 2, p. 81.
2. Malawska, B., Kulig, K., Filipek, B., Sapa, J., Maciag, D., Zygmunt, M., and Antkiewicz-Michaluk, L., *Eur. J. Med.*

Chem., 2002, vol. 37, p. 183.
3. Korotkikh, I.I., Losev, G.A., and Shvaika, O.P., *Azotistye geterotsikly i alkaloidy* (Nitrogen-containing Heterocycles and Alkaloids), Kartsev, V.G. and Tolstikov, G.A., Ed., Moscow: Iridium-Press, 2001, vol. 1, p. 350.
4. Kreighbaum, W.E., Matier, L., Dennis, R.D., Minielli, J.L., Deitch-man, D., Perhach, J.L., and Comer, W.T.Jr., *J. Med. Chem.,* 1980, vol. 23, p. 285.
5. Korotkikh, I.I. and Shvaika, O.P., *Zh. Org. Khim*., 1996, vol. 32, p. 1076.
6. Rovkina, N.M., Zherebtsov, I.P., Lopatinskii, V.P., and Batyrova, L.M., Gella, I.M., *Azotistye geterotsikly i alkaloidy* (Nitrogen-containing Heterocycles and Alkaloids), Kartsev, V.G. and Tolstikov, G.A., Moscow: Iridium-Press, 2001, vol. 2, p. 251.
7. Zhungietu, G.I., Budylin, V.A., and Kost, A.N., *Preparativnaya khimiya indola* (Preparative Chemistry of Indole), Kishinev: ShTIINTsA, 1975, p. 197.