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# SYNTHESIS OF 3-(2-ARYL-OXAZOLIDIN-3-YL)TROPANES

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*We obtained 3-(2-aryloxazolidin-3-yl)tropanes by reaction of aromatic aldehydes with 3-[N-(2-hydroxyethyl)amino]tropane. We obtained 3-benzyloxazolidine-2-spiro-3'-(8'-carbethoxy)-nortropane by reaction of benzylaminoethanol with 8-carbethoxynortropan-3-one.*

**Keywords:** oxazolidines, oxazolidine tropanes, spiro-oxazolidine tropane, tropan-3-one.

Tropane derivatives exhibit a broad spectrum of biological activity: tranquilizing, spasmolytic, antiarrhythmic, etc. effects. Oxazolidines in turn also are of interest as anticonvulsants. Accordingly, synthesis of new tropane derivatives containing a 2-aryloxazolidine moiety is of interest not only from the standpoint of searching for novel compounds with potential biological activity but also from a chemical standpoint, opening up the possibility of arriving at previously unknown polycyclic compounds based on tropane alkaloids.

Aromatic aldehydes reacted with N-(1,2,5-trimethyl-4-piperidyl)aminoethanol form 2-aryl-3-(1,2,5-trimethyl-4-piperidyl)-substituted oxazolidines [1].

By reaction of tropan-3-one (**1**) with aminoethanol, we obtained the corresponding Schiff's base of tropanone **2**, the hydrogenation of which at room temperature and normal pressure above $PtO_2$ probably, in analogy with the data in [2, 3], leads to a mixture of *endo* and *exo* isomers, although in the $^1$H NMR spectrum we do not observe a double set of signals and we cannot separate them by gas–liquid chromatography. By reaction of the obtained 3-[N-(2-hydroxyethyl)amino]tropane (**3**) with aromatic aldehydes (benzaldehyde, 4-methoxy-, 4-bromo-, 3,4-dimethoxy-, and 4-dimethylaminobenzaldehydes) in the presence of catalytic amounts of *p*-toluenesulfonic acid, we obtained 3-(2-aryloxazolidin-3-yl)tropanes **4-8** (see Scheme 1).

An attempt to obtain a spiro tropane containing an oxazolidine moiety by reaction of tropan-3-one **1** with benzylaminoethanol was unsuccessful due to the effect of the electron pair of the nitrogen on the nearby carbonyl group of the ketone [4]. In fact, using urethane **9** as the starting compound [5] leads to formation of 3-benzyloxazolidine-2-spiro-3'-(8'-carbethoxy)nortropanone (**10**) under the conditions indicated above.

The proton signals in the $^1$H NMR spectra from compounds **4-8, 10** were assigned based on double resonance experiments; the signals for the protons of the four methylene groups of the tropane ring appear in the spectrum in the 1.40-2.15 ppm region (Table 2). The signals from the protons of the N–$CH_2$–$CH_2$–O moiety of the oxazolidine ring are multiplets in the 2.85-4.00 ppm range. A characteristic feature of the spectra of compounds **4-8** is the presence of a multiplet signal from the 3-H proton of the tropane ring at 3.05 and a singlet in the 5.30 ppm region for the 2-H proton of the oxazolidine ring. The absence of the above-indicated signals in the $^1$H NMR spectrum of compound **10** suggests a spiro linkage between the tropane and oxazolidine rings.

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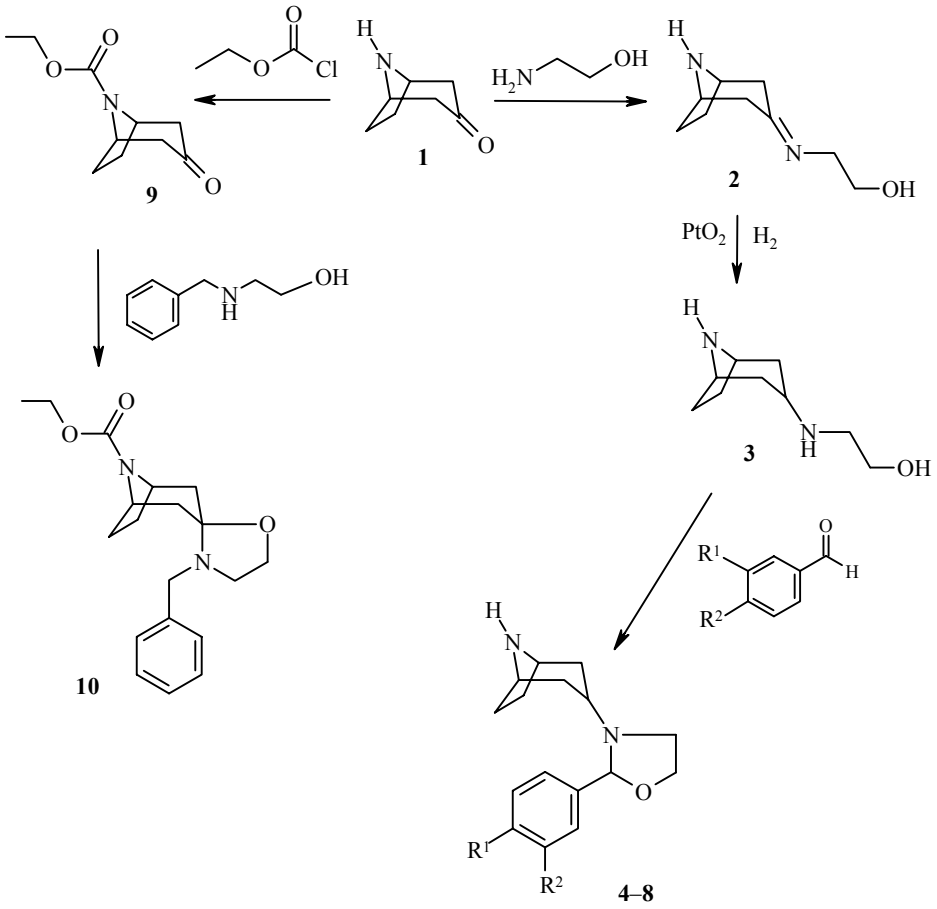
Scheme 1




**4** $R^1 = R^2 = H$; **5** $R^1 = MeO$, $R^2 = H$; **6** $R^1 = R^2 = MeO$; **7** $R^1 = Br$, $R^2 = H$; **8** $R^1 = NMe_2$, $R^2 = H$

TABLE 1. Characteristics of Oxazolidine Tropanes **4-8, 10**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C* | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **4** | $C_{16}H_{24}N_2O$ | 73.99 / 73.8 | 8.89 / 9.93 | 10.7 / 10.76 | 171-174 | 69 |
| **5** | $C_{18}H_{26}N_2O_2$ | 70.5 / 70.58 | 8.63 / 8.49 | 9.31 / 9.15 | 188-190 | 61 |
| **6** | $C_{19}H_{28}N_2O_3$ | 68.83 / 68.67 | 8.63 / 8.4 | 8.27 / 8.4 | 202-204 | 40 |
| **7** | $C_{17}H_{23}BrN_2O$ | 58.3 / 58.13 | 6.38 / 6.55 | 7.74 / 7.97 | 201-202 | 30 |
| **8** | $C_{19}H_{29}N_3O$ | 72.42 / 72.38 | 9.47 / 9.2 | 13.22 / 13.33 | 200-202 | 7 |
| **10** | $C_{19}H_{26}N_2O_3$ | 69.34 / 69.09 | 7.89 / 7.87 | 8.28 / 8.48 | 194-197 | 49 |

* For compounds **4-8**, a pressure of 1 mm Hg; for compound **10**, 2 mm Hg.

TABLE 2. $^{1}$H NMR Spectra of Oxazolidine Tropanes **4-8, 10**

| Compound | Chemical shifts, δ, ppm. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tropane ring | | | | Oxazolidine ring | | | H of aromatic system, $A_2X_2$, m | Substituents on aromatic ring (s) |
| | $CH_2$ (8H, m) | N–$CH_3$ | CH (1H, m) | 1-, 5-H (2H) | N–$CH_2$ (2H) | O–$CH_2$ (2H, m) | CH (1H, s) | | |
| **4** | 1.45-2.10 | 2.16 (3H, s) | 3.05 | 2.90 (m) | 2.90 and 3.22 (two m) | 3.87 | 5.35 | 7.25-7.60 (5H) | |
| **5** | 1.45-2.10 | 2.17 (3H, s) | 3.05 | 2.81 (m) | 2.82 and 3.20 (m) | 3.84 | 5.25 | 6.80-7.45 (4H) | 3.80 (3H, $OCH_3$) |
| **6** | 1.45-2.15 | 2.2 (3H, s) | 3.1 | 2.82 and 2.90 (two m) | 2.90 and 3.22 (two m) | 3.87 | 5.25 | 6.80-7.10 (3H) | 3.86 (6H, $(OCH_3)_2$) |
| **7** | 1.40-2.15 | 2.20 (3H, s) | 3.05 | 2.85 and 2.91 (two m) | 2.91 and 3.15 (two m) | 3.86 | 5.30 | 7.30-7.50 (4H) | |
| **8** | 1.40-2.10 | 2.2 (3H, s) | 3.05 | 2.90 (m) | 2.90 and 3.20 (two m) | 3.87 | 5.20 | 6.65-7.35 (4H) | 2.95 (6H, $(NCH_3)_2$) |
| **10** | 1.60-2.20 | —* | | 4.36 (m) | 2.75 (m) | 3.90 | | 7.20-7.95 (5H) | 3.55 (2H, $C\underline{H_2}$–Ar) |

* N(C=O)$CH_2$–$CH_3$: 1.25 (3H, t, $CH_3$); 4.15 (2H, q, $CH_2$).

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker A-250 spectrometer (250 MHz), solvent $CDCl_3$, internal standard TMS. GLC analysis of all the compounds was carried out on a Tsvet-152 chromatograph (column *l* 0.7 m, *d* 3 mm, liquid phase SE-30/5% on Chromaton-N-AW 0.16-0.20 mm). Carrier gas, nitrogen; temperature programming 75-300°C, 20°C/min.

**3-[N-(2-Hydroxyethyl)imino]tropane (2).** A mixture of tropan-3-one (**1**) (16 g, 0.11 mol) and aminoethanol (7 g, 0.11 mol) was refluxed for 6 h in benzene (100 ml) with a Dean–Stark attachment until liberation of water stopped. The reaction mixture was evaporated down and the residue was distilled under vacuum. Obtained 13 g (63%) of imine **2**; bp 129-131°C (1 mm Hg).

**3-[N-(2-Hydroxyethyl)amino]tropane (3).** $PtO_2$ (0.3 g) was added to a solution of imine **2** (13 g, 0.07 mol) in ethanol (70 ml). This was hydrogenated with stirring at room temperature until exhaustive absorption of hydrogen was achieved (1.6 l $H_2$). Then the catalyst was filtered out, the ethanol was evaporated off, and the residue was distilled under vacuum. Obtained 10.8 g (82%) of compound **3**; bp 140-141°C (1 mm Hg). $^1$H NMR spectrum, δ, ppm: 1.5-2.15 (8H, m, CH-2 tropane ring); 2.25 (3H, s, N–$CH_3$); 2.65-2.75 (2H, m, 1-, 5-H tropane ring); 2.8-2.9 (1H, m, 3-H tropane ring); 3.0-3.1 (2H, m, N–$\underline{CH_2}$); 3.6-3.7 (2H, m, $C\underline{H_2}OH$).

**3-(2-Aryloxazolidin-3-yl)tropanes 4-8.** A catalytic amount of *p*-toluenesulfonic acid was added to an equimolar solution of compound **3** and the corresponding benzaldehyde in benzene, and the mixture was refluxed with a Dean–Stark attachment until maximum liberation of water was achieved (6-8 h). The mixture was cooled, washed with water, and dried with $CaCl_2$. The solvent was distilled off, the residue was distilled under vacuum, and we obtained aryloxazolidine tropanes **4-8**.

**3-Benzyloxazolidine-2-spiro-3'-(8'-carbethoxy)nortropane (10).** A solution of N-carbethoxytropan-3-one (**9**) (4.5 g, 0.025 mol) and benzylaminoethanol (4.49 g, 0.03 mol) in toluene (35 ml) was refluxed in the presence of *p*-toluenesulfonic acid for 8 h until liberation of water stopped. The reaction mixture was treated by the method described above. The solvent was distilled off and the residue was distilled under vacuum. Obtained 4 g (49%) of compound **10**.

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