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# SYNTHESIS OF N-SUBSTITUTED AMINOALKYL DERIVATIVES OF SOME EPOXYISOINDOLES AS POTENTIAL PHARMACOLOGICAL AGENTS

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**Abstract:** Grogan and Rice reported a number of imides of epoxyisoindole sort. Some pharmacological testing was performed which revealed their bioactivity. Except of their work, only scattered examples of derivatives with oxygen-bridged ring have appeared in the literature; this approach has also been used by us in the synthesis of some new potential drugs. This paper reports the synthesis of a number of epoxyisoindole derivatives, as well as *in vitro* tests of some selected representants.

**Keywords:** epoxyisoindoles; anticancer and anti-HIV tests; oxygen-bridged rings

The derivatives of epoxyisoindoles were earlier tested as the compounds with an expected pharmacological activity. The research on these compounds was carried out in many ways. First of all, some epoxyisoindoles derivatives (Figure 1) were primarily synthesized as the potential chemotherapeutic agents (1). Some representative compounds were next submitted for the primary rodent tumor screens (consisting of murine sarcoma 180, adrenocarcinoma 755, and lymphoid leukemia 1210) (2). A number of the compounds were also assayed for the growth inhibitory activity against the KB cell line in tissue culture (2,3). Pharmacological screening of these compounds (other than anticancer) showed that hydrogen imides possessed in varying degrees a central nervous stimulant and anticonvulsant activity (4,5). Moreover, what is worthy of mention, the said compounds possessed a hypotensive activity (1,2). In addition to this, the properties of oxygen bridged rings have been reported in the literature and derivatives of the 4,7-epoxyisoindole ring system displayed a high physiological activity, accompanied by a low toxicity (2).

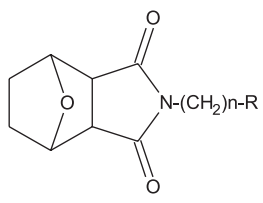


Figure 1. R represents the dialkyl group containing from 1 to 6 carbon atoms, or it may represent a heterocyclic rest, namely: piperidinyl, morpholinyl, while „n" is a number from 2 to 6.

The aforesaid information has encouraged us to design and to synthesise the a two new series of derivatives of epoxyisoindoles (Figure 2). Moreover, we have made some structural modifications within the imide group, and we have extended the mentioned fragment of the agents by adding there a cyclohexane ring. The aim of this study was to determine the influence of the said structural modifications of the synthesized compounds on their biological activity and cytotoxicity.

## EXPERIMENTAL

Melting points (uncorrected) were determined in an Electrothermal 9100 capillary apparatus; $^1$H NMR spectra were registered in $CDCl_3$ with BRUCKER (400 MHz) and UNITYplus-500 „carlos" (200 MHz) apparatuses; elemental analyses: a CHN model 2400 Perkin-Elmer; mass spectrometry: a Micromass apparatus.

### SYNTHESIS OF 5,8-DIMETHYL-3B, 9-EPOXY--3A, 4,5,6,7,8,9,9A-OCTAHYDRO-1*H*-BENZO [e] ISOINDOLE-1,3 (2*H*)-DIONE **(I)** AND 6,7-DIMETHYL-4,9-EPOXY-3A, 4,5,8,9,9A-HEXAHYDRO-1*H*-BENZO [f] ISOINDOLE-1,3 (2*H*)-DIONE **(II)**

A mixture of 3,6-dimethyl-4,5,6,7-tetrahydrobenzo [b] furan (5 g, 0.034 mole) / 5,6-dimethyl-4,7-dihydroisobenzofuran (10 g, 0.067 mole) and male-

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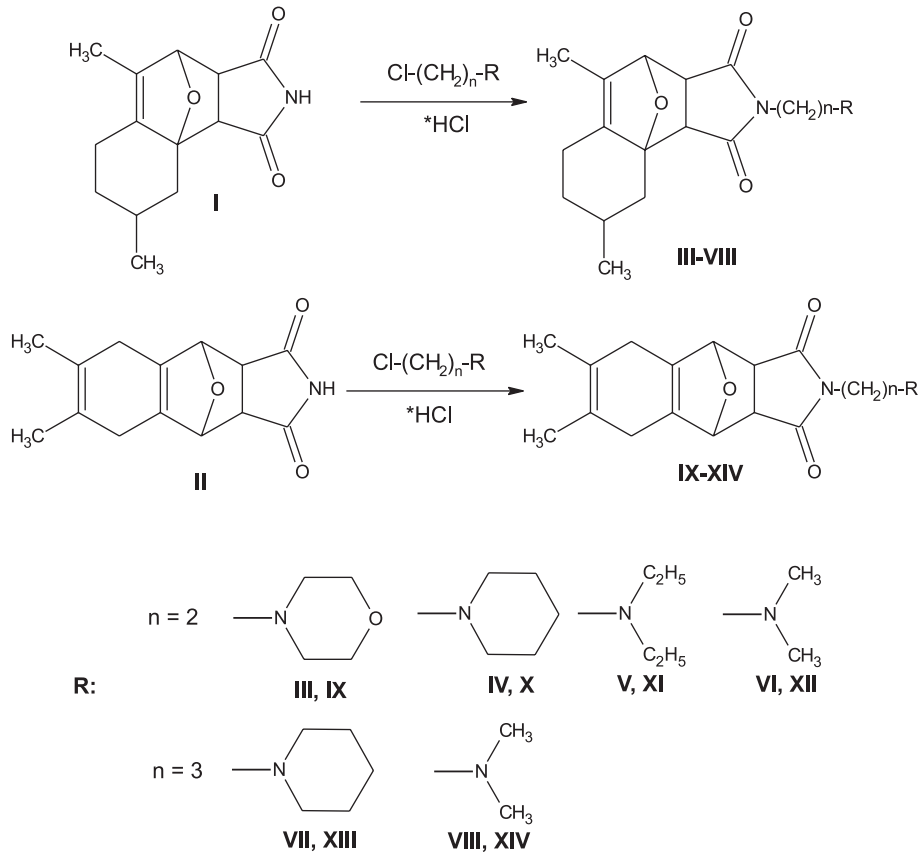


Figure 2. Scheme for preparing the reported compounds.

imide (3.3 g, 0.034 mole/ 6.5 g, 0.067 mole) in benzene (20 $cm^3$ / 50 $cm^3$) was refluxed for 2 / 1 h. Products **I** and **II** were collected by filtration and recrystallized from benzene.

**I** (yield 89 %, m. p. 152 $^0$C); $^1$H NMR (200 MHz, $CDCl_3$): 9.31 (s, 1H, NH); 4.90 (s, 1H, C1-H); 2.97 (d, J = 6.4 Hz, 1H, C3-H); 2.77 (d, J = 6.4 Hz, 1H, C2-H); 2.47 (m, 2H, C10-H); 1.82 (m, $3H_{cyclohexane}$); 1.73 (s, 3H, C6-$CH_3$); 1.47 (t, J = 12.8 Hz, $1H_{cyclohexane}$); 1.14 (m, $1H_{cyclohexane}$); 1.07 (d, J = 6.4 Hz, 3H, C8-$CH_3$).

$C_{16}H_{17}NO_3$ (247.3): calcd. C 68.00, H 6.83, N 5.65; found C 67.7, H 6.5, N 5.4.

**II** (yield 94 %, m. p. 247-248 $^0$C); $^1$H NMR (200 MHz, $CDCl_3$): 5.13 (s, 2H, C1-H, C4-H); 2.90 (s, 2H, C2-H, C3-H); 2.85 (m, 2H, C7-H, C10-H); 2.61 (m, 2H, C7-H, C10-H); 1.70 (s, 6H, C8-$CH_3$, C9-$CH_3$).

$C_{14}H_{15}NO_3$ (245.3): calcd. C 68.44, H 6.12, N 5.71; found C 68.2, H 6.0, N 5.6.

GENERAL METHOD FOR PREPARING N-AMINOALKYL DERIVATIVES OF 5,8-DIMETHYL--3B, 9-EPOXY-3A, 4,5,6,7,8, 9,9A-OCTAHYDRO--1*H*-BENZO [e] ISOINDOLE-1,3 (2*H*)-DIONE AND 6,7-DIMETYLO-4,9-EPOXY-3A, 4,5,8,9,9 A-HEXAHYDRO-1*H*-BENZO [f] ISOINDOLE-1,3 (2*H*)-DIONE

A mixture of 0.4 g (0.0016 mole) of 5,8-dimethyl-3b, 9-epoxy-3a, 4,5,6,7,8,9,9a-octahydro-1*H*--benzo [e] isoindole-1,3 (2*H*)-dione / 6,7-dimetylo--4,9-epoxy-3a,4,5,8,9,9a-hexahydro-1*H*-benzo[f]isoindole-1,3 (2*H*)-dione, 30 $cm^3$ of acetone, 0.2 g (0.0013 mole) of 98% 1,8-dizabicyclo [5.4.0] undec--7-en, 0.4 g (0.0029 mole) of $K_2CO_3$ and 0.0016 mole of an appropriate salt of secondary amine was stirred. The solvent and the excess of the amine were distilled off, and the precipitate was collected by filtration, purified by chloroform: methanol (99: 1) to give compounds **III-XIV**.

**III** (yield 71 %, oil); $^1$H NMR (400 MHz, $CDCl_3$): 4.86 (s, 1H, C1-H); 3.66 (m, 6H, C1-H, C5"-H, C6"-H); 2.94 (s, 1H, C3-H); 2.75 (d, J = 4.4 Hz, 1H, C2-H); 2.53 (m, 6H, C10-H, C3"-H, C4"-H); 1.87 (m, $3H_{cyclohexane}$, 2H, C2"-H); 1.73 (s, 3H, C6-$CH_3$); 1.47 (t, J = 12.6 Hz, $1H_{cyclohexane}$); 1.14 (m, $1H_{cyclohexane}$); 1.09 (d, J = 5.2 Hz, 3H, C8-$CH_3$).

$C_{20}H_{28}N_4O_4 \times 2H_2O$ (396.5): calcd. C 60.58, H 7.12, N 7.08; found C 60.5, H 7.1, N 7.2.

**IV** (yield 52 %, oil); $^1$H NMR (400 MHz, $CDCl_3$): 4.85 (s, 1H, C1-H); 3.66 (m, 2H, C1"-H); 2.91 (s, 1H, C3-H); 2.75 (d, J = 3.6 Hz, 1H, C2-H); 2.53 (m, 6H, C10-H, C2"-H, C3"-H, C4"-H); 1.91 (m, $3H_{cyclohexane}$); 1.72 (s, 3H, C6-$CH_3$); 1.56 (s, 6H, C5"-H, C6"-H, C7"-H); 1.46 (t, J = 12.6 Hz, $1H_{cyclohexane}$); 1.16 (m, $1H_{cyclohexane}$); 1.08 (d, J = 6.4 Hz, 3H, C8--$CH_3$).

$C_{21}H_{30}N_2O_3 \times 2H_2O$ (394.5): calcd. C 67.35, H 8.02, N 7.27; found C 67.1, H 8.0, N 7.3.

**V** (yield 69 %, oil); $^1$H NMR (400 MHz, $CDCl_3$): 4.85 (s, 1H, C1-H); 3.55 (t, J = 6.8 Hz, 2H, C1"-H); 2.92 (d, J = 6.4Hz, 1H, C3-H); 2.73 (d, J = 6.4 Hz, 1H, C2-H); 2.59 (m, 8H, C10-H, C2"-H, N $(CH_2)_2$); 1.89 (m, $3H_{cyclohexane}$); 1.72 (s, 3H, C6-$CH_3$); 1.46 (t, J = 12.8 Hz, $1H_{cyclohexane}$); 1.16 (m, $1H_{cyclohexane}$); 1.08 (d, J = 6.4 Hz, 3H, C8-$CH_3$); 1.00 (t, J = 7.0 Hz, 6H, 2*$CH_3$).

$C_{20}H_{26}N_2O_3 \times 4H_2O$ (418.5): calcd. C 67.63, H 8.51, N 7.88; found C 67.7, H 8.5, N 7.9.

**VI** (yield 49 %, m. p. 103-104$^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 4.86 (s, 1H, C1-H); 3.59 (t, J = 6.8 Hz, 2H, C1"-H); 2.94 (d, J = 6.4Hz, 1H, C3-H); 2.75 (d, J = 6.4 Hz, 1H, C2-H); 2.56 (m, 4H, C10-H, C2"-H); 2.26 (s, 6H, N $(CH_3)_2$); 1.91 (m, $3H_{cyclohexane}$); 1.73 (s, 3H, C6-$CH_3$); 1.47 (t, J = 12.8 Hz, $1H_{cyclohexane}$); 1.17 (m, $1H_{cyclohexane}$); 1.09 (d, J = 6.4 Hz, 3H, C8--$CH_3$).

$C_{18}H_{26}N_2O_3$ (318.4): calcd. C 67.89, H 8.23, N 8.80; found C 67.5, H 8.2, N 8.8.

**VII** (yield 51 %, m. p. 77-78 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 4.86 (s, 1H, C1-H); 3.50 (t, J = 7.2 Hz, 2H, C1"-H); 2.99 (d, J = 6.2Hz, 1H, C3-H); 2.69 (d, J = 6.6 Hz, 1H, C2-H); 2.50 (m, 2H, C10-H); 2.33 (m, 6H, C3"-H, C4"-H, C5"-H); 1.86 (m, $3H_{cyclohexane}$, 5H, C6-$CH_3$, C2"-H); 1.61 (m, 7H, $1H_{cyclohexane}$, C6"-H, C7"-H, C8"-H); 1.17 (m, $1H_{cyclohexane}$); 1.08 (d, J = 6.4 Hz, 3H, C8-$CH_3$).

$C_{22}H_{32}N_2O_3$ (372.5): calcd. C 70.93, H 8.66, N 7.52; found C 71.0, H 8.6, N 7.3.

**VIII** (yield 44 %, m. p. 102-103 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 4.87 (s, 1H, C1-H); 3.52 (t, J = 6.8 Hz, 2H, C1"-H); 2.90 (d, J = 6.4Hz, 1H, C3-H); 2.70 (d, J = 6.4 Hz, 1H, C2-H); 2.57 (m, 2H, C10--H); 2.29 (m, 2H, C3"-H); 2.21 (s, 6H, N $(CH_3)_2$); 1.85 (m, $3H_{cyclohexane}$, 5H, C6-$CH_3$, C2"-H); 1.43 (t, J = 13.2 Hz, $1H_{cyclohexane}$); 1.16 (m, $1H_{cyclohexane}$); 1.08 (d, J = 6.4 Hz, 3H, C8-$CH_3$).

$C_{19}H_{28}N_2O_3$ (332.4): calcd. C 68.65, H 8.49, N 8.43; found C 68.7, H 8.4, N 8.2.

**IX** (yield 66 %, m. p. 154-155 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 5.08 (s, 2H, C1-H, C4-H); 3.67 (m, 6H C1"-H, C5"-H, C6"-H); 2.91 (m, 4H, C2-H, C3-H, C7-H, C10-H); 2.61 (m, 8H, C7-H, C10-H, C2"-H, C3"-H, C4"-H); 1.68 (s, 6H, C8-$CH_3$, C9--$CH_3$).

$C_{20}H_{26}N_2O_4$ (358.4): calcd. C 67.02, H 7.31, N 7.82; found C 67.1, H 7.2, N 7.8.

**X** (yield 46 %, m. p. 149-150 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 5.07 (s, 2H, C1-H, C4-H); 3.65 (m, 2H C1"-H); 2.90 (m, 4H, C2-H, C3-H, C7-H, C10-H); 2.61 (m, 8H, C7-H, C10-H, C2"-H, C3"-H, C4"-H); 1.68 (s, 6H, C8-$CH_3$, C9-$CH_3$); 1.53 (s, 4H, C5"-H, C6"-H); 1.40 (s, 2H, C7"-H).

$C_{21}H_{28}N_2O_3$ (356.5): calcd. C 70.76, H 7.92, N 7.86; found C 70.7, H 8.0, N 7.5.

**XI** (yield 39 %, m. p. 110-111 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 5.07 (s, 2H, C1-H, C4-H); 3.58 (m, 2H C1"-H); 2.90 (m, 4H, C2-H, C3-H, C7-H, C10-H); 2.61 (m, 8H, C7-H, C10-H, C2"-H, N $(CH_2)_2$); 1.68 (s, 6H, C8-$CH_3$, C9-$CH_3$); 1.00 (s, 6H, 2*$CH_3$).

$C_{20}H_{28}N_2O_3$ (344.4): calcd. C 69.74, H 8.19, N 8.13; found C 69.4, H 8.3, N 8.2.

**XII** (yield 29 %, m. p. 143-144 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 5.07 (s, 2H, C1-H, C4-H); 3.65 (m, 2H, C1"-H); 2.95 (m, 4H, C2-H, C3-H, C7-H, C10-H); 2.60 (m, 4H, C7-H, C10-H, C2"-H); 2.30 (s, 6H, N $(CH_3)_2$); 1.68 (s, 6H, C8-$CH_3$, C9-$CH_3$).

$C_{18}H_{24}N_2O_3$ (284.4): calcd. C 76.02, H 8.51, N 9.85; found C 76.0, H 8.4, N 9.9.

**XIII** (yield 51%, m. p. 113-115$^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 5.06 (s, 2H, C1-H, C4-H); 3.55 (m, 2H C1"-H); 2.91 (m, 4H, C2-H, C3-H, C7-H, C10-H); 2.59 (m, 8H, C7-H, C10-H, C3"-H, C4"-H, C5"-H); 1.90 (s, 2H, C2"-H); 1.67 (s, 10H, C8-$CH_3$, C9-$CH_3$, C6"-H, C7"-H); 1.46 (s, 2H, C8"-H).

$C_{22}H_{30}N_2O_3$ (370.5): calcd. C 71.32, H 8.16, N 7.56; found C 71.1, H 8.0, N 7.6.

**XIV** (yield 49 %, m. p. 132-133 $^0$C); $^1$H NMR (400 MHz, $CDCl_3$): 5.07 (s, 2H, C1-H, C4-H); 3.53

Table 1. Percent growth of the treated cells as compared to the untreated control cells

| Comp. | Concentration (Molar) | Percent growth | | |
|---|---|---|---|---|
| | | MCF-7 | NCI-H460 | SF-268 |
| **VI** | $1.00\times10^{-4}$ | 114 | 119 | 105 |
| **XIV** | $1.00\times10^{-4}$ | 99 | 115 | 85 |

Table 2. Approximate values for 50% inhibitory concentration $IC_{50}$ for cell growth

| Comp. | $IC_{50}$ (Molar) | Comp. | $IC_{50}$ (Molar) |
|---|---|---|---|
| **I** | $>2.00\times10^{-4}$ | **V** | $>2.00\times10^{-4}$ |
| **II** | $>2.00\times10^{-4}$ | **IX** | $>2.00\times10^{-4}$ |
| **III** | $>2.00\times10^{-4}$ | **XI** | $>2.00\times10^{-4}$ |
| **IV** | $>2.00\times10^{-4}$ | **XIII** | $1.22\times10^{-4}$ |

(t, J = 7.1 Hz, 2H C1”-H); 2.90 (m, 4H, C2-H, C3-H, C7-H, C10-H); 2.60 (m, 2H, C7-H, C10-H); 2.28 (m, 2H, C3”-H); 2.21 (s, 6H, N $(CH_3)_2$); 1.74 (m, 2H, C2”-H); 1.68 (s, 6H, C8-$CH_3$, C9-$CH_3$).

$C_{19}H_{26}N_2O_3$ (339.4): calcd. C 69.06, H 7.93, N 8.48; found C 69.2, H 8.1, N 8.3.

## CONCLUSIONS

We designed and synthesized two series of N-substituted aminoalkyl derivatives of some epoxyisoindoles. Compounds **VI** and **XIV** were submitted for cytotoxicity testing in the National Cancer Institute in *in vitro* drug discovery screen. Initially, they had been evaluated in the 3-cell line panel consisting of the MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS) (6). Table 1 is showing the result of anticancer test. Compounds **VI** and **XIV** which did not reduce the growth of any one of the cell lines, not passed on to further testing for the full panel of 60 cell lines over 5-log dose range.

Compounds **I**-**V**, **IX**, **XI**, **XIII** were tested for anti-HIV activity by NCI. The antiviral assay basically involves the killing of T4 lymphocytes by HIV (7). All anti-HIV test results are presented in Table 2. With the exception of **XIII** ($IC_{50} = 1.22\times10^{-4}$), the values for the remaining compounds were not determined ($IC_{50} > 2.00\times10^{-4}$. The therapeutic index has not been calculated for each test. Considering, none of the compounds showed antiviral activity.

**Acknowledgements**

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