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Synthesis and Conformational Studies on some Nitro- and Aminophthalideisoquinoline Derivatives

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Summary. Nitro- and Aminophthalideisoquinolines were synthesized with a new efficient method. The molecular conformation of these derivatives was studied by ^{1}H NMR methods. On the basis of these studies tritoqualine was to be found the *erythro* racemate.

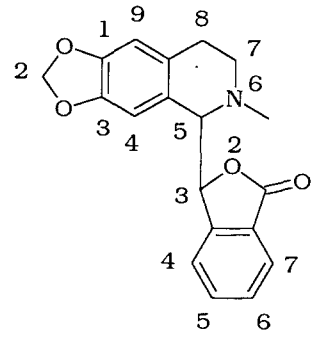
Keywords. Aminophthalideisoquinolines; Conformational analysis; Nitrophthalideisoquinolines; Reduction with ammonium formate.

Synthese und Konformationsuntersuchungen von Nitro- und Aminophthalidisochinolin

Zusammenfassung. Nitro- und Aminophthalidisochinoline wurden nach einem neuen effizienten Verfahren hergestellt. Konformationsuntersuchungen dieser Verbindungen wurden mit Hilfe von ^{1}H-NMR-Methoden vorgenommen.

Introduction

Synthetic aminophthalideisoquinolines represent an important group of phthalideisoquinolines. The favourable pharmacological properties of these compounds have been known for a long time. Tritoqualine (**5b**) has been used in Europe as an anti-allergic agent since 1963 [1]. Japanese authors reported about the hepatoprotective activity of these compounds [2]. All the nitro and aminophthalideiso-

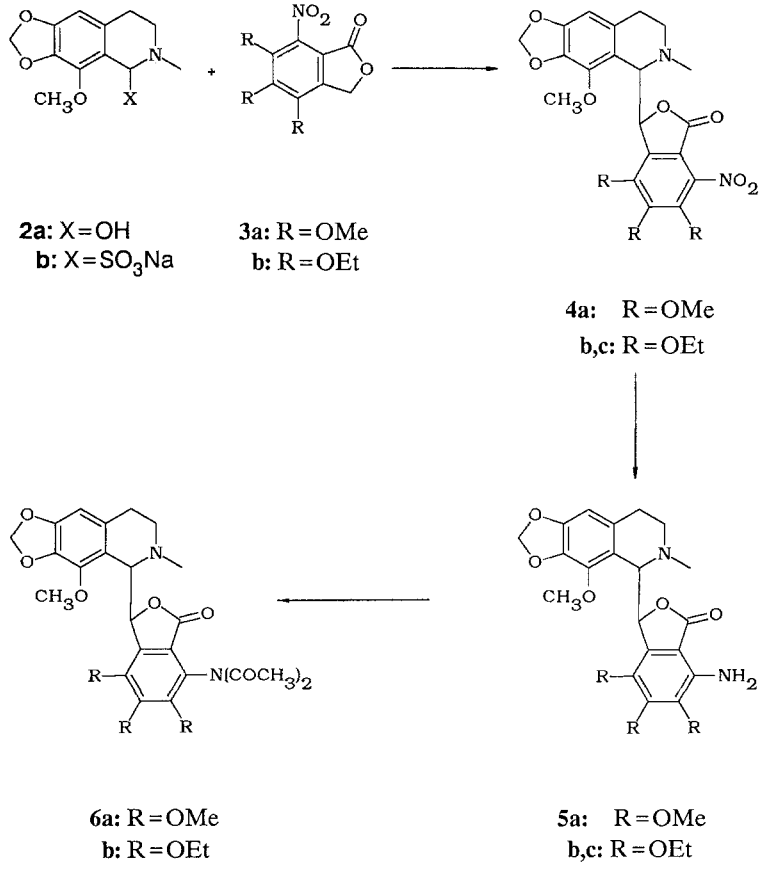


quinolines contain the skeleton depicted in formula **1**. Nitro and aminophthalide-isoquinolines have two chiral centers. They exist as two diastereomeric pairs of enantiomers i.e. (−)-*erythro* (3*S*,5*R*), (+)-*erythro* (3*R*,5*S*), (−)-*threo* (3*R*,5*R*), (+)-*threo* (3*S*,5*S*) and two racemates *erythro* (3*SR*,5*RS*) and *threo* (3*RS*,5*RS*). Here we report a new practical synthesis and conformational studies of tritoqualine and some analogues.

Results and Discussion

7-Nitro-4,5,6-triethoxyphthalide (**3b**) and cotarnine (**2a**) are key intermediates of the tritoqualine synthesis. **3b** can be prepared from gallic acid as a starting material by reacting with diethyl sulfate, and the triethoxybenzoic acid obtained is then reacted with formaldehyde in the presence of catalytic amounts of mineral acid. Nitration of the triethoxyphthalide yields then **3b** [10–16].

Cotarnine (**2a**) was prepared for the first time by the oxidative degradation of noscapine with mangan dioxyde in diluted sulfuric acid or with nitric acid. The reaction resulted in cotarnine (**2a**) and opianic acid. Salway [3a] reported the first total synthesis of cotarnine: since then several methods have been published [3b] using myristicin aldehyde as starting material. In these syntheses the Bischler–Napieralski reaction was applied to construct the isoquinoline skeleton. Several publications have appeared recently describing the total synthesis of cotarnine



[4, 5] and reaction intermediates [6, 7, 8] starting from 2-methoxy-3,4-(methylenedioxy)-benzaldehyde (croweacin aldehyde) and using a modified Pomeranz–Fritsch isoquinoline synthesis as a key step.

The key intermediates are generally reacted in aliphatic alcohol. In the condensation reaction either (3*RS*,5*RS*) A-mer or (3*SR*,5*RS*) B-mer can be

Table 1. Physical constants of compounds **4a–6b**

Comp.	Mol. formula	M.w.	M.p. (°C)	R_f[a]	MS
4a	$C_{23}H_{24}N_2O_{10}$	488.44	191	0.54	488(M^+, 12), 269(100)
4b	$C_{26}H_{30}N_2O_{10}$	530.52	148–49	0.66	530(M^+, 3), 220(100)
4c	$C_{26}H_{30}N_2O_{10}$	530.52	147–50	0.29	530(M^+, 2), 220(100)
5a	$C_{23}H_{26}N_2O_8$	458.56	192–93	0.42	458(M^+, 2), 220(100)
5b	$C_{26}H_{32}N_2O_8$	500.54	184–85	0.62	500(M^+, 2), 220(100)
5c	$C_{26}H_{32}N_2O_8$	500.54	96–97	0.35	500(M^+, 4), 200(100)
6a	$C_{27}H_{30}N_2O_{10}$	542.53	140–41	0.38	543$(M+H)^+$[b]
6b	$C_{30}H_{36}N_2O_{10}$	584.61	143–44	0.39	585$(M+H)^+$[b]

[a] Benzene–methanol = 8:2 (*v*/*v*)

[b] With thermospray technique

Table 2. ^{1}H-NMR data of compounds **4a–6b** (200 MHz, $CDCl_3$, δ in ppm relative to *TMS*, *J* in Hz)

Comp.	^{1}H-NMR Data
4a	H-5 (4.47, 1 H, d, $J_{5,3} = 1.7$), H-3 (5.71, 1 H, d, $J_{3,5} = 1.7$), H-9 (6.35, 1 H, s), OCH_2O (5.89, 2 H, m), OCH_3(4) (4.0–4.15, 12 H, s), NCH_3 (2.10, 3 H, s), CH_2-7,8 (2.3–3.2, 4 H, m)
4b	H-5 (4.53, 1 H, d, $J_{5,3} = 1.8$), H-3 (5.66, 1 H, d, $J_{3,5} = 1.8$), H-9 (6.32, 1 H, s), OCH_2O (5.86, 2 H, m), OCH_3 (4.10, 3 H, s), NCH_3 (2.08, 3 H, s), OCH_2(3) (4.1–4.4, 6 H, m), CH_3(3) (1.3–1.5, 9 H, m), CH_2-7,8 (2.3–3.1, 4 H, m)
4c	H-5 (4.55, 1 H, d, $J_{5,3} = 1.7$), H-3 (5.84, 1 H, d, $J_{3,5} = 1.7$), H-9 (6.26, 1 H, s), OCH_2O (5.83, 2 H, s), OCH_3 (3.68, 3 H, s), NCH_3 (2.57, 3 H, s), OCH_2(3) (4.0–4.35, 6 H, m), CH_3(3) (1.3–1.5, 9 H, m), CH_2-7,8 (2.2–3.1, 4 H, m)
5a	H-5 (4.52, 1 H, d, $J_{5,3} = 1.74$), H-3 (5.65, 1 H, d, $J_{3,5} = 1.74$), H-9 (6.35, 1 H, s), OCH_2O (5.87, 2 H, m), OCH_3(4) (3.8–4.1, 12 H, s), NCH_3 (2.16, 3 H, s), CH_2-7,8 (2.3–3.2, 4 H, m), NH_2 (5.11, 2 H, s)
5b	H-5 (4.54, 1 H, d, $J_{5,3} = 1.74$), H-3 (5.58, 1 H, d, $J_{3,5} = 1.74$), H-9 (6.34, 1 H, s), OCH_2O (5.82, 2 H, m), OCH_3 (4.05, 3 H, s), NCH_3 (2.15, 3 H, s), OCH_2(3) (3.9–4.3, 6 H, m), CH_3(3) (1.3–1.5, 9 H, m), CH_2-7,8 (2.3–3.1, 4 H, m), NH_2 (5.05, 2H, s)
5c	H-5 (4.59, 1 H, d, $J_{5,3} = 1.6$), H-3 (5.77, 1 H, d, $J_{3,5} = 1.6$), H-9 (6.27, 1 H, s), OCH_2O (5.8, 2 H, s), OCH_3 (3.54, 3 H, s), NCH_3 (2.56, 3 H, s), OCH_2(3) (3.8–4.4, 6 H, m), CH_3(3) (1.2–1.5, 9 H, m), CH_2-7,8 (2.4–3.2, 4 H, m), NH_2 (4.97, 2 H, s)
6a	H-5 (4.43, 1 H, d, $J_{5,3} = 1.4$), H-3 (5.64, 1 H, d, $J_{3,5} = 1.4$), H-9 (6.54, 1 H, s), OCH_2O (5.89, 2 H, m), OCH_3(4) (3.8–4.2, 12 H, s), NCH_3 (1.99, 3 H, s), CH_2-7,8 (2.2–3.0, 4 H, m), $N(COCH_3)_2$ (2.11, 2.52, 6 H, s)
6b	H-5 (4.48, 1 H, d, $J_{5,3} = 1.58$), H-3 (5.59, 1 H, d, $J_{3,5} = 1.58$), H-9 (6.36, 1 H, s), OCH_2O (5.9, 2 H, m), OCH_3 (4.11, 3 H, s), NCH_3 (1.99, 3 H, s), OCH_2(3) (3.8–4.4, 6 H, m), CH_3(3) (1.2–1.6, 9 H, m), CH_2-7,8 (2.2–3.0, 4 H, m), $N(COCH_3)_2$ (2.09, 2.51, 6 H, s)

Table 3. ^{1}H-(^{1}H) NOE values of compounds **4a–6b**

Comp.	NOE data[a]
4a, 4b, 5a, 5b	$f_{H\text{-}5}(H\text{-}3) = 19–23\%$, $f_{H\text{-}3}(H\text{-}5) = 12–15\%$
6a, 6b	$f_{H\text{-}5}(NCH_3) = 2–4\%$, $f_{NCH_3}(H\text{-}5) = 15–19\%$, $f_{OCH_3}(H\text{-}3) = 3–7\%$
4c, 5c	$f_{H\text{-}5}(H\text{-}3) = 11–13\%$, $f_{H\text{-}3}(H\text{-}5) = 11–12\%$
	$f_{H\text{-}5}(NCH_3) = 2–3\%$, $f_{NCH_3}(H\text{-}5) = 16–17\%$, $f_{NCH_3}(H\text{-}3) = 6–8\%$

[a] The irradiated protons are given in subscript, while the protons which show intensity enhancement are in brackets

produced. The A/B ratio depends on the reaction period and the concentration of the solution [13–16]. This type of reaction was first reported by Robinson and Hope. The condensation reaction of cotarnine and nitro meconine gave almost a quantitative yield of β-nitro gnoscopine [9]. The mixture of **4b** and **4c** is reduced by a method generally used for the reduction of aromatic nitro compounds [10–16]. Then the epimerization of the aminophthalideisoquinoline can be performed in aliphatic alcohol by an alkali hydroxide. In this way the **5c** component of the mixture can be converted into **5b**.

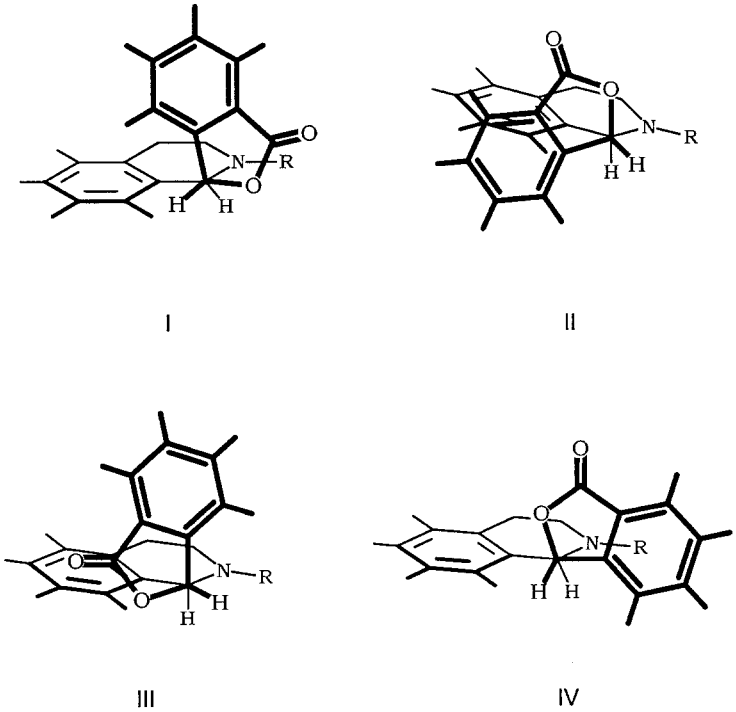


Fig. 1. Alternative conformations (partial formulae) of nitro and aminophthalideisoquinolines. **I** and **II** *erythro* configuration; **III** and **IV** *threo* configuration

In our experiment **2b** and **3b** were condensed in methanol at 80 °C resulting in a mixture of **4b** and **4c**. The mixture was separated by column chromotography or by fractional crystallization. In our experiment the condensation of **2b** and **3a** resulted in the formation of the *erythro* racemate **4a**. For the reduction of nitro phthalideisoquinolines we introduced two new methods: compounds **4a, 4b, 4c** were reduced with hydrazine hydrate in hot methanol in the presence of Raney-Ni or with ammonium formate in a methanol/tetrahydrofuran mixture in the presence of Pd/C. The advantage of these procedures is the short reaction time. The separation of the mixture of **5b** and **5c** was carried out by column chromatography. The characteristics of the prepared compounds are summarized in Table 1.

The determination of the structure and the stereochemistry of the phthalide-isoquinoline derivatives **4a–6b** was carried out by ^{1}H-NMR methods. The ^{1}H-NMR data are given in Table 2. The relative configuration of the chiral centers (C-5 and C-3) and the favoured conformation of the studied compounds were corroborated by 1 D ^{1}H-(^{1}H)NOE difference experiments. The predominance of conformation **I**, (Fig. 1) for compounds **4a, 4b, 5a, 5b, 6a, 6b** is verified by the strong dipole–dipole interactions observed between H-5 and H-3 protons, and H-5 and NCH_3 protons respectively (Table 3). The NOE effect measured between OCH_3(4) and H-3 and the absence of observable NOE between H-3 and NCH_3 protons also corroborate the preference of conformation **I** for these derivatives. In the case of compounds **4c** and **5c** the NCH_3 protons contribute to the dipolar relaxation of both H-3 and H-5 protons indicating the predominance of conformation **III**. The absence of a NOE effect between OCH_3(4) and H-3 protons, and the strong dipolar interaction observed between H-5 and H-3 protons also support conformer III as a preferred conformation of these derivatives.

Experimental Part

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Thin-layer chromatography was performed on Silica gel 60 F_{254} (MERCK 5554) layer using benzene–*methanol* = 8:2 (*v/v*) as eluant. Mass spectra were obtained on a VG 7035 instrument in EI mode at 70 eV. All ^{1}H-NMR experiments were carried out on a BRUKER WP 200 SY spectrometer. ^{1}H-NMR spectra were obtained at ambient temperature for ca. 0.1 *M* solutions in $CDCl_3$. Nuclear Overhauser enhancement (NOE) experiments were performed in the difference mode using the line selective, frequency jumping saturation technique [17, 18].

7-Nitro-4,5,6-trimethoxy-3(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo(4,5-g)-isoquinolin-5-yl)-1(3H)-isobenzofuranone (**4a**)

A mixture of 4.3 g **3a** (16 mmol), 5.2 g **2b** (16 mmol), 2.65 g potassium carbonate and 160 ml methanol was stirred at 80 °C for 4 h and then cooled. H_2O (96 ml) was added with stirring, and the deposited solid was collected by filtration and washed with cold methanol. Yield 4.45 g (57%).

7-Nitro-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo(4,5-g)-isoquinolin-5-yl)-1(3H)-isobenzofuranone (**4b, 4c**)

A mixture of 5 g **3b** (16 mmol), 5.2 g **2b**, 2.65 g potassium carbonate and 160 ml methanol was stirred at 80 °C for 4 h. The mixture was cooled to room temperature and H_2O (96 ml) was added with stirring. The solid was collected by filtration and washed with cold methanol. Yield 5.28 g (62%). The mixture

of *erythro* and *threo* racemates was either separated by column chromatography on Kieselgel using benzene–methanol = 8:2 (*v/v*) or by fractional crystallization from methanol.

7-Amino-4,5,6-trimethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo(4,5-g)-isoquinolin-5-yl)-1(3H)-isobenzofuranone (**5a**)

3.9 g **4a** (8 mmol) was added to the suspension of 0.39 g Raney-Ni and 95 ml methanol. To the resulting suspension a solution of 1.95 ml 98% hydrazine hydrate in 95 ml methanol was added at 0 °C. The reaction mixture was refluxed for 15–20 min. The catalyst was removed by filtration. The resulting solution was allowed to stand at 0 °C for 2 h. The crystalline product was separated by filtration. Yield 3.07 g (84%).

7-Amino-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo(4,5-g)-isoquinolin-5-yl)-1(3H)-isobenzofuranone (**5b**, **5c**)

A. A mixture of 4.24 g **4b** and **4c** (8 mmol) (or separately **4b** and **4c**) was added to the suspension of 0.42 g Raney-Ni and 95 ml methanol. 1.95 ml 98% hydrazine hydrate was added in 95 ml methanol to the resulting suspension. The mixture was boiled for 15–20 min. The catalyst was filtered out and the resulting solution was treated the same way as described above for **5a**. Yield 3.16 g (79%).

B. A mixture of 2.65 g **4b** and **4c** (5 mmol) (or separately **4b** and **4c**) was dissolved in 20 ml tetrahydrofuran. The resulting solution was added to a suspension of 0.26 g Pd/C and 20 ml methanol. 1.57 g (25 mmol) finely powdered anhydrous ammonium formate was added in small portions under nitrogen. The mixture was stirred at 35 °C for 1 h. The catalyst was removed by filtration, then the solution was evaporated to dryness. The residue was dissolved in 25 ml water and the solution was extracted with chloroform. The combined organic phase was washed with saturated sodium chloride solution and dried with Na_2SO_4. The yellow oil obtained after the evaporation of the solvent was crystallized from methanol. Yield 1.50 g (60%). **5b** and **5c** was separated on a Kieselgel column using benzene–methanol = 8:2 (*v/v*).

7-Diacetamido-4,5,6-trimethoxy-3(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo-(4,5-g)-isoquinolin-5-yl)-1(3H)-isobenzofuranone (**6a**)

2 g **5a** (4.3 mmol) was dissolved in 50 ml acetic anhydride. The solution was stirred for 5 h at 100 °C and then cooled to room temperature. The mixture was poured into ice water, made alkaline with ammonia and extracted with chloroform. The combined organic phase was dried with Na_2SO_4. The solvent was evaporated and the residue was crystallized from methanol. Yield 1.30 g (59%).

7-Diacetamido-4,5,6-triethoxy-3(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo-(4,5-g)-isoquinolin-5-yl)-1(3H)-isobenzofuranone (**6b**)

2.94 g **5b** (tritoqualine, 5.8 mmol) was stirred in 70 ml acetic anhydride at 100 °C for 5 h. The resulting solution was treated as described above. The yellow oil was crystallized from methanol. Yield 1.60 g (50%).

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