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Nenitzescu Synthesis of Carbamate Indole Derivatives from *N*,*N′*-Bis(methoxycarbonyl)-*p*-benzoquinone Diimine

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Abstract—*N*,*N′*-Bis(methoxycarbonyl)-*p*-benzoquinone diimine reacted with 4-(cyclohex-1-en-1-yl)- and 4-(cyclopent-1-en-1-yl)morpholines in methylene chloride at room temperature to give morpholino-substituted cyclohexane- and cyclopentane-fused indole derivatives. Heating of the latter in boiling 10% hydrochloric acid led to the formation of methyl 6-(methoxycarbonylamino)-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole-9-carboxylate and methyl 7-(methoxycarbonylamino)-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole-4-carboxylate, respectively. The reaction of *N*,*N′*-bis(methoxycarbonyl)-*p*-benzoquinone diimine with 4-benzylaminopent-3-en-2-one in CH_2Cl_2 in the presence of $BF_3 \cdot Et_2O$ on heating gave methyl 3-acetyl-2-methyl-(5-methoxycarbonylamino)-1*H*-indole-1-carboxylate.

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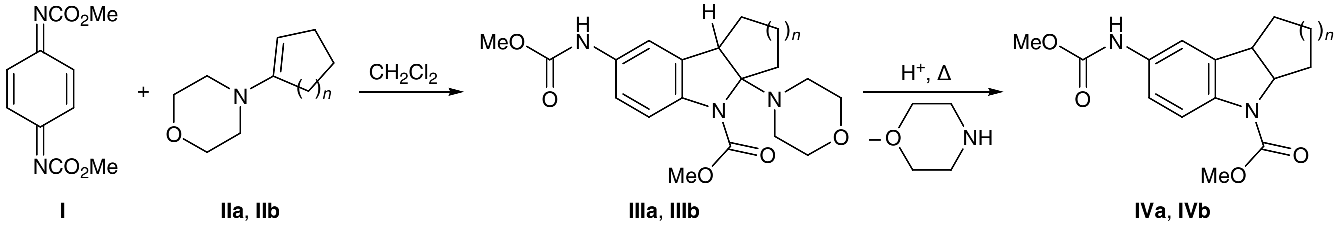
Nenitzescu reaction, i.e., condensation of quinones and quinoid compounds with enamines and some other derivatives, underlies the most important procedure for the synthesis of 5-hydroxyindoles [1]. Its synthetic potential was considered in detail in [2–5]. Nenitzescu reactions involving various heterocyclic quinones [6, 7] and *N*-arylsulfonyl-1,4-benzoquinone monoimines [8] were also reported.

The behavior of *N*,*N′*-(dialkoxycarbonyl)benzoquinone diimines in the Nenitzescu reaction was not stidued previously. To fill this gap we examined reactions of *N*,*N′*-bis(methoxycarbonyl)-*p*-benzoquinone diimine (**I**) with 4-(cyclohex-1-en-1-yl)morpholine (**IIa**) and 4-(cyclopent-1-en-1-yl)morpholine (**IIb**) in methylene chloride at room temperature and with 4-benzylaminopent-3-en-2-one (**IIc**) in the presence of $BF_3 \cdot Et_2O$ on heating. We have found that enamines **IIa** and **IIb** react with quinone diimine **I** to give initially morpholino-substituted indole derivatives **IIIa** and **IIIb**; on heating in 10% hydrochloric acid, compounds **IIIa** and **IIIb** lose morpholine molecule to form indoles **IVa** and **IVb** (Scheme 1). Unlike initial quinone diimine **I**, the IR spectra of **IIIa** and **IIIb** contain absorption bands typical of NH groups and aromatic ring at 3330 and 1610–1525 cm^{-1}, respectively.

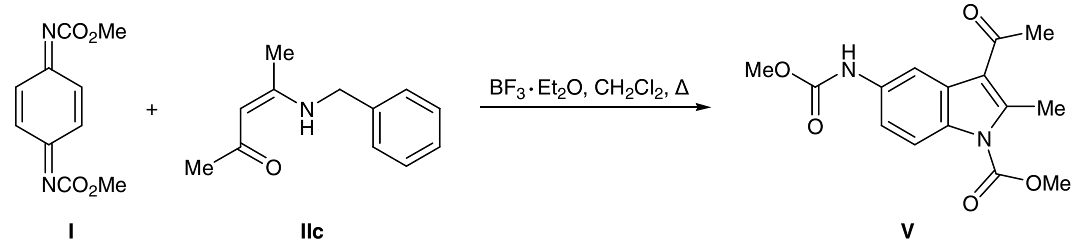
By heating a mixture of equimolar amounts of quinonediimine **I** and 4-benzylaminopent-3-en-2-one (**IIc**) in methylene chloride in the presence of boron trifluoride–ether complex we obtained methyl 3-acetyl-2-methyl-(5-methoxycarbonylamino)-1*H*-indole-1-carboxylate (**V**) (Scheme 2). Compound **V** was synthesized by us previously [9] by reaction of **I** with acetylacetone in the presence of sodium methoxide,

Scheme 1.



$n = 2$ (**a**), 1 (**b**).

Scheme 2.



followed by cyclization of the initially formed Michael adduct on heating in boiling 22% hydrochloric acid. The structure of compounds **IVa**, **IVb**, and **V** was confirmed by the IR and ^{1}H NMR spectra and elemental analyses.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.13 MHz from solutions in DMSO-d_6; the chemical shifts were measured relative to tetramethylsilane as internal reference. The IR spectra were measured in the range from 4000 to 400 cm^{-1} from samples dispersed in mineral oil on an IKS-29 spectrophotometer. The purity of the products was checked by TLC on Silufol UV-254 plates.

Methyl 6-(methoxycarbonylamino)-9a-morpholino-1,2,3,4,4a,9a-hexahydrocarbazole-9-carboxylate (IIIa). 4-(Cyclohex-1-en-1-yl)morpholine (**IIa**), 0.76 ml (4.5 mmol), was added to a solution of 1 g (4.5 mmol) of compound **I** in methylene chloride. The mixture was kept for 8 h at 20°C and poured into 25 ml of petroleum ether, and the precipitate was filtered off, dried in air, and recrystallized from methylene chloride–petroleum ether (1:1, by volume). Yield 1.3 g (75%), colorless crystals, mp 192–194°C. IR spectrum, ν, cm^{-1}: 3300 (NH); 1720 (C=O); 1610, 1540 (C=C$_{\mathrm{arom}}$). Found, %: C 61.61; H 6.48; N 11.00. $C_{20}H_{27}N_3O_5$. Calculated, %: C 61.70; H 6.94; N 10.80.

Methyl 7-(methoxycarbonylamino)-3a-morpholino-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole-4-carboxylate (IIIb) was synthesized in a similar way from 1 g (4.5 mmol) of quinone diimine **I** and 0.66 ml (4.5 mmol) of enamine **IIb**. Yield 1.2 g (72%), colorless crystalline substance, mp 158–159°C. IR spectrum, ν, cm^{-1}: 3330 (NH); 1710 (C=O); 1610, 1525 (C=C$_{\mathrm{arom}}$). Found, %: C 61.04; H 6.58; N 11.00. $C_{19}H_{25}N_3O_5$. Calculated, %: C 60.80; H 6.67; N 11.20.

Methyl 6-(methoxycarbonylamino)-1,2,3,4,4a,9a-hexahydrocarbazole-9-carboxylate (IVa). A suspension of 1 g (2.57 mmol) of compound **IIIa** in 25 ml of 10% hydrochloric acid was heated for 1 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, dried in air, and purified by column chromatography on neutral alumina using ethyl acetate as eluent. Yield 0.65 g (84%), colorless crystals, mp 206–207°C. IR spectrum, ν, cm^{-1}: 3310 (NH); 1710 (C=O); 1570, 1510 (C=C$_{\mathrm{arom}}$). ^{1}H NMR spectrum, δ, ppm: 8.68 br.s (1H, NH), 7.83 d (1H, H$_{\mathrm{arom}}$, $J = 9.8$ Hz), 7.65 s (1H, H$_{\mathrm{arom}}$), 7.55 d (1H, H$_{\mathrm{arom}}$, $J = 9.8$ Hz), 3.95 s (3H, NCO$_2$Me), 3.74 s (3H, NHCO$_2$**Me**), 3.15–3.38 m (2H, CH$_2$), 2.53–2.76 m (2H, CH$_2$), 2.00–1.65 m (4H, CH$_2$). Found, %: C 63.37; H 6.04; N 9.59. $C_{16}H_{18}N_2O_4$. Calculated, %: C 63.58; H 5.96; N 9.27.

Methyl 7-(methoxycarbonylamino)-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole-4-carboxylate (IVb) was synthesized in a similar way from 0.8 g (2.1 mmol) of compound **IIIb**. Yield 0.49 g (80%), colorless crystals, mp 202–203°C. IR spectrum, ν, cm^{-1}: 3310 (NH); 1715, 1720 (C=O); 1590, 1515 (C=C$_{\mathrm{arom}}$). ^{1}H NMR spectrum, δ, ppm: 8.72 br.s (1H, NH), 7.84 d (1H, H$_{\mathrm{arom}}$, $J = 9.8$ Hz), 7.67 s (1H, H$_{\mathrm{arom}}$), 7.58 d (1H, H$_{\mathrm{arom}}$, $J = 9.8$ Hz), 3.98 s (3H, NCO$_2$Me), 3.74 s (3H, NHCO$_2$**Me**), 3.61 m (2H, CH$_2$), 3.15 m (2H, CH$_2$), 2.18 m (2H, CH$_2$). Found, %: C 62.27; H 5.81; N 10.01. $C_{15}H_{16}N_2O_4$. Calculated, %: C 62.50; H 5.56; N 9.72.

Methyl 3-acetyl-5-(methoxycarbonylamino)-2-methyl-1*H*-indole-1-carboxylate (V). 4-Benzylaminopent-3-en-2-one (**IIc**), 0.85 g (4.5 mmol), and boron trifluoride–ether complex, 2–3 drops, were added to a solution of 1 g (4.5 mmol) of compound **I** in 10 ml of methylene chloride, and the mixture was heated for 1.5 h under reflux. The precipitate was filtered off, dried in air, and recrystallized from glacial acetic acid. Yield 1.15 g (84%), colorless crystals, mp 223°C. IR spectrum, ν, cm^{-1}: 3300 (NH); 1755, 1730 (C=O); 1605, 1560, 1540 (C=C$_{\mathrm{arom}}$). ^{1}H NMR spectrum, δ, ppm: 9.25 br.s (1H, NH), 8.25 s (1H, 4-H), 7.94 d (1H, H_{arom}, $J = 9.8$ Hz), 7.48 d (1H, H_{arom}, $J = 9.8$ Hz), 4.06 s (3H, NCO_2Me), 3.67 s (3H, $NHCO_2$**Me**), 2.82 s (6H, Me). Found, %: C 59.40; H 5.09; N 9.31. $C_{15}H_{16}N_2O_5$. Calculated, %: C 59.21; H 5.26; N 9.21.

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