MONO(m-SUBSTITUTED) CHLOROACETYLDIARYLAMINES IN THE STOLLÉ REACTION

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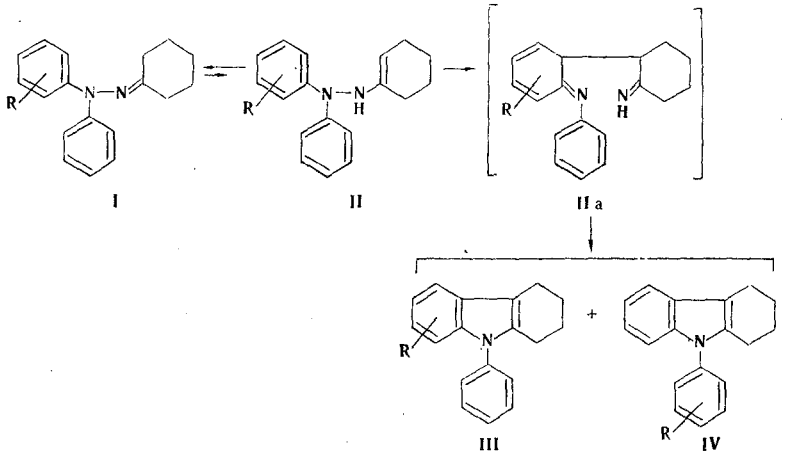
The effect of substituted (OCH_3, Cl) on the ratio of the isomeric N-aryloxindoles formed in the Stollé reaction from mono(m-substituted) chloroacetyldiarylamines was studied. It was shown by means of gas–liquid chromatography (GLC) and PMR spectroscopy that in the case of the methoxy group electrophilic substitution occurs only in the ring activated by the substituent. The presence of a halogen atom leads only to 1-(m-chlorophenyl)oxindole. The results show that high selectivity of the attack by the carbonium ion on the phenyl rings with electron-donor and electron-acceptor substituents is also retained in the case of intramolecular electrophilic substitution under conditions of kinetic control.

In a previous study of the mechanism of the principal step in the Fischer indolization we showed [1, 2] that substituents with different electronic natures (CH_3, OCH_3, Cl) in the meta or para position of one of the benzene rings of the diarylhydrazone (I) have relatively little effect on the ratio of the resulting isomeric tetrahydrocarbazoles (III/IV). On the basis of the data obtained it was concluded that the step involving the formation of a carbon–carbon bond (II → IIa) in this reaction has concerted character ([3, 3] sigmatropic rearrangement).



An alternative point of view exists with respect to the mechanism of this step: the formation of the C–C bond is regarded as electrophilic attack of the enehydrazine fragment on the aromatic ring [3, 4]. We felt that this approach to the reaction mechanism is unsuitable, since it is well known that the difference in the rates of electrophilic substitution reactions for monosubstituted benzenes with donor and acceptor substituents is always greater than 10^7. However, the question as to whether this difference is also retained in intramolecular electrophilic substitution has remained unanswered.

It seemed to us that the Stollé reaction [5], which is widely used for the synthesis of various oxindole derivatives [6], is suitable for the solution of this problem. Moreover, data on the effect of substituents on the ratio of isomeric N-aryloxindoles formed under the conditions of the Stollé reaction from monosubstituted chloroacetyldiarylamines V are not available in the literature.

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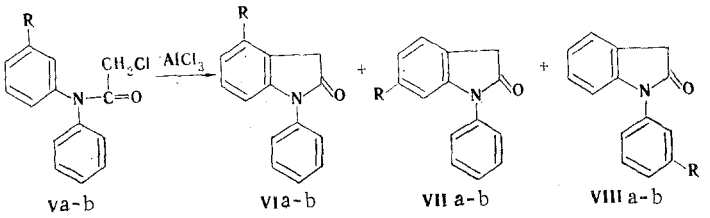


Va-b VIa-b VII a-b VIII a-b

a R = OCH_3; b R = Cl

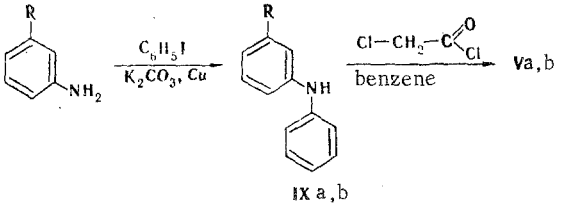
In the Stollé cyclization of m-methoxychloroacetyldiphenylamine (Va) in the presence of aluminum chloride at 150-160°C one might have expected the primary formation of a mixture of 1-phenyl-4- and 1-phenyl-6-methoxyoxindoles (VIa and VIIa), whereas one might have expected the formation of 1-(m-chlorophenyl)oxindole (VIIIb) in the case of amine Vb (R = Cl), since it is known that one isomer is formed in the electrophilic intramolecular acylation of monosubstituted β,β-diarylpropionic acids [7, 8]. Thus 5-methoxy-3-phenylindan-1-one was obtained when β-(m-methoxyphenyl)-β-phenylpropionic acid was treated with polyphosphoric acid at 100°C for 2 h [7], whereas 3-(p-chlorophenyl)indan-1-one is formed from β-(p-chlorophenyl(-β-phenylpropionyl chloride in the presence of $AlCl_3$ [8], i.e., only the activated (or nonactivated) benzene ring is acylated. Hydroxy derivatives of oxindoles, which are readily methylated by dimethyl sulfate in an alkaline medium [9] to give a mixture of isomers VIa and VIIa, are formed when m-methoxychloroacetyldiphenylamine (Va) is heated with 2 moles of aluminum chloride at 150-160°C for 2 h. Only oxindole VIIIb is formed under similar conditions from m-chloroacetyldiphenylamine (Vb).

The composition of the products of the investigated reactions was established by means of PMR spectroscopy and gas–liquid chromatography (GLC) and was confirmed by alternative syntheses. The assignment of the signals was made on the basis of the spectra of the individual compounds and model artificial mixtures of isomers VIa,b-VIIIa,b.

In the case of methoxy-substituted oxindoles a signal was observed at 3.70 ppm (isomers VIa + VIIa) in the PMR spectrum of the reaction mixture; however, a singlet at 3.80 ppm corresponding to the protons of the OCH_3 group of isomer VIIIa is absent.

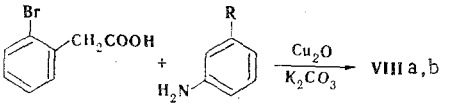
The PMR spectrum of the products of the reaction of amine Vb with $AlCl_3$, on the other hand, is characterized by only one signal at 3.55 ppm, which belongs to the protons of the methylene group of the pyrrolidone ring of isomer VIIIb (similar signals at 3.45 ppm are not observed for isomers VIb and VIIb).

It was demonstrated by special experiments that isomers of the VI, VII, and VIII type do not undergo interconversion under the reaction conditions and that consequently the process takes place under conditions of kinetic control. These data indicate clearly the strong effect of the nature of the substituent on the direction of intramolecular electrophilic substitution. Starting diarylamines Va,b were synthesized from the corresponding m-substituted anilines by Ullman arylation with subsequent treatment with chloroacetyl chloride. Oxindoles VIIIa, b

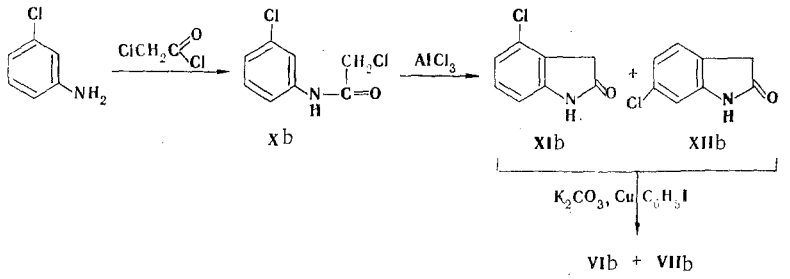


IX a,b

were obtained by the method presented in [11] from o-bromophenylacetic acid and m-anisidine and m-chloroaniline, respectively. Isomeric oxindoles VIb and VIIb were synthesized by an



independent method from m-chloroaniline via the scheme



EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. Analysis by GLC was carried out with a Pye-Unicam series 204 chromatograph with SE-30 (3%) on Chromosorb W as the stationary phase and nitrogen as the carrier gas; the flow rate was 32 ml/min, the column temperature was 230°C, the vaporizer temperature was 300°C, the detector temperature was 250°C, and the retention time (τ) was presented in seconds. The IR spectra of KBr pellets of the compounds were recorded with a Jasco-IR-S spectrometer. The UV spectra of solutions of the compounds in isopropyl alcohol were recorded with a Hitachi EPS-37 spectrophotometer. Thin-layer chromatography (TLC) was carried out on activity II aluminum oxide or Silufol UV-254 plates.

m-Methoxydiphenylamine (IXa). This compound, with mp 70-71°C [from benzene–petroleum ether (1:1)], was obtained in 60% yield from m-anisidine by Ullman arylation with iodobenzene [2].

m-Chlorodiphenylamine (IXb). This compound, with bp 149-152°C (2 mm), was similarly obtained in 50% yield from m-chloroaniline [2].

N-Chloroacetyl-N-phenyl-m-anisidine (Va). A solution of 5 g (0.045 mole) of chloroacetyl chloride in 30 ml of absolute benzene was added dropwise to a refluxing solution of 9.8 g (0.05 mole) of amine IXa in 50 ml of absolute benzene, after which the mixture was refluxed until HCl evolution ceased (8-10 h). The solvent was removed by distillation, and the resulting oil was purified with a column filled with Al_2O_3 by elution initially with petroleum ether and then with benzene to give 5.4 g (65%) of Va with mp 57-58°C (from methanol) and R_f 0.31 [Al_2O_3, benzene–acetone (20:1)]. PMR spectrum: 3.70 (3H, s, OCH_3), 3.95 (2H, s, CH_2Cl), and 6.70-7.20 ppm (9H, m). IR spectrum: 1700, 1600, 1240, and 710 cm^{-1}. UV spectrum, λ_{max} (log ε): 218 (4.35) inflection, 275 (3.60), 283 (3.57) inflection, and 240 nm (4.05) inflection. The retention time was 287 sec. Found: C 65.6; H 5.25%. $C_{15}H_{14}ClNO_2$. Calculated: C 65.3; H 5.1%.

N-Chloro-N-phenyl-m-chloroaniline (Vb). This compound, with mp 94-95°C (from methanol) and R_f 0.40 [Al_2O_3, benzene–acetone (20:1)], was obtained from amine IXb by a method similar to that used to prepare Va. PMR spectrum 3.95 (2H, s) and 7.10-7.45 ppm (9H, m). UV spectrum, λ_{max} (log ε): 240 (4.02) and 275 nm (3.72) inflection. IR spectrum: 1700, 1600, 1500, and 710 cm^{-1}. The retention time was 239 sec. Found: C 60.1; H 3.9%. $C_{14}H_{11}ClN_2O$. Calculated: C 60.0; H 4.0%.

N-Chloroacetyl-m-chloroaniline (Xb). This compound, with mp 100-101°C (from benzene) (mp 101°C [11]) and R_f 0.30 [Al_2O_3, benzene–acetone (20:1)], was obtained in 62% yield from m-chloroaniline by a method similar to that used to prepare Va.

Cyclization of α-Chloroacetanilides Va, b under the Conditions of the Stollé Reaction. A) A mixture of 2 g (0.007 mole) of amide Va and 4 g (0.014 mole) of anhydrous powdered aluminum chloride was heated at 50-60°C for 10 min and then at 150-160°C for 2 h. It was then cooled and decomposed with ice (30 g), and the precipitate was removed by filtration and crystallized from water to give 1.4 g (90%) of a mixture of isomeric hydroxy derivatives of oxindoles VIa-VIIIa with mp 188-189°C. Found: C 74.6; H 4.9%. $C_{14}H_{11}NO_2$. Calculated: C 74.3; H 5.0%.

B) Half of a solution of 0.75 g (3.5 mmole) of the mixture of oxindoles (see the preceding experiment) and a solution of 0.15 g (3.5 mmole) of NaOH in 3 ml of water were placed in a small three-necked flask equipped with a mechanical stirrer, a dropping funnel and a reflux condenser, and 0.5 g (3.5 mmole) of dimethyl sulfate was added dropwise with stirring

at 3-5°C in the course of 10 min. The mixture was then heated on a water bath at 90°C for 30 min, after which the second half of the solution was added, and the mixture was heated for 4 h. It was then cooled and extracted with ether (three 20-ml portions), and the extract was dried with magnesium sulfate. The solvent was removed by distillation, and the residue crystallized from methanol to give 0.67 g (80%) of oxindoles VIa + VIIa with mp 96-98°C and R_f 0.43 [Al_2O_3, benzene–acetone (10:1)]. PMR spectrum: 3.70 (6H, s, 4-OCH_3 and 6-OCH_3), 3.58 (2H, s, 3-H) and 3.60 (2H, s, 3-H) for the 4- and 6-OCH_3 isomers, respectively, and 7.05-7.35 ppm (8H, m). Found C 75.5 H 5.4%. $C_{15}H_{13}NO_2$, Calculated C 75.3 H 5.5%. The retention time was 253 sec.

Stollé Cyclization of N-Chloroacetyl-N-phenyl-m-chloroanile (Vb). This reaction was carried out in the same way as the cyclization of Va (step A). The product was 1-(m-chlorophenyl)oxindole (VIIIb), with was completely identical to the sample synthesized from o-bromophenylacetic acid and m-chloroaniline. The retention time was 218 sec.

Mixture of 4-Chlorooxindole and 6-Chlorooxindole (XIb and XIIb). This mixture, with mp 115-116°C (from methanol) and R_f 0.44 (Al_2O_3, ether), was obtained in 60% yield by a method similar to that used to prepare oxindole Va (step A). According to GLC, the ratio of the 4-chloro and 6-chloro isomers was 1:5. The retention times were 59 and 78 sec, respectively. Found: C 57.2; H 3.8; N 8.3%. C_8H_6ClNO. Calculated: C 57.3; H 3.6; N 8.3%.

Mixture of 1-Phenyl-4-chloro- and 1-Phenyl-6-chlorooxindoles (VIb and VIIb). This mixture, with mp 112-115°C (from methanol), was obtained in 65% yield from the mixture of oxindoles XIb and XIIb by Ullman arylation with iodobenzene. PMR spectrum 3.45 (2H, s, CH_2) and 6.85-7.20 ppm (8H, m). The retention time was 201 sec.

1-(m-Methoxyphenyl)oxindole (VIIIa). A mixture of 1.1 g (0.005 mole) of o-bromophenylacetic acid, 3 g (0.025 mole) of m-anisidine, 0.8 g (0.006 mole) of anhydrous potassium carbonate, and 0.1 g of Cu_2O was heated with stirring at 220-240°C for 4 h, after which the excess amine was removed by steam distillation, and the residue was extracted with ether. The ether was removed, and the residue was purified with a column filled with Al_2O_3 by elution initially with benzene and then with benzene–acetone (10:1). The solvent was removed by distillation, and the residue was recrystallized from methanol to give 1 g (82%) of oxindole VIIIa with mp 101-102°C and R_f 0.42 [benzene–acetone (10:1)]. PMR spectrum: 3.80 (3H, s, OCH_3), 3.65 (2H, s, 3-H), and 6.65-7.30 ppm (8H, m). IR spectrum: 1720, 1250, 1500, and 1600 cm^{-1}. UV spectrum, λ_{max} (log ε): 249 (4.06) and 290 nm (3.58) inflection. The retention time was 260 sec. Found: C 75.1; H 5.2%. $C_{15}H_{13}NO_2$. Calculated: C 75.3; H 5.5%.

1-(m-Chlorophenyl)oxindole (VIIIb). This compound, with mp 116-117°C and R_f 0.58 [benzene–acetone (10:1)], was obtained in 75% yield from o-bromophenylacetic acid and m-chloroaniline by a method similar to that used to prepare oxindole VIIIa. PMR spectrum 3.55 (2H, s, 3-H) and 6.60-7.15 ppm (8H, m). UV spectrum, λ_{max} (log ε): 253 (3.60) and 289 nm (3.98). IR spectrum: 1680, 1600, 1500, and 690 cm^{-1}. The retention time was 218 sec. Found: C 69.0; H 3.8%. $C_{14}H_{10}ClNO$. Calculated: C 69.0; H 4.1%.

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