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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of 6-Methyl-4-(1-methyl-2-buten-1-yl)-2-(2-cyclohexen-1-yl)- and 6-Methyl-4-(1-methyl-2-buten-1-yl)-2-(1-cyclohexen-1-yl)anilines

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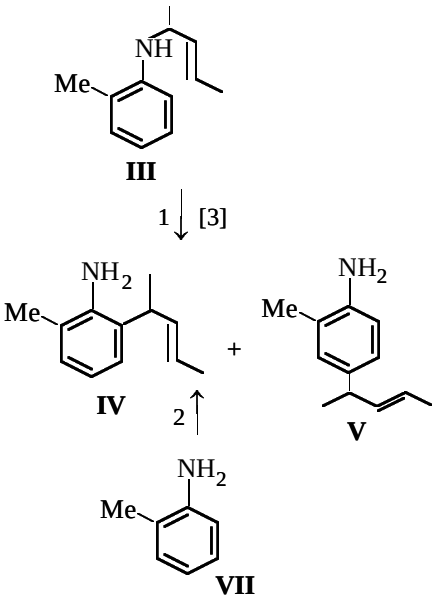
Abstract—Alkenylation of 6-methyl-2-(2-cyclohexen-1-yl)- and 2-(1-cyclohexen-1-yl)anilines with piperylene in the presence of $AlCl_3$ and transformation of the resulting cyclohexenylanilines into carbazole structures were studied.

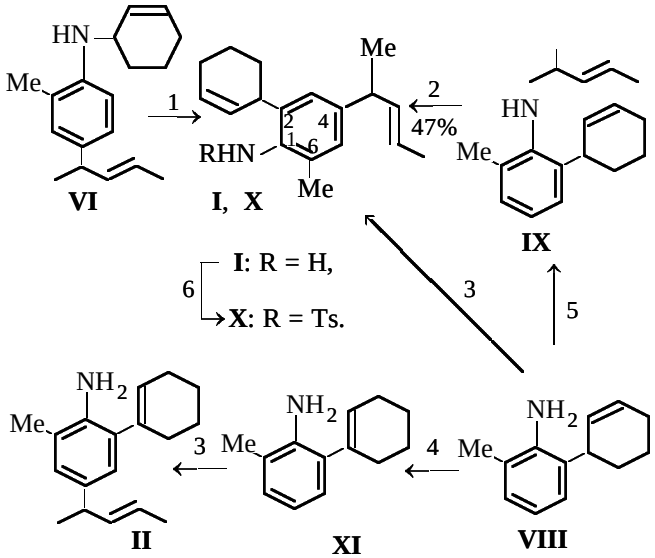
Major attention is given to synthesis of heterocyclic systems of the pyridocarbazole series, as such derivatives (e.g., ellipticine, olivacine, and their isomers) show antitumor activity. One of the main routes to such compounds involves as intermediates 6-substituted carbazoles or their partially hydrogenated analogs [1] prepared from 2-cyclohexenylanilines [2].

To develop a procedure for preparing amines **I** and **II**, which are key substances in the synthesis of olivacine and its isomers, we examined several routes. Aromatic Claisen amino rearrangement of **III** yields amines **IV** and **V** [3]:



Conditions and reagents: (1) HCl, then excess toluidine, 140°C; (2) piperylene, $AlCl_3$, benzene, 135°C, 3 h.

The ratio of the *ortho* and *para* isomers is approximately 85 : 15; therefore, cyclohexenylation of the minor *para* isomer **V** followed by the rearrangement of the resulting N-substituted product **VI** into the desired amine **I** is of little preparative use:



Conditions and reagents: (1) HCl, then excess **V** or *o*-xylene, 140°C; (2) HCl, then excess **VIII**, 165–170°C, 6 h; (3) piperylene, $AlCl_3$, benzene, 135°C, 3 h; (4) KOH, 300°C, 1 h; (5) 3-chloro-2-pentene; (6) TsCl, Py, 20°C.

In alkenylation of toluidine **VII** with piperylene in the presence of excess $AlCl_3$, the isomer ratio **IV** : **V** becomes inverse (15 : 85), but the problem of their separation remains.

The reaction of cyclohexenyltoluidine **VIII** with 3-chloro-2-pentene yields *N*-pentenyl derivative **IX**.

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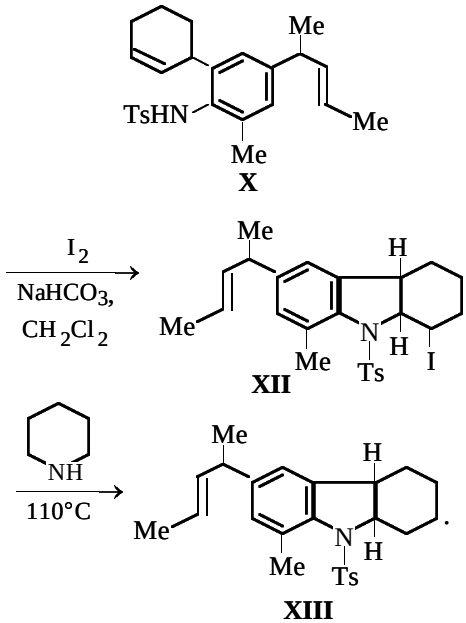
Heating of the hydrochloride of **IX** at 170°C also gives dialkenylaniline **I** in 47% yield based on the reacted amine **VIII**. Alkenylation of **VIII** with piperylene in the presence of $AlCl_3$ appeared to be the most efficient; the yield of **I** was 88%. Cyclohexenylaniline derivatives with the vinyl location of the double bond can be successfully used for the synthesis of relatively complex heterocyclic systems of the carbazole series. Proceeding with such studies [5], we also performed alkenylation of aniline **XI** with piperylene in the presence of $AlCl_3$. The product is formed in 85% yield by heating of **VIII** with KOH at 300°C. The reaction of amine **XI** with piperylene gives compound **II** in 87% yield.

The reaction of amine **I** with TsCl in pyridine gives *N*-tosyl derivative **X**, which, when treated with electrophilic agents (in particular, with molecular iodine), yields hexahydrocarbazole system **XII**, with the double bond in the methylbutenyl moiety remaining intact. Refluxing of **XII** in piperidine results in *trans* elimination with the formation of tetrahydrocarbazole **XIII** in 90% yield:



The compositions and structures of the compounds prepared were proved by IR and NMR spectroscopy and by elemental analysis.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Bruker AM-300 spectrometer (operating frequencies 300 and 75 MHz, respectively; solvent $CDCl_3$; internal reference TMS), and the IR spectra, on a UR-20 spectrometer. The product purity was monitored on a Chrom-5 chromatograph (stationary phase SE-30 on Chromaton N-AW-DMCS, 1200 × 3-mm column, flame ionization detector, heating rate 12 deg min^{-1}, carrier gas He). Qualitative analysis was performed with Sorbfil UV 254 plates (Lyuminofor Private Company, Krasnodar, Russia), eluent CH_2Cl_2. A mixture of *cis* and *trans* isomers of piperylene (Kaustik plant, Sterlitamak, Bashkortostan, Russia) was used for alkenylation without additional purification.

6-Methyl-4-(1-methyl-2-buten-1-yl)-2-(2-cyclohexen-1-yl)aniline I. (a) A 17-ml pressure vessel was charged with 1 g of aniline **VIII**, 10 ml of benzene, 0.69 g of $AlCl_3$, and 0.68 g of piperylene. The mixture was heated on an oil bath at 135°C for 3 h and cooled to room temperature, after which 30 ml of 20% aqueous NaOH was added, the mixture was stirred, 30 ml of benzene was added, and the organic phase was separated and dried over KOH. The solvent was evaporated to a minimal volume (2–3 ml). Yield of amine **I** after chromatographic purification on a short (1 × 1 cm) silica gel column (eluent hexane) 1.2 g (88%).

(b) To 35 g of amine **VIII** was added 9.5 g of 3-chloro-2-pentene. After the condensation completion (GLC monitoring of reaction mixture samples treated with a NaOH solution), the mixture was heated on an oil bath at 160–170°C. The consumption of **IX** was monitored by GLC. After the rearrangement completion, the mixture was cooled and neutralized with 20% aqueous NaOH (50 ml); the organic layer was dried over KOH. Vacuum distillation gave 20 g of the unchanged amine **VIII** (42% conversion) and 9.6 g (47% based on the reacted amine **VIII**) of dialkenylated product **I**, bp 140–145°C (2 mm Hg).

(c) To 32.37 g of **V** was added 14.9 g of 3-bromo-1-cyclohexene. The mixture was heated on a water bath at 90°C for 1 h and cooled to room temperature; 50 ml of 20% aqueous NaOH was added, and the mixture was shaken in a separating funnel. The organic layer was dried over KOH, filtered, and saturated with gaseous HCl. The resulting hydrochloride of **VI** was heated in excess amine **V** or in *o*-xylene at 140°C until aniline **VI** disappeared (GLC monitoring of reaction mixture samples neutralized with a NaOH solution). After the isomerization completion, the mixture was cooled to room temperature, 100 ml of 20% aqueous NaOH was added, the mixture was shaken in a separatory funnel, and the organic phase was dried over KOH. Vacuum distillation gave 15 g of the unchanged amine **V** and 10.8 g (42% based on

the reacted amine **V**) of dialkenylaniline **I**, bp 140–145°C (2 mm Hg).

6-Methyl-4-(1-methyl-2-buten-1-yl)-2-(1-cyclohexen-1-yl)aniline II was prepared similarly to **I** by procedure (a) from 1 g of **XI**; yield 1.19 g (87%).

***N*-Tosyl-6-methyl-4-(1-methylbut-2-en-1-yl)-2-(2-cyclohexen-1-yl)aniline X.** To a solution of 1.27 g of amine **I** in 10 ml of pyridine was added 1.7 g of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at room temperature for 24 h, 0.5 ml of H_2O was added, the mixture was stirred for 30 min, and the solvent was vacuum-evaporated. The residue was diluted with 5 ml of H_2O and 50 ml of CH_2Cl_2. The organic phase was separated, washed with 30 ml of 5% HCl and water (2 × 10 ml), and dried over $MgSO_4$. After vacuum evaporation of the solvent, 2 g of crude **X** was obtained; the product slowly solidified in air and was sufficiently pure for the subsequent syntheses. Recrystallization from EtOH gave 0.63 g of crystalline **X**, mp 124–126°C (from EtOH). An additional 0.4-g crop of **X** was obtained from the mother liquor after its prolonged storage; mp 126–130°C.

6-Methyl-2-(1-cyclohexen-1-yl)aniline XI. 6-Methyl-2-(2-cyclohexen-1-yl)aniline (10 g) [3] and KOH (10 g) were heated for 1 h on a silicone bath (300°C) in a steel test tube equipped with a reflux air condenser. After cooling, the product was decanted from KOH and vacuum-distilled. Yield 9.5 g (95%), bp 118–120°C (3 mm Hg).

***N*-Tosyl-1-iodo-6-(1-methyl-2-buten-1-yl)-1,2,3,-4,4a,9a-hexahydrocarbazole XII.** To a solution of 0.41 g of amide **X** in 20 ml of CH_2Cl_2, we added 0.85 g of $NaHCO_3$ and 0.51 g of I_2. After the complete consumption of the starting amide **X** (~6–7 h), the precipitate was filtered off, and the solution was washed with 10% aqueous $Na_2S_2O_3$ (2 × 20 ml) and water (2 × 10 ml) and dried over $MgSO_4$. The solvent was vacuum-evaporated. Compound **XII** was obtained as an amorphous mass; yield 0.51 g (95%), R_f 0.4 (eluent CH_2Cl_2).

***N*-Tosyl-6-(1-methyl-2-buten-1-yl)-3,4,4a,9a-tetrahydrocarbazole XIII.** A solution of 0.377 g of 1-iodohexahydrocarbazole **XII** in 3 ml of piperidine was heated at 110°C for 3 h. After the dehydroiodination completion, the solvent was vacuum-evaporated, and the residue was dissolved in 50 ml of CH_2Cl_2 and washed with water (2 × 20 ml). The organic phase was dried over Na_2SO_4, and the solvent was vacuum-evaporated; yield of **XIII** 0.26 g (90%), R_f 0.7 (eluent CH_2Cl_2).

CONCLUSIONS

(1) Alkenylation of 6-methyl-2-(2-cyclohexen-1-yl)- and -2-(1-cyclohexen-1-yl)anilines with piperylene in the presence of $AlCl_3$ gives the corresponding 4-(1-methyl-2-buten-1-yl)anilines in 87–88% yields.

(2) The reaction of the synthesized 6-methyl-2-(2-cyclohexen-1-yl)-4-(1-methyl-2-buten-1-yl)aniline with I_2 gave iodohexahydrocarbazole in 95% yield. On refluxing in piperidine, it transformed into the tetrahydrocarbazole in 90% yield.

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