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Synthesis of 2-Ethyl-2-methyl-2,3-dihydro-1*H*-indole, a New Insecticide Exhibiting Juvenile Hormone Activity

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Abstract — Catalytic hydroamination of isoprene gave *N*-(1,2-dimethylprop-2-en-1-yl)aniline in a preparative yield. By heating at 260°C the product was converted into 2-ethyl-2-methyl-2,3-dihydro-1*H*-indole, a new ecologically safe insecticide exhibiting a juvenile hormone activity. Its insecticide properties against Tenebrio Molitor L. chrysalises were estimated at 7.5 points according to the Schmialek 9-point scale.
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In the recent time, chemists and biologists give much attention to the preparation of up-to-date insecticides which are characterized by high selectivity, satisfactory resistance to natural factors, and the lowest possible toxicity toward all participants of biocenosis. Considerable attention is also given to economic aspects, such as accessibility of starting materials and "green chemistry" requirements. Moreover, the main goal of modern studies is to control over the magnitude of populations of insect pests rather than their complete elimination. Advances in agrochemical science over the past decades have led to the discovery of insect growth regulators, i.e., ecologically safe insecticides that simulate two kinds of insect hormones, steroid 20-hydroxyecdysone (20E) and sesquiterpenoid juvenile hormones. The low persistence of juvenile hormones and their analogs (juvenoids) to photochemical degradation and oxidation, as well as very expensive manufacture of sesquiterpenoids, imposes strong limitations on the application of juvenoids in agricultural practice. An efficient way of enhancing the stability of juvenoids is to introduce a heterocyclic fragment into their molecules. Active insect esterase inhibitors whose mechanism of action is similar to that of juvenile hormones were found among *N*-terpenyl-substituted benzimidazoles [1–3], while indole derivatives were reported to effectively inhibit biosynthesis of chitin, thus corrupting the investment of insects during molt [4–5]. In continuation of our studies on the synthesis of practically important biologically active compounds on the basis of butadiene and isoprene (which are large-scale products in oil processing), in the present work we made an attempt to prepare in several steps dihydroindole derivatives and test them for juvenile activity.

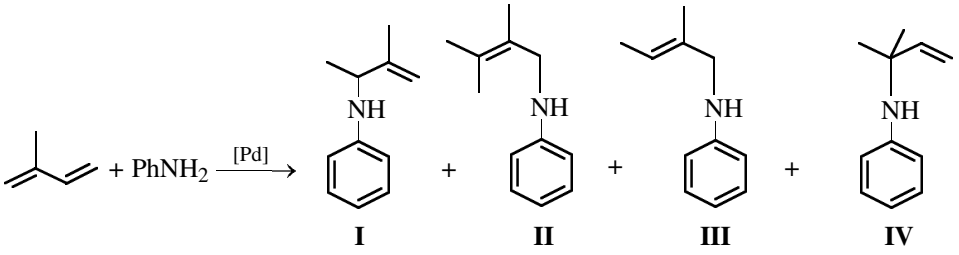
An effective method for building up dihydroindole or indole ring is based on heterocyclization of 2-(alk-2-en1-yl)anilines. The latter can be prepared in turn from *N*-(alk-2-en-1-yl)anilines by the amino-Claisen rearrangement. The goal of the present study was to synthesize indole derivatives possessing a juvenile hormone activity from *N*-(alk-2-en-1-yl)anilines. A one-step catalytic procedure for the preparation of *N*-(alk-2-en-1-yl)anilines from isoprene and aniline was described in [6–9]. Thus the key sage of our study was investigation of the amino-Claisen rearrangement of *N*-(alk-2-en-1-yl)anilines that are available via direct amination of isoprene with aniline. The main advances in the field of studying the amino-Claisen rearrangement were reviewed in [10] (see also references therein). The direction of the rearrangement is determined by the nature and position of substituents in allyl fragment, and in some cases these factors facilitate the subsequent heterocyclization of 2-(alk-2-en-1-yl)anilines thus formed. For example, Bunina-Krivorukova et al. [11] showed that the presence of a methyl group in the γ- rather than β-position of the allyl substituent leads to anomalous product compositions in both thermal and catalytic ($ZnCl_2$) Claisen rearrangements of β-methyl-, α,β- and β,γ-dimethyl-, and β,γ,γ-trimethylallyl *p*-methylphenyl ethers. When two γ-methyl groups are present in the allyl fragment, the Claisen rearrangement follows a path different from the classical one. In this case, the rearrangement

was accompanied by heterocyclization only in the presence of an acid catalyst. According to [12, 13], acid-catalyzed (concentrated hydrochloric acid or polyphosphoric acid) amino-Claisen rearrangement of *N*-allylaniline, as well as of *N*-(but-2-en-1-yl)aniline (γ-methyl-substituted allyl fragment) gives only substituted dihydroindoles as products of heterocyclization involving the most substituted carbon atom at the double bond in the corresponding intermediate of the classical amino-Claisen rearrangement. Jolidon and Hansen [14] believe that α- and γ-substituents in the allyl fragment of *N*-allylanilines play the key role in the thermal and catalytic amino-Claisen rearrangement. Thus almost no amino-Claisen rearrangement products are formed from *N*-(γ-methylallyl) and *N*-(γ,γ-dimethylallyl)anilines at 260–335°C, but elimination of aniline occurs mainly. However, the thermal rearrangement of *N*-(α,α-dimethylallyl)aniline at 200–260°C smoothly affords the classical Claisen rearrangement product, while *N*-(α-methylallyl)aniline requires more severe conditions (290°C). The Claisen rearrangement of *N*-(α,α-dimethylallyl)aniline in the presence of organic acids in a 10 : 1 acetonitrile–water mixture gives up to 70% of the normal rearrangement product [15] and no hydration products which are sometimes formed in the presence of aqueous mineral acids. Katayama et al. [16, 17] studied the effect of alkyl substituents in the *N*-allyl fragment of 1-allyl-1,2,3,4-tetrahydroquinoline and 1-allyl-6-methoxy-1,2,3,4-tetrahydroquinoline in the reaction performed in anhydrous boron trifluoride–ether complex. Introduction of one or two γ-methyl groups into the allyl fragment increased the yield of nonclassical Claisen rearrangement products (*para*-substituted) and products resulting from elimination of the substituted allyl fragment. Here, the Claisen rearrangement was not accompanied by heterocyclization. As shown in [18, 19], the rearrangement of *N*-(α,γ-dimethylallyl)-anilines in the presence of HCl does not involve inversion of the allyl fragment with formation, and both *ortho*- and *para*-substituted anilines are formed. *N*-(Cyclopent-2-en-1-yl)aniline hydrochloride having an α,γ-dimethylallyl fragment at 200–220°C gives rise to dihydroindole derivative, and the reaction mixture contained *o*-cyclopentenylaniline which gradually disappeared, being converted into the corresponding dihydroindole [20]. Thus the available published data indicate that the presence of an α-substituent in the allyl fragment facilitates the amino-Claisen rearrangement, γ-substituents hamper the process, while β-substituents exert almost no effect on the course of the rearrangement.

No effective and convenient method for the synthesis of all possible *N*-(mono-, di-, and trimethylallyl)anilines has been proposed so far. The conventional procedure for the preparation of *N*-(methyl- or dimethylalk-2-en-1-yl)anilines by reaction of aniline with the corresponding substituted allyl chlorides does not always lead to the desired products (see, e.g., [18]). Probably, this is the reason for the lack of data for amino-Claisen rearrangement of *N*-(α,β-dimethylallyl)aniline. An alternative synthetic route to such compounds may be direct amination of isoprene with aniline, catalyzed by palladium complexes (Scheme 1). In the presence of PdX_2–R_3P–HX (HX is an acid) as catalytic system, the main products are adducts **I**–**IV**: *N*-(1,2-dimethylprop-2-en-1-yl)aniline (**I**), *N*-(3-methylbut-2-en-1-yl)aniline (**II**), *N*-(2-methylbut-2-en-1-yl)aniline (**III**), and *N*-(1,1-dimethylprop-2-en-1-yl)aniline (**IV**). The selectivity of the process toward formation of amines **I**–**IV** can be changed by varying the nature and ratio of the components of the catalytic system and solvent nature. In such a way, we recently obtained aniline **I** in acetonitrile with a selectivity of 31% [7, 8]. In the present article we describe the synthesis of compound **I** in methanol with a slightly lower selectivity (27%). As follows from the published data considered above, the amino-Claisen rearrangement of adducts **II** and **IV** is well studied; adduct **III** might be expected to give rise to a complex mixture of products due to the presence of a γ-substituent in the allyl fragment. We presumed that previously unknown rearrangement of compound **I** should follow the classical scheme (see above), taking into account that α-substituents facilitate the process and that β-substituent should exert no appreciable effect.

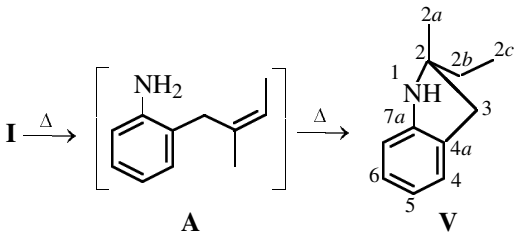
In most experiments, by heating amine **I** in a sealed ampule at 220–350°C we obtained dihydroin-

Scheme 1.



dole **V** as the major product (Scheme 2). The data in table show that the reaction performed in the temperature range from 300 to 350°C is accompanied by considerable elimination of aniline (33–41%) and that dihydroindole **V** is formed with a selectivity of 50–52%. Heating of aniline **I** for 30 min at 260°C gave a complex mixture containing initial amine **I**, product **V**, and unknown compound A. Presumably, the latter is the normal Claisen rearrangement product. Upon subsequent heating at 260°C (6 h), compound **A** disappeared from the reaction mixture together with initial aniline **I**, being converted into product **V**. When aniline **I** was heated at 250–254°C, dihydroindole **V** was formed with a selectivity of 47–57%. The contribution of the aniline elimination process did not exceed 5% at 200–220°C; however, the conversion of aniline **I** reached 97% only after prolonged heating (19 h), and the products were compound **A** and dihydroindole **V**.

Scheme 2.



Two protons on C^3 in molecule **V** are diastereotopic due to the presence of the neighboring chiral C^2 atom. Their signals appear in the ^{1}H NMR spectrum as an *AB* quartet with a coupling constant *J* of 15.5 Hz; this value is typical of a CH_2 group linked to aromatic ring in 2,2-disubstituted dihydroindoles (see, e.g., [21]). In keeping with the above discussed published data, heterocyclization products are formed (with a few exceptions) with participation of the most substituted carbon atom at the double bond. Therefore, we can assure with a high degree of certainty that compound **V** is formed from the classical amino-Claisen rearrangement product (**A**). Abdrakhmanov et al. [22] previously reported that compound **V** was formed as anomalous product of the reaction of 2-(α,γ-dimethylallyl)aniline with polyphosphoric acid; this was rationalized [22] in terms of 1,2-methyl group shift in allyl fragment, followed by heterocyclization at the most substituted carbon atom. However, the ^{1}H NMR spectrum of **V** given in [22] contained a singlet from the C^3H_2 protons, which contradicts their diastereotopic character. Presumably, the product isolated [22] is not dihydroindole **V**. Comparison of our results with published data revealed some specific features of the amino-Claisen rearrangement. For instance, the presence of two methyl groups in the α- and β-positions of the allyl fragment, as well as of two methyl groups at the α-carbon atom [14], facilitates the process, so that it can be performed at a lower temperature (200–260°C), as compared to compounds having only one α-substituent in the allyl fragment. The thermal rearrangement of *N*-(α,β-dimethylallyl)aniline is accompanied by heterocyclization to dihydroindole derivative.

Amino-Claisen rearrangement of *N*-(1,2-dimethylprop-2-en-1-yl)aniline

Temperature, °C	Time, min	Unreacted aniline **I**, %	Product composition,[a] %		
			$PhNH_2$	**V**	**A**
350	10	7	38	50	5
302	40	6	41	52	1
300	20	9	33	50	8
260	30	7	13	15	65
254/250	60/300	21	12	56	11
250	360	25	11	47	13
250	540	10	8	60	22
220	80	42	5	2	51
220/200	60/180	31	5	6	58
220/200	60/1080	4	3	54	39

[a] According to the GLC data.

Compound **V** was tested for juvenile hormone activity in Tenebrio molitor L. chrysalises (laboratory strain, AllRussian Research Institute of Chemical Means for Plant protection). The insecticide activity was estimated by applying 4.4 μg of an acetone solution containing 10 g l^{-1} of compound **V** to the terminal abdomen segment of a chrysalis in 0 to 6 h after its delivery. Compound **V** was tested on two series each containing 15 species. The effect was determined according to the Schmialek 9-point scale [23] by the imago delivery. Point 0 was assigned to a chrysalis delivering a normal imago, and point 9 was given to a chrysalis producing no imago and not differing from the intact chrysalis. Intermediates points corresponded to different degrees of morphogenetic disorders in the transformation of chrysalises into imago. After examination of morphological variations of each species, an average estimate (*N*) was calculated by the formula

$$N = \frac{x_1 \cdot 1 + x_2 \cdot 2 + x_3 \cdot 3 + \ldots + x_n \cdot n}{A}.$$

The absolute error (Δ*N*) was calculated by the formula

$$\Delta N = \frac{x_1|N-1| + x_2|N-2| + \ldots + x_n|N-n|}{A}.$$

Here, 1, 2, 3, ..., n are estimates in points from 0 to 9; x_1, x_2, x_3, ..., x_n are the numbers of chrysalises assigned the corresponding point; and **A** is the overall number of chrysalises. As a result of biological tests for juvenile hormone activity, compound **V** in solution with a concentration of 10 g l^{-1} was assigned N = 7.5 (from 9 possible), ΔN = 0.38, relative error $\Delta N/N$ = 5.1%.

EXPERIMENTAL

The reagents used in this work had a purity of 99%; the solvent and liquid reagents were distilled just before use and were stored under argon; Pd(*acac*)$_2$ was prepared as described in [24]. All reactons were carried out under argon. GLC analysis was performed on an LKhM-8MD (5) chromatograph equipped with a 2000 × 3-mm steel column; stationary phase 15% of SKTFT-50 on Chromaton N-AW; carrier gas helium. The NMR spectra were recorded from solutions in $CDCl_3$ on Bruker WR-200SY and Varian VXR-400 spectrometers using TMS as internal reference. The IR spectra were measured from thin films on a UR-20 instrument. The electronic absorption spectrum of compound **V** was recorded on a Specord M-40 spectrophotometer from a solution in ethanol ($c = 10^{-3}$ M).

Reaction of isoprene with aniline in methanol in the presence of the catalytic system Pd(*acac*)$_2$–P(OEt)$_3$–CF$_3$CO$_2$H. A mixture of 0.92 g Pd(*acac*)$_2$, 2.0 g P(OEt)$_3$, 120 ml of isoprene, 55.8 g aniline, 3.4 g CF_3COOH, and 150 ml of methanol was stirred at 20°C under argon until it became homogeneous. The resulting solution was transferred under argon into a 250-ml steel high-pressure reactor, and the reactor was heated for 34 h at 100°C. The low-boiling fraction was distilled off under atmospheric pressure, and the residue was distilled under reduced pressure (water-jet pump) to obtain 70 g of a mixture of products with bp 91–108°C (8 mm). Amines **I**–**IV** were isolated through transformation into the corresponding hydrochlorides. For this purpose, the product mixture was dissolved in hexane, the solution was treated with cold dilute hydrochloric acid, the aqueous phase was separated and treated with a cold solution of potassium hydroxide, an oily material separated and was extracted into benzene, the extract was dried over Na_2SO_4 and evaporated, and the residue was distilled under reduced pressure. We thus isolated 48.8 g (60%) of a mixture of compounds **I**–**IV** with bp 104–118°C (15 mm), which contained 27% of aniline **I**, 37% of **II**, 25% of **III**, and 11% of **IV**. Their retention times (GLC) were consistent with those reported in [6]. Aniline **I** was isolated by fractional distillation through a laboratory rectification column; a fraction boiling at 104°C (15 mm) was collected; its ^{1}H NMR spectrum was identical to that given in [6]; IR spectrum, ν, cm^{-1}: 1660 (C=C); 1520, 1615 (C=C$_{arom}$); 2960, 2990, 3070 br (C–H$_{arom}$); 3440 (NH); 700 [δ(=CH$_2$)].

2-Ethyl-2-methyl-2,3-dihydro-1*H*-indole (V). Aniline **I**, 1.98 g, was heated in a sealed ampule for 9 h at 250°C. According to the GLC data, the resulting mixture contained 60% of compound **V**. Distillation gave 1.19 g (60%) of dihydroindole **V** with bp 144–146°C (15 mm). Electronic absorption spectrum, λ_{max}, nm ($\varepsilon \times 10^{-3}$): 233 (7.4), 244 (7.4), 294 (2.7). IR spectrum, ν, cm^{-1}: 1490, 1618 (C=C$_{arom}$), 2990 br (C–H$_{arom}$), 3400 (N–H), 765 [δ(C=C$_{arom}$)]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 t (3H, 2-CH$_2$CH$_3$, *J* = 7.4), 1.39 s (3H, 2-CH$_3$), 1.76 q (2H, 2-CH$_2$CH$_3$, *J* = 7.4); 2.89 and 3.08 (1H each, 3-H, *AB* system, J_{AB} = 15.5), 3.68 s (1H, NH), 6.70 d (1H, 4-H, *J* = 7.7), 6.84 d.d (1H, 5-H, *J* = 7.4), 7.17 d.d (1H, 6-H, *J* = 7.4), 7.21 d (1H, 7-H, *J* = 7.7). ^{13}C NMR spectrum, δ_C, ppm: 8.82 (2-CH$_2$CH$_3$), 26.23 (2-CH$_3$), 34.41 (2-CH$_2$CH$_3$), 41.67 (C^3), 63.67 (C^2), 108.83 (C^4), 117.81 (C^5), 124.65 (C^6), 127.17 (C^7), 127.96 (C^{4a}), 150.11 (C^{7a}); the signals were assigned using APT pulse sequence. Found, %: C 81.74; H 9.25; N 8.67. $C_{11}H_{15}N$. Calculated, %: C 81.94; H 9.38; N 8.67.

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