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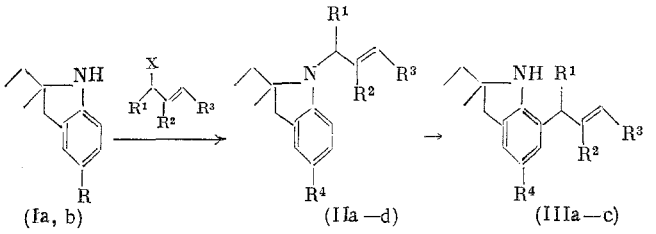
CLAISEN REARRANGEMENT OF STERICALLY HINDERED N-ALKENYLINDOLINES

I. B. Abdrakhmanov, A. G. Mustafin, G. A. Tolstikov, L. V. Spirikhin, and L. M. Khalikov

UDC 542.951.1:547.754:541.63

Despite the development of several methods for carrying out the amino-Claisen rearrangement [1, 2], this reaction remains insufficiently studied, especially for the series of nitrogen-containing heterocyclic compounds. In the present paper our goal was to investigate the Claisen rearrangement in a series of sterically hindered 2-methyl-2-ethyl- (Ia) and 2,5-dimethyl-2-ethylindolines (Ib) in order to elucidate its feasibility for the synthesis of complex heterocyclic derivatives.

In most cases, N-alkenylated materials are required for carrying out Claisen rearrangements. Indolines (Ia, b) are N-alkenylated under harsher conditions than necessary for aromatic amines [3].



(Ia, b) (IIa–d) (IIIa–c)

R = H(a), CH_3(b); X = Cl or Br $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$(a), $R^1 = R^3 = R^4 = CH_3$, $R^2 = H$(b), $R^1 = R^2 = R^3 = R^4 = H$(c) $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$(d)

Thus, (IIa-d) were prepared by heating indolines (Ia, b) with alkenyl halides, specifically, allyl bromide, methallyl chloride, and 4-chloro-2-pentene, at 150°C in an autoclave. Compounds (IIa and b) underwent rearrangement at rearrangement at room temperature in the presence of mineral acids to give 2-methyl-2-ethyl-7-(1'-methyl-2'-butenyl)- (IIIa) and 2,5-dimethyl-2-ethyl-7-(1'-methyl-2'-butenyl)indoline (IIIb) in 90% yields [4]; in contrast, N-allylanilines rearrange at significant rates only upon heating above 100°C [5, 6].

The ease of this isomerization process was further demonstrated by the rearrangement of the hydrochloride salt of (IIc) to give (IIIc) at 150°C; the hydrochloride salt of N-allylaniline does not rearrange under these conditions. Heating allyl bromide with excess indoline (Ia) also led to rearrangement to give (IIIc). Monitoring this reaction by GLC revealed the stable presence of (IIc) in the reaction mixture. Apparently, the limiting step of this process is the rearrangement step, since treatment of 4-chloro-2-pentene with (Ia, b) led to the

Institute of Chemistry, Bashkir Affiliate, Academy of Sciences of the USSR, Ufa. Bashkir Agricultural Institute, Ufa.

Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 613-618, March, 1987. Original article submitted July 24, 1985.

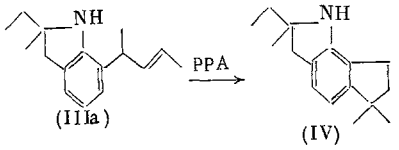
TABLE 1. Effect of Solvent on the Rearrangement of Hydrochloride (IIa) at 20°C

Solvent	Yield, %			Nucleophilicity [7]
	(IIIa)	(IIa)	(Ia)	
Benzene	91	–	9	48
1,4-Dioxane	38,2	58,8	3	237
Ethanol	37,9	57,1	5	235
Nitrobenzene	33,5	66,5	–	67
Water	22,6	77,4	–	156
DMF	18,6	81,4	–	291
DMSO	8,1	91,9	–	362

Thermal rearrangement of (IIa and b) also occurred much more readily than the analogous reactions of corresponding N-allylanilines. For instance, N-(1'-methyl-2'-butenyl)aniline rearranged at 290°C to give the ortho product in 30% yield after 22 h; in the case of (III), a 35% yield was obtained after 6 h at 250°C. In addition, (IIa) was also found to undergo photochemical rearrangement, albeit in low yield.

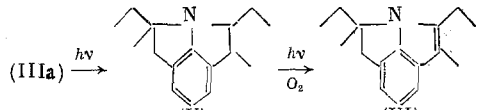
The ease of the amino-Claisen rearrangement of indolines (IIa, b) can be explained in terms of decreased strength of the N–C bond due to steric hindrance. This bond weakening is less prominent, apparently, in the case of compounds (IIc and d). It should be noted that N-(2'-methyl-2'-propene)-2-ethylindoline (IId) does not rearrange under these conditions.

The alkenylindoline derivatives synthesized in this way could be cyclized by a variety of methods to generate more complex heterocyclic systems. For instance, heating (IIIa) in polyphosphoric acid (PPA) led to the formation of (IV) in 90% yield via isomerization of the alkenyl fragment.



(IIIa) (IV)

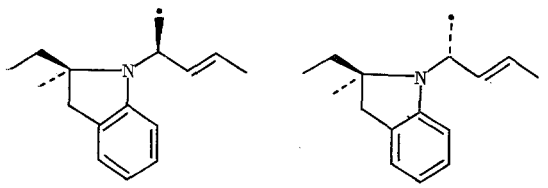
UV irradiation of a solution of (IIIa) in benzene, followed by oxidation of the intermediate product (V), resulted in the formation of compound (VI) in 55% yield.



(V) (VI)

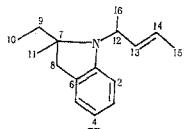
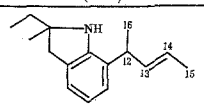
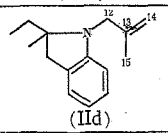
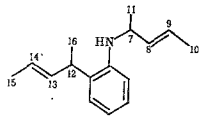
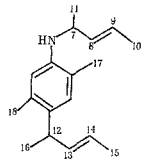
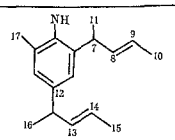
The formation of (V) was confirmed by GLC analysis, as well as by IR and mass spectroscopic analysis of the isolated compound. The absence of bands in the 3400 cm^{-1} region characteristic of amines, as well as the molecular weight (229), provided unequivocal evidence for the structure shown above.

The presence of two chiral carbon atoms at C^7 and C^{12} in compounds (IIa, b) and (IIIa, b) would be expected to lead to the formation of diastereomeric pairs of erythro and threo isomers.



In fact, the ^{13}C-NMR spectrum of compound (IIa) exhibited a double set of signals, which could be assigned to a set of two diastereomers differing in the orientation of the methyl group (C^{16}) (Table 2). The diastereomeric effect for the C^{16} methyl group was 1.09 ppm, which is significantly greater than the error involved in the measurements (0.03 ppm). An analogous effect was observed in the spectrum of compound (IIIa). In this case, the greater distance between the two chiral centers at C^7 and C^{12} resulted in a maximum diastereomeric effect for the C^8 methyl group of only 0.85 ppm. The diastereomeric effects for compounds (VII)-(IX) also substantiated this view. Thus, in the case of compound (VII) the diasteromeric effect was 0.26 ppm for C^{14}, whereas for compounds (VIII) and (IX) it did not exceed 0.09 ppm.

TABLE 2. ^{13}C Nuclear Chemical Shifts for Compounds (IIa, d), (IIIa), and (VII)-(IX) (δ, ppm)

Compound	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9
 (IIa)	148,54s 148,67s	126,91s 126,99s	126,1d	114,69d	124,83d 125,22d	107,10d 107,36d	67,44s 67,62s	40,35t 40,44t	31,86t
 (IIIa)	148,56s	125,67s 125,80s	123,70d 123,81d	122,60d 122,66d	124,44d 124,51d	128,17s 128,32s	63,74s 63,91s	42,96t 42,11t	34,35t 34,75t
 (IId)	151,79	127,48	127,13d	116,21d	123,74d	106,06d	68,22s	40,61t	31,55t
 (X)	145,07 145,29	128,56	126,96	116,73	124,49	111,61	50,11 50,32	135,28 135,45	124,61
 (XI)	143,23	132,12 132,20	127,80	119,31	133,54	112,78	50,30	136,57 136,62	124,59
 (XII)	140,41	135,93	126,80	122,32	124,07	128,97	37,64	137,09	123,10

Compound	C^{10}	C^{11}	C^{12}	C^{13}	C^{14}	C^{15}	C^{16}	C^{17}	C^{18}
(IIa)	8,93q	25,18q 25,44	48,59d	132,98d 133,16d	124,14d	17,77q	16,94q 18,03q		
(IIIa)	9,08q 8,69q	26,35d 26,79q	37,86d 38,03d	135,06d	118,22d	17,75d	18,84q 18,88q		
(IId)	9.15q	23,19q	49,37t	142,43	110,44t	20,29q			
(X)	17,64	22,28 22,11	37,19 37,32	134,58 134,37	126,52 126,26	17,64	19,45 19,25		
(XI)	17,68	22,19	36,99	134,74	122,45	17,25	17,90	20,96 20,87	19,44
(XII)	17,81 17,90	21,72	41,81	136,36	122,60	17,86	21,76	19,52	

The PMR spectra of the diastereomers of (IIa) differed with respect to the chemical shifts of the methyl group signals; the methyl group at C^7 appeared as two singlets (δ_1 = 1.178, δ_2 = 1.197 ppm), the methyl group at C^{12} exhibited two doublets with J = 7.0 Hz (δ_1 = 1.434, δ_2 = 1.387 ppm), and the methyl group on the double bond also as two doublets with J = 4.7 Hz (δ_1 = 1.695, δ_2 = 1.676 ppm). In the case of compound (IIIa), the greatest chemical shift difference occurred for the ethyl fragment at C^7. The methyl group appeared as two triplets (δ_1 = 0.86, δ_2 = 0.91 ppm, J = 7.0 Hz), and the methylene group signal as two quartets (δ_1 = 1.53, δ_2 = 1.6 ppm). The singlet signals at δ_1 = 1.18 and δ_2 = 1.23 ppm belong to the methyl group at C^7. In contrast to compound (IIa), the methyl groups attached to the double bond (δ = 1.65 ppm, J = 3.6 Hz) and to C^{12} (δ = 1.31 ppm, J = 7.0 Hz) in compound (IIIa) appeared as doublets and were identical for the diastereomeric pair.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer for thin films; mass spectra were obtained on an MX-13-06 spectrometer at an electron ionization energy of 70 eV and an ionization temperature of 200°C. PMR spectra were recorded on a Tesla BS-567A spectrometer for $CDCl_3$ and CCl_4 solutions vs TMS, while ^{13}C-NMR spectra were obtained on a Jeol X-90Q (22.50 Hz) spectrometer with broadband as well as partial proton suppression in the monoresonance mode. The field width was 4000 Hz; the resolution of the analog-digital transducer was 0.50 Hz. $CDCl_3$ was used as solvent vs TMS as standard. GLC analyses were conducted on an LKHM-8MD chromatograph using a 3 m × 3 mm column filled with SE-30 on N-AW-DMCS chromatone with a helium flow rate of 30 ml/min.

General Method for N-Alkenylation. A mixture of 3 g (Ia) or (Ib), 6 ml Et_3N, and a one-and-a-half excess of the required haloalkene was heated at 150°C in a bantam autoclave (volume 15 ml) for 5 h. The mixture was cooled and washed 2-3 times with water; the organic layer was extracted into ether, dried over $CaCl_2$, and evaporated. Yield of product, 85-90%.

Catalytic Rearrangement of (IIa, b). 1) The hydrochloride of (II), prepared in pentane, was dried in vacuo for 30 min, and then dissolved in the appropriate solvent (see Table 1) with an internal standard, pentadecane. The reaction was carried out with stirring at 20°C and was monitored by GLC.

2) To 10 ml of 2N HCl or H_2SO_4 was added 0.5 g (IIa) or (IIb). The course of the reaction was followed by GLC. Yield of the desired product, up to 90%. In addition to (IIIa, b), (Ia, b) were also detected, in amounts not exceeding 7-8%.

Preparation of (IIIa, c) Without Intermediate Isolation of (IIa-c). A mixture of 0.0372 mole of the corresponding indoline and 0.019 mole of the haloalkene was heated at 150°C for several hours. The mixture was worked up with conc. KOH solution, and the organic layer was extracted with ether, dried over $CaCl_2$, and evaporated.

Cyclization of (IIIa) with PPA. PPA was prepared from 9 g (H_3PO_4 (85%) and 5 g P_2O_5, and was treated with 3.5 g (0.0153 mole) of (IIIa); the mixture was heated at 135-140°C for 6 h. Water was added to the reaction mixture and it was carefully neutralized with conc. KOH under cooling. The upper layer was extracted with ether (4 times), dried over $CaCl_2$, and evaporated. Yield of (IV), 90%.

Photochemical Cyclization of (IIIa). A solution of 1.5 g (IIIa) in 750 ml benzene was placed in an 850 ml reactor and irradiated under Ar atmosphere with a DRT-375 lamp for 30 min. (V) was formed during this process. Air was then allowed into the reactor in place of Ar, and the mixture was irradiated another 30 min, which resulted in the oxidation of the intermediate compound (IV) to (VI). The benzene was evaporated and the residue was chromatographed on SiO_2 by extraction with a 1:4 benzene–pentane mixture. Yield of (VI), ca. 55% at 90% conversion.

Photochemical Rearrangement of (IIa). A solution of 0.5 g (0.0022 mole) (IIa) in 500 ml benzene was irradiated as in the previous example for 15 min. The following were identified in the reaction mixture: (Ia), 22%, (IIa), 43%, (IIIa) + (IV), 10-12%.

Thermal Rearrangement of (IIa). A 3 ml solution of (IIa) in undecane with a concentration of 0.150 ml* (pentadecane as internal standard) was heated in a sealed tube at 250°C for 6 h. The reaction mixture consisted of 24% (Ic), 12% (IIa), and 35% (IIIa); other components were not identified.

2-Methyl-2-ethyl-N-(1'-methyl-2'-butenyl)indoline (IIa). η_D^{20} 1.5382, bp 115-116°C (1 mm Hg). IR spectrum (ν, cm^{-1}): 750, 980, 1610. PMR spectrum (δ, ppm): 0.86 t (3H, CH_3), 1.178 s (3H, CH_3), 1.197 s (3H, CH_3) 1.387 d (3H, CH_3), 1.434 d (3H, CH_3), 1.56 q (2H, CH_2), 1.676 d (3H, CH_3), 1.695 d (3H, CH_3), 2.70 d (1H, CH_2), 2.98 d (1H, CH_2), 4.025 m (1H, CH), 5.4-5.9 m (2H, CH=CH), 6.3-7.1 m (4H, Ar). M^+ 229.

2-Methyl-2-ethyl-7-(1-methyl-2-butenyl)indoline (IIIa). η_D^{20} 1.5335, bp 117-119°C (1 mm Hg). IR spectrum (ν, cm^{-1}): 750, 980, 1600, 3385 (N–H). PMR spectrum (δ, ppm): 0.86 t (3H, CH_3, J=7 Hz) 0.91 t (3H, CH_3, J=7 Hz, 1.18 s (3H, CH_3), 1.23 s (3H, CH_3), 1.31 d (3H, CH_3, J=7 Hz, 53 q (2H, CH_2), 1.60 (2H, CH_2, J=7 Hz, 1.65 d (3H, CH_3, J=3.6 Hz), 2.74 d (1H, CH_2, J=15 Hz, 1.88 d (1H, CH_2, J=15 Hz, 3.29 (1H, CH, J=6 Hz), 3.66 s (1H, NH), 5.2-5.8 m (2H, CH=CH), 6.54.7.04 m (3H, Ar). M^+ 229.

*As in Russian original – Publisher.

2,5-Dimethyl-2-ethyl-1-(1-methyl-2-bentenyl)indoline (IIb). Bp 120-123°C (1 mm Hg). IR spectrum (ν, cm^{-1}): 750, 975, 1590, 2970. PMR spectrum (δ, ppm): 0.85 t (3H, CH_3, J = 7 Hz), 1.166 s (3H, CH_3), 1.20 s (3H, CH_3), 1.350 d (3H, CH_3, J = 7 Hz, 1.40 d (3H, CH_3, J = 7 Hz, 1.567 q (2H, CH_2, J = 7 Hz), 1650 d (3H, CH_3, J = 4 Hz, 2.20 s (3H, CH_3), 2.62 d (1H, CH_2, J = 15.5 Hz, 2.95 d (1H, CH_2, J = 15.5 Hz, 3.85 q, (1H, CH, J = 7 Hz, 5.45-5.73 m (2H, CH = CH), 6.28 d (1H, Ar), 6.75 d (1H, Ar), 6.83 s (1H, Ar). M^+ 243.

2,5-Dimethyl-2-ethyl-7-(1-methyl-2-butenyl)indoline (IIIb). Bp 121-124°C (1 mm Hg). IR spectrum (ν, cm^{-1}): 750, 980, 1600, 3370 (N—H). PMR spectrum (δ, ppm): 0.892 t (3H, CH_3, J = 7 Hz), 0.925 t (3H, CH_3, J = 7 Hz, 1.183 s (3H, CH_3), 1.208 s (3H, CH_3), 1.317 d (3H, CH_3, J = 7 Hz), 1.58 q (2H, CH_2, J = 7 Hz, 1.65 q (2H, CH_2, J = 7 Hz, 1.68 d (3H, CH_3, J = 4 Hz, 2.27 s (3H, CH_3), 2.82 s (2H, CH_2), 3.36 q (1H, CH, J = 7 Hz), 5.33 m (2H, CH = CH), 6.80 s (2H, Ar). M^+ 243.

2-Methyl-2-ethyl-1-(2-propene)indoline (IIc). η_D^{20} 1.5497. IR spectrum (ν, cm^{-1}): 750, 1610, 1650, 3085. PMR spectrum (δ, ppm): 0.83 t (3H, CH_3, J = 7 Hz) 1.12 s (3H, CH_3), 1.55 q (2H, CH_2, J = 7 Hz) 2.625 d (1H, CH_2, J = 15 Hz, 2.91 d (1H, CH_2, J = 15.5 Hz, 3.43-3.67 m (2H, CH_2), 4.90-5.85 (3H, $CH=CH_2$), 6.03-7.0 m (4H, Ar). M^+ 201.

2-Methyl-2-ethyl-7-(2-propene)indoline (IIIc). IR spectrum (ν, cm^{-1}): 750, 1610, 3085, 3370 (N—H). PMR spectrum (δ, ppm): 0.83 t (3H, CH_3, J = 7 Hz), 1.10 s (3H, CH_3), 1.50 q (2H, CH_2, J = 7 Hz, 2.725 s (2H, CH_2), 3.22 s (1H, N-H), 3.45-3.68 m (2H, CH_2), 4.83-6.0 m (3H, $CH=CH_2$) 6.33-7.0 m (3H, Ar). M^+ 201.

2-Methyl-2-ethyl-1-(2-methyl-2-propene)indoline (IId). η_D^{20} 1.5445. IR spectrum (ν, cm^{-1}): 750, 1610, 1660, 3080. PMR spectrum (δ, ppm): 0.83 t (3H, CH_3, J = 7 Hz) 1.12 s (3H, CH_3), 1.56 q (2H, CH_2, J = 7 Hz, 1.75 s (3H, CH_3), 2.65 d (1H, CH_2, J = 15.5 Hz, 2.92 d (1H, CH_2, J = 15.5 Hz), 3.42 s (2H, CH_2), 4.67-5.08 s (2H, $=CH_2$) 5.92-7.0 m (4H, Ar). M^+ 215.

6,6-Dimethylperhydrocyclopent[g]-2-methyl-ethylindoline (IV). Bp 115-118°C (1 mm Hg). IR spectrum (ν,cm^{-1}): 1605, 3370 (N—H). PMR spectrum (δ, ppm): 0.90 t (3H, CH_3, J = 7 Hz) 1.16 s (9H, $3CH_3$), 1.56 m (2H, CH_2), 1.90 t (2H, CH_2), 2.50 t (2H, Ar-CH_2), 2.68 s (2H, Ar-CH_2), 3.13 s (1H—H), 6.30 d (1H, Ar), 6.73 d (1H, Ar). Found: C 83.98; H 10.10; N 6.05%. $C_{16}H_{23}N$. Calc.: C 83.84; H 10.04; N 6.11%. M^+229.

8-Methyl-8-ethylpyrrolidino(h, i)-3-methyl-2-ethylindole (VI). IR spectrum (ν, cm^{-1}): 755, 770, 1500, 2940, 2980. PMR spectrum (δ, ppm): 0.80 t (3H, CH_3, J = 7 Hz), 1.25 t (3H, CH_3, J = 7 Hz), 1.55 s (3H, CH_3), 1.88 q (2H, CH_2, J = 7 Hz, 2.20 s (3H, CH_3), 2.72 q (2H, CH_2, J = 7 Hz), 3.33 d (1H, CH_2, J = 16 Hz, 3.60 d (1H, CH_2, J = 16 Hz), 6.47-7.17 m (3H, Ar). M^+ 227.

CONCLUSIONS

Claisen rearrangement of N-(1'-methyl-2'-butenyl)-2-methyl-2-ethylindoline occurs under mild conditions upon treatment with acids at 20°C. Tricyclic compounds, namely, 6,6-dimethylperhydrocyclopent[g]-2-methyl-2-ethylindoline and 8-methyl-8-ethylpyrrolidino[h, i]-3-methyl-2-ethylindole, were obtained from 7-(1'-methyl-2'-butenyl)-2-methyl-2-ethylindoline.

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