Chemistry of Heterocyclic Compounds, Vol. 33, No. 7, 1997

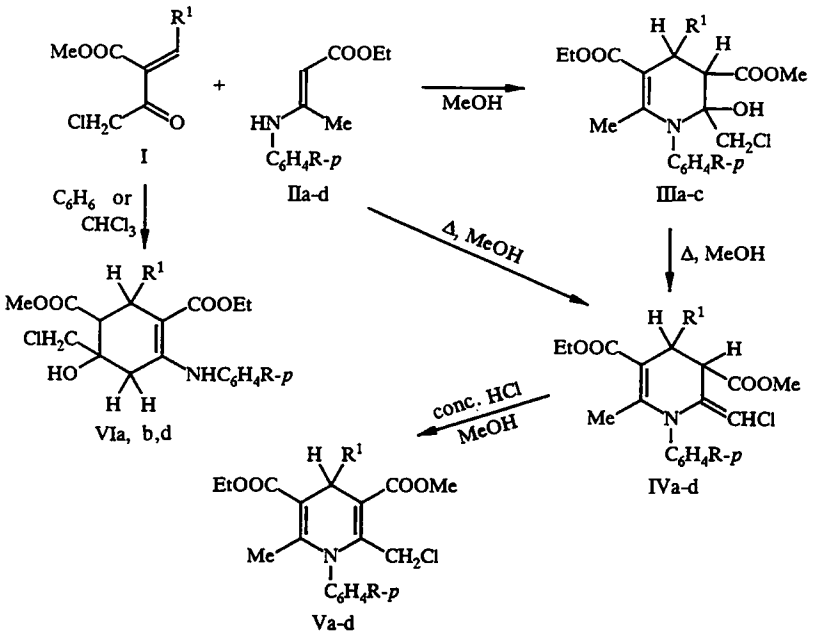
N-ARYL-2-HYDROXY-1,2,3,4-TETRAHYDROPYRIDINES AND N-ARYL-2-CHLOROMETHYLENE-1,2,3,4-TETRAHYDRO-PYRIDINES — SUCCESSIVE INTERMEDIATES IN THE HANTZSCH SYNTHESIS OF 1,4-DIHYDROPYRIDINES

B. Chekavichus, Yu. Popelis, E. Shebenina, A. Sausin'sh, R. Verkhe, and G. Duburs

Esters of 4-chloro-2-arylideneacetoacetic acid I and esters of N-arylaminocrotonic acid II form stable N-aryl-3,4-trans-2-hydroxy-1,2,3,4-tetrahydropyridines III. Their regio- and stereoselective dehydration results in N-aryl-2-chloromethylene-1,2,3,4-tetrahydropyridines with an exocyclic bond, IV. Compounds IV isomerize to the corresponding N-aryl-2-chloromethyl-1,4-dihydropyridines V in acid medium. Michael addition of compounds I and II in chloroform or benzene forms carbocyclic derivatives of cyclohexene VI.

1,4-Dihydropyridines are a well-known class of biologically active compounds used in clinical practice as cardiovascular agents [1]. The most common method of their preparation is the Hantzsch synthesis, during which various products of heterocyclization, i.e., derivatives of N-unsubstituted 2-hydroxy- and 2-methylene-1,2,3,4-tetrahydropyridines, are formed [2-8].

The object of this work was to study the heterocyclization products in the Hantzsch synthesis in a series of N-substituted compounds which thus far have been mentioned only in a brief communication [9].



II–VI a R = NMe_2, b R = OMe, c R = OEt, d R = Cl; I, III–VI R^1 = $C_6H_4NO_2$-*m*

Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 915-920, July, 1997. Original article submitted January 3, 1997.

0009-3122/97/3307-0799$18.00

TABLE 1. Characteristics of Compounds III-VI

Compound	Empirical formula	Found, % / Calculated, %				T, °C	Method	Yield, %
		C	H	N	Cl			
IIIa	$C_{26}H_{30}ClN_3O_7$	58.35 58,71	5.62 5,64	7.91 7,90	6.24 6,67	124...125		35
IIIb	$C_{25}H_{27}ClN_2O_8$	57.87 57,85	5.23 5,24	5.30 5,39	6.71 6,84	113...115		39
IIIc*	$C_{26}H_{29}ClN_2O_8$	58.69 58,58	5.49 5,48	5.26 5,25	6.67 6,66	136...137		38
IVa	$C_{26}H_{28}ClN_3O_6$	59.98 60,76	5.52 5,49	7.97 8,17	6.46 6,90	170...172	A/B	72/87
IVb*	$C_{25}H_{25}ClN_2O_7$	60.42 59,93	4.98 5,03	5.48 5,59	6.46 7,08	123...125	A/B	63/52
IVc	$C_{26}H_{27}ClN_2O_7$	60.52 60,63	5.15 5,28	5.30 5,44	6.95 6,89	118...120	A/B	65/56
IVd	$C_{24}H_{22}Cl_2N_2O_6$	57.50 56,99	4.43 4,44	5.58 5,54	13.24 14,03	148...150	B	56
Va	$C_{26}H_{28}ClN_3O_6$	60.29 60,76	5.44 5,49	7.94 8,17	7.31 6,90	162...164	A_1	80
Vb*	$C_{25}H_{25}ClN_2O_7$	59.94 59,93	5.03 5,03	5.59 5,59	7.07 7,08	136...137	A_1/A_2/ B	60/49/61
Vc*	$C_{26}H_{27}ClN_2O_7$	59.94 60,63	5.03 5,28	5.60 5,44	7.07 6,89	125...126	A_2/B	54/91
Vd	$C_{24}H_{22}Cl_2N_2O_6$	57.03 56,99	4.33 4,44	5.50 5,54	13.29 14,03	130...132	A_2	44
VIa	$C_{26}H_{30}ClN_3O_7$	58.61 58,69	5.72 5,68	7.89 7,89	6.59 6,67	124...125	A_1	36
VIb	$C_{25}H_{27}ClN_2O_8$	57.60 57,85	5.18 5,24	5.29 5,39	6.02 6,84	153...154	A_1	39
VId	$C_{24}H_{24}Cl_2N_2O_7$	54.97 55,07	4.59 4,62	5.29 5,35	12.61 13,56	177...178	A_1/A_2	94/58

*m/z, (M^+) for the compounds: IIIc) 533; IVb) 500; Vb) 500; Vc) 514.

It was possible for the first time to isolate two successive series of stable N-aryl-1,2,3,4-tetrahydropyridines leading to N-aryl-1,4-dihydropyridines: N-aryl-2-hydroxy-1,2,3,4-tetrahydropyridines III and N-aryl-2-chloromethylene-1,2,3,4-tetrahydropyridines IV were obtained in a two-component Hantzsch cyclization of esters of 4-chloro-2-arylideneacetoacetic (I) and N-arylaminocrotonic (II) acids (scheme, Table 1) [9].

Thanks to specific structural elements—a substituent at the nitrogen atom—compounds III and IV are stable when isolated and studied, but at the same time, subsequent dehydration and isomerization reactions of compounds III and IV take place readily, with the formation of an exocyclic C=C bond (the 2-chloro substituent promotes chlorovinylamino coupling) and N-aryl-substituted compounds IVa-d are more stable in various solvents (chloroform, benzene, acetone at room temperature as well as at the boiling points of the solvents) than are their N-unsubstituted analogues [5].

The isomerization of 2-chloromethylene-1,2,3,4-tetrahydropyridines IV to 2-chloromethyl-1,4-dihydropyridines V takes place readily in acid medium and in good yields. When 1,4-dihydropyridines V were treated with camphorsulfonic acid, reverse isomerization to 1,2,3,4-tetrahydropyridines IV was not observed.

N-Aryl-2-chloromethyl-1,4-dihydropyridines V are stable compounds which do not cyclize into a lactone either after many hours of heating or in the molten state. This is consistent with the reactivity, which we elucidated earlier, of 2-bromomethyl-1,4-dihydropyridines [10], associated with their steric strain, the latter being caused by the substituent at the nitrogen atom, despite the high reactivity of the halogen of the allyl group of compounds V.

The Stewart-Brigleb models show that in N-aryl-2-chloromethyl-1,4-dihydropyridines [10], associated with their steric strain, the latter being caused by the substituent at the nitrogen atom, despite the high reactivity of the halogen of the allyl group of compounds V.

The Stewart-Brigleb models show that in N-aryl-2-chloromethyl-1,4-dihydropyridines V, rotation of the CH_2Cl group is impossible, and apparently, as a result, there is little probability that the reaction centers will come closer together to close

TABLE 2. ESR Spectra of Compounds IIIa-c in $CDCl_3$

Compound	Chemical shifts, δ, ppm, and SSCC (J, Hz)								
	2-OH	2-CH_2Cl	3-H	4-H	5-$COOCH_2CH_3$	3-$COOCH_3$	6-CH_3	$C_6H_4NO_2$-*m*, C_6H_4R-*p*	H_R
IIIa	4,47	3,25, 3,10 (13,2)	4,35 (d, 12,2) (q, 1,6)	3,45 (d, 12,2)	3,43, 0,72 (6,8)	3,40	2,01 (d, 1,6)	7,1...8,1, 6,65, 7,19 (8,1)	2,94
IIIb	4,51	3,18, 3,08 (13,7)	4,33 (d, 11,6) (q, 1,5)	3,43 (d, 11,6)	3,66, 0,71 (6,9)	3,39	1,97 (d, 1,5)	6,8...8,1, 6,83, 7,13 (8,3)	3,77
IIIc	4,57	3,25, 3,17 (11,6)	4,40 (d, 11,1) (q, 1,5)	3,51 (d, 11,1)	3,73, 0,76 (6,6)	3,48	2,03 (d, 1,5)	7,3...8,2, 6,90, 7,27 (8,9)	4,06, 1,44 (6,7)

TABLE 3. ESR Spectra of Compounds IVa-d in $CDCl_3$

Compound	Chemical shifts, δ, ppm, and SSCC (J, Hz)							
	2-CHCl	3-$COOCH_3$	3-H	4-H*	5-$COOCH_2CH_3$	6-CH_3	$C_6H_4NO_2$-*m*, C_6H_4R-*p*	H_R
IVa	5,02	3,79	4,21 (2,2)	4,90	4,06, 1,13 (6,6)	2,23	7,2...8,2, 6,76, 7,07 (9,1)	3,01
IVb	4,99	3,84	4,26 (2,1)	4,92	4,07, 1,14 (7,2)	2,22	7,3...8,2, 7,00, 7,17 (8,3)	3,86
IVc	4,95	3,80	4,20 (2,2)	4,87	4,02, 1,10 (6,6)	2,19 (b)	6,8...8,1, 6,93, 7,05 (8,2)	4,02 1,42 (6,6)
IVd	4,94	3,80	4,22 (2,05)	4,90	4,03, 1,10 (7,2)	2,18 (0,6)	7,3...8,2, 7,19, 7,46 (8,9)	

*The signals have an additional SSCC with the 6-CH_3 group, and therefore, $J_{3,4}$ were determined only for the 3-H signals.

the lactone ring. The inhibition of the rotation of the CH_2Cl group is indicated in the ESR spectra by signals (AB-type) of the methylene group in the 2 position at 3.9-4.1 ppm and 4.8-4.9 ppm.

In a two-component reaction between esters of 4-chloro-2-arylidene-acetoacetic acid I and esters of N-arylaminocrotonic acid II at room temperature or after brief boiling in methanol, N-aryl-3,4-trans-2-hydroxy-1,2,3,4-tetrahydropyridines IIIa-c were obtained. The structure of compounds IIIa-c was confirmed by the ^1H and ^{13}C spectra (for compound IIIb). The ^1H NMR signals (Table 2) of the ring protons (3)-H, (4)-H have a coupling constant J = 11.2-12.2 Hz, which is characteristic of their transdiaxial arrangement (the dihedral angle is almost 180°). The axial position of 4-H is also confirmed by its long-range SSCC with the methyl-group protons in the 6 position (J = 1.5-1.6 Hz).

The structure of compounds IVa-d was proven by their spectroscopic data. In the UV spectra of tetrahydropyridines IV, only one peak appears at 311-315 nm, in contrast to dihydropyridines V, and in the IR spectra, absorption of carbonyl groups at 1740 cm^{-1} and 1700 cm^{-1} is observed. In the ^1H NMR spectra, one can clearly identify the proton signals of C=CHCl at 4.9-5.0 ppm, and the signals of 3-H and 4-H, respectively, in the form of doublets at 4.2-4.3 ppm and 4.8-4.9 ppm; the spin-spin coupling constants J = 2.0-2.2 Hz remain unchanged in the temperature range 271-333 K (Table 3). The long-range SSCC between 4-H and the methyl group in the 6 position is less than 0.2 Hz. From this one can conclude that tetrahydropyridines IV exist as a single isomer with a diequatorial arrangement of 3-H and 4-H.

The solvent polarity in the two-component condensation between the initial substances I and II has a decisive effect on the course of the reaction—carbocyclic derivatives of cyclohexene were obtained in the course of the synthesis (Tables 1 and 4).

The structure of compounds VIa,b,d was proven by ESR spectra (Table 4). The doublets in the range 2.8-2.9 ppm and 4.2-4.3 ppm are due to the absorption of 4-H and 3-H, respectively, and the value 11.0 Hz of the SSCC indicates a transdiaxial arrangement of the protons. For compound VIa, a 2-D NEO spectrum was recorded; the absence from this spectrum of the correlation peaks for 6-H protons suggests that a skewed chair conformation takes place.

EXPERIMENTAL

The ESR spectra were recorded on the instruments Bruker WH (90 MHz) and AM 360 (360 MHz) in $CDCl_3$, and the chemical shifts are given in ppm relative to TMS internal standard. The IR spectra were recorded on a Perkin-Elmer 580 B spectrometer in the form of a suspension in Nujol, and the UV spectra were recorded on a Specord M-40 Carl Zeiss/Jena spectrometer in ethanol. The mass spectra were taken with an AE/MS-50 instrument.

The course of the reaction and the purity of the synthesized compounds were monitored on 0.25-mm Merck Kieselgel 60 F_{254} plates. Solvent systems: 9:7:1 chloroform—hexane—acetone and 20:1 benzene—ethyl acetate.

TABLE 4. ESR Spectra of Compounds VIa,b,d in $CDCl_3$

Compound	Chemical shifts, δ, ppm, and SSCC (J, Hz)									
	1-NH	3-H	4-H	5-OH	5-CH_2Cl	6-H	2-$COOCH_2CH_3$	4-$COOCH_3$	$C_6H_4NO_2$-*m* C_6H_4R-*p*	H_R
VIa	10,6	4,27 (d, 10,8) (d, 1,1)	2,85 (d, 10,8)	3,77 (d, 2,2)	3,37, 3,32 (11,7)	2,46, 2,75* (17,7)	3,82, 0,75 (7,1)	3,53	8,1...7,4, 7,03, 6,71 (9,0)	2,98
VIb	9,3	4,27 (d, 11,0) (d, 1,8)	2,86 (d, 11,0)	3,79 (d, 2,0)	3,36, 3,32 (11,9)	2,44, 2,75* (17,6)	3,85, 0,75 (6,8)	3,54	8,1...7,4, 7,08, 6,92 (8,0)	3,84
VId	10,9	4,29 (d, 11,0) (d, 1,2)	2,75 (d, 11,0)	3,81 (d, 1,8)	3,39	2,54, 2,89* (17,4)	3,83, 0,77 (6,8)	3,55	8,1...7,4, 7,40, 7,13	—

*An additional splitting with SSCC of 1.8 Hz and 2.0 Hz is observed for the signal.

The data of the ultimate analysis of the compounds obtained for C, H, N, and Cl correspond to the calculated data. The characteristics of compounds III-VI are correlated in Tables 1-4.

N-Aryl-3,4-trans-2-hydroxy-1,2,3,4-tetrahydropyridines (III). Obtained by boiling 10 mmole of the esters of 4-chloro-2-arylideneacetoacetic acid I and 10 mmole of N-arylaminocrotonic acid II for 20 min in 20 ml of methanol or by stirring the reaction mixture for 4 h at room temperature. The mixture is cooled, and the crystals are filtered off. Crystallization from methanol.

N-Aryl-2-chloromethylene-1,2,3,4-tetrahydropyridines (IV). A. The isolated compounds III (5 mmole) are boiled for 3 h in 10 ml of methanol.

B. Equimolar amounts (5 mmole) of initial substances I and II are dissolved in 10 ml of methanol and boiled for 2 h. The reaction mixture is cooled, and the precipitate is filtered off (methods A and B). Crystallization from methanol.

N-Aryl-2-chloromethyl-1,4-dihydropyridines (V). A. Obtained from the initial compounds (10 mmole) I and II with isolation (method A_1) or without isolation (method A_2) of compounds IV, followed by addition of a few drops of conc. HCl and boiling in 20 ml of methanol for 30 min.

B. Equimolar amounts (10 mmole) of initial substances I and II in 20 ml of methanol are boiled for 10 h. After cooling, the precipitate is filtered off and crystallized from methanol (methods A and B).

N-Aryl-5-chloromethyl-5-hydroxycyclohexenes (VI). Equimolar amounts (5 mmole) of initial substances I and II are boiled for 4 h in 15 ml of benzene or chloroform (solvents: method A_1 – benzene, method A_2 – chloroform). After evaporation of the reaction mixture in a vacuum, the residue is ground up with methanol and crystallized from methanol.

The authors are grateful to ISF (Grants LF 2000 and LJ 2100) and the Science Council of Latvia (Grant 93-468) for their financial support.

REFERENCES

1. A. E. Sausin'sh and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 1, 435 (1992).
2. B. Sigh and G. Y. Lesher, J. Heterocycl. Chem., **17**, 1109 (1980).
3. European Pat. Appl. 125,803; A. L. G. Boxter, J. Dixon, K. J. Gould, T. McInally, and A. C. Tinker, Chem. Abstr., **102**, 203874 (1985).
4. T. Ogawa, K. Matsumoto, K. Hatayama, K. Kitamura, and Y. Kita, J. Chem. Soc. Perkin Trans. I (1993), p. 3033.
5. M. Frigerio, A. Zaliani, C. Riva, G. Palmisano, T. Pilati, and C. A. Gandolfi, Tetrah. Lett., **29**, 6335 (1988).
6. J. A. M. Christiaans, A. D. Windhorst, P. M. Groenenberg, H. Van der Goot, and H. Timmermann, Eur. J. Med. Chem., **28**, 859 (1993).
7. M. D. Taylor, E. W. Badger, R. P. Steffen, S. J. Haleen, T. A. Pugsley, Y. H. Shih, and R. E. Weishaar, J. Med. Chem., **31**, 1659 (1983).
8. J. W. Patterson and J. T. Nelson, J. Heterocycl. Chem., **25**, 125 (1988).
9. B. S. Chekavichus, I. S. Birgele, A. E. Sausin'sh, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 7, 1000 (1992).
10. B. S. Chekavichus, A. E. Sausin'sh, I. P. Skrastin'sh, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 10, 1442 (1989).