SYNTHESIS AND ACYLATION OF TERTIARY ENAMINES: 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES

V. S. Shklyaev, B. B. Aleksandrov,
M. S. Gavrilov, A. G. Mikhailovskii,
and M. I. Vakhrin

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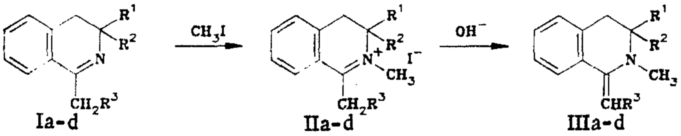
N-methyl-3,3-R^1R^2-1-(R^3-methylene)-1,2,3,4-tetrahydroisoquinolines were obtained; they react with acylating agents forming enaminocarbonyl derivatives.

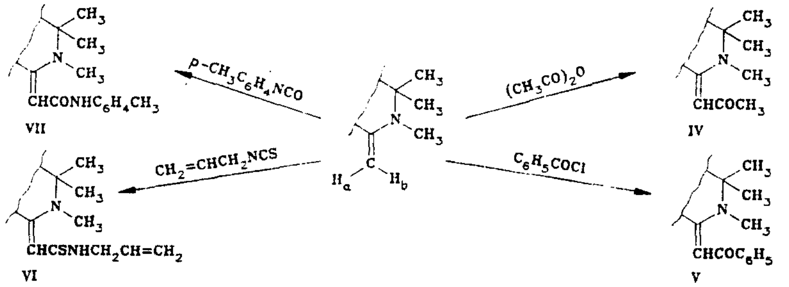
We obtained earlier secondary enamines of the 3,4-dihydroisoquinoline series [1, 2]. Investigations showed that the possibility of acylating these latter was limited to reactions with aroyl ketenes [3], oxalyl chloride [4] and aryl isocyanates. In continuing our investigation of the reactivity of 1-methyl-3,3-dialkyl-3,4-dihydroisoquinolines Ia-Id, we discovered that they could be easily methylated at the nitrogen atom forming iodomethylates IIa-IId, which upon treatment with caustic solutions were converted to anhydrous bases IIIa-IIId.



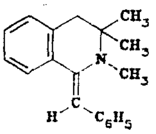
I, II, III a $R^1=R^2=CH_3$, $R^3=H$; b $R^1=CH_3$, $R^2=C_2H_5$, $R^3=H$; c $R^1+R^2=(CH_2)_5$, $R^3=H$; d $R^1=R^2=CH_3$, $R^3=C_6H_5$

Tertiary enamines IIIa-IIId are unstable as compared to the corresponding starting Ia-Id compounds; the former rapidly oxidize in air and actively react with various acylating reagents. This increase in reactivity can be explained by the fact that the produced bases IIIa-IIId have an enamine structure rather than an azomethine structure as do the starting compounds Ia-Id [1-4].

We used compound IIIa as the example of our investigation. This compound reacts with acetic anhydride, benzoyl chloride, allyl isothiocyanate, and n-tolyl isocyanate, forming enamines IV-VII:



In PMR spectra of enamines IIIa-IIIc our attention was drawn to the difference in the chemical shifts of a-H and b-H protons.



IIId

Proceeding from calculated data [5], the values of chemical shifts for these olefinic protons are 4.43 ppm (a-H) and 3.99 ppm (b-H), which agree with experimental data (Table 1). Two spatial configurations are possible for the molecules of enamine IIId: Z and E. According

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TABLE 1. PMR Spectra of Compounds III-VIII (in $CDCl_3$, ppm)

Compound	Protons of group $C_3R^1R^2$	s, 2H, 4-H	a-H	b-H	m, Ar	s, 1H $CHC_{(1)}$	s, 3H, CH_3N	Protons of other groups
IIIa	1,03 (s, $2CH_3$)	2,67	4,47	3,64	6,60—7,63	—	2,54	—
IIIb	1,02 (s, CH_3); 0,8 (t, CH_3); 1,40 (q, CH_2)	2,55	4,48	3,70	6,67—7,77	—	2,53	—
IIIc	0,9—1,83 (width s, $5CH_2$)	2,60	4,38	3,64	6,68—7,60	—	2,60	—
IIId	1,07 (s, $2CH_3$)	2,60	—	—	6,65—7,87	5,87	2,40	—
IV	1,17 (s, $2CH_3$)	2,67	—	—	6,80—7,56	5,03	2,98	2,10 (s, CH_3CO)
V	1,15 (s, $2CH_3$)	2,70	—	—	6,87—7,98	5,00	3,05	—
VI	1,13 (s, $2CH_3$)	2,70	—	—	6,83—7,75	4,97	2,70	—*
VII	1,14 (s, $2CH_3$)	2,62	—	—	6,78—7,87	5,54	2,77	2,17 (s, CH_3Ar) 9,23 (s, NH)
VIII	1,20 (s, $2CH_3$)	2,74	—	—	6,70—7,83	5,05	—	2,22 (s, CH_3Ar) 9,60 (NH of the ring 6,57 (s, CONH)

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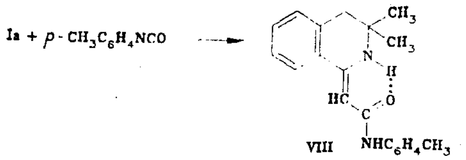
*4.23 (d, CH_2N); 11.02 (s, NH amine); 5.17 (s); 5.28 (s); 5.60 (t, $H_2C{=}CH-$).

to [6], the calculation of the chemical shift of the vinyl proton gave 5.78 ppm for the Z configuration and 5.30 ppm for the E configuration. Because in the PMR spectrum of compound IIId this signal is found at 5.87 ppm, the most probable configuration of this molecule is Z. The fact that base IIId is a Z isomer can be explained by the mutual repulsion of the isoquinoline and phenyl rings.

We made an attempt to determine the configurations of compounds IV-VII. The individuality of isomers IV-VII, obtained after having been recrystallized, was confirmed by their melting points (Table 2) and by TLC in the system chloroform—acetone, 9:1, as well as by PMR spectral data (Table 1) which exhibited the signals of only a single isomer. Investigations of compounds IV-VII immediately following the reaction by TLC and PMR, before their recrystallization, did not allow us to make any conclusion about the presence of a second isomer. The PMR pattern did not change either when heating solutions of enamines IV-VII in $CDCl_3$ up to 60°C, and in DMSO-D_6 up to 80°C, demonstrating thus the configurational stability of these compounds.

The following chemical shift values were calculated for the vinyl proton in enamines IV-VII, in ppm: for E isomers, 4.99 (IV); 5.05 (V); 5.36 (VII). For Z isomers: 5.44 (IV); 5.40 (V); 5.71 (VII). The additive parameters for thioamide VI is not known [5]. A comparison of these values with those of Table 1 allowed us to conclude the existence of compounds IV and V in the E configuration. In order to determine the configuration of compound VII, we synthesized the secondary enamine VIII for which we ascertained, by PMR and IR data, (0.01 M), the Z configuration stabilized by an intramolecular hydrogen bond:



VIII

Based on the difference in chemical shifts of the vinyl proton in amides VII and VIII, amounting to 0.49 ppm (Table 1), it can be assumed that compounds VII and VIII have opposite configurations. This assumption agrees with the known rule about the displacement of cis olefinic protons with respect to the electronegative nitrogen atom [6].

EXPERIMENTAL

The IR spectra were taken in $CHCl_3$ using a UR-20 spectrometer, and the PMR spectra with a PC-60 instrument using HMDS as the internal standard. The TLC analysis was carried out on Silufol UV-254 plates; the development was conducted with bromine vapors.

TABLE 2. Characteristics of Compounds II-VIII

Compound	mp, *°C	Found, %			Gross formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIa	217—219	49,5	5,7	4,4	$C_{13}H_{18}IN$	49,5	5,8	4,4	97
IIb	205—207	51,0	6,1	4,2	$C_{14}H_{20}IN$	51,1	6,1	4,3	91
IIc	193—194	54,0	6,1	3,8	$C_{16}H_{22}IN$	54,1	6,2	3,9	89
IId	150—151	58,1	6,0	3,6	$C_{19}H_{23}IN$	58,2	5,9	3,6	87
IV	172—173	78,4	8,3	5,3	$C_{15}H_{19}NO$	78,6	8,4	6,1	86
V	163—164	82,2	7,2	4,7	$C_{20}H_{21}NO$	82,4	7,3	4,8	78
VI†	142—144	52,7	5,9	7,2	$C_{17}H_{23}ClN_2O_4S$	52,8	6,0	7,2	73
VII	155—156	78,6	7,4	8,7	$C_{21}H_{24}N_2O$	78,7	7,6	8,7	92
VIII	183—185	78,1	7,3	9,0	$C_{20}H_{22}N_2O$	78,4	7,2	9,1	78

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*All compounds were recrystallized from isopropyl alcohol.
†Identified as perchlorate. Found, %: Cl 9.1; S 8.2. Calculated, %: Cl 9.2; S 8.3.

Compounds Ia-Id were prepared using the methods described in [1-4]. Enamines III were identified as hydroiodides II. The characteristics of compounds III-VIII are shown in Table 2.

N-Methyl-3,3-R^1-R^2-methylene)-1,2,3,4-tetrahydroisoquinolines IIIa-IIId. General Method. A mixture of 10 mmole of base Ia-Id and 0.8 ml (13 mmole) of CH_3I was tightly closed and kept at 20°C for 4 h. The formed precipitate was filtered and, after recrystallization, iodides IIa-IId were obtained. To prepare bases IIIa-IIId, the corresponding iodomethylate was treated with a 20% NaOH solution, extracted with ether, the ether extract was dried with NaOH, and after driving off the ether, bases IIIa-IIId were obtained. Their IR spectra were: 1640-1650 cm^{-1} (C=C).

2,3,3-Trimethyl-1-(acetylmethylene)-1,2,3,4-tetrahydroisoquinoline (IV). 1.87 g (10 mmole) of enamine IIIa was mixed with 1.03 ml (11 mmole) of acetic anhydride. After 30 min, the precipitated ketone IV was filtered out and recrystallized. The IR spectrum showed: 1730 (C=O) and 1655 cm^{-1} (C=C).

2,3,3-Trimethyl-1-(benzoylmethylene)-1,2,3,4-tetrahydroisoquinoline (V). 0.5 g NaOH in 30 ml of water was added to 1.87 g (10 mmole) of base IIIa with 30 ml acetone. To the so obtained solution 1.27 ml (11 mmole) of benzoyl chloride, dissolved in 20 ml of a water–acetone (1:1) mixture, was added. After 20 min, the formed yellow crystalline precipitate was filtered out and recrystallized. Its IR spectrum showed: 1650 (C=C) and 1645 cm^{-1} (C=O).

2,3,3-Trimethyl-1-[(N-allyl)thiocarbamoylmethylene]-1,2,3,4-tetrahydroisoquinoline (VI) Perchlorate. A mixture of 1.87 g (10 mmole) of base IIIa with 1.07 ml (11 mmole) allyl isothiocyanate was left for 4 h. The thickened mass was dissolved in 30 ml of ethanol, and 1 ml of a 72% $HClO_4$ solution was added. Thioamide VI perchlorate was obtained. The IR spectrum of the base showed: 1640 (C=C) and 3420 cm^{-1} (NH).

2,3,3-Trimethyl-1-[(N-p-Tolyl)Carbamoylmethylene]-1,2,3,4-Tetrahydroisoquinoline (VII). 1.87 g (10 mmole) of base IIIa was mixed with 1.22 ml (10 mmole) of p-tolyl isocyanate in 30 ml of benzene. After 5 min, the precipitated amide VII was filtered out and recrystallized. The IR spectrum showed: 1645 (C=C), 1640 (C=O), and 3430 cm^{-1} (NH).

3,3-Dimethyl-1-[N-p-tolyl)carbamoylmethylene]-1,2,3,4-tetrahydroisoquinoline (VIII). This compound was prepared similarly to VII, but with the difference that the mixture had to be left for one day at 20°C or boiled for 1 h. The IR spectrum showed: 1650 (C=C), 1620 (C=O), 3260 (NH of the ring), and 3440 cm^{-1} (NH of the amide).

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CYCLIZATION REACTIONS OF NITRILES.

28.* SYNTHESIS AND REACTIONS OF 3β-ACETOXY-2'-METHYL-5'-CYANOANDROST-5-ENO[17,16-c]PYRIDINE-6'(1'H)-THIONE

Yu. A. Sharanin and G. V. Klokol

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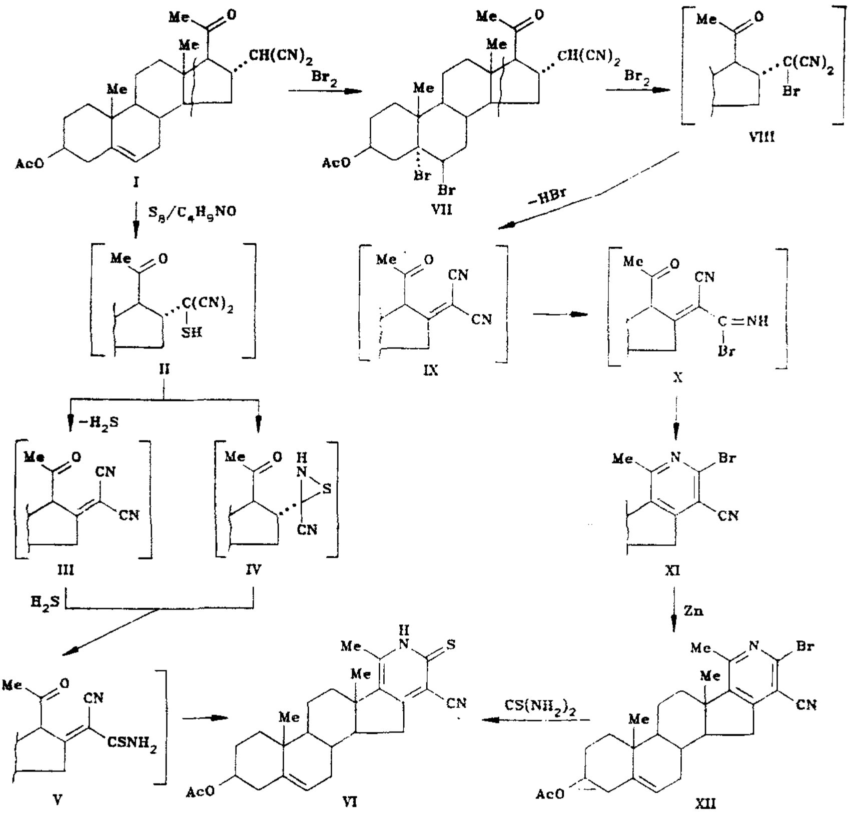
3β-Acetoxy-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine-6'(1'H)-thione was obtained by thiylation of 16α-dicyanomethyl-3β-hydroxypregn-5-en-20-one acetate, and its alkylation by chloroacetonitrile and phenacyl bromide was studied. The same thione was also synthesized by treating the corresponding 6'-bromo-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine with urea.

Derivatives of 1,5-ketonitriles are readily thiylated and brominated to the corresponding pyridine-2(1H)-thiones and 2-bromopyridines, which are used in the synthesis of various heterocyclic compounds [2, 3]. It was interesting to study the behavior of 16α-dicyanomethyl-3β-hydroxypregn-5-en-20-one acetate (I) [1] in these reactions.



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*Communication 27, see [1].

T. G. Shevchenko Voroshilovgrad State Pedagogical Institute, Voroshilovgrad 348011.
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