FORMATION OF NITROGEN HETEROCYCLES IN THE HYDROAMINATION OF 1,5-DIKETONES

V. G. Kharchenko, A. P. Kriven'ko,
O. V. Fedotova, and T. G. Nikolaeva

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It was established that the principal pathway in the catalytic hydro(alkyl,aryl)-amination of 1,5-diketones is, depending on the structure of the diketone and the amine component, the stereospecific formation of substituted piperidines, octa- and decahydroquinolines, and perhydroacridines or pyridine and tetrahydro- and benzodihydroquinoline structures.

It is known [1] that the principal products in the reaction of 1,5-diketones with hydeoxylamine are compounds of the pyridine series; mixtures of piperidine and pyridine bases with significant preponderance of the latter are formed under the conditions of the Chichibabin reaction with ammonium acetate [2], while the reactions with primary amines proceed with the formation of dihydropyridines or pyridines [3, 4]. Ammonia or amines and various reducing agents — formic acid, formamide (the Leuckart reaction) [5, 6], and alkali metal borohydrides [7] — are used to obtain saturated six-membered heterocycles on the basis of 1,5-diketones.

The catalytic hydroamination of 1,5-diketones has not been previously investigated. In order to make the transition from 1,5-dioxo compounds to saturated azaheterocycles we investigated the reductive amination under heterogeneous catalysis conditions of 1,5-diketones of the noncyclic and semi- and bicyclic series: 1,5-diphenylpentane-1,5-dione (I), 1-phenyl-3R-3-(2-oxocyclohexyl)propan-1-ones (II, III), 1,3R-propanonyltetralones (IV, V), 2,2'-methylenebiscyclohexanone (VI), 2,2'-methylenebiscyclopentanone (VII), and 2-(2-cyclohexanonylmethyl)-cyclopentanone (VIII). Hydroamination was carried out in an autoclave at high temperatures and hydrogen pressures in the presence of ruthenium and nickel catalysts. Ammonia, methylamine, and aniline in methanol were used as the aminating agents; the diketone—ammonia (or methylamine) molar ratio was 1:2, and the diketone—aniline molar ratio was 1:1.

We established that the direction of the process is determined by the structure of the starting diketone and the amine component.

The directed synthesis of saturated azaheterocycles occurs in the catalytic hydroamination of 1,5-diketones I, II, and IV-VI with methylamine as the aminating reagent. We obtained compounds of the piperidine, octa- and decahydroquinoline, and perhydroacridine series in high yields (Table 1) by this method: N-methyl-2,6-diphenylpiperidine (IX), N-methyl-2,4-diphenyldecahydroquinoline (X), N-methyl-2,4-diphenyl- (XI) and N-methyl-2-phenyl-4-dimethoxyphenyl-7,8-benzooctahydroquinoline (XII), and β-N-methylperhydroacridine (XIII).

The catalytic hydroarylamination of 1,5-dicarbonyl compounds (I, VI-VIII) with aniline proceeds smoothly only in the case of 2,2'-methylenebiscyclohexanone (VI). N-Phenylperhydroacridine (XIV) is formed from the threo form of the latter in 50% yield. N-Heterocyclization is not observed for the other bicyclic diketones VII and VIII and noncyclic ketone I, and the principal reaction pathway is hydrogenation to the corresponding diols XV-XVII.

Completely different character of the transformations of 1,5-diketones I-VI is noted when ammonia is used as the aminating agent. Either substituted pyridines or mixtures of the latter with piperidine bases are formed in this case. Thus piperidine XVIII and pyridine XX or perhydroacridine XIX and sym-octahydroacridine XXI, respectively, were isolated as the products of the reaction of diketones I and VI with ammonia under the investigated conditions.

A peculiarity of unsymmetrical semicyclic 1-phenyl-3R-3-(2-oxocyclohexyl)propan-1-ones (II, III) and 2-(1-phenyl-3R-propan-1-on-3-yl)tetralones (IV, V), in contrast to dioxo com-

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N. G. Chernyshevskii Saratov State University, Saratov 410601. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 944-947, July, 1982. Original article submitted July 29, 1981; revision submitted December 10, 1981.

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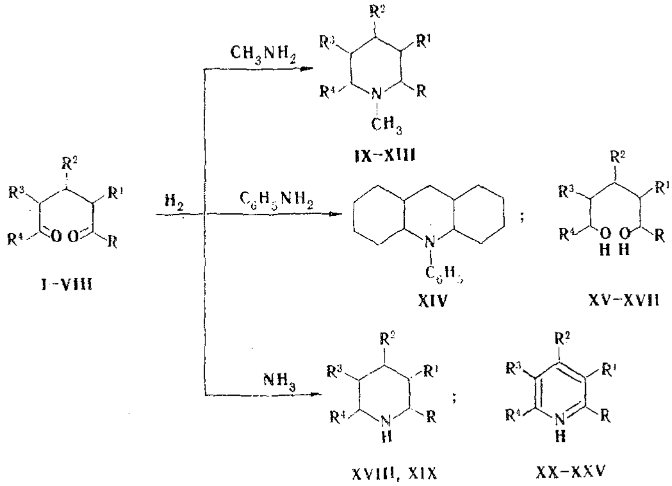
pounds I and VI, which are symmetrically constructed, was the formation of only aromatic structures — substituted 5,6,7,8-tetrahydro- (XXII, XXIII) and 7,8-benzo-5,6-dihydroquinolines (XXIV, XXV) in 50-70% yields.



I, IX, XV, XVIII, XX $R=R^4=C_6H_5$, $R^1=R^2=R^3=H$; II, X, XXII $R=R^2=C_6H_5$, $R^1=H$, $R^3+R^4=-(CH_2)_4-$; III, XXIII $R=C_6H_5$, $R^1=R^2=H$, $R^3+R^4=-(CH_2)_4-$; IV, XI, XXIV $R=R^2=C_6H_5$, $R^1=H$, $R^3+R^4=$ 2,3-benzotetramethylene; V, XII, XXV $R=C_6H_5$, $R^1=H$, $R^2=C_6H_3(OCH_3)_2$, $R^3+R^4=$ 2,3-benzotetramethylene; VI, XIII, XIV, XIX, XXI $R+R^1=R^3+$ $+R^4=-(CH_2)_4-$, $R^2=H$; VII, XVI $R+R^1=R^3+R^4=-(CH_2)_3-$, $R^2=H$; VIII, XVII $R+R^1=-(CH_2)_4-$, $R^3+R^4=-(CH_2)_3-$, $R^2=H$

The saturated bases that we obtained are formed in one of the possible geometrical forms - cis-2,6-diphenylpiperidine (XVIII) and β-perhydroacridine (XIX) — which constitutes evidence for the definite stereospecificity of the process and is an advantage as compared with the Leuckart reaction [5, 6]. This result is evidently due to the preferableness of cis addition of hydrogen in reactions involving the hydrogenation of unsaturated compounds and is in agreement with the rule of maximum compactness [8].

The catalysts used in the investigated reactions were 5% Ru/C, RuO_2, Raney nickel, and ruthenium-promoted nickel. The most effective catalyst for hydro(alkyl)amination is 5% Ru/C, in the presence of which saturated N-methyl-substituted azaheterocycles IX-XIII are formed in good yields (33-98%); only two compounds — cis-2,6-diphenylpiperidine (XVIII) and 2,6-diphenylpyridine (XX) — are formed in the case of diketone I in the presence of this catalyst, whereas a complex mixture is obtained when RuO_2 and Raney nickel are used. Ruthenium-promoted Raney nickel displayed high activity under catalytic hydroarylamination conditions. The results of the studies are presented in Table 1.

The different character of reductive amination and methylamination can be explained on the basis of the general principles of the hydroamination of oxo compounds. Both processes take place through a step involving the formation of dihydropyridine systems. The latter, inasmuch as they are unstable compounds, readily undergo further transformations to give more stable pyridine structures in the case of dehydrogenation or dealkylation or are hydrogenated to the piperidine base.

The peculiar behavior of dioxo compounds I and VI-VIII in hydroarylamination is due, on the one hand, to the low basicity of the nucleophile (aniline) and, on the other, to the decreased electrophilicity of the carbon atom of the carbonyl group (for diketone I) or the conformational peculiarities of substrates VII and VIII.

The assignment of the reaction products was accomplished by comparison of their constants (melting points, boiling points, and n_D^{20} values) with the values presented in the literature [5, 9-11], from the results of elementary analysis, and from IR and PMR spectroscopic data; the ratios of the perhydro- and heteroaromatic bases were determined by gas—liquid chromatography (GLC). The retention times of the peaks in the chromatograms were compared with the retention times of pure samples of XVIII and XIX obtained by alternative synthesis by the Leuckart reaction and XXIV and XXV obtained by refluxing the corresponding propanonyltetralones IV and V with hydroxylamine hydrochloride [12].

TABLE 1. Hydro(alkyl, aryl)amination of 1,5-Diketones (P_{H_2} = 1.013•10^4 hPa, 100°C)

Diketone	Catalyst	Aminating agent	Reaction products	Yield, %
I	Ru/C	NH_3	cis-XVIII	36
			XX	63
I	Ni$_{raney}$	NH_3	cis-XVIII	27
II	RuO_2	NH_3	Mixture of products	—
VI	Ni$_{raney}$	NH_3	β-XIX	15
			XXI	59
VI	RuO_2	NH_3	β-XIX	10
			XXI	90
I	Ru/C	CH_3NH_2	IX	63
II	Ru/C	CH_3NH_2	X	33
IV	Ru/C	CH_3NH_2	XI	74
V	Ru/C	CH_3NH_2	XII	59
VI	Ru/C	CH_3NH_2	β-XIII	98
VI	Ru/C	$C_6H_5NH_2$	XIV	35
VI	Ni/Ru	$C_6H_5NH_2$	XIV	50
I	Ni/Ru	$C_6H_5NH_2$	XV	88
I	Ru/C	$C_6H_5NH_2$	XV	63
VII	Ni/Ru	$C_6H_5NH_2$	XVI	76
VIII	Ni/Ru	$C_6H_5NH_2$	XVII	81

A band of stretching vibrations of the NH bond at 3320 cm^{-1} is present in the IR spectra of the nitrogen heterocycles that include a secondary amino group, viz., XVIII and XIX. Bases XX-XXV are characterized by vibrations of the pyridine ring at 1590 and 3020-3070 cm^{-1}, while IX-XIII are characterized by vibrations of the N—CH_3 bond at 2820 cm^{-1}. The IR spectra of diols XV-XVII contain a broad intense absorption band of an associated hydroxy group at 3300 cm^{-1}.

Singlets at 7.45 ppm, which were assigned to the 3-H proton of the pyridine ring, are observed in the weak-field part of the PMR spectra of XXIV and XXV in addition to signals of aromatic protons at 7.20 and 8.09-8.50 ppm. A broad singlet with an integral intensity corresponding to four methylene protons is observed in the high-field part of the spectra at 2.81 ppm. The PMR spectra of octahydroquinolines XI and XII do not contain signals of a vinyl proton; the protons of the heteroring appear at 3.69-4.01 ppm, while the protons of the N-methyl group show up in the form of a singlet at 3.26 ppm. The chemical shifts of the protons of the aromatic rings and the alicyclic ring are observed at 7.10 and 2.30-2.50 ppm, respectively.

EXPERIMENTAL

Gas—liquid chromatography (GLC) was carried out with Chrom-31 and LKhM-8MD chromatographs with a flame-ionization detector and stainless steel columns with a diameter of 0.6 cm and a length of 1-2.4 m; the sorbent was TND-TS-M Inza brick modified with 2% KOH and impregnated with 15% Apiezon-L, the temperature was 220-250°C, and the carrier-gas (helium) flow rate was 1.2 liters/h. The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in deuteroacetone were recorded with an RYa-2306 spectrometer (60 MHz) at 20°C with hexamethyldisiloxane as the internal standard.

Typical Method for the Hydro(alkyl, aryl)amination of 1,5-Diketones I-VIII. A 150-ml autoclave was charged with 0.05 mole of the 1,5-diketone, 60-80 ml of methanol containing 0.05-0.1 mole of the amine (ammonia, methylamine, aniline), and the catalyst (10% of the weight of the starting diketone). The initial hydrogen pressure was 1.013•10^4 hPa, and the temperature was 100°C. After the calculated (2 moles) amount of hydrogen had been absorbed (7-8 h), the catalyst was separated by filtration (or by hot filtration in the case of diketone VI). Bases IX-XIV and XX and mixtures of XIX, XXI, and XXII-XXV precipitated from the hydrogenated mixtures when they were evaporated. The methanol was removed from the mother liquor by distillation, and XVIII and additional amounts of IX and XXII were isolated when the residues were distilled in vacuo. The separation of β-perhydroacridine XIX and sym-octahydroacridine XXI was realized with a column filled with activity II Al_2O_3 by elution with hexane—ether—chloroform (2:1:1). Diols XV-XVII were obtained by vacuum distillation

TABLE 2. Characteristics of the Substances Obtained

Compound	mp, °C	Found, %			Empirical formula	Calc., %		
		C	H	N		C	H	N
IX	108—110	86,2	8,4	6,4	$C_{18}H_{21}N$	86,1	8,4	6,6
X	82—82,5	86,9	8,3	4,8	$C_{22}H_{27}N$	86,5	8,8	4,6
XI	118—119	88,4	7,6	3,7	$C_{26}H_{27}N$	88,4	7,7	3,9
XII	140—141	81,6	7,6	3,7	$C_{28}H_{31}NO_2$	81,3	7,6	3,4
XV	70—70,5	79,4	8,1	—	$C_{17}H_{20}O_2$	79,7	7,9	—
XXV	145—146	82,7	6,1	3,8	$C_{27}H_{23}NO_2$	82,5	5,9	3,6

of the corresponding hydrogenated mixtures. 1,5-Diphenylpentane-1,5-diol (XV) crystallized on standing.

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2,3,3-TRIMETHYL-3H-PYRROLO[3,2-c]QUINOLINES AND POLYMETHINE DYES BASED ON THEM

F. A. Mikhailenko, L. I. Shevchuk,
V. S. Tolmacheva, and F. S. Babichev

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2,3,3-Trimethyl-3H-pyrrolo[3,2-c]quinoline and its 8-methoxy derivative were obtained from methyl isopropyl ketone 4-quinolylhydrazones. These bases form quaternary salts at the azine nitrogen atom, from which polymethine dyes were obtained. The changes in the absorption spectra of the dyes in solutions with various acidities were examined.

Luminescence and the generation of deeply colored form IA have been achieved in the case of dye I, which is a 3H-pyrrolo[2,3-b]pyridine derivative, by excitation of the more highly colored protic salt (IB) in connection with the loss by the latter of a proton in the excited state [1]. Such systems should be of promise as active laser media [2].

T. G. Shevchenko Kiev State University, Kiev 252017. Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 948-951, July, 1982. Original article submitted July 20, 1981.

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