1-Methyl-4-arylisoquinolines (II, Table 1). A mixture of 0.3 g of I, 3 g of P_2O_5, and 10 ml of absolute toluene was refluxed on a metal bath for 3 h, after which it was cooled, made alkaline with 30% NaOH, and extracted thoroughly with ether. The ether layer was treated repeatedly with 10% HCl, and the acidic layer was made alkaline and extracted repeatedly with ether. The ether layer was dried with KOH, and the ether was removed by successive distillation and evaporation.

Ethyl (4-Arylisoquinolyl)pyruvates (IV, Table 1). A 4-g (0.1 mole) sample of potassium was dissolved in a mixture of 25 ml of absolute ether and 18 ml (0.3 mole) of absolute ethanol, after which a solution of 7.5 g (0.05 mole) of freshly distilled diethyl oxalate in 50 ml of absolute ether was added dropwise. After 15 min, a solution of 0.05 mole of isoquinoline II in ether was added dropwise, and the mixture was allowed to stand for 4 days. The crystalline precipitate was removed by vacuum filtration, and 200 ml of 50% acetic acid was added to the precipitate. After a few hours, the completely liberated ester IV was removed by filtration and recrystallized from ethanol.

(4-Arylisoquinolyl)[3-(4H)-oxoquinoxalyl]methanes (VI, Table 1). A mixture of 0.15 mmole of ester IV, 0.15 mmole of o-phenylenediamine (V), and 10 ml of amyl alcohol was refluxed for 45 min, after which it was cooled, and the resulting precipitate was removed by filtration and recrystallized from xylene.

LITERATURE CITED

1. E. Yu. Posyagina, E. V. Dormidontova, and V. S. Shklyaev, Khim. Khim. Tekhnol., 19, 35 (1976).
2. A. Bischler and B. Napieralski, Chem. Ber., 26, 1903 (1893).
3. M. Gordon, J. H. Jamilton, C. Adkins, and D. E. Pearson, J. Heterocycl. Chem., 4, 410 (1967).
4. V. Hensler, Heterocyclic Compounds, Vol. 4, Wiley.
5. W. E. Donahue, Dissert. Abstr., 15, 2011 (1955).
6. H. Zellner, M. Pailer, and G. Pruckmayr, US Patent No. 3028384; Chem. Abstr., 57, 841 (1962).
7. O. Hirotaka and M. Toru, Japanese Patent No. 7019907; Chem. Abstr., 73, 98988 (1970).
8. H. Zellner, Austrian Patent No. 1804328; Chem. Abstr., 71, 70642 (1969).
9. N. Masaru, K. Shigenari, and J. Hisao, Japanese Patent No. 7143783; Chem. Abstr., 76, 59650 (1972).

AZAHETEROCYCLES BASED ON 1,5-DIKETONES, CYCLIC β-KETOLS, AND ETHANOLAMINE

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

UDC 547.834'787.31'835.2'836.3:542.941.4.7'958.3:543.422

The peculiarities of the hydroxyethylamination of 1,5-diketones and three-ring β-ketols under heterogeneous-catalysis conditions as a function of the type of carbonyl compound were ascertained. Catalytic hydroxyethylamination is a convenient preparative method for the production of N-β-hydroxyethyl derivatives of 2,3,5,6-dicycloalkanopiperidines and 9-substituted perhydroacridines.

The synthesis of saturated six-membered nitrogen-containing heterocycles by means of catalytic hydroxyalkyl(aryl)amination of 1,5-diketones was reported in [1].

The present communication is devoted to a study of the catalytic reductive amination of dioxo compounds of the indicated type and three-ring β-ketones in the presence of a binucleophilic reagent, viz., ethanolamine. The substrates were 2,2'-methylenedicyanones (I-III), 2-hydroxy-2,3-tetramethylene-4-alkyl(furyl)bicyclo[3.3.1]nonan-9-ones (IV-VII),

N. G. Chernyshevskii Saratov State University, Saratov 410601.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1370-1372, October, 1983. Original article submitted February 9, 1983.

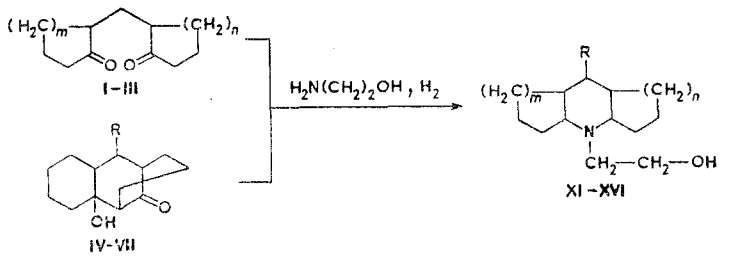
0009-3122/83/1910-1090$07.50

TABLE 1. Hydroxyethylamination of 1,5-Diketones and Cyclic β-Ketols (P_{H_2} = 1.013·10⁴ hPa, 100°C)

Starting oxo compound	Reaction products	Catalyst	Yield, %
I	β-XI	Ru/C	70
		Ni/Ru	82
II	XII	Ni/Ru	74
III	XIII	Ni/Ru	75
IV	β-XI	Ni/Ru	98
V	XIV	Ni/Ru	70
VI	XV	Ni/Ru	70
VII	XVI	Ni/Ru	95
VIII	XVII	Ru/C	62
		Ni/Ru	98
IX	XVIII	Ru/C	40
		Ni/Ru	90
X	XIX	Ru/C	40
		Ni/Ru	54

oxocyclohexylpropanones (VIII, IX), and 1,5-diphenyl-1,5-pentanedione (X). Hydroxyethylamination was accomplished in methanol at high temperatures and hydrogen pressures in the presence of nickel and ruthenium catalysts at a diketone (cyclic β-ketol):ethanolamine:hydrogen ratio of 1:1:4.

Under the reaction conditions methylenedicyclanones I-III are converted smoothly to the corresponding N-(β-hydroxyethyl)-2,3,5,6-dicycloalkanopiperidines (XI-XIII) in 70-80% yields, regardless of the size of the alicyclic ring.



I, IV, XI R=H, $m=n=2$; II, XII R=H, $m=n=1$; III, XIII R=H, $m=2$, $n=1$; V, XIV R=CH_3, $m=n=2$; VI, XV R=C_2H_5, $m=n=2$; VII, XVI R=2-furyl, $m=n=2$

The transition to 9-substituted perhydroacridines by the indicated pathway is possible only on the basis of three-ring β-ketols, since alkylidene(arylidene)dicyclohexanones are still difficult to obtain because they readily undergo intramolecular aldol condensation.

For the first time we have shown that the use of cyclic β-ketols IV-VII in hydroxyethylamination makes it possible to obtain both unsubstituted and 9-alkyl(furyl)-substituted N-(β-hydroxyethyl)perhydroacridines in 70-98% yields. The results obtained constitute evidence for retroaldol cleavage of cyclic β-ketones under the reaction conditions to give the corresponding 1,5-diketones as intermediates, which then undergo hydroxyethylamination via the usual scheme.

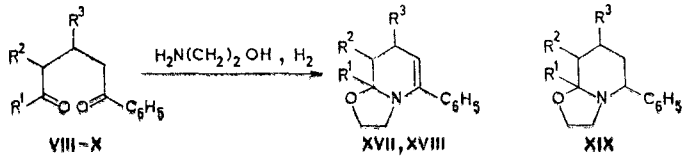
Thus we have synthesized new representatives of condensed piperidine derivatives (XII-XVI), as well as the previously known N-(β-hydroxyethyl)perhydroacridine (XI), the yield of which exceeds the yield indicated in [2] by a factor of more than three.

According to the results of gas–liquid chromatography (GLC), hydroxyethylamination proceeds stereospecifically with the primary formation of one of the possible stereoisomers. In conformity with the literature data [2] we isolated the β isomer (trans-anti-cis) of XI.

In contrast to two-ring diketones I-III, semicyclic diketones VIII and IX and noncyclic diketone X behave peculiarly under the reaction conditions. Ethanolamine reacts with substrates of this type with participation of both nucleophilic centers to give oxazolopyridine derivatives XVII-XIX:

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C, or bp, °C (hPa)	Found, %			Empirical formula	Calc., %		
		C	H	N		C	H	N
XII	131—132 (3,99)	79,9	11,2	6,8	$C_{13}H_{23}NO$	74,6	11,0	6,7
XIII	167—169 (6,65)	75,4	11,5	6,2	$C_{14}H_{25}NO$	75,3	11,2	6,3
XIV	166—167 (2,66)	76,0	11,5	5,5	$C_{16}H_{29}NO$	76,5	11,6	5,6
XV	162—164 (1,33)	76,6	11,5	4,9	$C_{17}H_{31}NO$	77,0	11,7	5,3
XVI	157—158	74,7	9,3	4,4	$C_{19}H_{29}NO_2$	75,2	9,6	4,6
XVIII	132—133	80,4	7,6	4,2	$C_{24}H_{27}NO_2$	80,0	7,5	3,9
XIX	61,5—62,5	82,1	7,8	5,0	$C_{19}H_{21}NO$	81,7	7,6	5,0



VIII, XVII $R^1—R^2=—(CH_2)_4—$, $R^3=C_6H_5$; IX, XVIII $R^1—R^2=—(CH_2)_4—$, $R^3=p\text{-}C_6H_4OCH_3$; X, XIX $R^1=C_6H_5$, $R^2=R^3=H$

This unusual reaction pathway can be explained by the formation of intermediate dihydropyridine systems, in which the olefin double bond is stabilized by conjugation with the phenyl substituent and, as a consequence of this, is hydrogenated more slowly, so that not only N-heterocyclization but also O-heterocyclization can occur; when phenyl substituents are present in the 1 and 3 positions in dioxo compounds VIII and IX, only amination occurs because of steric hindrance.

We used 5% Ru/C and nickel promoted with ruthenium as the catalysts in hydroxyethylamination. The greatest activity was displayed by Ni/Ru, in the presence of which saturated azaheterocycles are formed in higher yields. When Ru/C was used, hydrogenation of the starting carbonyl compounds was observed in a number of cases. The results of the studies are presented in Table 1.

The structures of the reaction products were proved from the results of elementary analysis, GLC data, and IR and PMR spectroscopic data, as well as by comparison of their constants with the literature data [2, 3] (in the case of known XI and XVIII).

A broad intense band of stretching vibrations of an associated hydroxy group at 3350-3460 cm^{-1} is present in the IR spectra of heterocyclic amino alcohols XI-XVI; the band at 1035-1055 cm^{-1} corresponds to the stretching vibrations of the C—O bond in primary alcohols. Base XVI is characterized by vibrations of a furan ring at 1585 and 3120-3170 cm^{-1}. The IR spectra of oxazolohydropyridines XVII-XIX do not contain absorption bands of an OH group, but absorption bands of phenyl substituents appear at 1610 and 3020-3080 cm^{-1}. The band at 1640 cm^{-1} in the spectra of XVII and XVIII confirms the presence of a double band conjugated with an aromatic ring. This absorption is absent in the IR spectrum of oxazolohydropyridine XIX.

In the PMR spectra of amino alcohols XI-XVI the chemical shift of the proton of the hydroxy group appears in the form of a singlet at 3.07 ppm for XII, at 3.09 for XIII, at 3.23 ppm for XI, at 3.28 ppm for XVI, at 3.83 ppm for XIV, and at 3.85 ppm for XV. Signals of protons of the CH_3 group in 9-alkyl-substituted amino alcohols XIV and XV are observed at 0.8-0.85 ppm. Signals of protons of a furan ring at 7.23, 6.21, and 5.88 ppm are present in the weak-field part of the spectrum of XVI. The chemical shift of the methylene protons of alicyclic ring and heteroring is observed at 1.05-1.9 ppm. The signals of the methylene protons of the N-β-hydroxyethyl substituent appear in the high-field part of the spectra at 3.46-3.55 ppm (—CH_2—O—) and 2.66-2.81 ppm (—CH_2—N<).

EXPERIMENTAL

Gas—liquid chromatography (GLC) was carried out with an LKhM-8MD chromatograph with a flame-ionization detector and a 1-2-m-long column (the sorbent was TND-TS-M Inza brick modified with 2% KOH and impregnated with 15% Apiezon-L) at 200-240°C; the carrier-gas (argon)

flow rate was 1.2 liters/h. The IR spectra of suspensions of the compounds in hexachlorobutadiene and mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in deuterochloroform were recorded with a Varian FT80A spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

Typical Method for the Hydroxyethylamination of 1,5-Diketones I-III and VIII-X and Cyclic β-Ketols IV-VII. A 150-ml autoclave was charged with 0.05 mole of oxo compound I-X, 0.05 mole of ethanolamine, 80 ml of methanol, and the catalyst (10% of the mass of the starting oxo compound). The initial hydrogen pressure was 1.013 hPa, and the temperature was 100°C. When hydrogen absorption had ceased (0.1 mole for XI-XVI and 0.05 mole for XIX; H_2 absorption was not observed for XVII and XVIII) (after 7-10 h), the catalyst was removed by filtration. Bases XI and XVI-XVIII, which were obtained as crystalline precipitates when the hydrogenation products were evaporated, were recrystallized from methanol. Compounds XII-XV and XIX were obtained by vacuum distillation of the corresponding hydrogenation products. Base XIX crystallized on standing. The characteristics of the synthesized compounds are presented in Table 2.

LITERATURE CITED

1. V. G. Kharchenko, A. P. Kriven'ko, O. V. Fedotova, and T. G. Nikolaeva, Khim. Geterotsikl. Soedin., No. 7, 944 (1982).
2. V. I. Vysotskii, Khim. Geterotsikl. Soedin., No. 9, 1236 (1970).
3. L. M. Eremeeva, T. V. Moskovkina, Yu. V. Vasilenko, A. N. Saverchenko, V. A. Kaminskii, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 2, 240 (1979).

AROMATIC CHLORINATION AND IODINATION OF 8-METHYLQUINOLINE. BENZYL BROMINATION OF 5-HALO-8-METHYLQUINOLINES

A. I. Tochilkin, I. N. Gracheva, I. R. Kovel'man, and E. P. Prokof'ev

UDC 547.831.2:542.944.2:543.422.25

5-Chloro- and 5-iodo-8-methylquinoline were obtained by chlorination or iodination of 8-methylquinoline with chlorine or iodine in concentrated sulfuric acid in the presence of silver sulfate. 5-Fluoro-8-methylquinoline was synthesized from 5-amino-8-methylquinoline. 5-Chloro-, 5-bromo-, and 5-fluoro-8-methylquinoline were converted to the corresponding 5-halo-8-(bromomethyl)quinolines by bromination with N-bromosuccinimide. Partial displacement of iodine by bromine to give a mixture of 5-bromo- and 5-iodo-8-(bromomethyl)quinoline occurs in the analogous bromination of 5-iodo-8-methylquinoline.

Numerous studies have been devoted to the halogenation of various quinoline derivatives [1]. However, insufficient study has been devoted to halo-substituted (in the benzene part of the molecule) 8-methylquinolines. Only the synthesis of 5-bromo-8-methylquinoline has been described [2], and this compound was obtained only recently by the direct bromination of 8-methylquinoline [3]. The study of compounds of this class is of definite interest, since they can be used for the preparation of some biologically active compounds, such as monoamine oxidase inhibitors.

In the present research we synthesized 5-chloro- and 5-iodo-8-methylquinolines (Ia, b), as well as 5-fluoro-8-methylquinoline (Ic), for the first time and studied the benzyl bromination of 5-halo-8-methylquinolines (Ia-d).

Aromatic halogenation under the influence of halonium ions [4], which has been successfully used for the halogenation of quinoline [5-7], was used for the chlorination and iodina-

Institute of Biological and Medicinal Chemistry, Academy of Medical Sciences of the USSR, Moscow 119121.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1373-1376, October, 1983. Original article submitted July 19, 1982; revision submitted February 22, 1983.

0009-3122/83/1910-1093$07.50