LITERATURE CITED

1. A. I. Kuznetsov, B. A. Kamaritskii, V. Ya. Vainshtein, and B. V. Unkovskii, Zh. Obshch. Khim., 12, 227 (1976).
2. J. Kuthan and J. Palecek, Collect. Czech. Commun., 28, 2261 (1963).
3. P. F. Yakushev, A. I. Kuznetsov, V. V. Tolstikov, and B. V. Unkovskii, Zh. Obshch. Khim., 13, 2542 (1977).
4. K. Hiroi, Y. Matsuda, and S. Sato, Synthesis, 621 (1979).
5. T. Kato, M. Sato, and H. Kimura, J. Chem. Soc., Perkin Trans. I, 529 (1979).
6. A. I. Kuznetsov, P. F. Yakushev, and B. V. Unkovskii, Zh. Obshch. Khim., 10, 841 (1974).
7. H. Stetter, K. Dieminger, and E. Rauscher, Chem. Ber., 92, 2057 (1951).

DIAZABICYCLOALKANES WITH NITROGEN ATOMS AT THE NODAL POSITIONS. 12.* STEPHENS REARRANGEMENT IN SUBSTITUTED 1,4-DIAZABICYCLO[2.2.2]OCTANES

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UDC 547.895'861.04.543.422.25

The ylides formed from phenacyl derivatives of substituted diazabicyclooctanes decompose to the initial base or give products of the Stephens rearrangement, leading to an expansion of the ring. The direction of the reaction is determined by the presence of C-substituents in the bicyclic fragment. C-Phenyl groups, which are capable of stabilizing the transition state, ensure the occurrence of the rearrangement reaction.

Continuing an investigation of the influence of C-substituents on the properties of quaternary salts of compounds in the diazabicyclooctane series — 1,4-diazabicyclo[2.2.2]octane (I), trans-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (II) and its cis isomer (III), and benzo[b]1,4-diazabicyclo[2.2.2]octene (IV)[2] — we have synthesized the monophenacyl derivatives of these compounds ((V-VIII), Table 1) and have studied their behavior under the conditions of the Stephens rearrangement [3]. There have been several publications devoted to this rearrangement for ammonium ylides with a nitrogen atom forming part of a bicyclic system [4-7]. Pine et al. [7] studied the behavior of mono- and bisquaternary salts of the bicyclic compound (I) under the action of butyllithium. This formed in very small yields ring-expansion products and the initial base.

The monophenacyl derivatives (V-VIII) were synthesized by the action of phenacyl bromide on the corresponding bicyclic amines (I-IV). The ylides (IX-XII) were obtained by treating compounds (V-VIII) with potassium tert-butanolate in tert-butanol or with caustic potash in methanol. The formation of the ylides (IX) and (XII) was shown by IR spectroscopy: the C=O absorption at 1700 cm^{-1} had disappeared and two bands had appeared in the 1500-1600 cm^{-1} region [8]. After the careful acidification of these ylides, the reaction products corresponded in their spectral properties and chromatographic behavior completely to the phenacyl derivatives (V) and (VIII).

The ylide (IX) is a stable compound withstanding heating to 200°C in the solid form in vacuum and also resistant to boiling in aqueous alkali and toluene. On being boiled in o-xylene, the ylide (IX) decomposed in 3 h and the only decomposition product isolated that possessed basic properties was the initial amine (I) (42% yield). A similar direction of the decomposition of ylides has been reported previously [7, 9].

*For Communication 11, see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 664-668, May, 1985. Original article submitted May 24, 1984.

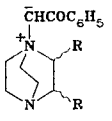
0009-3122/85/2105-0559$09.50

TABLE 1. Phenacyl Derivatives of 1,4-Diazabicyclo[2.2.2]-octane and Its C-Substituted Derivatives (V-VIII)

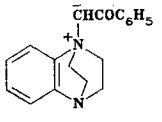
Compound	Amt. initial amine, mmole	Reaction time, h	mp, °C	Rf, (system)	νC=O, cm^{-1}	PMR spectrum (60 MHz, D_2O), ppm: ring CH_2s	CH_2—C=O	aromatic protons	Yield, %
V	11	2	252—255[b]	0,39 (D)	1700	4,01—4,68 (m, 12H)	5,74 (s, 2H)	7,80—8,42 (m 5H)	82
VI	4,2	170	139—144[c]	0,74 (A)	1700	3,40—4,74 (m, 10H)		7,05—7,96 (m, 15H)[d]	97
VII	2,2	24	137—139[d]	0,48 (A)	1700	3,40—4,84 (m 10H)		6,69—8,07 (m, 15H)[e]	97
VIII	10	120	126—128[f]	0,19 (A)	1700	3,44 (s, 4H) 3,60 (s, 4H)	4,85 (s, 2H)	6,15—8,20 (m 9H)	89

[a]After reprecipitation with ether from methanol. From ethanol: the correct elementary analysis was obtained. [c]No analytical sample was obtained. [d]In CD_3OD, benzyl protons: 4.85 ppm (d, 1 H, 3-H) and 5.56 ppm (d, 1 H, 2-H, J = 10 Hz). [e]In CD_3OD, benzyl protons: 5.29 ppm (d, 1 H, 3-H) and 6.25 ppm (d, 1 H, 2-H, J = 10 Hz). [f]For an analytically pure sample.

The ylide (XII) also proved to be fairly stable, but it decomposed on being boiled in toluene for 2 h, forming a complex mixture of readily oxidizable substances difficult to separate from which it was possible to isolate only the initial base (IV) (38% yield). The benzodiazabicyclooctene (IV) was stable under the reaction conditions and, consequently, the mixture of compounds was formed as the result of the decomposition of the ylide (XII).



IX–XI



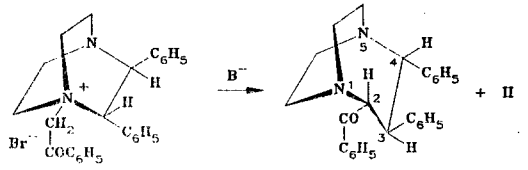
XII

IX R=H; X R=C_6H_5 (trans); XI R=C_6H_5 (cis)

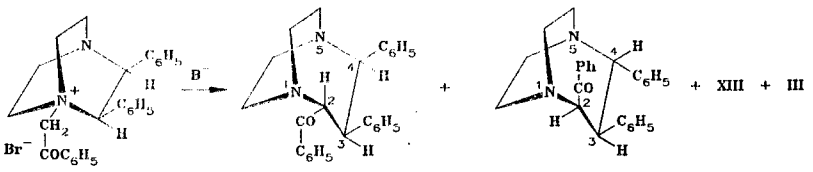
The ylides (X) and (XI) were not isolated, since they rapidly underwent rearrangement under the conditions of formation. On the basis of elementary analysis and IR and PMR spectroscopy, the formula of 2-benzoyl-3,5-diphenyl-1,5-diazabicyclo[3.2.2]nonane (XIII) is proposed for the product of the rearrangement of the ylide (X), which was isolated with a yield of 92%. In addition, base (II) was isolated with a 4% yield.

The rearrangement of the ylide (XI) took place in more complex fashion. Together with compound (XIII) (yield 19%) we succeeded in isolating from the reaction mixture with the aid of preparative TLC another three substances, two of which — (XIV) (yield 27%) and (XV) (yield 5%) — proved to be isomers of the amino ketone (XIII), while the third was the base (III) (yield 8%).

Differences in the PMR spectra in the region of methine protons of the isomers (XIII-XV) enabled us to suggest structures for these compounds.



VI XIII + II



VII XIV XV + XIII + III

TABLE 2. Isomeric 2-Benzoyl-3,4-Diphenyl-1,5-diazabicyclo-[3.2.2]nonanes (XIII-XV)

Compound	mp, °C	Rf (system B)	νC=O, cm⁻¹	PMR spectrum (acetone-d_6, 200 MHz), δ, ppm					M a	Yield, %
				aromatic protons	2-H	4-H	3-H	ring CH_2		
XIII	222—225[b]	0,74	1679	7,91—6,77 (m, 15H)	4,96 (d, 1H, J = 11 Hz)	4,52 (d, 1H, J = 12 Hz)	4,36 (d.d, 1H, J = 11 and 12 Hz)	3,67—2,87 (m, 8H)	382,2129	92
XIV	90[d]	0,26	1685	8,28—6,74 (m, 15H)	5,71 (d, 1H, J = 12,5 Hz)	4,96 (d, 1H, J = 8 Hz)	4,54 (d.d, 1H, J = 8 and 12,5 Hz)	3,70—2,36 (m, 8H)	382,2125	27
XV	127—131[e]	0,1	1689	8,62—6,80 (m, 15H)	6,12 (d, 1H, J = 8 Hz)	6,05 (d, 1H, J = = 12,5 Hz)	5,01 (d.d, 1H, J = 8 and 12,5 Hz)	4,27—3,00 (m, 8H)	382,1892	5

[a]Mass-spectrometrically. $C_{26}H_{26}N_2O$. Calculated: mol. wt. 382.2045. [b]From tert-butanol. The correct elementary analysis was obtained. [c]The yield of amino ketone from the phenacyl derivative (VII) was 19%. [d]Purified by TLC. [e]From a mixture of chloroform and hexane.

In the PMR spectrum of compound (XIII) (Table 2), the methine protons gave two groups of signals — a doublet at 4.96 ppm (J = 11 Hz, 1 H) and a multiplet at 4.27-4.57 ppm (2 H). When the 4.96 ppm signal was suppressed, the multiplet was converted into two doublets with J = 12 Hz, while the doublet present in the weaker field split slightly when the signal at 4.96 ppm was incompletely suppressed. Consequently, the doublet present in the stronger field could belong only to 3-H. The high SSCCs are characteristic for protons located axially [10, 11]. It may be assumed that the doublet at 4.96 ppm corresponded to 2-H (inductive influence of the benzoyl group). Then all three voluminous substituents occupied the most suitable e-positions and the initial transoid position of the phenyl groups at the $C_{(3)}$ and $C(_4)$ carbon atoms was retained.

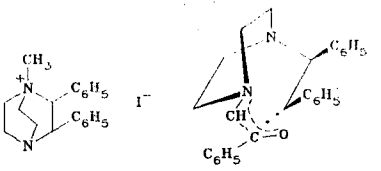
In the PMR spectrum of compound (XIV) the methine protons gave three groups of signals (Table 2) with ratios of their integral intensities of 1:1:1. A doublet of doublets with J = 12.5 Hz and 8 Hz at 4.54 ppm related to 3-H. A doublet at 5.71 ppm with J = 12.5 Hz related to 2-H. In the stronger field at 4.96 ppm there was a doublet with J = 8 Hz corresponding to 4-H. The SSCC values showed that the 2-H and 3-H were located axially and 4-H equatorially. It may be assumed that the downfield shift of the 4-H signal as compared with the corresponding signal in the amino ketone (XIII) was caused by a change in its position from axial in compound (XIII) to equatorial in the amino ketone (XIV) [12]. The downfield shift of the 2-H signal could be caused by a change in the influence of the magnetic anisotropy of the phenyl group at $C(_4)$ on this proton [13]. On Stuart—Briegleb models it can be seen that 2-H and C_6H_5—$C(_4)$ are close.

The methine protons of the isomer (XV) gave two groups of signals in the PMR spectrum (Table 2). At 5.01 ppm there was a doublet of doublets at J = 12.5 and 8 Hz, which apparently related to 3-H. Two close doublets were observed in the weaker field at 6.05 ppm (J = 12.5 Hz, 1 H) and 6.12 ppm (J = 8 Hz, 1 H). It may be assumed that a signal at 6.12 ppm related to 2-H, occupying the e-position, and the signal at 6.05 ppm to 4-H, which has the α-orientation. The formation of this compound and also of the amino ketone (XIII) from an ylide with a cis arrangement of the phenyl groups can be explained by isomerization when, during rearrangement, the phenyl groups pass into the trans position and then the benzoyl group becomes either axial (XV) or equatorial (XIII).

To determine the possibility of such isomerization, we took a model compound — the methiodide of cis-2,3-diphenyl-1,4-diazabicyclo[2.2.2] octane (XVI). After it has been boiled with potassium tert-butanolate in tert-butanol for 2 h, the trans isomer was obtained with a yield of about 50%. The ketones (XIII) and (XIV) did not isomerize under the conditions of the rearrangement reaction. The relatively low rate of isomerization of the salt (XVI) as compared with the rate of rearrangement (reaction 10-15 min), and also the high acidity of the proton in the phenacyl group (which means the predominant formation of the ylide) force us to give preference to the second possible route for the formation of the

amino ketones (XIII) and (XV) from the ylide (XI) – rotation around the C-C bond in a biradical of type (XVII), similar to that proposed for the Stephens rearrangement in substituted quinuclidines [6].

It is known that in the bicyclic systems (I-IV) a definite strain of the ring exists [14], which could serve as the motive force for the rearrangement of the ylides (IX-XII), leading to ring expansion. Nevertheless, the main role in the choice of the direction of the reaction of an ylide containing a diazabicyclooctane residue is probably played by the capacity of the substituent for stabilizing the transition state on rearrangement [15].



XVI XVII

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument in KBr, and PMR spectra on Varian A 56/60A (60 MHz) and Bruker WP-200SY (200 MHz) instruments with TMS as external standard. Mass spectra were recorded on a MS-902 instrument at an energy of 10-70 eV, a current of 100 mA, and a temperature of 100-170°C. TLC was performed on Silufol UV-254 in the following systems: A) ethanol–ammonia (5:1); B) chloroform–acetone (1:1); C) chloroform–methanol (9:1); and D) tert-butanol–methyl ethyl ketone–formic acid–water (40:30:15:15). The spots were detected with the Dragendorff reagent [16] and in UV light. Preparative TLC was performed on 25 × 40 cm glass plates coated with silica gel with the addition of the phosphor K-35 in system B or C, the bands being detected in UV light.

Phenacyl Derivatives of 1,4-Diazabicyclo[2.2.2]octane and its C-Substituted Derivative (V-VIII) (Table 1). Equimolar amounts of one of the amines (I-IV) and of phenacyl bromide were dissolved in 100-200 ml of ether, and the solution was kept at room temperature until the initial amine had disappeared (monitoring by TLC in system A; 2-170 h). The precipitate was filtered off, washed with ether, and crystallized from ethanol or reprecipitated from methanol with ether.

The Ylides (IX-XII). The phenacyl derivatives (V) and (VIII) were kept with an excess of potassium tert-butanolate (2:3) in tert-butanol for 5-120 h, and the phenacyl derivatives (VI) and (VII) were boiled for 10 min. The solutions of the first two substances were filtered and evaporated. Ylides (IX) and (XII) were obtained and were used without additional purification for the subsequent transformations. Ylide (IX) was also obtained from the phenacyl derivative (V) by boiling in 1% NaOH (1 h).

Decomposition of the Ylides (IX) and (XII). A. The ylide (IX) (0.03 g; 0.13 mmole) was boiled in 10 ml of o-xylene until it had disappeared completely (monitoring with the aid of TLC in system A). The resulting precipitate was filtered off, and the filtrate was acidified with a solution of hydrogen chloride in methanol. The white precipitate was filtered off. This gave 0.01 g (42%) of a substance corresponding completely according to its IR and PMR spectra, and also in chromatographic behavior, with an authentic sample of the dihydrochloride of the amine (I).

B. A mixture of 1.4 g (5 mmole) of the ylide (XII) and 150 ml of toluene was boiled for 2 h. The precipitate was filtered off, and the filtrate was evaporated. The 0.74 g of a dark oil that remained was separated with the aid of preparative TLC in system B. The fractions corresponding to the amine (IV) (monitoring with the aid of TLC on Silufol in the same system) were combined and recrystallized from acetone. This yielded 0.3 g (38%) of a crystalline substance the spectra and chromatographic behavior of which coincided with those of an authentic sample of the base (IV), with which it gave no depression of the melting point. It was impossible to isolate individual substances from the other fractions.

The Isomeric 2-Benzoyl-3,4-diphenyl-1,5-diazabicyclo[3.2.2]nonanes (XIII-XV) (Table 2). A. A mixture of 0.92 g (2 mmoles) of the phenacyl derivative (VI) and 0.34 g (3 mmole) of potassium tert-butanolate was boiled in 50 ml of tert-butanol for 10 min. The resulting precipitate was filtered off and washed with acetone. The acetone solution was evaporated and combined with the product, isolated with the aid of preparative TLC (system B), from the alcoholic filtrate.

The total yield of the amino ketone (XIII) was 92%. In addition, on chromatography 0.02 g (4%) of a viscous oil which crystallized on standing was obtained. Its PMR spectrum and R_f value (0.32, system B) agreed completely with those for the amine (II).

B. A mixture of 0.44 g (0.95 mmole) of the phenyl derivative (VII), 0.075 g (1.33 mmole) of caustic potash, and 25 ml of methanol was boiled under reflux for 15 min (with monitoring by TLC in system A). The solution was evaporated to dryness, the residue was extracted with ether, and the extract was evaporated. This gave 0.26 g of an oil, which was boiled in 60 ml of petroleum ether. The solution was separated from the brown mass (see below) and evaporated, and the residue was separated preparatively by TLC in system B. The bands were revealed in the UV spectrum, and they were collected and eluted with methanol. The fraction third from the front (0.07 g; 19%) had IR and PMR spectra agreeing completely with those of the amino ketone (XIII) obtained previously. The fraction fourth from the front was substance (XIV); yield 0.1 g (27%). The fraction at the start corresponded completely in its chromatographic properties and IR and PMR spectra to the amine (III). Yield 0.02 g (8%). The brown mass obtained above (weighing 0.03 g) was dissolved in chloroform, the solution was filtered, and the filtrate was treated with hexane. This gave 0.02 g (5%) of the amino ketone (XV).

Isomerization of the Monomethiodide of cis-2,3-Diphenyl-1,4-diazabicyclo[2.2.2]octane (XVI). The methiodide of the base (II) and also the base (III) and its monomethiodide (XVI) were obtained by a method described previously [17]. A solution of 0.35 g (0.9 mmole) of the salt (XVI) and 0.3 g (2.7 mmole) of potassium tert-butanolate in 30 ml of tert-butanol was boiled under reflex for 2 h and was then kept at room temperature for 17 h. The resulting precipitate was filtered off, giving 0.14 g (54%) of a substance the spectral characteristics of which were close to those of an authentic sample of the monomethiodide of trans-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane. The filtrate was evaporated. This gave a residue the spectral characteristics of which were close to those of the initial salt (XVI).

LITERATURE CITED

1. G. V. Shishkin, Khim. Geterotsikl. Soedin., No. 10, 1407 (1984).
2. V. I. Vysochin and G. V. Shishkin, Khim. Geterotsikl. Soedin., No. 2, 250 (1982).
3. K. V. Vatsuro and G. L. Mishchenko, Name Reactions in Organic Chemistry [in Russian], Khimiya, Moscow (1976), p. 382.
4. S. Mageswaran, W. D. Ollis, I. O. Sutherland, and J. Thebtaranonth, J. Chem. Soc. Chem. Commun., No. 20, 1494 (1971).
5. W. D. Ollis, I. O. Sutherland, and J. Thebtaranonth, Chem. Commun., No. 9, 657 (1973).
6. W. D. Ollis, M. Rey, and I. O. Sutherland, Chem. Commun., No. 8, 675 (1978).
7. S. H. Pine, J. Cheney, B. Catto, and J. D. Petersen, J. Org. Chem., 39, 130 (1974).
8. R. W. Jemison, S. Mageswaren, W. D. Ollis, S. E. Potter, A. Pretty, I. O. Sutherland, and J. Thebtaranonth, J. Chem. Soc., Chem. Commun., No. 11, 1201 (1970).
9. A. R. Lepley and A. G. Giumanini, J. Org. Chem., 32, 1706 (1976).
10. F. A. Bovey, Nuclear Magnetic Resonance Spectroscopy, Academic Press, New York (1969).
11. H. M. R. Hoffmann and H. Vathke, Chem. Ber., 113, 3416 (1980).
12. A. Gaudemer, M. Golfier, A. Mandelbaum, and R. Partharasathy, in: Stereochemistry. Fundamentals and Methods (ed. H. B. Kagan), G. Thieme, Stuttgart, (1977), p. 99.
13. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, High Resolution NMR Spectroscopy, Pergamon, Oxford, Vol. 1 (1965).
14. H. K. Hall, J. Org. Chem., 28, 223 (1963).
15. T. I. Temnikova and S. N. Semenova, Molecular Rearrangements in Organic Chemistry [in Russian], Khimiya, Leningrad (1983), p. 149.
16. H. Thies and F. W. Reuther, Naturwissenschaften, 41, 230 (1954).
17. G. V. Shishkin, I. I. Naumenko, I. L. Anisimova, O. B. Yudina, and V. G. Storozhenko, Khim. Geterotsikl. Soedin., No. 1, 95 (1982).