Russian Chemical Bulletin, International Edition, Vol. 56, No. 3, pp. 527—531, March, 2007

Synthesis and properties of bicyclic aziridines, derivatives of triacetoneamine

L. A. Krinitskaya

N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences,
4 ul. Kosygina, 119991 Moscow, Russian Federation.
Fax: +7 (495) 938 2484. E-mail: amserebr@sky.chph.ras.ru

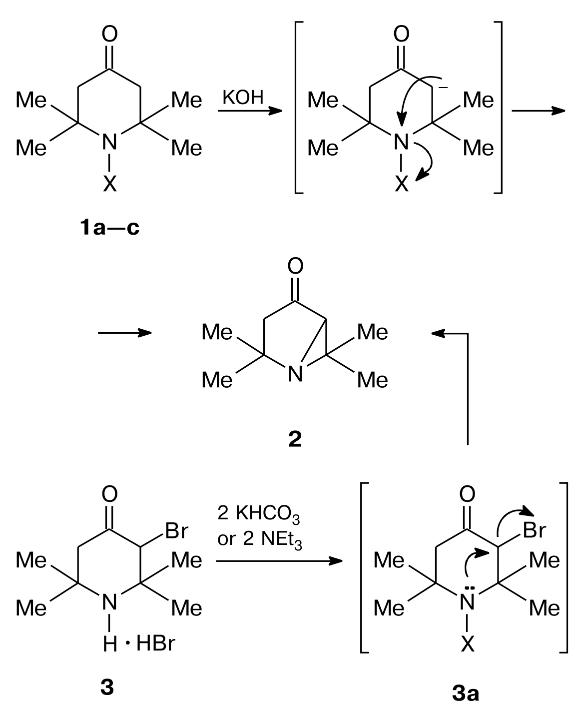
Bicyclic aziridines, derivatives of 2,2,6,6-tetramethyl-4-piperidone (triacetoneamine), are synthesized, which by acids treatment undergo the N—C(1) or N—C(2) bonds cleavage to form the corresponding pyrrolines, pyrrolidines, and piperidines.

Key words: triacetoneamine, aziridines, ring opening, pyrrolines, pyrrolidines, piperidines.

2,2,6,6-Tetramethyl-4-piperidone (triacetoneamine, TAA) shows a peculiar chemical reactivity. The absence of hydrogen atoms in positions 2 and 6 of the ring makes it possible to oxidize TAA and its derivatives into stable nitroxyl radicals.[1—3] In addition, Me groups in these positions affect the reactivity of 3- and 5-CH_2 groups, as well as of substituents attached to them. For example, halogen atoms in these positions cannot be substituted by treatment with nucleophilic reagents.[4] Instead, the products of intramolecular nucleophilic substitution reaction emerge. Thus pyrroline[5] and pyrrolidine[6] derivatives are formed as a result of the Favorskii rearrangement.

We were first to show the possibility of the intramolecular cyclization of triacetoneamine derivatives with formation of 1-azabicyclo[3.1.0]hexane.[7,8] The only known compound of this series, 1-azabicyclo[3.1.0]hexane-5-carboxylic acid ethyl ester, was synthesized[9,10] from 1-chloropiperidine-3-carboxylic acid ethyl ester and MeONa. A base treatment of 1-chloro-, 1-tosyloxy-, and 1-acetoxy-2,2,6,6-tetramethyl-4-piperidones (**1a—c**) led to 2,2,6,6-tetramethyl-1-azabicyclo[3.1.0]hexan-4-one (**2**) (Scheme 1), though the procedure was not described in the communication.[7] The alternative method for the synthesis of compound **2** by cyclization of 3-bromo-2,2,6,6-tetramethyl-4-piperidone (**3a**) was given by us in the communication[8] (see Scheme 1). In the present work all the detailed procedures for the synthesis of ketone **2** are described and the best of them are highlighted. In addition, its analogs are also synthesized, as well as a ring opening process in compounds of this series by cleavage of the N—C(1) or N—C(2) bonds with formation of the corresponding pyrrolines, pyrrolidines, and piperidines was studied.

Scheme 1



X = Cl (**1a**), OTs (**1b**), OAc (**1c**)

The rate of aziridine **2** formation from compounds **1a—c** increases with the increase of the leaving group ability at the N atom of compound **1** (OTs > Cl > OAc). The most pure product **2** was obtained from *N*-acetoxy derivative **1c**, however, to synthesize aziridine **2** from 3-bromotriacetoneamine hydrobromide **3** is preparatively more convenient (the yield was 76%). In this case, a base ($KHCO_3$ or Et_3N) is necessary for conversion of bromoketone **3** into **3a** and further for reaction with the arising HBr (to avoid side reaction of HBr with aziridine **2**). The use of stronger bases (alkali or alkoxides) causes the Favorskii rearrangement[5,6] in bromoketone **3** (or **3a**).

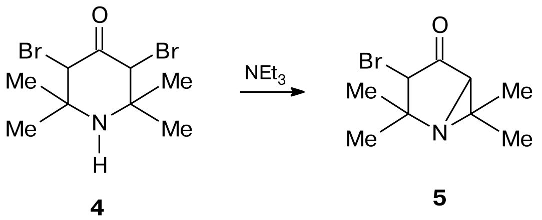
Aziridine **2** is a liquid stable at room temperature and during vacuum distillation with b.p. 79 °C (10 Torr) with good solubility in water and organic solvents. Compound **2** forms crystalline hydrate, relatively stable in solid state

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 508—511, March, 2007.

picrate, oxalate, tosylate, and perchlorate, as well as a blue complex with copper(II) acetate.

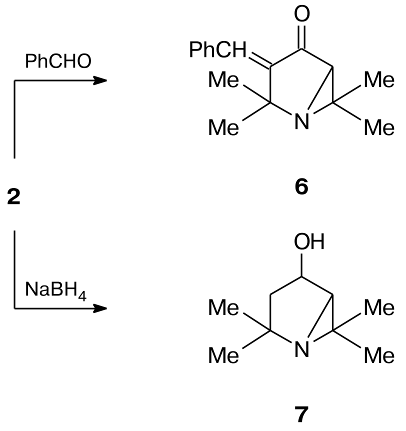
Similarly, from 3,5-dibromotriacetoneamine **4** or its hydrobromide in the presence of Et_3N was obtained 3-bromo derivative of aziridine **2**, compound **5** (Scheme 2).

Scheme 2



Compound **2** can be involved into some reactions characteristic of ketones with the aziridine ring remained intact. Thus it was converted into benzylidene derivative **6**, as well as into alcohol **7** by reduction of the carbonyl group (Scheme 3).

Scheme 3

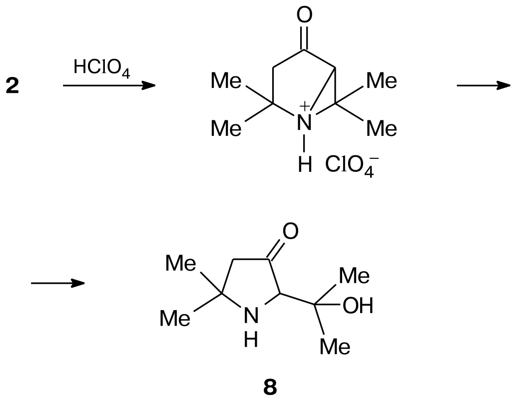


However, attempted conversion of aziridine **2** into the corresponding oxime by reaction with hydroxylamine failed. Bromination of ketone **2** as well as the Favorskii rearrangement of bromoketone **5** were also unsuccessful.

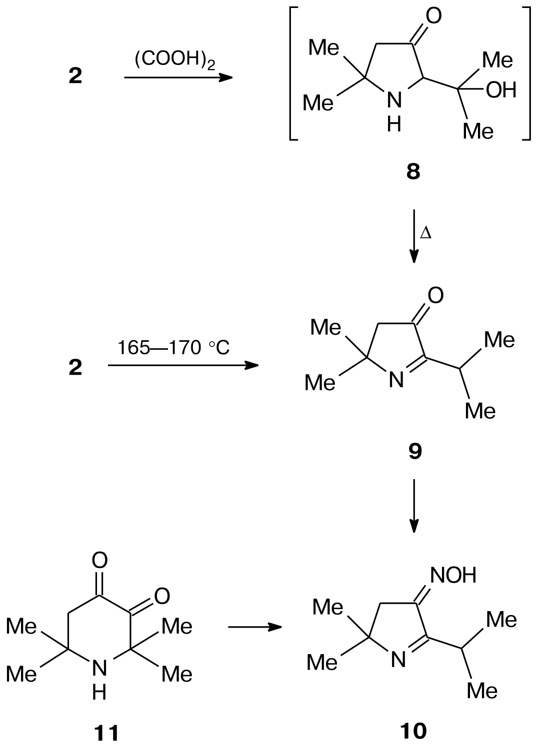
It is known[11] that aziridine ring can be open by reaction with a large number of acids. Reaction of aqueous solution of aziridine **2** with perchloric acid leads to precipitation of its perchlorate, which completely dissolves in the solution during 24 h. Ketoalcohol **8** was isolated after neutralization of the solution and its extraction with ether (Scheme 4).

Reflux of aqueous solution of aziridine **2** with oxalic acid, through the intermediate formation of compound **8** and its dehydration, produces extremely volatile pyrrolin-3-one (**9**), which can be formed by heating of aziridine **2** at 165—170 °C as well (Scheme 5).

Scheme 4



Scheme 5

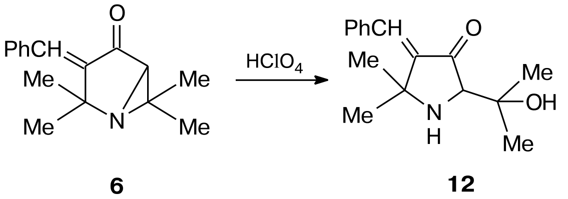


Compound **9** was converted into oxime **10**, which was also synthesized[12] earlier by reflux of aqueous solution of diketone **11** with a large excess of $NH_2OH \cdot HCl$ and CH_3COONa (see Scheme 5).

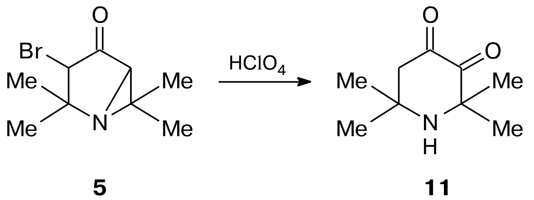
Benzylidene derivative of ketone **2**, compound **6**, under perchloric acid treatment undergoes the similar rearrangement to give compound **12** (Scheme 6).

Quite the contrary, bromoketone **5** does not undergo ring contraction under acid treatment, rather changing into diketone **11** described also earlier[12] (Scheme 7).

Scheme 6



Scheme 7



In conclusion, hydrolysis of bicyclic ketone **2** and its benzylidene derivative **6** leads to the products of pyrrolidine series, that is, the three-membered ring opening with a cleavage of the N—C_{Me2} bond takes place. In the bromoketone **5** case the aziridine ring opening occurs at the N—C_H bond, producing compound of the piperidine series.

Experimental

IR spectra were recorded on a Specord M-80 spectrometer, ^{1}H NMR spectra were recorded on a Jeol C-60 HL, Brucker WP-80-SY, Brucker WH-360, and Brucker WM-400 spectrometers, mass-spectrum was recorded on a Finnigan 4021 instrument.

1-Hydroxy-2,2,6,6-tetramethyl-4-piperidone,[13] dibromotriacetoneamine hydrobromide,[5] 2,2,6,6-tetramethylpiperidin-3,4-dione,[12] 1-chloro-2,2,6,6-tetramethyl-4-piperidone (**1a**),[14] and 2,2,6,6-tetramethyl-1-tosyloxy-4-piperidone (**1b**)[13] were synthesized by procedures described earlier.

1-Acetoxy-2,2,6,6-tetramethyl-4-piperidone (1c). Triethylamine (5 mL) and $(CH_3CO)_2O$ (4 mL) were added to a solution of 1-hydroxy-2,2,6,6-tetramethyl-4-piperidone hydrochloride (6.21 g, 0.03 mol) in $CHCl_3$ (30 mL) under stirring and cooling by ice-cold water. The mixture was stirred for 1 h at 20 °C and left staying for ~14 h. The solvent and excess of the reagents were removed *in vacuo*, water (50 mL) was added to the residue, and the product was extracted with benzene. The extract was dried with anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue (6.4 g) was recrystallized from hexane. Acetoxy derivative **1c** (5.05 g, 79%) was obtained, m.p. 99—100 °C, after sublimation, 100.5—101 °C. Found (%): C, 62.01; H, 9.04; N, 6.49. $C_{11}H_{19}NO_3$. Calculated (%): C, 61.93; H, 8.98; N, 6.57. ^{1}H NMR (60 MHz, $CDCl_3$), δ: 1.17 (s, 12 H, 2,2,6,6-Me_4); 2.02 (s, 3 H, OMe); 2.42, 2.62 (both s, 2 H each, 2 CH_2).

2,2,6,6-Tetramethyl-1-azabicyclo[3.1.0]hexan-4-one (2). ***A* (from compound 1a).** A solution of KOH (250 g) in water (1500 mL) was cooled down to −10 °C with an ice—salt mixture and chlorine gas obtained by a gradual addition of conc. HCl (800 mL) to potassium permanganate (130 g) was bubbled through it to produce an aqueous solution of KOCl. This aq. KOCl (130 mL) was added dropwise to a stirred solution of triacetoneamine hydrochloride (19.1 g, 0.1 mol) in water (100 mL) cooled down with an ice—salt mixture. After addition of entire hypochlorite, the reaction mixture was stirred for 30 min and extracted with ether, the extract was dried with Na_2SO_4 in refrigerator. The drying agent was filtered off and the ether solution was concentrated. Compound **1a** (18.8 g, 89%) was obtained. A solution of KOH (10 g) in EtOH (100 mL) was added to compound **1a** (18.8 g, 99 mmol) under stirring and cooling with an ice—salt mixture. The reaction mixture was kept for 3 days at 0 °C, then EtOH was evaporated, and benzene (100 mL) was added. The precipitate of KCl was filtered off, the benzene filtrate was concentrated, and the residue was twice distilled *in vacuo*. Compound **2** (7.06 g, 46%) was obtained, b.p. 77—78 °C (9 Torr), n_D^{20} 1.4675. Found (%): C, 70.64; H, 9.98; N, 9.18. $C_9H_{15}NO$. Calculated (%): C, 70.55; H, 9.87; N, 9.14. ^{1}H NMR (360 MHz, C_6D_6), δ: 0.95, 1.01, 1.08, 1.11 (all s, 3 H each, 2,2,6,6-Me_4); 1.86, 1.97 (both d, 1 H each, CH_2, ^2J = 19 Hz); 2.23 (s, 1 H, CH). ^{13}C NMR (90.6 MHz, C_6D_6), δ: 17.61, 24.60, 28.78, 33.62 (all q, 2,2,6,6-Me_4, ^1J = 127.0 Hz); 44.30 (s, C(6)); 49.61 (t, CH_2, ^1J = 129.4 Hz); 55.12 (d, CH, ^1J = 180.7 Hz); 59.14 (s, C(2)); 210.22 (s, CO). IR (CCl_4), ν/cm^{-1}: 1720 (C=0). MS, *m/z* (I_{rel} (%)): 153 $[M]^+$ (5)), 138 (15), 110 (9), 98 (9), 97 (24), 96 (17), 70 (14), 69 (100), 55 (13), 41 (7).

***B* (from compound 1b).** A solution of KOH (0.14 g, 2 mmol) in MeOH (3 mL) was added to a suspension of compound **1b** (0.65 g, 2 mmol) in MeOH (5 mL) under cooling with an ice—salt mixture. After 30 min the reaction mixture was concentrated *in vacuo*, the product was washed off the precipitate with ether. The ether extract was concentrated *in vacuo*. The product was obtained as a residual oil (0.30 g, 100%). Properties of the product are identical with those of compound **2** synthesized by method *A*.

***C* (from compound 1c).** Potassium hydroxide (1.4 g, 20 mmol) was added to a solution of compound **1c** (4.26 g, 20 mmol) in MeOH (10 mL). The mixture was refluxed with a reflux condenser for 15 min and concentrated *in vacuo*. Benzene was added to the residue, precipitate of KCl was filtered off, and benzene extract was distilled *in vacuo*. The product (2.90 g, 94%) was obtained; its properties are identical with those of compound **2** synthesized by method *A*.

***D* (from 3-bromo-2,2,6,6-tetramethyl-4-piperidone hydrobromide (3)).** Triethylamine (46.5 mL, 0.33 mol) was added dropwise to a stirred and cooled with ice-cold water solution of compound **3** obtained by the described earlier procedure[6] by bromination of triacetoneamine hydrochloride (19.15 g, 0.1 mol) in $CHCl_3$ (50 mL). The mixture was kept for 6 h, then chloroform and excess of Et_3N were evaporated *in vacuo*. Benzene was added to the residue, the precipitate was filtered off and additionally was washed with benzene. The combined benzene solutions were concentrated *in vacuo*. Product **2** (11.68 g, 76%) was obtained; its properties are identical with those of compound **2** synthesized by method *A*.

3-Bromo-2,2,6,6-tetramethyl-1-azabicyclo[3.1.0]hexan-4-one (5). Triethylamine (4.2 mL, 30 mmol) was added to a suspension of dibromotriacetoneamine hydrobromide **4** (3.94 g, 10 mmol) in acetone (20 mL), the mixture was stirred for 6 h at ~20 °C and left in refrigerator for 14 h. Then the mixture was concentrated to dryness and suspended in ether (20 mL). The precipitate of $NEt_3 \cdot HBr$ was filtered off, washed with ether on the filter, the combined ether extract was concentrated to dryness. After crystallization from hexane compound **5** was obtained (1.47 g, 64%), m.p. 88—89 °C. Found (%): C, 46.95; H, 6.23; N, 5.82. $C_9H_{14}BrNO$. Calculated (%): C, 47.11; H, 6.08; N, 6.04. ^1H NMR (400 MHz, C_6D_6), δ: 0.90, 0.92, 1.09, 1.52 (all s, 3 H each, 2,2,6,6-Me_4); 2.20 (s, 1 H, CH); 4.25 (s, 1 H, CHBr). IR (CCl_4), ν/cm^{-1}: 1765 (C=0).

3-Benzylidene-2,2,6,6-tetramethyl-1-azabicyclo[3.1.0]-hexan-4-one (6). Potassium hydroxide (0.3 g, 5 mmol) was added to a solution of compound **2** (0.92 g, 6 mmol) and freshly distilled benzaldehyde (0.64 g, 6 mmol) in EtOH (10 mL). The reaction mixture was stirred for 3 days at ~20 °C, then the solvent was removed *in vacuo*, ether (10 mL) was added, KOH was filtered off, and filtrate was concentrated *in vacuo*. Compound **6** (0.83 g, 57.4%) was obtained, m.p. 88.5—89.5 °C. Found (%): C, 79.56; H, 8.07; N, 6.11. $C_{16}H_{19}NO$. Calculated (%): C, 79.66; H, 7.93; N, 5.81. ^1H NMR (60 MHz, $CDCl_3$—CCl_4), δ: 1.29, 1.38, 1.40, 1.51 (all s, 3 H each, 2,2,6,6-Me_4); 2.60 (s, CH); 7.34 (m, Ph); 7.38 (s, HC=). IR (CCl_4), ν/cm^{-1}: 3074 (CH=); 1725 (C=0); 1630 (C=C).

4-Hydroxy-2,2,6,6-tetramethyl-1-azabicyclo[3.1.0]hexane (7). Sodium borohydride (0.08 g, 2.1 mmol) was added to a solution of compound **2** (0.31 g, 2 mmol) in EtOH (5 mL) at 0 °C, which was stirred for 1 h. Then the mixture was kept at ~20 °C for 15 h, the solvent was removed *in vacuo*, and the product was extracted from the solid residue with benzene. Benzene extract was concentrated *in vacuo* and the residue was crystallized from hexane. Compound **7** was obtained (0.31 g, ~100%), m.p. 121—122 °C. Found (%): C, 69.44; H, 10.86; N, 9.12. $C_9H_{17}NO$. Calculated (%): C, 69.65; H, 11.04; N, 9.03. ^1H NMR (360 MHz, C_6D_6), δ: 1.05, 1.10, 1.12, 1.48 (all s, 3 H each, 2,2,6,6-Me_4); 1.52, 1.83 (both dd, 1 H each, 2 CH_2, ^2J = 13.8 Hz, ^3J = 7.8 Hz); 2.12 (d, 1 H, CH, ^3J = 6.3 Hz); 4.65 (ddd, CHOH, ^3J = 6.3 Hz).

2-(2-Hydroxyprop-2-yl)-5,5-dimethyl-3-pyrrolidinone (8). Perchloric acid (aq. 48%, 1.4 mL) was added dropwise to a solution of compound **2** (0.61 g, 4 mmol) in water (5 mL) at 20 °C, during which the precipitate of perchlorate of compound **2** was formed. The reaction mixture was kept at 20 °C for 24 h, during which the precipitate was gradually dissolving. The solution was neutralized with NH_4OH (1 mL), extracted with ether, and the extract was dried with anhydrous $MgSO_4$. The drying agent was filtered off and filtrate was concentrated *in vacuo*. Compound **8** was obtained (0.64 g, 94%) as colorless crystals, m.p. 62.5—63 °C (after crystallization from hexane and sublimation *in vacuo*). Found (%): C, 63.20; H, 9.88; N, 8.06. $C_9H_{17}NO_2$. Calculated (%): C, 63.14; H, 10.01; N, 8.18. ^1H NMR (80 MHz, $CDCl_3$), δ: 1.17, 1.21 (both s, 3 H each, 5,5-Me_2); 1.24, 1.36 (both s, 3 H each, CMe_2); 2.20 (s, 2 H, CH_2—C=O); 3.29 (s, 1 H, CH—N). ^1H NMR ($CDCl_3$—CF_3COOH), δ: 1.43 (s, 3 H, Me); 1.46 (s, 6 H, 5,5-Me_2); 1.75 (s, 3 H, Me); 2.61 (s, 2 H, CH_2—C=O); 3.88 (br.s, 1 H, CH—N). IR (CCl_4), ν/cm^{-1}: 3270 (NH); 1730 (C=O); 3430 (OH).

2-Isopropyl-5,5-dimethyl-1-pyrrolin-3-one (9). ***A.*** A solution of compound **2** (0.31 g, 2 mmol) and oxalic acid (0.32 g, 2.5 mmol) in water (5 mL) was refluxed for 5 h. The solution was cooled down, $NaHCO_3$ (0.5 g, 6 mmol) was added, and the resulting mixture was extracted with ether. The ether extract was dried with anhydrous $MgSO_4$, after which ether was evaporated *in vacuo*. Compound **9** was obtained (0.32 g, ~100%), n_D^{20} 1.4420. Found (%): C, 70.33; H, 9.77; N, 9.46. $C_9H_{15}NO$. Calculated (%): C, 70.55; H, 9.87; N, 9.14. ^1H NMR (80 MHz, $CDCl_3$), δ: 1.14 (d, 2×3 H, $CH(C\underline{H}_3)_2$, ^3J = 7.0 Hz); 1.31 (s, 6 H, 5,5-Me_2); 2.23 (s, 2 H, CH_2—CO); 2.82 (sept, 1 H, $C\underline{H}(CH_3)_2$, ^3J = 7.0 Hz). IR (CCl_4), ν/cm^{-1}: 1660 (C=N); 1750 (C=O).

B. Compound **2** (10.7 g, 70 mmol) was placed into a distillation apparatus and heated up to 175 °C, then the temperature was gradually raised up to 205 °C. During heating the product was distilled, which by its refractive index and chromatographic behaviour was identical with the product of rearrangement of compound **2** in the presence of oxalic acid.

3-Hydroxyimino-2-isopropyl-5,5-dimethyl-1-pyrroline (10). Potassium acetate (0.2 g) and hydroxylamine chlorohydrate (0.14 g) were added to a solution of compound **9** (0.32 g) in water (10 mL). The mixture was kept for 24 h. The formed precipitate of oxime was filtered off and dried. Compound **10** (0.12 g, 32%) was obtained. The product can be sublimed at the temperatures higher 100 °C without melting. Found (%): C, 64.61; H, 9.58; N, 16.38. $C_9H_{16}N_2O$. Calculated (%): C, 64.27; H, 9.52; N, 16.66.

2,2,6,6-Tetramethylpiperidin-3,4-dione (11). A suspension of compound **5** (0.16 g, 0.7 mmol) in water (5 mL) was cooled down with ice-cold water and 48% aq. $HClO_4$ (0.2 mL) was added to it. The mixture was stirred for 6 h, kept at ~20 °C for ~14 h, neutralized with $NaHCO_3$ (0.2 g), and the product was extracted with ether. The extract was dried with $MgSO_4$, concentrated *in vacuo*, and the residue was sublimed *in vacuo*. Product was obtained (0.071 g, 61%) by all characteristics identical with compound **11** synthesized by Rassat method.[12]

4-Benzylidene-2-(2-hydroxyprop-2-yl)-5,5-dimethyl-3-pyrrolidinone (12). Water (2 mL) and 48% aq. $HClO_4$ (0.5 mL) were added to a cooled with ice-cold water solution of benzylideneketone **6** (0.18 g, 0.75 mmol) in EtOH (5 mL). The mixture was kept at ~20 °C for 24 h, after which EtOH was evaporated *in vacuo*. Water (5 mL) and $NaHCO_3$ (0.25 g) were added to a stirred residue. The product was extracted with ether, the extract was dried with $MgSO_4$, ether was evaporated *in vacuo*, the residue was washed with hexane, and the hexane solution was discarded. After washing with hexane the solid product was remained. After recrystallization from hexane compound **12** was obtained (0.091 g, 50%), m.p. 85 °C. Found (%): C, 78.91; H, 8.50; N, 5.38. $C_{16}H_{21}NO$. Calculated (%): C, 79.01; H, 8.64; N, 5.76. ^1H NMR (60 MHz, $CDCl_3$—CCl_4), δ: 1.23, 1.53 (both s, 3 H each, 5,5-Me_2); 1.31 (s, 6 H, Me_2COH); 3.50 (s, 1 H, CH—N); 7.38 (s, 5 H, Ph); 7.50 (s, 1 H, CH=).

References

1. O. L. Lebedev and S. N. Kazarnovskii, *Trudy po khimii i khimicheskoy tekhnologii* [*Chemistry and Chemical Technology Transactions*], Gor´kii State University Publ., Gor´kii, 1959, p. 649.
2. M. B. Neiman, E. G. Rozantsev, and Yu. G. Mamedova, *Nature*, 1963, **200**, 256.
3. E. G. Rozantsev and L. A. Krinitskaya, *Tetrahedron*, 1965, **21**, 491.

4. L. A. Krinitskaya and L. B. Volodarskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 1619 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33** (Engl. Transl.)].
5. H. Pauly, *Ann.*, 1902, **322**, 77.
6. L. A. Krinitskaya and L. B. Volodarskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 443 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31**, 401 (Engl. Transl.)].
7. L. A. Krinitskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1685 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 1566 (Engl. Transl.)].
8. L. A. Krinitskaya, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1189 [*Russ. Chem. Bull.*, 1997, **46** (Engl. Transl.)].
9. O. C. Dermer and D. E. Ham, *Ethylenimine and other Aziridines. Chemistry and Applications*, Acad. Press, New York—London, 1969, 437 pp.
10. Germ. Pat. 1054088, 1959; *Chem. Abstr.*, 1959, **55**, 843.
11. P. A. Gembitskii, D. S. Zhuk, and V. A. Kargin, *Khimiya etilenimina* [*Chemistry of Ethyleneimine*], Nauka, Moscow, 1996, 254 pp.
12. D. Pilo-Veloso and A. Rassat, *Bull. Soc. Chim. Fr.*, 1978, **11**, 621.
13. E. G. Rozantsev and V. A. Golubev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966, 891 [*Bull. Acad Sci. USSR, Div. Chem. Sci.*, 1966, **15**, 1566 (Engl. Transl.)].
14. T. Toda, E. Mori, H. Horiuchi, and K. Murayama, *Bull. Chem. Soc. Jpn*, 1972, **45**, 1802.

Received October 6, 2006;
in revised form January 31, 2007