no absorption above 3000 $cm^{-1}$. PMR spectrum ($CDCl_3$): 3.76 (3H, s, 1-$CH_3$); 3.71 (3H, s, 9-$CH_3$); 3.54 (3H, s, 7-$CH_3$); 3.51 ppm (3H, s, 3-$CH_3$). Mass spectrum, m/z (%): 344 $M^+$ (100), 287 (8), 259 (12), 233 (15), 232 (12), 230 (12). Found, %: C 45.6; H 3.8; N 32.8. $C_{13}H_{12}N_8O_4$. Calculated, %: C 45.5; H 3.5; N 32.6.

## LITERATURE CITED


1. V. V. Kuz'menko, T. A. Kuz'menko, G. G. Aleksandrov, A. F. Pozharskii, and A. V. Gulevskaya, Khim. Geterotsikl. Soedin., No. 6, 836 (1987).
2. J. W. Jones and R. K. Robins, J. Am. Chem. Soc., 82, 3773 (1960).
3. E. M. Karpitschka, G. Smole, and W. Klötzer, Sci. Pharm., 49, 453 (1981).
4. A. F. Pozharskii, V. V. Kuz'menko, and I. M. Nanavyan, Khim. Geterotsikl. Soedin., No. 11, 1564 (1983).
5. W. Klötzer, H. Baldinger, E. M. Karpitschka, and J. Knoflach, Synthesis, No. 7, 592 (1982).
6. A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, Usp. Khim., 35, 261 (1966).
7. C. Temple, C. L. Kussner, and J. A. Montgomery, J. Org. Chem., 34, 2102 (1969).
8. A. K. Sheinkman, A. P. Kucherenko, I. V. Kurkurina, N. A. Klyuev, and E. N. Kurkugova, Khim. Geterotsikl. Soedin., No. 2, 229 (1977).
9. J. B. Barat, R. J. Blade, A. J. Boulton, J. Epstein, A. R. Katritzky, J. Lewis, P. Molina-Buendia, Nie Pai-Lin, and C. A. Ramsden, Tetrahedron Lett., No. 31, 2691 (1976).
10. Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, J. Hetrocycl. Chem., 11, 781 (1974).
11. B. Pullman and A. Pullman, Quantum Biochemistry, Wiley Interscience, New York (1963).
12. F. Yoneda and S. Nishigaki, Chem. Pharm. Bull., 19, 1060 (1971).


# SYNTHESIS AND $^{13}C$ NMR SPECTRA OF 5-ALKYL-1,4-DIAZA- AND 5-ALKYL-1-AZA-4-OXABICYCLO[3.3.0]OCTAN-8-ONES


V. A. Sedavkina, I. V. Lizak, and N. N. Sorokin



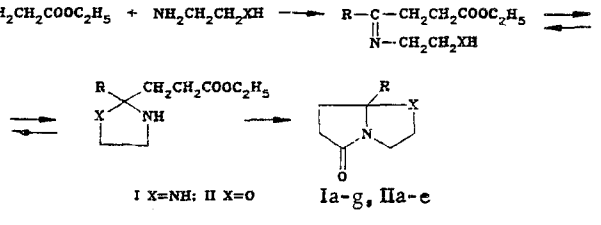
UDC 547.415.1'435.1'484.2'745.04:543.422.25



A group of previously unreported 5-alkyl-1,4-diaza- and 5-alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones have been synthesized from the ethyl esters of γ-ketocarboxylic acids and ethylenediamine or ethanolamine.


The wide range of biological activities of 2-pyrrolidones [1-4] accounts for the extensive studies of their methods of synthesis. The bicyclic analogs 5-alkyl-1,4-diaza- and 5-alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones are practically unknown, only 5-methyl-1,4-diazabicyclo[3.3.0]octan-8-one having been reported [5].

We have obtained a new series of 5-alkyl-1,4-diaza- and 5-alkyl-1-aza-4-oxabicyclo-[3.3.0]octan-8-ones (Ia-g, IIa-e, Table 1) by condensation of the ethyl esters of γ-ketocarboxylic acids with ethylenediamine or ethanolamine.




I X=NH; II X=O  Ia-g, IIa-e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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1405-1408, October, 1987. Original article submitted April 28, 1986.

TABLE 1. 5-Alkyl-1,4-diaza- and 5-Alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones

| Compound | R | $T_{bp}$, °C (8 mm Hg) | $n_D^{20}$ | $d_4^{20}$ | $MR_D$ | | Found, % | | | Empirical formula | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | found | calc. | C | H | N | | C | H | N | |
| Ia* | $C_3H_7$ | 173—174 | 1,5040 | 1,0490 | 46,710 | 46,914 | 64,2 | 9,8 | 16,5 | $C_9H_{16}N_2O$ | 64,3 | 9,6 | 16,6 | 70 |
| Ib | $C_4H_9$ | 176—178 | 1,5025 | 1,0380 | 51,400 | 51,533 | 65,8 | 10,0 | 15,4 | $C_{10}H_{18}N_2O$ | 65,9 | 9,9 | 15,3 | 67,5 |
| Ic | $C_4H_9$-*i* | 174—175 | 1,5020 | 1,0328 | 51,596 | 51,533 | 65,8 | 10,1 | 15,6 | $C_{10}H_{18}N_2O$ | 65,9 | 9,9 | 15,3 | 71 |
| Id | $C_5H_{11}$ | 180—181 | 1,5020 | 1,0248 | 56,144 | 56,151 | 67,8 | 10,4 | 14,2 | $C_{11}H_{20}N_2O$ | 67,9 | 10,2 | 14,2 | 77 |
| Ie | $C_5H_{11}$-*i* | 178—179 | 1,5030 | 1,0120 | 56,320 | 56,151 | 66,6 | 10,3 | 14,5 | $C_{11}H_{20}N_2O$ | 67,9 | 10,2 | 14,2 | 73 |
| If | $C_6H_{13}$ | 183—184 | 1,5010 | 1,0050 | 60,723 | 60,769 | 69,4 | 10,8 | 13,2 | $C_{12}H_{22}N_2O$ | 68,6 | 10,5 | 13,3 | 75 |
| Ig | $C_6H_{13}$-*i* | 181—182 | 1,5015 | 1,0040 | 60,820 | 60,769 | 68,5 | 10,7 | 13,4 | $C_{12}H_{22}N_2O$ | 68,6 | 10,5 | 13,3 | 72 |
| IIa | $C_3H_7$ | 138—139 | 1,4890 | 1,0755 | 44,740 | 44,853 | 63,8 | 8,8 | 8,3 | $C_9H_{15}NO_2$ | 63,9 | 8,9 | 8,2 | 76 |
| IIb | $C_4H_9$ | 141—142 | 1,4870 | 1,0600 | 49,178 | 49,461 | 65,6 | 9,5 | 7,9 | $C_{10}H_{17}NO_2$ | 65,6 | 9,3 | 7,6 | 74 |
| IIc | $C_4H_9$-*i* | 145—146 | 1,4860 | 1,0603 | 49,188 | 49,461 | 65,6 | 9,3 | 7,8 | $C_{10}H_{17}NO_2$ | 65,6 | 9,3 | 7,6 | 76 |
| IId | $C_5H_{11}$ | 140—141 | 1,4850 | 1,0480 | 53,799 | 54,069 | 66,8 | 9,9 | 7,1 | $C_{11}H_{19}NO_2$ | 67,0 | 9,7 | 7,1 | 74 |
| IIe | $C_6H_{13}$ | 141—142 | 1,4840 | 1,0345 | 58,563 | 58,677 | 68,4 | 10,2 | 6,5 | $C_{12}H_{21}NO_2$ | 68,3 | 10,0 | 6,6 | 72 |

*Hydrochloride mp 78-80°C. Found, %: Cl 17.7; N 13.5. $C_9H_{17}ClN_2O$. Calculated, %: Cl 17.5; N 13.7.

TABLE 2. $^{13}C$ Chemical Shifts of Pyrrolidones and Pyrrolidines

| Compound | δ, ppm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $C_{(2)}$ | $C_{(3)}$ | $C_{(5)}$ | $C_{(6)}$ | $C_{(7)}$ | $C_{(8)}$ | $C_{(9)}$ | $C_{(10)}$ | $C_{(11)}$ |
| Ia | 40,94 | 45,67 | 85,48 | 31,23 | 32,94 | 175,56 | 38,62 | 16,64 | 13,28 |
| IIa | 40,82 | 64,40 | 100,57 | 29,57 | 31,73 | 177,72 | 37,93 | 16,21 | 13,19 |
| III | 40,88 | 44,74 | 85,57 | 31,13 | — | 175,69 | 37,58 | 16,69 | 13,36 |
| IV* | 40,63 | 64,18 | 100,41 | 29,30 | 31,40 | 177,56 | 35,42 | 30,64 | 22,33 |
| V | 53,22 | 42,91 | 88,42 | 42,07 | 22,95 | 53,87 | 35,33 | 16,76 | 13,05 |
| VI | 54,20 | 43,92 | 89,76 | 42,99 | 23,97 | 54,51 | 26,34 | 17,90 | 14,14 |
| VII | 41,52 | 38,01 | 55,61 | 22,13 | 28,04 | 172,81 | 33;48 | 15,80 | 12,03 |
| VIII | 41,17 | 38,19 | 57,03 | 23,13 | 29,32 | 175,14 | 34,50 | 16,97 | 13,22 |
| IX | 40,49 | 64,49 | 57,17 | 29,95 | 21,82 | 53,72 | 36,30 | 19,30 | 14,07 |

*$C_{12}$ 21.32; $C_{13}$ 12.71 ppm.

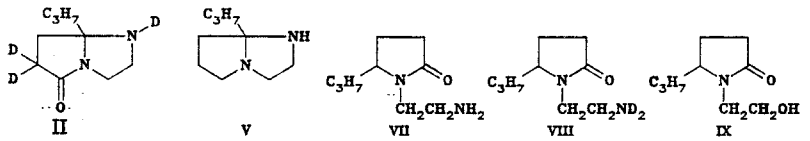
The reaction was studied using protic and aprotic solvents (ethanol, propanol, isopropanol, benzene, and dioxan) and in the absence of solvent. The best results were obtained using benzene with continuous azeotropic distillation of the evolved water and ethanol.

The bicyclic structure of the reaction products was confirmed by $^{1}H$ and $^{13}C$ NMR spectroscopic data. The absence in the $^{1}H$ NMR spectra of vinyl protons and of carbon signals for cyclic alkenes in the $^{13}C$ NMR spectra showed that they were not unsaturated eight-membered ring compounds and pyrrolones formed by the reaction of γ-keto esters with aminating agents possessing two nucleophilic centers. The $^{13}C$ NMR spectra showed singlets for the quaternary $C_5$ carbons at 85.48 ppm for Ia and 100.57 ppm for IIa (Table 2). Assignment of the $^{13}C$ spectra followed from a) off resonance (incompletely decoupled) experiments, b) $^{13}C$ [$^{1}H$] spectra of deuterated analogs III, VI, and VIII, c) the spectra of monocyclic 5-propyl-N-(β-aminoethyl)-2-pyrrolidone (VII) and 5-propyl(β-hydroxyethyl)pyrrolidine (IX), and d) $^{13}C$ [$^{1}H$] NMR data [6-9] for pyrrolidones, pyrrolidines, and alkyl substituted cyclopentanes.

Off resonance spectra of Ia permitted the assignment of the carbonyl carbon at 175.56, the quaternary carbon at 85.48, and the methyl group at 13.28 ppm. The remaining signals corresponded to methylene carbons of which the highest field at 16.64 ppm was due to $C_{10}$ of the alkyl radical [10]. In III (Table 2), which was deuterated at position 7 alpha to the carbonyl function, the spectrum had virtually lost the signal at 32.94 ppm which could thus be unambiguously assigned to $C_7$. The same deuterium exchange led to small (±0.1 ppm) high or low field shifts for the adjacent $C_6$ and $C_8$ carbons, respectively, in agreement with data from [11].

It is known that the gamma effect [12] for carbonyl groups in cyclic compounds falls within the range −10 to −12 ppm. For a comparison the carbonyl group of Ia was reduced using lithium aluminium hydride to give 5-propyl-1,4-diazabicyclo[3.3.0]octane V. Assignment of $C_2$ (40.94) and $C_6$ (31.23 ppm) in Ia was possible because of their low field shifts of ~12 ppm in V. In view of the greater electronegativity of the oxygen atom, the oxygen analog IIa should show stronger deshielding for $C_3$ and $C_5$ [13]. In fact, the spectrum of IIa showed two signals at 100.57 and 64.40 ppm low field shifted from 85.48 and 45.67 ppm in Ia which were assigned to $C_5$ and $C_3$, respectively. Thus, the remaining signal at 38.62 ppm in Ia must be $C_9$ of the alkyl substituent.

The monocyclic compounds VII-IX showed methine carbon signals in the region 55.61-57.17 ppm (Table 2).




Comparison of the spectra of Ia and VII showed that annelation of β-aminoethyl to the 2-pyrrolidone fragment led to low field shifts of 8.53 ppm for $C_6$, 29.13 ppm for $C_5$, and 7.24 ppm for $C_3$. This was in agreement with data concerning the effect of a strained, five-membered ring on their $^{13}C$ NMR chemical shifts [7].

## EXPERIMENTAL

GLC analysis was carried out on an LKhM-8 MD instrument using a flame ionization detector and a stainless steel column (0.6 cm × 1 m) with powdered brick type TND-TS-M modified with 2% KOH and impregnated with 15% apiezon-L. The temperature was 220-250°C and the helium gas velocity was 1.2 liter/h. IR spectra were recorded on a UR-20 instrument as Vaseline mulls or capillary films. $^1H$ and $^{13}C$ NMR spectra were measured on a Varian 80 MHz instrument with HMDS as internal standard.

Compound VII was obtained by [14] and IX by [15].

5-Alkyl-1,4-diaza and 5-Alkyl-1-aza-4-oxabicyclo[3.3.0]octan-8-ones (Ia-g, IIa-e). A mixture of the ethyl esters of γ-ketocarboxylic acid (0.058 mole) and ethanolamine or ethylenediamine (0.058 mole) in absolute benzene (80 ml) were heated in a flask fitted with a Dean and Stark head for 12 h at 90°C. GLC was used to monitor the progress of the reaction. The solvent was reduced at reduced pressure and the residue fractionally distilled in vacuo. IR spectrum (KBr), Ia 3330 (NH), 1720 $cm^{-1}$ (C=O), IIa 1690 (C=O), 1090-1080 $cm^{-1}$ (C–O–C). Parameters for these products are given in Tables 1 and 2.

Deuterated Ia. A solution of Ia (0.0035 mole) in absolute dioxan (4 ml) was poured into $D_2O$ (4 ml) and treated under argon with metallic sodium to pH 10-11. The mixture was decanted under argon into an ampul and heated on a steam bath for 40 h. The contents were then extracted with absolute ether, dried over ignited sodium sulfate, and the ether removed at 20°C to give III. The $^{13}C$ NMR spectra were taken without further purification.

Compounds VI and VIII were synthesized similarly from V and VII.

## LITERATURE CITED


1. J. Struble UK Patent 43,300, Russ. Zh. Khim., 190198P (1981).
2. T. V. Stezhko, V. G. Granik, R. G. Glushkov, L. F. Roshchina, A. I. Polezhaeva, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 3, 290 (1984).
3. T. V. Stezhko, V. G. Granik, R. G. Glushkov, L. F. Roshchina, A. I. Polezhaeva, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 7, 823 (1984).
4. T. V. Stezhko, V. G. Granik, R. G. Glushkov, L. F. Roshchina, A. I. Polezhaeva, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 10, 1198 (1984).
5. H. Wollwerber, Angew. Chem., 81, 34 (1969).
6. I. M. Skvortsov, J. Am. Chem. Soc., No. 11, 1589 (1969).
7. I. M. Skvortsov and I. V. Antipova, Zh. Org. Khim., 15, 868 (1970).
8. G. C. Levy and G. L. Nelson, Carbon-Thirteen Nuclear Magnetic Resonance for Organic Chemists, Wiley Interscience, New York (1974).
9. L. F. Jonson and W. C. Jankowski, Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra, Wiley Interscience, New York (1972).
10. E. L. Eliel and V. Rao, Org. Magn. Reson., 12, 461 (1979).
11. F. Wehrli and T. Wirthlin, Interpretation of $^{13}C$ NMR Spectra, Wiley Heyden, New York (1976), p. 310.
12. H. Beierbeck and J. K. Saunders, Can. J. Chem., 54, 2985 (1976).
13. A. V. German, V. V. Zorin, S. S. Zlotskii, D. L. Rakhmankulov, and A. B. Terent'ev, Khim. Geterotsikl. Soedin., No. 7, 900 (1982).
14. V. A. Sedavkina and I. V. Lizak, USSR Patent 513,972, Byull. Izobr., No. 18, 72 (1976).
15. V. A. Sedavkina and N. A. Morozova, USSR Patent 574,440, Byull. Izobr., No. 36, 63 (1977).