Chemistry of Heterocyclic Compounds, Vol. 48, No. 6, September, 2012 (Russian Original Vol. 48, No. 6, June, 2012)

5',6',7',8'-TETRAHYDRO-1'*H*,3'*H*-SPIRO[CYCLOHEXANE-1,2'-QUINAZOLIN]-4'-ONE IN MANNICH REACTION

V. I. Markov[1] and O. K. Farat[1]*

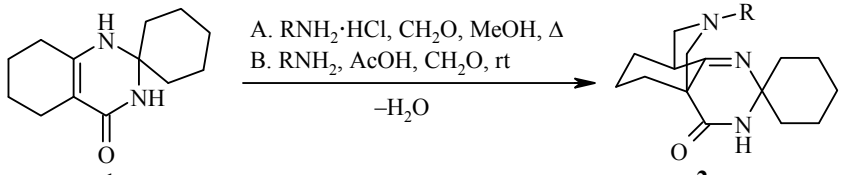
The Mannich aminomethylation of 5',6',7,'8'-tetrahydro-1'H,3'H-spiro[cyclohexane-1,2'-quinazolin]-4'-one leads to formation of a heterocyclic system containing an annelated azabicyclic fragment. Hydrolysis of the indicated spirans gives 3-azabicyclo[3.3.1]nonanes.

Keywords: alkaloids, 3-azabicyclo[3.3.1]nonane, cage amines, quinazolin-4(3*H*)-ones, Mannich reaction.

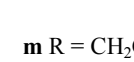
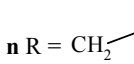
3-Azabicyclo[3.3.1]nonanes show a variety of biological activity (analgesic, antimicrobial), possess ganglioblocking and hypotensive properties, and behave as sedative and antipyretic agents [1-2]. In addition, the special interest in this group of compounds relates to the alkaloids of aconitine series, which also have a 3-azabicyclononane fragment and show high antiarrhythmic activity [2]. It is known that many contemporary antiarrhythmics used in medical practice have a number of drawbacks, the most significant of which is their high toxicity and hence a rather narrow field of therapeutic use. Hence there is significant interest in developing methods for preparing novel polycyclic 3-azabicyclo[3.3.1]nonanes.

Cyclic ketones are key synthons in the preparation of 3-azabicyclo[3.3.1]nonanes and a series of other biologically active heterocyclic compounds [2-8]. A synthon of this type is 5',6',7',8'-tetrahydro-1'*H*,3'*H*-spiro-[cyclohexane-1,2-quinazolin]-4'-one (**1**). Only one example has been reported in the literature of the reaction of compound **1** with formaldehyde and methylamine in ethanol to give the product **2a** in 44% yield [9].

We have studied in detail the Mannich aminoalkylation reaction of compound **1** with primary amines containing different aliphatic and heterocyclic substituents.



1 **2a–p**

a R = Me, **b** R = Et, **c** R = Pr, **d** R = *t*-Bu, **e** R = CH_2Ph, **f** R = CH_2CH_2Ph, **g** R = $CH(Ph)_2$, **h** R = CH_2CH_2Br, **i** R = CH_2COOEt, **j** R = C_6H_{11}, **k** R = $C_{18}H_{37}$, **l** R = CH_2CH_2OH, **m** R = $CH_2CH_2CH_2OH$, **n** R =  , **o** R =  , **p** R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$

*To whom correspondence should be addressed, e-mail: faratok@mail.ru.

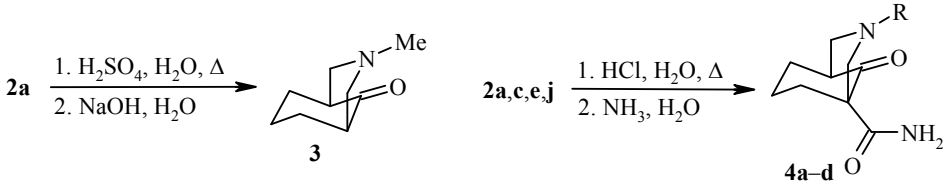
[1]Ukrainian State Chemical and Technological University, 8 Gagarin Ave., Dnepropetrovsk 49005, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 995-1000, June, 2012. Original article submitted April 16, 2011; revision submitted October 21, 2011.

The aminoalkylation was carried out using different alcohols (methyl, ethyl, isopropyl, and isobutyl). The best yield was obtained when methanol was used as solvent. In the case of the use of amines containing 3-aminopyridinyl, 4-amino-1,2,4-triazolyl, or 3-amino-1-phenylpyrazolyl heteroaryl fragments the reaction did not occur under the reported conditions.

The structure of the aminoalkylation products was proved by ^{1}H NMR spectroscopy and by elemental analysis (Tables 1 and 2). The ^{1}H NMR spectra of compounds **2a-p** showed a signal for the NH proton in the region 8.13-8.15 ppm, which did not contradict the proposed structure.

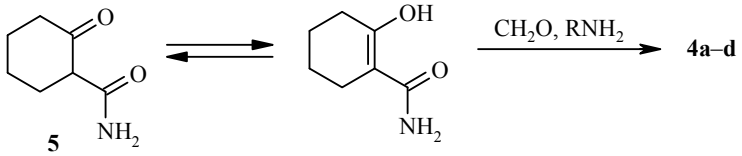
A more certain proof of the structure of the products obtained was reached through acid hydrolysis of the derivatives **2a,c,e,j**. Hence refluxing of the amine **2a** in 50% sulfuric acid gave compound **3**. Heating the amines **2a,c,e,j** with a 10% solution of hydrochloric acid gave the carboxamides **4a-d**.



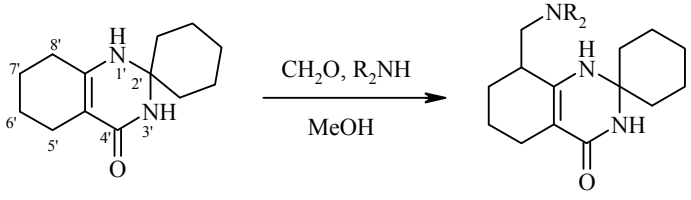
4 a R = Me, **b** R = Pr, **c** R = CH_2Ph, **d** R = C_6H_{11}

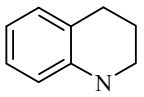
The structure of the compounds **4a-d** obtained was proved by spectroscopic methods (IR, ^{1}H NMR) and confirmed from elemental analysis data (Tables 1 and 2). The IR spectra of the products showed absorption bands for the carbonyl and for the carboxamide groups at 1703-1710 and 1648-1663 cm^{-1}, respectively. The ^{1}H NMR spectra showed the two carboxamide group protons at 7.85 ppm.

Derivatives **4a-d** were also obtained in good yields by a counter synthesis from the carboxamide **5**.



Based on a single example in the study [9], it was shown that the aminomethylation of compound **1** with dimethylamine occurs at the 1'-nitrogen atom. We have found that the analogous reaction gives the products of substitution **6a-f** at the C-8' carbon atom.



a R = Me, **b** R = Et, **c** R = CH_2Ph, **d** R_2N =  , **e** R_2N =  , **f** R_2N = 

The structures of compounds **6a-f** were confirmed from ^{1}H NMR spectroscopy and elemental analysis (Tables 1 and 2). The ^{1}H NMR spectra showed downfield signals for the two NH group protons to and so excludes the possibility of this reaction occurring at nitrogen atom.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield*, %
		C	H	N		
2b	$C_{17}H_{27}N_3O$	70.63 / 70.55	9.48 / 9.40	14.59 / 14.52	160-162	67
2c	$C_{18}H_{29}N_3O$	71.33 / 71.25	9.70 / 9.63	13.90 / 13.85	135-136	70
2d	$C_{19}H_{31}N_3O$	71.93 / 71.88	9.91 / 9.84	13.33 / 13.24	115-118	36
2e	$C_{22}H_{29}N_3O$	75.25 / 75.18	8.37 / 8.32	12.03 / 11.95	163-164	87
2f	$C_{23}H_{31}N_3O$	75.65 / 75.58	8.60 / 8.55	11.58 / 11.50	172-173	55
2g	$C_{28}H_{33}N_3O$	78.69 / 78.65	7.82 / 7.78	9.91 / 9.83	187-188	31
2h	$C_{17}H_{26}BrN_3O$	55.53 / 55.44	7.21 / 7.12	11.57 / 11.41	125-128	50
2i	$C_{19}H_{29}N_3O_3$	65.72 / 65.68	8.45 / 8.41	12.15 / 12.09	175-179	30
2j	$C_{21}H_{33}N_3O$	73.51 / 73.43	9.74 / 9.68	12.27 / 12.23	172-174	74
2k	$C_{33}H_{59}N_3O$	77.23 / 77.14	11.67 / 11.57	8.23 / 8.18	78-80	46
2l	$C_{17}H_{27}N_3O_2$	66.93 / 66.85	9.01 / 8.91	13.85 / 13.76	137-140	33
2m	$C_{18}H_{29}N_3O_2$	67.74 / 67.68	9.21 / 9.15	13.20 / 13.15	125-128	47
2n	$C_{20}H_{31}N_3O_2$	69.64 / 69.53	9.15 / 9.04	12.23 / 12.16	143-147	35
2o	$C_{20}H_{27}N_3O_2$	70.27 / 70.35	7.84 / 7.97	12.25 / 12.31	172-175	38
2p	$C_{25}H_{35}N_3O_3$	70.65 / 70.56	8.33 / 8.29	9.82 / 9.87	142-145	74
4a	$C_{10}H_{16}N_2O_2$	61.31 / 61.20	8.27 / 8.22	14.35 / 14.27	210-211	57
4b	$C_{12}H_{20}N_2O_2$	64.20 / 64.26	8.90 / 8.99	12.41 / 12.49	210-215	51
4c	$C_{16}H_{20}N_2O_2$	71.02 / 70.56	7.53 / 7.40	10.36 / 10.29	158-160	68
4d	$C_{15}H_{24}N_2O_2$	68.25 / 68.15	9.19 / 9.15	10.67 / 10.60	143-145	53
6a	$C_{16}H_{27}N_3O$	69.19 / 69.28	9.74 / 9.81	15.10 / 15.15	162-165	72
6b	$C_{18}H_{31}N_3O$	70.85 / 70.78	10.32 / 10.23	13.81 / 13.76	147-150	64
6c	$C_{28}H_{35}N_3O$	78.37 / 78.28	8.32 / 8.21	9.85 / 9.78	105-108	47
6d	$C_{19}H_{31}N_3O$	71.95 / 71.88	9.90 / 9.84	13.30 / 13.24	220-224	70
6e	$C_{18}H_{29}N_3O_2$	67.75 / 67.68	9.21 / 9.15	13.10 / 13.15	260-263	35
6f	$C_{23}H_{31}N_3O$	75.60 / 75.58	8.63 / 8.55	11.60 / 11.50	163-165	37

* Yield of compounds **2b-p** and **4a-d** by the method A.

Hence examples of an efficient strategy for using the Mannich reaction in a targeted synthesis of potentially biologically active 3-azabicyclo[3.3.1]nonanes and analogs of natural compounds have been described. It was also shown that the reaction of 5',6',7',8'-tetrahydro-1'*H*,3'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'-one with secondary amines under Mannich conditions occurs at a carbon atom rather than the nitrogen atom indicated previously.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)
2b	0.95 (3H, t, *J* = 6.8, CH_3); 1.21-3.21 (23H, m, 11CH_2, 8'-CH); 8.15 (1H, s, NH)
2c	0.93 (3H, t, *J* = 6.8, CH_3); 1.05-3.23 (25H, m, 12CH_2, 8'-CH); 8.14 (1H, s, NH)
2d	0.91 (9H, s, 3CH_3); 1.05-3.22 (21H, m, 10CH_2, 8'-CH); 8.15 (1H, s, NH)
2e	1.05-3.65 (23H, m, 11CH_2, 8'-CH); 7.33-7.51 (5H, m, H Ph); 8.15 (1H, s, NH)
2f	1.00-3.25 (25H, m, 12CH_2, 8'-CH); 7.11-7.46 (5H, m, H Ph); 8.15 (1H, s, NH)
2g	1.00-3.25 (22H, m, 10CH_2, 2CH); 7.52-7.83 (10H, m, H Ph); 8.13 (1H, s, NH)
2h	1.00-3.51 (25H, m, 12CH_2, 8'-CH); 8.15 (1H, s, NH)
2i	0.94 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.22-3.25 (23H, m, 11CH_2, 8'-CH); 4.23 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 8.15 (1H, s, NH)
2j	1.20-3.18 (32H, m, 15CH_2, 2CH); 8.15 (1H, s, NH)
2k	0.95-3.21 (58H, m, CH_3, 27CH_2, 8'-CH); 8.14 (1H, s, NH)
2l	1.10-3.25 (25H, m, 12CH_2, 8'-CH); 4.72 (1H, s, OH); 8.15 (1H, s, NH)
2m	1.07-3.15 (27H, m, 13CH_2, 8'-CH); 4.81 (1H, s, OH); 8.15 (1H, s, NH)
2n	1.10-3.19 (27H, m, 13CH_2, 8'-CH); 3.73 (2H, m, OCHC$\underline{H}_2$); 4.03 (1H, t, *J* = 7.1, OC$\underline{H}$$CH_2$); 8.15 (1H, s, NH)
2o	1.10-3.19 (23H, m, 11CH_2, 8'-CH); 6.06 (1H, d, *J* = 6.7, H-3"); 6.25 (1H, t, *J* = 7.0, H-4"); 7.32 (1H, d, *J* = 7.1, H-5"); 8.14 (1H, s, NH)
2p	1.10-3.24 (25H, m, 12CH_2, 8'-CH); 3.73 (6H, s, 2OCH_3); 6.52-6.61 (3H, m, H Ar); 8.15 (1H, s, NH)
4a*	1.50-2.60 (11H, m, 5CH_2, 5-CH); 2.27 (3H, s, CH_3); 7.85 (2H, s, NH_2)
4b*	0.95 (3H, s, CH_3); 1.21-2.58 (15H, m, 7CH_2, 5-CH); 7.85 (2H, s, NH_2)
4c*	1.50-2.60 (13H, m, 6CH_2, 5-CH); 7.21-7.63 (5H, m, H Ph); 7.85 (2H, s, NH_2)
4d*	1.20-2.74 (22H, m, 10CH_2, 2CH); 7.85 (2H, s, NH_2)
6a	0.95-2.60 (19H, m, 9CH_2, 8-CH); 2.27 (6H, s, 2CH_3); 6.70 (1H, s, NH); 7.73 (1H, s, NH)
6b	1.00 (6H, s, 2CH_3); 1.22-2.65 (23H, m, 11CH_2, 8-CH); 6.70 (1H, s, NH); 7.72 (1H, s, NH)
6c	1.20-2.65 (23H, m, 11CH_2, 8-CH); 6.71 (1H, s, NH); 7.06-7.14 (10H, m, H Ph); 7.73 (1H, s, NH)
6d	1.00-2.60 (29H, m, 14CH_2, 8-CH); 6.70 (1H, s, NH); 7.73 (1H, s, NH)
6e	1.00-2.60 (27H, m, 13CH_2, 8-CH); 6.70 (1H, s, NH); 7.72 (1H, s, NH)
6f	1.00-2.48 (25H, m, 12CH_2, 8-CH); 6.70 (1H, s, NH); 6.54-6.94 (4H, m, H Ar); 7.73 (1H, s, NH)

* IR spectra of compounds **4** (ν, cm^{-1}): **a** 1703, 1663; **b** 1705, 1648; **c** 1710, 1654; **d** 1710, 1650.

EXPERIMENTAL

IR spectra were recorded on a Bruker ALPHA FT-IR spectrometer in the ATR mode for KBr pellets. ^{1}H NMR spectra were recorded on a Varian VXR 200 instrument (200 MHz) using DMSO-d_6 with TMS as internal standard. The purity of the prepared compounds was established using TLC on Merck 60 F254 plates in the system chloroform–ethyl acetate (10:1).

The spiro compound **1** was prepared from cyclohexanone and urea with azeotropic distillation of water using toluene [10-11]. Compound **2a** was prepared in methanol using method [9] in 60% yield, and the carboxamide **5** was obtained by acid hydrolysis of the spirane **1** [12].

5',6',7',8'-Tetrahydro-4a',8'-(2-ethyl-2-azapropano)-3'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'-one (2b). A. Compound **1** (2.200 g, 0.01 mol) and a 36% formalin solution (1.6 ml) were added to a solution of $EtNH_2 \cdot HCl$ (0.815 g, 0.01 mol) in MeOH (10 ml) and refluxed on a water bath for 40 min. Solvent was distilled off under reduced pressure, and the residue was dissolved in water, filtered, and treated with 10% ammonia solution. The precipitated compound **2b** was filtered off, washed with water, and recrystallized from a mixture of water and methanol. Yield 1.940 g (67%).

Compounds **2c-f,h-k,n-p** were obtained similarly (in the case of compound **2g** using the amine hydrobromide). Compounds **2l,m** were obtained from the corresponding free amine with addition of an equivalent amount of HCl solution. After the completion of the process, the reaction mixture was neutralized and extracted with dichloromethane (3×10 ml). The combined extracts were washed with water, dried over $MgSO_4$, and the solvent was distilled off. The oil obtained was triturated with hexane.

B. A mixture of 70% aqueous $EtNH_2$ (0.65 g, 0.01 mol) and glacial acetic acid (3 ml) was cooled in an ice bath, and there were added in sequence formalin solution (36%, 1.6 ml, 0.02 mol) and compound **1** (2.20 g, 0.01 mol) at 5ºC. The reaction mixture was maintained for 1 day at 20ºC. Then the reaction mixture was neutralized with 10% KOH aqueous solution in the cold. The oily compound **2b** rapidly crystallized and was recrystallized from a mixture of water and methanol. Yield 1.73 g (60%).

Compounds **2c,f,i,j,n-p** were prepared similarly in the following yields: **2c** 59%, **2f** 51%, **2i** 33%, **2j** 63%, **2n** 41%, **2o** 58%, and **2p** 72%.

3-Methyl-3-azabicyclo[3.3.1]nonan-9-one (3). Compound **2a** (2.75 g, 0.01 mol) was dissolved in a 50% aqueous H_2SO_4 solution (15 ml) and gently refluxed for 5 h. The cooled solution was filtered and extracted with diethyl ether (1×10 ml). The aqueous layer was basified using a 40% aqueous NaOH solution to pH 8-9 and extracted with chloroform (3×10 ml). The obtained extract was washed with saturated NaCl solution and then water, and dried over $CaCl_2$. Removal of solvent by distillation gave the product **3** as a light-yellow oil, which was distilled *in vacuo* at 85ºC (2 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.21-2.33 (10H, m, $5CH_2$); 2.25 (3H, s, NCH_3); 2.68-2.80 (2H, m, 2CH). Found, %: C 70.49; H 9.83; N 9.10. $C_9H_{15}NO$. Calculated, %: C 70.55; H 9.87; N 9.14.

Reaction of compound **3** with 2,4-dinitrophenylhydrazine gave the corresponding hydrazone. Yield 0.69 g (45%); mp 178-180ºC (mp 178ºC [13]).

3-Methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxamide (4a). A. Compound **2a** (2.75 g, 0.01 mol) was dissolved in a 10% aqueous HCl solution (10 ml). The solution was placed in a Wurtz flask and heated until azeotropic distillation of cyclohexanone ceased. The cooled aqueous solution was treated with ammonia solution and extracted with CH_2Cl_2 (3×10 ml). The extract was washed with water and dried over $MgSO_4$. Solvent was distilled off and light petroleum ether was added to the oily compound **4a** obtained. The mixture was brought to reflux with vigorous stirring, and then it crystallized. Yield 1.12 g (57%). It was purified by recrystallization from hexanes.

The derivatives **4b-d** were prepared similarly. At the end of the reactions, the mixtures were neutralized. The precipitated solid products were collected by filtration and purified by recrystallization from water–methanol. A greater degree of purification was achieved by conversion of these compounds to their perchlorates with subsequent recrystallization from a water–DMF mixture and isolation of the free amines.

B. A mixture of compound **5** (1.41 g, 0.01 mol), 40% aqueous $MeNH_2$ solution (0.78 g), and a 36% formalin solution (1.6 ml, 0.02 mol) in AcOH (5 ml) was left for 1 day. Then the mixture was neutralized using a saturated K_2CO_3 solution. Subsequent workup and purification was carried out by the same procedure described in method A. Yield 1.05 g (54%).

Compounds **4b-d** were prepared similarly. Workup and purification of the compounds were carried out as described in method A. The yields were: **4b** 75%, **4c** 48%, **4d** 57%.

8'-(*N*,*N*-Dimethylaminomethyl)-5',6',7',8'-tetrahydro-1'*H*,3'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'-one (6a). A 36% formalin solution (0.8 ml) and compound **1** (2.203 g, 0.01 mol) were added to $Me_2NH{\cdot}HCl$ (0.815 g, 0.01 mol) in MeOH (10 ml). The mixture was refluxed on a water bath for 2 h. The reaction mixture was then cooled and poured into a solution of ammonia and ice. Compound **6a** (2.000 g, 72%) was filtered off and recrystallized from H_2O–MeOH,

Compounds **6b-f** were prepared similarly.

REFERENCES

1. H. Tecle and G. Hite, *Probl. Drug. Depend.*, 464 (1976). *Chem. Abstr.*, **88**, 69028z (1978).
2. R. Jeyaraman and S. Avila, *Chem. Rev.*, **81**, 149 (1981).
3. H. O. House, P. P. Wickham, and H. C. Muller, *J. Am. Chem. Soc.*, **84**, 3139 (1962).
4. A. V. Kharchenko, Yu. P. Stroev, and I. V. Markova, *Vopr. Khim. Khim. Tekhnol.*, No 5, 16 (2009).
5. G. R. Puchina, *Authors Abstr*., *Diss. Cand. Chem. Sci.*, Ufa (2007).
6. M. A. Titov, *Authors Abstr., Diss. Cand. Chem. Sci.*, Moscow (2008).
7. I. V. Shakhkel'dyan, . *Diss. Doct. Chem. Sci.*, Tula (2003).
8. L. I. Vlasova, *Authors Abst*., *Diss. Cand. Chem. Sci.*, Ufa (2007).
9. G. Zigeuner and G. Gübitz, *Monatsh. Chem.*, **101**, 1547 (1970).
10. A. F. McKay, E. J. Tarlton, and C. Podesva, *J. Org. Chem.*, **26**, 76 (1961).
11. H. C. Scarborough and W. A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).
12. C. Bischoff and H. Herma, *J. Prakt. Chem.*, **318**, 773 (1976).
13. S. Rossi and W. Butta, *Ann. Chim. (Rome)*, **52**, 381 (1962); *Chem. Abstr.*, **57**, 9810l (1962).