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SYNTHESIS AND STUDY OF LACTIM ETHERS OF 3,4-DIHYDROCARBOSTYRYL AND 2,3,4,5-TETRAHYDROBENZ[*b*]AZEPIN-2-ONE

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Alkylation of 3,4-dihydrocarbostyryl and 2,3,4,5-tetrahydrobenz[b]azepin-2-one using dimethyl sulfate and triethyloxonium fluoborate gives the corresponding lactim ethers. The reactions of lactim ethers with different compounds having primary amino groups (including ammonia, alkyl-, aralkyl-, and arylamines, amino acids, and related compounds) have been studied. Novel heterocyclic compounds based on the lactim ethers have been synthesized.

Keywords: dihydrocarbostyryl, lactim ether, tetrahydrobenz[*b*]azepinone, triethyloxonium fluoborate, alkylation.

One of the productive routes for development of the chemistry of heterocyclic compounds is the transformation of lactams to the corresponding lactim ethers, the high reactivity of which combined with their preparative availability has led to novel routes to the synthesis of various amidine and enamine derivatives and, based on them, to the preparation of a variety of azaheterocycles [1]. At the same time, data concerning the use of benzannelated lactim ethers which do not have functional substituents in the lactam ring are very limited. Of the published reports the following should be mentioned: the synthesis of O-ethyl-3,4-dihydrocarbostyryl (**1**) from 2-chloroquinoline [2] and by alkylation of 3,4-dihydrocarbostyryl (**2**) using triethyloxonium fluoborate [3]; the preparation of 1-ethoxyindolenine (**3**) [4] and O-ethylbenzo[1,4]thiazan-3-one (**4**) by the same method; and the synthesis of 2-methoxy-3,4-dihydroquinoline (**5**) [5] from the corresponding chloroimide. The preparation of 2-ethoxy-4,5-dihydro-3H-benzazepine (**6**) by the alkylation of the corresponding lactam – 2,3,4,5-tetrahydrobenzazepin-2-one (**7**) using triethyloxonium fluoborate has been described only in the report [6]. The properties of the previously obtained lactim ethers **1, 3-6** have been reported very fragmentarily [4-6].

The aim of our work was to study the reactions of the lactim ethers **1,6** with different compounds having a primary amino group including ammonia, alkyl-, aralkyl-, and arylamines, amino acids, and related materials. In the first step of the work we examined the alkylation of the lactams **2** and **7**. It was found that the six-membered lactam **2** did not react with dimethyl sulfate upon heating in dichloroethane whereas the seven-membered analog **7,** under these conditions, underwent partial O-alkylation. ^{1}H NMR spectroscopic data indicates that after 8 h a mixture of the corresponding methyl sulfate complex **8a** and the starting lactam is formed in the ratio 1:2. Triethyloxonium fluoborate has a much stronger alkylating potential [7] when compared with dimethyl sulfate and readily alkylates both lactams to form the corresponding fluoborate salts **8b,c** which readily undergo conversion to lactim ethers **1,6** upon the treatment with alkali.

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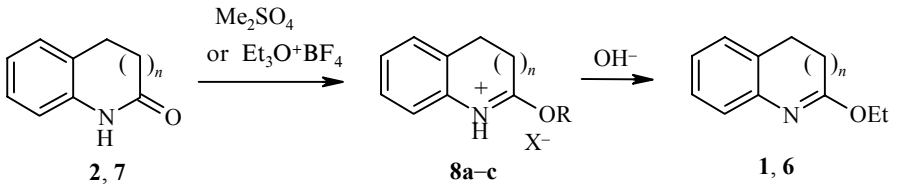
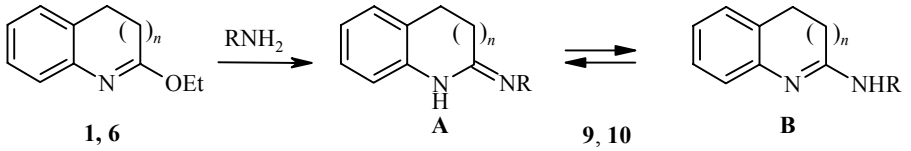


2, **7** **8a–c** **1**, **6**

1, **2** *n* = 1; **6**, **7** *n* = 2; **8 a** R = Me, X = $MeSO_4$, **b**, **c** R = Et, X = BF_4; **a**, **c** *n* = 2, **b** *n* = 1

In contrast to data in [5], according to which lactim ether **5** does not react with cyclohexylamine, ethers **1** and **6** react under usual conditions with various amines to give the corresponding amidines. Hence, reaction of ethers **1,6** with ammonia and different amines gave amidines **9a-g** and **10a-h**:

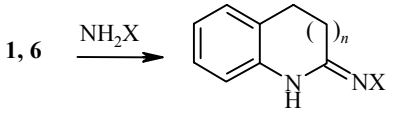


1, 6 **A** **9**, **10** **B**

9 *n* = 1, **10** *n* = 2; **9**, **10** **a** R = H, **b** R = *n*-Bu, **c** R = $PhCH_2$, **d** R = homoveratryl, **e** R = Ph, **f** R = *p*-MeC_6H_4, **g** R = *p*-$MeOC_6H_4$, **10 h** R = $CH_2CH_2NEt_2$

The structures of the derivatives obtained have been characterized by their ^{1}H NMR spectroscopic and mass spectrometric data (Tables 1 and 2). It is interesting to note the presence in the ^{1}H NMR spectrum of compound **9a** of a broad signal at 6.60 ppm with an intensity of 2H assigned to an amino group which may be connected with a significant shift of the tautomeric equilibrium **A** ↔ **B** towards the formation of the amino form **B**. In the spectra of the compounds **9e** and **10e** taken at room temperature in DMSO-d_6 strongly broadened signals for the *ortho* protons of the N-phenyl substituents (~7.80 ppm) are observed. The broadening is so marked that they do not show their multiplicity whereas the *meta* protons appear in the spectrum as narrow signals with clearly defined multiplicity. For the six-membered compound **9e** this broadening is observed also for the aromatic 6- and 8-H protons as well as the protons of the 4-CH_2 unit in the saturated ring whereas the protons of the 3-CH_2 unit appear as a narrow multiplet. In the ^{1}H NMR spectrum of the analyzed solution taken at an elevated temperature (70°C) the previously broadened signals are markedly narrowed: under these conditions the *ortho* protons of the N–Ph group are seen as a broadened doublet with a simultaneous shift to higher field. Upon cooling the solution the spectrum fully conforms to the starting spectrum. Such changes are very likely connected with a relatively slow amine-imine equilibrium (**A** ↔ **B**). To explain the dependence of the form of the signals in the spectra on the temperature of accumulation (as noted above) as an effect of hindered "rotation" around the PhN=C– or N–Ph bonds in the imino form **A** is unreasonable since, in the first case, this would affect the form of the 3-CH_2 group signals (in this case narrow multiplets not changing with an increase in the temperature of recording of spectra) and, in the second case, this would be unlikely to change the form of the 6- and 8-H signals.

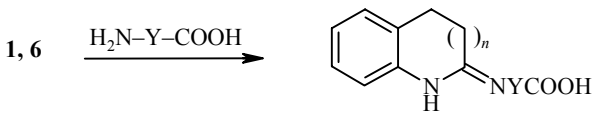
Lactim ethers react not only with primary amines but also with hydroxylamine, phenylhydrazine, and cyanamide and in these examples form the corresponding derivatives **11a-c** and **12a-c**:



11a–c, **12a–c**

n = 1, 2; **a** X = NHPh; **b** X = OH; **c** X = CN

A reaction with aliphatic amino acids also occurs quite readily to form amidino acids **13a-d** and **14a-e**.



13a–e, **14a–e**

n = 1, 2; **a** Y = –CH_2–, **b** Y = –CH_2CH_2–, **c** Y = –$(CH_2)_3$– , **d** Y = –$(CH_2)_5$–, **e** Y = –CH(Me)–

^{1}H NMR spectroscopic data for compounds **11-14** are given in Table 1.

TABLE 1. ^{1}H NMR and ^{13}C NMR Spectral Characteristics of the Synthesized Compounds.

Com-pound	δ, ppm (*J*, Hz), in DMSO-d_6
1	2
9a	2.25 (2H, t, 3-H); 2.64 (2H, t, 4-H); 6.60 (2H, br. s, NH_2); 6.72-6.78, 6.96-7.04 (two m, each 2H, 5-, 6-, 7-, 8-H)
9b	0.90 (3H, t, CH_3 side chain); 1.35 (2H, m, CH_2 side chain); 1,50 (2H, m, CH_2 side chain); 3.27 (2H, t, CH_2 side chain; $NCH_2CH_2CH_2CH_3$); 2.24 (2H, t, 3-H); 2.61 (2H, t, 4-H); 6.86 (1H, br. s, NH); 6.73 (1H, t, 6-H); 6.80 (1H, d, 8-H); 6.95 (1H, d, 5-H); 7.00 (1H, t, 7-H)
9d	2.84 (2H, m, 3-H); 2.90 (2H, m, 4-H); 2.91 (2H, t, CH_2 side chain); 3.87 (2H, br. t, CH_2 side chain; NCH_2CH_2); 3.68 (3H, s, OCH_3); 3.76 (3H, s, OCH_3); 6.80-6.97 (2H, m); 7.06 (1H, split, s); 7.10 (1H, t); 7.20-7.24 (2H, m); 7.70 (1H, d, H arom.); 10.60 (1H, br. s, NH); 11.68 (1H, br. s, NH^+)
9e	2.48 (2H, t, 3-H); 2.74 (2H, br. t, 4-H); 6.95 (1H, t, *p*-H arom.); 7.27 (2H, t, *m*,*m*'-H arom.); 7.94 (2H, strongly br. s, *o*,*o*'-H arom.; NPh); 6.85 (1H, strongly br. t, 6-H); 6.97 (1H, strongly br. d, 8-H); 7.05 (1H, d, 5-H); 7.09 (1H, t, 7-H); 9.05 (1H, strongly br. s, NH)
9f	2.46 (2H, t, 3-H); 2.73 (2H, br. t, 4-H); 2.24 (3H, s, CH_3); 7.80 (2H, strongly br. s, *o*,*o*'-H arom.); 7.07 (2H, d, *m*,*m*'-H arom.; N-C_6H_4-CH_3-*p*); 6.84 (1H, br. t, 6-H); 6.94 (1H, br. d, 8-H); 7.03 (1H, d, 5-H); 7.08 (1H, t, 7-H); 9.00 (1H, strongly br. s, NH)
9g	2.46 (2H, t, 3-H); 2.74 (2H, t, 4-H); 3.72 (3H, s, OCH_3); 6.86 (2H, d, *m*,*m*'-H arom.); 7.80 (2H, strongly br. s, *o*,*o*'-H arom.; N-C_6H_4-OCH_3-*p*); 6.82 (1H, br. t, 6-H); 6.92 (1H, br. d, 8-H); 7.04 (1H, d, 5-H); 7.08 (1H, t, 7-H); 8.92 (1H, strongly br. s, NH)
10d	2.00 (4H, m, 3-, 4-H); 2.40 (2H, br. t, 5-H); 2.80 (2H, t, CH_2 side chain); 3.44 (2H, br. t, CH_2 side chain; NCH_2CH_2); 3.71, 3.73 (3H, two OCH_3); 6.72-6.79 (3H, m); 6.85 (1H, split s); 6.86 (1H, d); 7.00-7.09 (2H, m, *o*,*o*'-H arom., *m*-H arom., 6-, 7-, 8-, 9-H); 6.95 (1H, br. signal, NH)
10e	2.18 (2H, br. m, 2-, 4-H); 2.25 (2H, br. t, 5-H); 2.51 (2H, br. t, 3-H); 6.81-6.88, 7.08-7.16 (two m, each 2H, 6-, 7-, 8-, 9-H); 6.94 (1H, t, *p*-H arom.); 7.26 (2H, t, *m*,*m*'-H arom.); 7.80 (2H, strongly br. s, *o*,*o*'-H arom.; NC_6H_5); 9.10 (1H, strongly br. s, NH)
10f	2.16 (2H, m, 4-H); 2.24 (2H, t, 3-H); 2.50 (2H, t, 5-H); 2.24 (3H, s, CH_3); 7.68 (2H, strongly br. s, *o*,*o*'-H arom.); 7.07 (2H, d, *m*,*m*'-H arom.; N-C_6H_4-CH_3-*p*); 6.80-6.88, 7.08-7.16 (two m, each 2H, 6-, 7-, 8-, 9-H); 9.00 (1H, strongly br. s, NH)
10h	2.20 (2H, m, 2-, 4-H); 2.46 (2H, t, 3-H); 2.74 (2H, t, 5-H); 1.27 (6H, t, CH_3, CH_3); 3.22 (4H, br. q, CH_2, CH_2; $N(CH_2CH_3)_2$); 3.47 (2H, br. t, β-CH_2); 4.10 (2H, br. q, α-CH_2; $NHCH_2CH_2N$); 7.22-7.40 (4H, m, 6-, 7-, 8-, 9-H); 10.98 (2H, br. s); 11.72 (1H, br. s; NH, $2NH^+$)
11a	3.00 (2H, t, 3-H); 3.15 (2H, t, 4-H); 6.92 (1H, t, *p*-H arom.); 7.00 (2H, d, *o*,*o*'-H arom.); 7.27 (2H, t, *m*,*m*'-H arom.); 9.00 (1H, s, NH; NHC_6H_5); 7.13 (1H, t); 7.24 (1H, t); 7.28 (1H, d); 7.42 (1H, d, 5-, 6-, 7-, 8-H); 11.81 (1H, s, 1-NH); 12.60 (1H, br. s, NH^+)
11b	2.37 (2H, t, 3-H); 2.71 (2H, t, 4-H); 6.72 (1H, m); 6.98-7.06 (3H, m, 5-, 6-, 7-, 8-H); 8.78 (1H, s); 9.44 (1H, s, NH, OH)
11c	2.80-3.00 (4H, m, 3-, 4-H); 6.95-7.05, 7.15-7.22 (two m, each 2H, 5-, 6-, 7-, 8-H); 11.36 (1H, s, NH)

TABLE 1 (continued)

1	2
13a*	2.65 (2H, t, 3-H); 2.77 (2H, t, 4-H); 3.89 (2H, s, CH_2 side chain); 6.90 (1H, t, 6-H); 7.00 (1H, d, 8-H); 7.07-7.17 (2H, m, 5-, 7-H)
13b*	2.40 (2H, t, 3-H); 2.69 (2H, t, 4-H); 2.50 (2H, t, β-CH_2); 3.48 (2H, t, α-CH_2; NCH_2CH_2COOH); 6.80-6.95, 7.03-7.10 (two m, each 2H, 5-, 6-, 7-, 8-H)
13c*	2.35 (2H, t, 3-H); 2.68 (2H, t, 4-H); 1.72 (2H, m, β-CH_2); 2.27 (2H, t, γ-CH_2), ~3.30*[2] (2H, α-CH_2; $NCH_2CH_2CH_2$-COOH); 6.80 (1H, t, 6-H); 6.90 (1H, d, 8-H); 7.01 (1H, d, 5-H); 7.05 (1H, t, 7-H)
13d*	2.27 (2H, t, 3-H); 2.63 (2H, t, 4-H); 1.33 (2H, m); 1.52 (4H, m, β-, γ-, σ-CH_2 side chain); 2.19 (2H, t, ω-CH_2 side chain); 3.27 (2H, t, α-CH_2 side chain; NCH_2,$CH_2CH_2CH_2CH_2COOH$); 6.72-6.86, 6.95-7.04 (two m, each 2H, 5-, 6-, 7-, 8-H)
14a*	2.17 (2H, m, 4-H); 2.33 (2H, t, 3-H); 2.58 (2H, t, 5-H); 3.90*[3] (s, CH_2 side chain); 6.98 (1H, d, 9-H); 7.03 (1H, t, 7-H); 7.20-7.26 (2H, m, 6-, 8-H)
14b*	2.08 (2H, m, 4-H); 2.16 (2H, t, 3-H); 2.50 (2H, t, 5-H); 2.46 (2H, t, β-CH_2); 3.48 (2H, t, α-CH_2; NCH_2CH_2COOH); 6.86-6.98, 7.10-7.20 (two m, each 2H, 6-, 7-, 8-, 9-H)
14c*	2.10 (2H, m, 4-H); 2.12 (2H, t, 3-H); 2.47 (2H, t, 5-H); 1.78 (2H, m, β-CH_2); 2.27 (2H, t, γ-CH_2); 3.30 (2H, t, α-CH_2; $NCH_2CH_2CH_2COOH$); 6.81-6.90, 7.06-7.16 (two m, each 2H, 6-, 7-, 8-, 9-H)
16*	2.71 (2H, br. t, 3-H); 2.80 (2H, br. t, 4-H); 7.80 (1H, strongly br. s, *o*-H arom.); 7.99 (1H, d); 7.54 (1H, t, *m*,*m*'-H arom.); 7.14 (1H, t, *p*-H arom.; NC_6H_4-COOH-*o*); 6.94 (1H, t, 6-H); 7.03 (1H, d, 7-H); 7.15 (1H, d, 5-H); 7.16 (1H, t, 8-H)
17*[4]	1.96 (1H, m, 6-H); 2.20 (1H, m, 6-H); 2.30 (1H, m, 7-H); 2.58 (1H, m, 7-H); 2.71 (2H, m, 5-H); 7.40 (3H, m); 7.47 (1H, m); 7.53 (1H, m); 7.67 (1H, d, split); 7.84 (1H, t, split); 8.16 (1H, d, split arom. protons). [28.4 (t, $^1J_{CH}$ = 132) and 28.5 (t, $^1J_{CH}$ = 132, $C_{(6)}$ and $C_{(7)}$); 33.2 (t, $^1J_{CH}$ = 132, $C_{(5)}$); 126.9 ($C_{(11)}$), 127.0, 127.1, 128.1, 129.1, 129.2 (C arom.), 121.2 (q, $C_{(12a)}$), 134.9 (d, $^1J_{CH}$ = 162, $C_{(12)}$), 135.6 and 135.8 (m, $C_{(4a)}$ and $C_{(14a)}$), 147.2 (q, $C_{(8a)}$), 156.4 (m, $C_{(7a)}$), 160.6 (split, C=O)]
18*[4]	2.40-2.56 (2H, m, 3-H); 2.68-2.80 (2H, m, 4-H); 3.65, 3.98 (2H, two s, CH_2CN)*[5]; 6.70-7.20 (4H, m, H arom.); 9.00, 9.08 (NH), 10.00, 10.20 (NH) [24.3 ($^1J_{CH}$ = 135.8); 25.1 ($^1J_{CH}$ = 136.6, $\underline{C}H_2CN$); 25.0, 25.2 ($^1J_{CH}$ = 125.9, $C_{(3)}$); 27.0, 27.5 ($^1J_{CH}$ = 127.4, $C_{(4)}$); 114.9, 115.4 (arom. C); 116.6, 116.7 (CN); 121.4, 121.6 (arom. C); 127.5, 127.6 (arom. C); 128.4, 128.8 (arom. C), ($C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$); 123.8, 124.2 ($C_{(4a)}$); 138.1, 137.9 ($C_{(8a)}$); 143.9, 151.5 ($C_{(2)}$); 158.4, 164.2 (CO)]
19*[4]	2.12 (2H, 5-H); 2.32 (2H, 4-H), 2.68, 2.98 (two br. signals, each 1H, 6-H); 4.30, 4.50 (two br. signals, each 1H, CH_2CN), 7.42-7.58 (4H, m, H arom.) [10.8 (t, $^1J_{CH}$ = 138, $\underline{C}H_2CN$); 16.8 (t, $^1J_{CH}$ = 132.7, $C_{(5)}$); 24.4, 24.8 (two t, $^1J_{CH}$ = 129.0, $C_{(4)}$ and $C_{(6)}$); 110.7 (t, $^2J_{CN,CH_2}$ = 11, CN); 119.0, 123.6, 125.0, 126.3 (four d, $C_{(7)}$, $C_{(8)}$, $C_{(9)}$, $C_{(10)}$); 128.6 (m, $C_{(6a)}$); 131.8 (m, $C_{(10a)}$); 140.2 (t, $^2J_{2\text{-}S,CH_2}$ = 8.4, $C_{(1)}$); 151.4 (m, $C_{(4a)}$)]

* The mobile NH and COOH group protons take part in rapid exchange between themselves and water in the solvent and form a general, intense, strongly broadened signal in the spectrum (3.30-5.50 ppm).

*[2] The signal for the α-CH_2 protons is partially overlapped by the strong signal from the solvent water (3.30 ppm).

*[3] The intensity of the signal is not given since it is partially overlapped by the signal from water in the solvent.

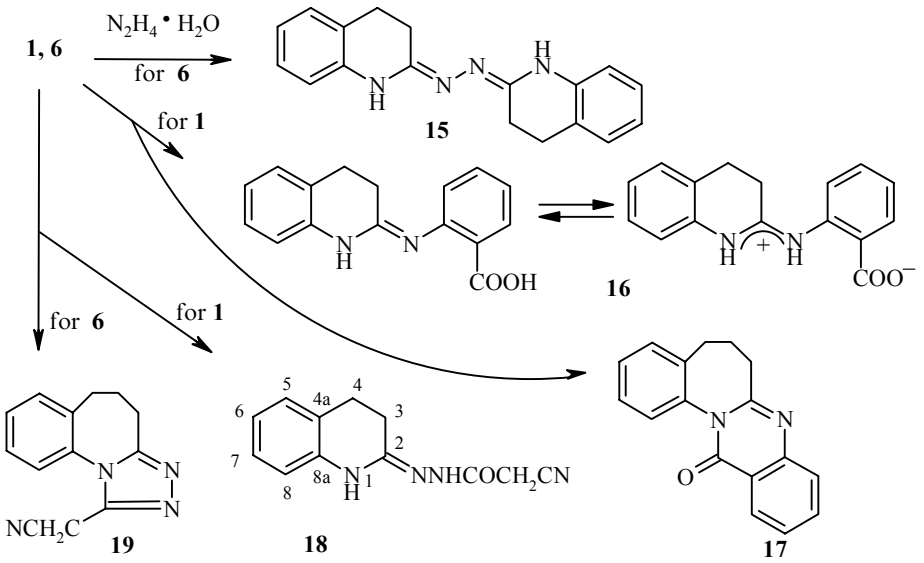
*[4] The ^{13}C NMR spectroscopic data are given in square brackets.

*[5] The CH_2CN group signals at 3.67 and 3.87 ppm correspond to the minor forms; the overall integrated intensity of the four signals of the CH_2CN group protons corresponds to 2H.

In the next stage of the work we undertook attempts to synthesize heterocycles based on lactim ethers **1** and **6**. The reaction of ether **1** with hydrazine was expected to yield the corresponding hydrazone which might further be converted to triazole and tetrazole derivatives [1]. However, in this case we isolated only azine **15** which was characterized using mass spectrometry, ^{1}H NMR spectroscopy, and elemental analysis data.

The ^{1}H NMR spectrum of compound **15** shows the presence of the following signals: 2.63 (2H, q, 3-H); 2.80 (2H, q, 4-H); 6.75-7.10 (4H, m, 5-, 6-, 7-, 8-H); 9.02 ppm (1H, s, NH). According to the mass spectrum this compound has a dimeric structure. Since the ^{1}H NMR spectrum shows one set of signals it is natural to propose that, firstly, the dimer has a symmetrical structure and, secondly, there must be minimal steric interaction, i.e. the bicyclic fragments apparently are *trans*-located at the central =N–N= bond. In solution the compound discussed is quite unstable and the hydrolysis products are formed in solution upon standing.

In other investigated processes there is a distinct difference in the reaction course depending on the size of the saturated ring [9] in the lactim ethers **1** and **6**. Hence the reaction of compound **1** with anthranilic acid gives amidine **16** which does not cyclize under the reaction conditions. According to mass spectroscopic data, besides the signal M^+ 266, a peak for M^+ 248 is observed, however the amount of this substance is negligible and it could be formed in the conditions of the recording of the mass spectrum. The ^{1}H NMR spectrum of compound **16** (Table 1) shows the presence of a strongly broadened signal (no multiplicity seen) for the *ortho* proton of the N-(*o*-carboxy)phenyl substituent at 7.80 ppm. Upon recording the spectrum at 70°C the signal is markedly narrowed but its position does not change. The mobile protons at the heteroatoms are observed as an overall signal at 3.60 ppm (due to rapid exchange between themselves and water in the solvent). The multiplet for the 3-CH_2 group at 2.71 ppm is markedly broadened and the multiplet for the 4-CH_2 at 2.80 ppm is broadened to a lesser degree. Such a signal broadening is characteristic of amidines due to the possibility of *syn-anti* isomerization around the C=N– double bond. The isomerization process is accelerated upon heating and the signals become narrowed when the spectrum is recorded at an increased temperature. It should be noted that protons of the 3-CH_2 group are sterically close to the N-aryl substituents in the predominant conformation as indicated by the results of a nuclear Overhauser effect (NOE) experiment. Irradiation of the signals from protons of the 3-CH_2 group at 2.71 ppm brings about a marked increase in the intensity of the multiplets for the *meta* protons of the N–C_6H_4–COOH-*p* unit at 7.59 (by 30%) and 7.99 ppm (by 4%). The effect is not observed for the *ortho* proton because of the significant broadening of the signal of the latter (see above). Irradiation of the signal for the 4-CH_2 group at 2.80 ppm leads to a 10% increase in the intensity of the 5-H signal at 7.15 ppm (d).



Another picture is seen when carrying out the reaction of lactim ether **6** with anthranilic acid. In this case 6,7,13,14-5H-tetrahydrobenz[*f*]azepino[1,2-*b*]quinazolin-13-one (**17**) is formed readily and in high yield. The structure follows from ^{1}H NMR and ^{13}C NMR spectroscopic data (Table 1) and from mass spectroscopy.

Since the condensation of the seven-membered lactim ether **6** with anthranilic acid to give tetracycle **17** occurs under more drastic conditions than the condensation of six-membered lactim ether **1** (see Table 3) we have carried out the condensation reaction of compound **1** with anthranilic acid under the conditions for preparing the tetracycle **17** and compound **6** in the conditions for preparing amidine **16** and we have studied the reaction products using ^{1}H NMR spectroscopy.

According to the ^{1}H NMR spectrum of the reaction product of the seven-membered derivative (in DMSO-d_6), in the solution discussed only signals for the starting compounds (lactim ether **6** and anthranilic acid) and ethanol are present in addition to those of the tetracycle **17** itself.

A different situation is observed when analyzing the reaction product formed in the course of preparation of the six-membered derivative. The ^{1}H NMR spectrum shows intense signals corresponding to the noncyclic derivative **16** along with clearly identified, low intensity signals for the cyclic derivative (analog of compound **17**) in the ratio 10:1. The solution also contains a small amount of both starting compound **1** and anthranilic acid as well as ethanol.

Hence, also in the case of the six-membered lactim ether **1** in the course of the studied reaction the formation of a tetracyclic product is observed, although its content is much less than that of the noncyclic compound **16**.

The difference in behavior of lactim ethers **1** and **6** is retained when studying their reactions with cyanoacetic acid hydrazide. According to mass spectroscopic data (Table 2) ether **1** forms compound **18**.

TABLE 2. Mass Spectral Characteristics of the Synthesized Compounds*

Com-pound	*m/z* (*I*, %)
9b	202 M^+ (93), 201 $[M–H]^+$ (44), 173 $[M–C_2H_5]^+$ (60), 159 $[M–C_3H_7]^+$ (80), 146 $[C_4H_8]^+$ (100), 130 $[M–C_4H_{10}N]^+$ (56), 118 $[CH_2CHC_6H_4NH]^+$ (10), 106 $[CH_2C_6H_4NH_2]^+$ (54), 103 $[CH_2CHC_6H_4]^+$ (20), 77 $[Ph]^+$ (21)
9d	310 M^+ (15), 164 $[CH_2=CHC_6H_3(OCH_3)_2]^+$ (100), 159 $[M–CH_2C_6H_3(OCH_3)_2]^+$ (20), 151 $[CH_2C_6H_3(OCH_3)_2]^+$ (10), 146 $[M–CH_2=CHC_6H_3(OCH_3)_2]^+$ (23), 130 $[M–NH(CH_2)_2C_6H_3(OCH_3)_2]^+$ (15), 106 $[CH_2C_6H_4NH_2]^+$ (8), 77 $[Ph]^+$ (7)
9f	236 M^+ (70), 235 $[M–H]^+$ (100), 130 $[M–NH–C_6H_4CH_3]^+$ (8), 117 $[M–H_2C–NC_6H_4CH_3]^+$ (10), 91 $[CH_2Ph]^+$ (10)
12a	251 M^+ (100), 159 $[M–NHPh]^+$ (8), 144 $[M–N_2H_2Ph]^+$ (68), 133 $[M–C=N–NHPh]^+$ (10), 106 $[CH_2C_6H_4NH_2]^+$ (17), 93 $[PhNH_2]^+$ (19)
12c	185 M^+ (80), 157 $[M–C_2H_4]^+$ (5), 144 $[M–NHCN]^+$ (100), 116 $[M–NHCN–C_2H_4]^+$ (15), 106 $[CH_2C_6H_4NH_2]^+$ (13), 91 $[C_6H_4NH]^+$ (8), 77 $[Ph]^+$ (10)
13b	218 M^+ (90), 217 $[M–H]^+$ (57), 173 $[M–COOH]^+$ (100), 159 $[M–CH_2COOH]^+$ (22), 146 $[M–CH_2CHCOOH]^+$ (60), 130 $[M–NHCH_2CH_2COOH]^+$ (50), 106 $[CH_2C_6H_4NH_2]^+$ (40), 77 $[Ph]^+$ (20)
16	266 $[M]^+$ (75), 265 $[M–H]^+$ (30), 247 $[M–H–H_2O]^+$ (80), 221 $[M–COOH]^+$ (100), 130 $[M–NHC_6H_4COOH]$+ (12), 116 $[M–HC–NC_6H_4COOH]$+ (15), 77 $[Ph]^+$ (15)
17	262 M^+ (80), 261 $[M–H]^+$ (100), 247 $[M–CH_3]^+$ (7), 234 $[M–CO]^+$ (10), 233 $[M–H–CO]^+$ (7), 205 $[M–H–CO–C_2H_4]^+$ (6), 89 $[C_7H_5]^+$ (7)
18	228 $[M]^+$ (70), 227 $[M–H]^+$ (40), 210 $[M–H_2O]^+$ (10), 188 $[M–CH_2CN]^+$ (100), 160 $[M–COCH_2CN]^+$ (14), 146 $[M–NCOCH_2CN]^+$ (19), 143 $[M–H–NH_2COCH_2CN]^+$ (23), 130 $[M–H_2NNCOCH_2CN]^+$ (55), 118 $[M–CHNNHCOCH_2CN]^+$ (12), 106 $[CH_2C_6H_4NH_2]^+$ (12), 77 $[Ph]^+$ (15)
19	224 $[M]^+$ (100), 223 $[M–H]^+$ (43), 209 $[N–CH_3]^+$ (16), 196 $[M–C_2H_4]^+$ (20), 184 $[M–CH_2CN]^+$, 168 $[M–C_2H_4–N_2]^+$ (10), 157 $[M–CH_2CN–HCN]^+$ (12), 143 $[M–CH_2CN–CHN_2]^+$ (10), 130 $[M–NCCH_2C_2H_2N_2]^+$ (45), 116 $[M–NCCH_2CHN_2–HCN]^+$ (12), 103 $[M–CH_2CNC_2H_2N_2–HCN]^+$ (20), 77 $[Ph]^+$ (15)

* DCI Mass spectra: **14b** - $[MH]^+$ 233, **14c** - $[MH]^+$ 247.

TABLE 3. Conditions for the Reaction of Lactim Ethers with Amines*

Compound	Molar ratio **1** (**6**) : amine	Reactions conditions		Compound	Molar ratio **1** (**6**) : amine	Reactions conditions	
		Time, min	T, °C			Time, min	T, °C
9c	1:1.03	40	120-125	**10h**	1:1	90	~170
9d	1:1	60	155-160	**11a**	1:1	180	195-200
9e	1:1	45	~200	**11c**	1:0.86	30	~100
9f	1.02:1	60	~130	**12a**	1:1	180	195-200
9g	1:1	60	~160	**12c**	1:0.86	30	~100
10c	1:1.03	40	120-125	**16**	1:0.83	10	~100
10d	1:0.83	60	125-130	**17***[2]	1:0.78	40	~110
10e	1:1	45	~200	**18**	1:1	30	95-100
10f	1.02:1	60	~150	**19**	1:1	20	95-100
10g	1:1	60	~160				

* For compounds **9a-g** and **10e-g** the reaction was carried out in the presence of a catalytic amount of *p*-TsOH.
*[2] The reaction product was then heated for 15 min at 130°C until complete disappearance of anthranilic acid on TLC.

Judged by the number of signals for the CH_2CN methylene proton signals in the ^1H NMR spectrum of compound **18** it exists as a mixture of four rotamers. The ^1H NMR spectra of the two main rotamers are given in Table 1. Heating the analyzed solution leads to a simplification of the spectrum. In the spectrum of the solution heated to 60°C the signals for two rotamers are clearly seen (in the case of the CH_2CN group at 3.62 and 3.93 ppm). The ^1H NMR spectrum of the cooled solution of **18** fully agrees with the starting spectrum.

A similarly complex situation is also observed for compound **18** in its ^{13}C NMR spectrum. As in the case of the ^1H NMR spectrum, a set of four is seen for a number of signals. In order to characterize the compound under investigation we report the signals of the two predominant rotamers. As in the ^1H NMR spectra, the recording of the spectra of the solution heated to 60°C leads to a simplification of the ^{13}C NMR spectrum – only the signals from two forms are present. The ^{13}C NMR spectrum of the cooled solution fully corresponds to the initial spectrum.

Hence the spectroscopic characterization considered above unambiguously shows that compound **18** is bicyclic. However, when the seven-membered lactim ether **6** is used in this reaction there occurs a cyclization involving the imino ether and hydrazide fragments to give 1-cyanomethyl-4H,5,6-dihydro-1,2,4-triazolo[4,3-*a*]-benz[*f*]azepine (**19**). The structure of the tricycle **19** follows from the mass spectroscopic data (Table 2) and the ^1H NMR and ^{13}C NMR spectra (Table 1).

The features of the ^1H NMR spectrum include very broad signals for the methylene protons in the seven-membered ring: 2.12 (2H, 5-H); 2.32 ppm (2H, 4-H) and two equal intensity, broad signals at 2.68 and 2.98 ppm (each 1H, 6-H). The methylene protons of the CH_2CN fragment in the spectrum also appear as two strongly broadened signals at 4.30 and 4.50 ppm (each 1H).

When 2 drops of DCl/D_2O are added to the analyzed solution a marked decrease in the intensity of the latter signals is observed (the intensity of the other signals being unchanged) and this is related to a deuterium exchange of the acidic protons of the CH_2CN group. In the spectrum taken at 70°C a clear narrowing of the signals for the 4-CH_2 and 6-CH_2 groups is seen and for the 5-CH_2 group protons (2.11 ppm) their characteristic quintet multiplicity is revealed. The form of the signals for the CH_2CN group protons also undergoes a significant change and these protons appear as a singlet at 4.34 ppm with a two proton unit intensity. The multiplicity of the aromatic protons in the range of 7.42-7.58 ppm (4H) is virtually unchanged upon heating the solution under investigation.

TABLE 4. Characteristics of the Synthesized Compounds

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C	Solvent for recrystallization	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
9a	$C_9H_{10}N_2$	73.99 / 73.94	6.83 / 6.90	19.35 / 19.16	109-112	Heptane	70
9b	$C_{13}H_{18}N_2$	77.22 / 77.18	9.00 / 8.97	13.97 / 13.85	58-60	Heptane	77
9c	$C_{16}H_{16}N_2$	81.38 / 81.32	6.90 / 6.82	11.77 / 11.85	130-133	Heptane	75
9d	$C_{19}H_{22}N_2O_2 \cdot HCl$	65.96 / 65.79	6.87 / 6.68	8.25 / 8.08	233-234.5	Ethanol	79
9e	$C_{15}H_{14}N_2$	80.78 / 81.05	6.44 / 6.35	12.64 / 12.60	160-162	Propan-2-ol	~100
9f	$C_{16}H_{16}N_2$	81.15 / 81.32	6.93 / 6.83	11.86 / 11.85	165-167	Heptane	85
9g	$C_{16}H_{16}N_2O$	76.01 / 76.16	6.46 / 6.39	11.11 / 11.10	181-182	Propan-2-ol	87
10a	$C_{10}H_{12}N_2$	74.90 / 74.96	7.72 / 7.55	17.47 / 17.49	124-127	Heptane	72
10b	$C_{14}H_{20}N_2$	77.56 / 77.73	9.57 / 9.32	12.66 / 12.95	69-72	Heptane	73
10c	$C_{17}H_{18}N_2$	81.44 / 81.56	7.63 / 7.25	11.01 / 11.19	123-125	Heptane	~100
10d	$C_{20}H_{24}N_2O_2$	74.00 / 74.04	7.51 / 7.46	8.61 / 8.64	121-123	33% aqueous propan-2-ol	15
10e	$C_{16}H_{16}N_2$	81.57 / 81.32	7.01 / 6.82	11.52 / 11.85	143-147	Heptane	56
10f	$C_{17}H_{18}N_2$	81.60 / 81.56	7.32 / 7.25	11.24 / 11.19	146-147.5	Heptane	55
10g	$C_{17}H_{18}N_2O$	76.38 / 76.66	7.08 / 6.81	10.54 / 10.52	141-143	Heptane	74
10h	$C_{16}H_{25}N_3 \cdot 2HCl$	57.90 / 57.83	8.20 / 8.19	12.83 / 12.64	236-239	Acetonitrile	54
11a	$C_{15}H_{15}N_3 \cdot HCl$	65.98 / 65.81	5.70 / 5.89	15.65 / 15.35	231-236	Ethanol	76
11b	$C_9H_{10}N_2O$	66.55 / 66.65	6.18 / 6.22	17.28 / 17.27	126-129	Acetonitrile	90
11c	$C_{10}H_9N_3$	70.06 / 70.15	5.43 / 5.30	24.45 / 24.55	183-185	Propan-2-ol	83
12a	$C_{16}H_{17}N_3 \cdot HCl$	66.71 / 66.77	6.51 / 6.30	14.66 / 14.60	245-247 (dec. from 205)	Ethanol	42
12b	$C_{10}H_{12}N_2O$	68.00 / 68.18	6.90 / 6.86	15.82 / 15.90	121-122	Acetonitrile	75
12c	$C_{10}H_9N_3$	70.06 / 70.15	5.43 / 5.30	24.45 / 24.55	183-185	Propan-2-ol	83
13a*[2]	$C_{11}H_{12}N_2O_2 \cdot H_2O$	59.62 / 59.45	6.26 / 6.35	12.62 / 12.61	239-239.5	Water	78
13b	$C_{12}H_{14}N_2O_2$	66.13 / 66.04	6.41 / 6.47	12.80 / 12.84	236-237	Water	97
13c	$C_{13}H_{16}N_2O_2$	67.14 / 67.22	6.98 / 6.94	11.80 / 12.06	265.5-270.5	Methanol	80
13d	$C_{15}H_{20}N_2O_2 \cdot$ $\cdot 0.5$ *i*-PrOH	68.09 / 68.24	8.55 / 8.33	9.20 / 9.65	85-89	Propan-2-ol	100
14a	$C_{12}H_{14}N_2O_2$	66.15 / 66.04	6.61 / 6.47	13.10 / 12.84	215-217	96% aqueous ethanol	78
14b*[3]	$C_{13}H_{16}N_2O_2 \cdot H_2O$	62.27 / 62.38	7.28 / 7.25	11.17 / 11.19	136-140	Water	77
14c	$C_{14}H_{18}N_2O_2 \cdot$*i*-PrOH	66.54 / 66.64	8.43 / 8.55	9.49 / 9.14	195-196	Propan-2-ol	97
14d	$C_{16}H_{22}N_2O_2$	70.22 / 70.04	8.48 / 8.08	10.33 / 10.21	165-167	DMF	100
14e	$C_{13}H_{16}N_2O_2$	66.86 / 67.22	7.01 / 6.94	12.14 / 12.06	213-216	DMF	26

TABLE 4 (continued)

1	2	3	4	5	6	7	8
15	$C_{18}H_{18}N_4$	74.14 74.45	6.29 6.25	19.54 19.30	214-217.5	Acetonitrile	80
16	$C_{16}H_{14}N_2O_2$	71.86 72.16	5.37 5.30	10.54 10.52	207.5-210.5	DMF	94
17	$C_{17}H_{14}N_2O$	77.61 77.84	5.70 5.38	10.76 10.68	160-161	Propan-2-ol	67
18	$C_{12}H_{12}N_4O$	63.08 63.14	5.05 5.29	24.61 24.55	160-162	Acetonitrile	96
19	$C_{13}H_{12}N_4$	69.50 69.63	5.50 5.39	25.11 24.99	182-184	Propan-2-ol	89

* Compound **9d** - Cl. Found, % 10.30. Calculated, %: 10.22. **10h** - Cl. Found, %: 21.36. Calculated, %: 21.34. **11a** - Cl. Found, %: 13.01. Calculated, %: 12.95. **12a** - Cl. Found, %: 12.03. Calculated %: 12.32.
*[2] H_2O. Found, %: 7.96. Calculated, %: 8.10.
*[3] H_2O. Found, %: 7.70. Calculated, %: 7.20.

The ^{13}C NMR spectrum of compound **19** agrees well with the proposed structure. In contrast to the ^1H NMR spectrum, all of the signals in the ^{13}C NMR spectrum are narrow and this allows us to propose that the broadening of the signals in the proton spectrum is related to a slowed inversion of the seven-membered ring. The high conformational freedom of the seven-membered ring is also possibly the reason for the difference in the reactivity of lactim ethers **1** and **6**, as manifested in the examples of their reactions with anthranilic acid and cyanoacetic acid hydrazide.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian Unity+400 spectrometer (working frequencies 400 (^1H) and 100 MHz (^{13}C)) using DMSO-d_6 with TMS internal standard. EI and DCI mass spectra were taken on a Finnigan-MAT SSQ-710 instrument with direct introduction of the sample into the ion source (ionizing voltage 70 eV, ionization chamber temperature 150°C). Melting points were determined on a Boetius heating block.

Physicochemical and spectroscopic parameters for the synthesized compounds are given in Tables 1, 2, and 4.

Alkylation of 1H,2,3,4,5-Tetrahydrobenz[*c*]azepin-2-one by Dimethyl Sulfate. Mixture of compound **7** (1.61 g, 0.01 mol) and dimethyl sulfate (1.72 ml, 2.32 g, 0.018 mol) in dichloroethane (15 ml) was refluxed for 3 h, dimethyl sulfate (1.2 ml) was added, and refluxing continued for a further 5 h. The reaction product was evaporated and the residue was washed with heptane and then ether and dried in vacuo to give a mixture of compounds **8a** and **7** in the ratio 1:2 (according to ^1H NMR spectroscopic data).

General Method for the Preparation of Compounds 9c-g, 10c-h, 11a,c 12a,c, and 16-19 (Table 3). Mixture of lactim ether **1** or **6** and the corresponding amine was heated to the temperature of the start of the condensation and held at this temperature with distillation of alcohol formed to the conclusion of the reaction (cessation of the distillation). The reaction product was triturated with heptane (for compounds **9c,e-g, 10c,e-g, 11c, 12c,** and **16**), with heptane and then absolute ether (for compounds **10d, 18,** and **19**) or with propan-2-ol (for compound **17**). Compounds **9d**, **10h**, and **11a** were isolated as hydrochlorides by solution of the reaction product in ethyl acetate (for compounds **9d** and **10h**) or absolute ether (for compound **11a**) with subsequent acidification with a saturated solution of HCl in ethyl acetate (for compounds **9d** and **10h**) or in alcohol (for compound **11a**).

General Method for the Preparation of Compounds 11b and 12b. Mixture of the corresponding lactim ether **1** or **6**, hydroxylamine hydrochloride, and $NaHCO_3$ (molar ratio 1:1.39:1.39) in DMF was stirred at 60°C (for compound **11b**) or refluxed (for compound **12b**) for 3 h. The precipitate was filtered off, the mother liquor was evaporated, and the residue was triturated with water to give compound **11b** or **12b**.

General Method for the Preparation of Compounds 13a-d and 14a-e. Mixture of lactim ether **1** or **6** and the corresponding amino acid (molar ratio 1:0.89) in alcohol was refluxed for 4 h (for compounds **14b,d**), 3.5 h (for compound **14a**), 6 h (for compound **14c**), 7 h (for compound **14e**), 1 h (for compounds **13b-d**), or 1.5 h (for compound **13a**). The reaction product was cooled, the corresponding amidines **14a,b,e** and **13a-d** were filtered off or evaporated in vacuo and the residue triturated with ether (for compound **14c**) or with heptane and then propan-2-ol (for compound **14d**).

General Method for the Preparation of Compounds 9b, 10b. Mixture of lactim ether **1** or **6** (11.5 mmol) and butylamine (10 ml) was heated in a bomb for 4 h at 115-120°C. The reaction product was evaporated and the residue was triturated with heptane to give the compound **9b** or **10b**.

General Method for the Preparation of Compounds 9a, 10a. Mixture of lactim ether **1** or **6** (5 ml) and saturated solution of ammonia in methanol (20 ml) was heated in a bomb for 6 h at 120-125°C. The reaction product was evaporated and the residue was triturated with heptane to give the compound **9a** or **10a**. Compound **9a** was additionally purified by reprecipitation with 2 N NaOH from an aqueous HCl solution.

N,N,N',N'-Bis(1,2,3,4-tetrahydroquinol-2-en)azine (15). Solution of compound **1** (0.95 g, 5.4 mmol) in toluene (10 ml) was added dropwise to solution of hydrazine hydrate (6 ml) in toluene (10 ml) at 105°C. The reaction product was refluxed for 1.25 h, cooled, and compound **15** was filtered off.

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