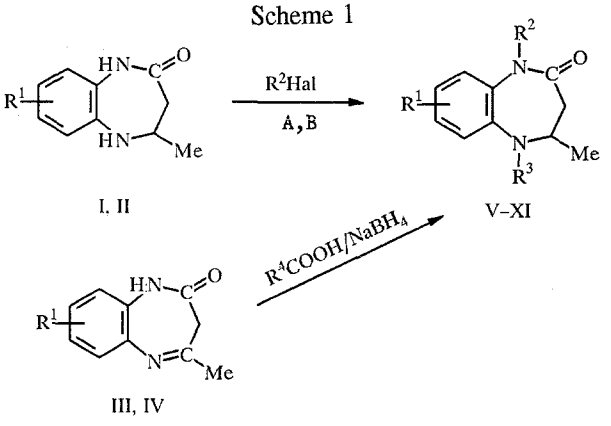
# SYNTHESIS AND SPECTRAL PROPERTIES OF N-ALKYL-4-METHYL-7(8)-NITRO-2,3,4,5-TETRAHYDRO-(1H)-1,5-BENZODIAZEPIN-2-ONES

**B. A. Puodzhyunaite, R. A. Yanchene, P. B. Terent'ev, K. A. Abdurakhmanov, and G. Dzhumakuliev**

*Alkylation of 4-methyl-7(8)-nitro-2,3,4,5-tetrahydrobenzodiazepin-2-ones under phase transfer catalytic conditions or in dry acetone occurs only at position 1. The 5-alkyl isomers are obtained by reductive alkylation of 4-methyl-7(8)-nitro-2,3-dihydro-1,5-benzodiazepin-2-ones. The UV, IR, PMR, and mass spectra of the isomeric compounds are reported.*

The alkylation of biologically active 2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-ones (THB) has been reported in [1]. It was shown that 3- or 4-methyl-THB unsubstituted in the aromatic ring form 1,3(4),5-trimethyl-THB with methyl iodide independently of the reaction conditions. Only by reacting the same reagent with 4-phenyl-THB, in which the nitrogen at position 5 is more sterically hindered, was it possible to obtain the monomethylation product at position 1 [1]. Introduction of an electron-accepting nitro group into the aromatic ring may show a significant effect on the nature and direction of the alkylation. In this connection we have studied the reaction of isomeric 4-methyl-7(8)-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-ones (I, II) [2, 3] with alkylating reagents both under phase-transfer-catalytic conditions (A) and in dry acetone in the presence of solid potassium hydroxide (B) (Scheme 1).

Scheme 1




I, II — V–XI

III, IV

I, III, V, VI, VIII, IX, XI $R^1$ = 7-$NO_2$; II, IV, VII, X $R^1$ = 8-$NO_2$; V—VII $R^2$ = $CH_3$; VIII $R^2$ = $CH_2C_6H_5$; IX—XI $R^2$ = H; VI $R^2$ = $CO(CH_2)_2Br$; V, VII, VIII $R^3$ = H; IX, X $R^3$ = = $CH_3$; XI $R^3$ = $CH_2CF_3$; $R^4$ = H, $CF_3$

We have also shown that isomer I is alkylated in high yields under conditions A and B only at amide nitrogen 1 (Scheme 1). By contrast, the 8-isomer (II) reacts with methyl iodide under conditions B to form approximately equal amounts of the monomethyl derivative (VII) and 8-nitro-1,4,5-trimethyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (PMR data). The

Lithuanian Institute of Biochemistry, Vilnyus 232600. Chemistry Faculty, M. V. Lomonosov State University, Moscow 117234. Turkmenistan Institute of National Economy, Ashkhabad 744001. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 959-963, July, 1992. Original article submitted February 26, 1992.

 0009-3122/92/2807-0798$12.50 

TABLE 1. Properties of V-XI

| Compound | mp, °C* | IR spectrum, $\nu_{C=O}$ | IR spectrum, $\nu_{N-H}$ | UV spectrum, nm (log ε) | PMR spectrum, δ, ppm: 4-$CH_3$ (d) | N—$CH_3$ (s) | 4-CH (m) | 3-$CH_2$ (m) | other protons** | Yield % (method) |
|---|---|---|---|---|---|---|---|---|---|---|
| V | 160...162 | 1650 | 3320 | 208 (4,36); 264 (4,17); 305 (3,86); 357 (3,58) | 1,28 | 3,31 | 4,08 | 2,22...2,54 | 3,82 (5-NH) | 57 (A), 66 (B) |
| VI | 191...193 | 1660, 1670 | – | 306 (4,07) | 1,10 | 3,27 | 5,18 | 1,95...2,78 and ($COCH_2$) | 3,48 (t) ($CH_2Br$) | 61 |
| VII | 140...142 | 1650 | 3330 | 222 (4,27); 270 (3,76); 385 (3,98) | 1,18 | 3,23 | 3,92 | 2,17...2,62 | – | 25 (B) |
| VIII | 144...146 | 1660 | 3330 | 264 (4,15); 308 (3,89); 367 (3,66) | 1,18 | 5,05 (benzyl) | 3,94 | 2,20...2,50 | 5,62 (5-NH) | 83 (A) |
| IX | 215...217 | 1670 | 3185 | 209 (4,30); 270 (4,25); 309 (3,9), 373 (3,55) | 1,20 | 2,84 | 3,83 | 2,21...2,58 | 9,77 (s) (1-NH) | 78 |
| X | 191...193 | 1680 | 3200 | 223 (4,39); 274 (3,89); 389 (4,08) | 1,28 | 2,86 | 3,85 | 2,27...2,58 | 9,48 (s) (1-NH) | 53 |
| XI | 176...178 | 1680 | 3200 | 266 (4,15); 308 (3,89); 347 (3,70) | 1,08 | 3,73 ($CH_2CF_3$) | 3,87 | 2,20...2,46 | 8,85 (s) (1-NH) | 49*** |

*Recrystallized from ethyl acetate (XI from benzene).

**In addition to low field aromatic signals at 7-8 ppm.

***Based on the consumption of III in the reaction.

TABLE 2. Mass Spectra of I, II, V, and VII-XI

| Compound | m/z (relative intensity, %) |
|---|---|
| I | 221 (70), 206 (45), 178 (15), 164 (100), 132 (12), 118 (53), 105 (7), 78 (10), 69 (36), 52 (11), 51 (10) |
| II | 221 (83), 206 (38), 178 (21), 164 (100), 132 (15), 118 (54), 105 (8), 78 (12), 69 (47), 65 (14), 52 (11) |
| V | 235 (57), 220 (14), 192 (62), 178 (100), 146 (17), 132 (12), 78 (11), 77 (11), 69 (45), 51 (9) |
| VII | 235 (93), 220 (11), 192 (79), 178 (100), 146 (19), 132 (47), 131 (10), 104 (7), 78 (9), 69 (49), 51 (8) |
| VIII | 311 (40), 268 (15), 254 (9), 193 (5), 178 (4), 164 (4), 132 (3), 91 (100), 69 (10), 65 (9) |
| IX | 235 (45), 220 (28), 178 (100), 177 (13), 146 (15), 132 (52), 131 (16), 78 (14), 77 (14), 69 (64), 51 (13) |
| X | 235 (33), 220 (45), 192 (7), 178 (100), 148 (7), 146 (9), 132 (49), 131 (9), 78 (7), 77 (8), 69 (25) |
| XI | 303 (42), 288 (30), 246 (100), 242 (100), 200 (44), 192 (13), 131 (9), 118 (8), 78 (7), 77 (6), 69 (28), 51 (7) |

TABLE 3. Characteristic Peak Ion Intensities in the Mass Spectra of I, II, V, and VII-XI (% $\Sigma_{50}$)

| Compound | $W_M$ | $\Phi_1$ | $\Phi_2$ | $\Phi_3$ | $\Phi_4$ | $\Phi_5$ | $\Phi_6$ | $\Phi_7$ | $\Phi_8$ |
|---|---|---|---|---|---|---|---|---|---|
| I | 14,2 | 8,9 | 17,6 | 2,6 | 6,2 | 0,6 | 0,9 | 10,3 | 2,2 |
| II | 9,7 | 5,0 | 12,8 | 3,0 | 5,4 | 0,4 | 0,6 | 6,9 | 1,7 |
| V | 8,5 | 2,1 | 14,2 | 9,2 | 6,2 | 0,5 | 0,1 | 8,4 | 2,4 |
| VII | 19,3 | 2,0 | 19,7 | 16,2 | 9,2 | 0,6 | — | 9,0 | 3,3 |
| VIII | 18,9 | 0,5 | 3,3 | 5,7 | 3,6 | 0,5 | — | — | — |
| IX | 4,7 | 3,0 | 9,8 | 4,0 | 5,8 | 0,1 | 0,2 | 5,3 | 1,3 |
| X | 5,5 | 6,1 | 15,0 | 0,8 | 3,3 | 0,1 | 0,7 | 6,2 | 1,2 |
| XI | 7,5 | 5,2 | 17,0 | 0,8 | 4,2 | 0,1 | 0,8 | 7,6 | 0,5 |

first of these can be partially separated from the mixture by column chromatography. Alkylation at position 1 is confirmed by both PMR spectral data (Table 1) and by the ready alkylation of V by 2-bromopropionyl chloride forming VI. The isomeric 5-monoalkyl derivatives IX-XI could only be prepared by reductive alkylation [3, 4] of the isomeric 4-methyl-7(8)-nitro-2,3-dihydro-1,5-benzodiazepin-2-ones (III and IV) using formic (IX, X) or trifluoroacetic acids (XI) in the presence of sodium borohydride. All of the 7-nitro compounds (V, VI, VIII, IX, XI) showed characteristic [5] absorption maxima at 305-309 nm. A longer wavelength absorption at 347-367 nm can be assigned to an electronic transition typical of m-nitroanilines [6]. This absorption band disappears in the acylated product VI. The UV spectra of the 8-nitro isomers (VII, X) show a longer wavelength absorption (385-389 nm), typical of p-nitroanilines.

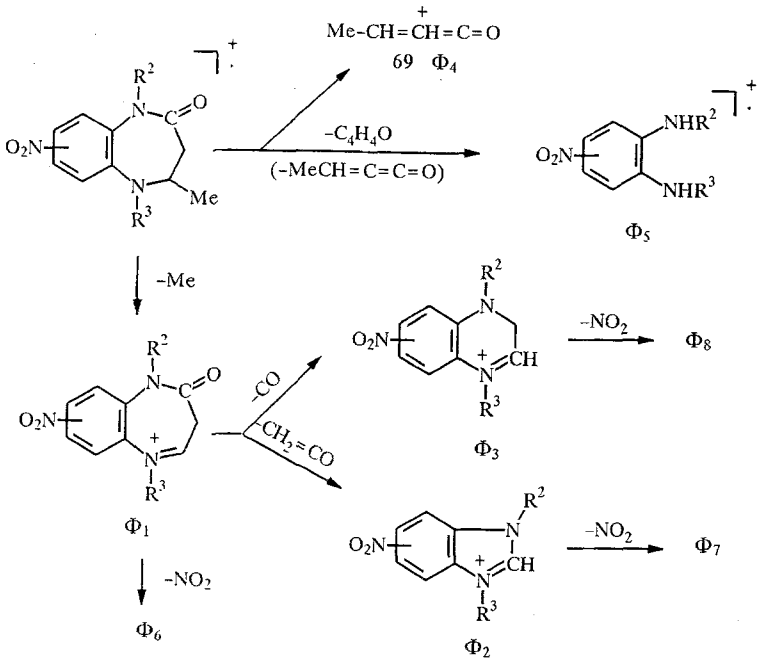
The IR spectra of V-XI showed absorption for the amide carbonyl group (amide-I) [7]. The absorption frequencies for the 1-alkyl compounds (V-VIII) were lower (1650-1660 $cm^{-1}$) than for the 5-alkyl isomers IX-XI (1670-1680 $cm^{-1}$). They also differ in their N–H stretching frequencies, those for 1-alkyl isomers being higher (3320-3330 $cm^{-1}$) than for the 5-alkyl isomers (3185-3200 $cm^{-1}$).

Differences of the same kind are also seen in the PMR spectra of the 1- and 5-alkyl compounds. For the former, the N-methyl proton signals are seen at lower field than the 5- isomers. In addition, the chemical shifts of the 5-NH group protons (V, VII, VIII) are found at higher field than the 1-NH groups in IX-XI. The slightly lower field shift for the 5-NH proton in VIII is most probably due to the steric arrangement of the 1-benzyl group. The molecular mechanics optimized structure shows that the phenyl ring substituent sits predominantly over the nitrobenzene part of the molecule. As a result, the N–H proton falls in the anisotropic cone of the benzyl benzene group.

Mass spectral analysis of V-XI (Tables 2 and 3) shows that the stability of the molecular ions of the 1-methyl substituted compounds is higher than the 5-methyl isomers. Fragmentation of all compounds under electron impact takes place similarly (Scheme 2) by two routes. The first of these involves initial loss of the 4-methyl group (ion $\Phi_1$), typical of 1,5-tetrahydrobenzodiazepines [8], followed by elimination of ketene ($\Phi_2$) or carbon monoxide ($\Phi_3$). The other fragmentation route involves fission of the heterocyclic ring at the C–H bonds concurrently with migration of one ($\Phi_4$) or two ($\Phi_5$) protons of the alkyl fragments on the arylamino groups. Bearing in mind that ions $\Phi_3$ and $\Phi_2$ lose a nitro group, the part of the full ion flow involved in the first route exceeds the overall ion fraction arising in the first stage of heterocycle decomposition by 4-8 times.

Loss of nitro at the first stage of molecular ion dissociation is extremely unlikely (ion $\Phi_6$) with nitronitrite rearrangement [9] being suppressed in all cases.

Scheme 2




Thus introduction of a nitro group, particularly in position 7 of the benzene ring of THB, significantly increases the reactivity of the amide nitrogen atom and makes selective alkylation possible.

## EXPERIMENTAL

UV Spectra were measured on a Specord UV-vis instrument using ethanol solvent. IR Spectra were taken on a 71 IR spectrometer for KBr tablets. PMR Spectra were recorded on a Hitachi R-22 instrument (90 MHz) using DMSO-$D_6$ (VII, VIII), deuterochloroform (X, XI), or a mixture (V, VI, IX) as solvents and HMDS as internal standard. Mass spectra were taken on MKh-1321, MKh-1321A, and LKB-2091 machines at an ionization energy of 70 eV and direct sample introduction into the ion source. Spectra of the same compounds on different instruments differed by not more than 15% in their relative peak intensities.

**1,4-Dimethyl-7-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one (V). A.** A mixture of I (4.4 g, 20 mmole), tetrabutylammonium bromide (TBAB, 1.6 g, 5 mmole), benzene (200 ml), and sodium hydroxide solution (50%, 30 ml) was treated with methyl iodide (2.5 ml, 40 mmole) with stirring and the reaction mixture refluxed for 4 h. The aqueous layer was separated and the benzene solution washed with water, dried, evaporated to dryness, and the residue recrystallized.

**B.** A mixture of I (4.4 g, 20 mmole), methyl iodide (2.5 ml, 40 mmole), powdered KOH (5.6 g, 100 mmole), and absolute acetone (100 ml) was stirred at reflux for 4 h. The product was filtered, the solvent evaporated, and the residue dissolved in chloroform and washed with water to neutral pH. The solvent was evaporated and the residue recrystallized.

**1,4-Dimethyl-8-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one (VII).** Obtained by method **B**. After evaporation of chloroform the residue was separated on a silica gel column collecting three fractions eluted with a mixture of chloroform and ethyl acetate (1:2). After evaporation of solvent the first fraction gave VII with $R_f$ 0.58 and the second and third gave a solid (1.2 g) containing substances with $R_f$ 0.58 and 0.66. The PMR spectra of the mixture gave two high field signals for the methyl group protons at 3.25 (1-$CH_3$) and 2.87 ppm (5-$CH_3$) with relative integrated intensities of 2:1.

**1-Benzyl-4-methyl-7-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one (VIII)** was obtained by method **A** from THB (2.2 g, 10 mmole), TBAB (0.5 g, 1.5 mmole), benzyl bromide (3.2 ml, 20 mmole), benzene (150 ml), and NaOH solution (50%, 15 ml).

**5-(ω-Bromopropionyl-1,4-dimethyl-7-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one (VI).** β-Propionyl chloride (6.9 g, 40 mmole) was added dropwise with stirring at 0°C to a solution of V (4.2 g, 18 mmole) and pyridine (3.8 ml) in dry chloroform (250 ml). The product was left for 2 h at room temperature and then refluxed for 8 h. The precipitate was filtered and the filtrate washed successively with water, HCl solution (10%), and KOH solution (10%). The organic layer was dried, evaporated, and the residue recrystallized.

**4,5-Dimethyl-7-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one(IX).** Sodium borohydride (6.5 g, 140 mmole) was added portionwise with stirring at −8°C to a solution of III (4.4 g, 20 mmole) in formic acid (90 ml). The mixture was held at room temperature for 3 h, poured onto ince, and neutralized to pH 7 with saturated sodium hydroxide solution. The precipitate was filtered and recrystallized.

**4,5-Dimethyl-8-nitro-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one (X)** was obtained similarly from IV but after holding at room temperature the mixture was held for 5 h at 50°C on a water bath.

**4-Methyl-7-nitro-5-(β,β,β-trifluoroethyl)-2,3,4,5-tetrahydro-(1H)-1,5-benzodiazepin-2-one (XI)** was obtained similarly from III (4.4 g, 20 mmole) but formic acid was exchanged for trifluoroacetic acid (90 ml). After washing, the precipitate was dissolved in ethanol and starting III (2.5 g) separated (mp 240-242°C) [4]. The filtrate was evaporated to dryness and the residue chromatographed on a silica gel column eluting XI with chloroform−ethyl acetate (1:1).

## REFERENCES


1. B. A. Puodzhyunaite, R. A. Yanchene, and A. S. Zaks, Khim.-farm. Zh., No. 9, 1077 (1988).
2. B. A. Puodzhyunaite, R. A. Yanchene, and Z. S. Stumbovichute, Khim. Geterotsikl. Soedin., No. 7, 957 (1988).
3. Z. F. Solomko, V. S. Tkachenko, A. N. Kost, V. A. Budylin, and V. L. Pikalov, Khim. Geterotsikl. Soedin., No. 4, 533 (1975).
4. B. A. Puodzhyunaite and Z. A. Talaikite, Khim. Geterotsikl. Soedin., No. 6, 833 (1974).
5. T. S. Chmilenko, Z. F. Solotko, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 4, 525 (1977).
6. M. J. Kamlet (ed.), Organic Electronic Spectral Data, Vol. 1, New York (1957), p. 86.
7. L. Bellamy, New IR Spectral Data for Complex Molecules [Russian translation], Mir, Moscow (1971), p. 197.
8. W.-G. Chai, G.-H. Wang, S. Jin, and Z. Ming. Org. Mass Spectrometry, **22**, No. 10, 660 (1987).
9. R. A. Khmel'nitskii and P. B. Terent'ev, Usp. Khim., **48**, No. 5, 854 (1979).