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SYNTHESIS OF 1,3-DIHYDRO-5(R)-7,8-ETHYLENEDIOXY-2H-1,4-BENZO-DIAZEPIN-2-ONES

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1,4-Diazepin-2-ones have been prepared from 1,4-benzodioxane for the first time.

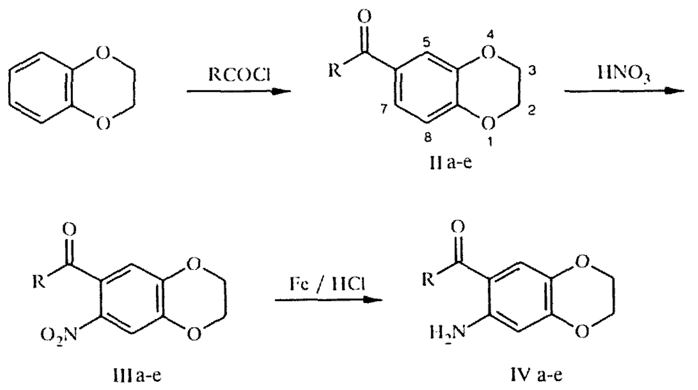
It is known that 1,4-benzodioxanes containing alkylaminoalkyl groups in different positions of the heterocycle show marked α-adrenoblocking, analgesic, and CNS depressant properties [1]. Moreover, an ethylenedioxy fragment in the 1,4-benzodioxan can play an important part in the occurrence of biological activity. The tranquillizing and sedative properties of benzodiazepinones are widely used in medicine [2].

With these factors in mind, the problem became that of synthesizing 1,4-diazepinones based on 1,4-benzodioxane, i.e., to combine both pharmacophoric fragments in one molecule and then to investigate how this affects the biological activity of the compounds obtained.

To resolve this problem, we have used one of the most widely employed methods for building the 1,4-benzodiazepinone ring, i.e., the intramolecular cyclization of 2-acylhaloacetamido-benzenes using ammonia [3].

A key feature of this synthetic scheme is preparation of ortho-acylanilines (precursors of the benzodiazepinones) which are usually synthesized from the corresponding ortho-nitroacyl-benzenes. As is known, the latter are difficult to prepare and are made in poor yields by nitration of acylbenzenes.

In this work we have used the specific properties of 6-substituted 1,4-benzodioxanes to form 6,7-disubstituted derivatives under electrophilic reaction conditions regardless of the nature of the substituent in position 6 of the starting 1,4-benzodioxane [1]. We have shown that 6-acyl substituted 1,4-benzodioxanes IIa-e are nitrated to give a good yield of almost exclusively 7-nitro derivatives IIIa-e, from which the needed 7-amino-6-acyl-1,4-benzodioxanes IVa-e can readily be prepared.



(1)

II—IV a R = CH_3; b R = C_2H_5; c R = Ph; d R = 2-ClC_6H_4; e R = 2-BrC_6H_4

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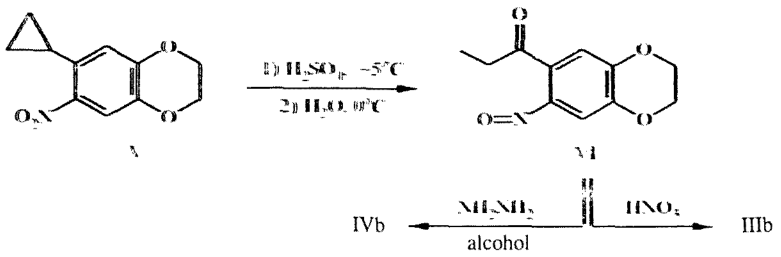
It was found that nitration of IIa-e, containing even such bulky substituents as 2-chloro-(IId) or 2-bromobenzoyl (IIe), gave the nitro derivative almost exclusively at position 7.

Of the synthesized compounds II-IV only 6-acetyl- and 6-propionyl-1,4-benzodioxanes (IIa, b) have been reported in the literature, even though electrophilic reactions of 1,4-benzodioxane and changes in their substituents have been widely studied [1].

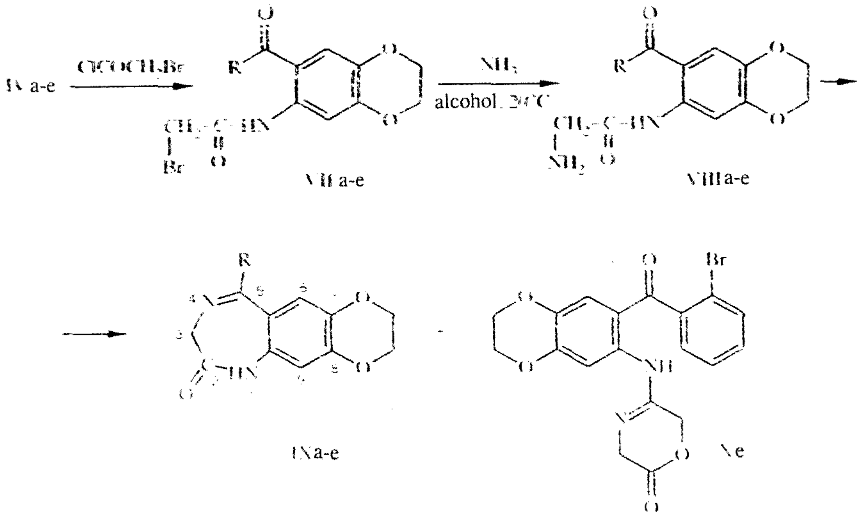
To add to the physicochemical data confirming the structures of the 7-nitro- and 7-amino-6-acyl-1,4-benzodioxanes (IIIa-e and IVa-e, see Table 1) we have studied an alternative synthesis of IIIb and IVb from 7-nitro-6-cyclopropyl-1,4-benzodioxane (V), the structure of which has been identified as the 6,7-disubstituted derivative [4].



(2)

1,4-Benzodiazepinones have basically been obtained by cyclization of the corresponding ortho-acylchloroacetanilide precursors using ammonia [3]. However, it is known that the conversion to the 1,4-benzodiazepinones occurs more efficiently if the reaction with ammonia is carried out on the bromo- rather than the chloro-acetyl ortho-acylanilines [5]. Hence reaction of 6-acyl-7-amino-1,4-benzodioxanes (IVa-e) with bromoacetyl chloride gave the bromo substituted acetanilides VIIa-e which were used as benzodiazepinone precursors.

In fact, treatment of VIIa-e with alcoholic ammonia solution gave good yields of the 7,8-ethylenedioxy-1,4-benzodiazepin-2-ones (XIa-3).



(3)

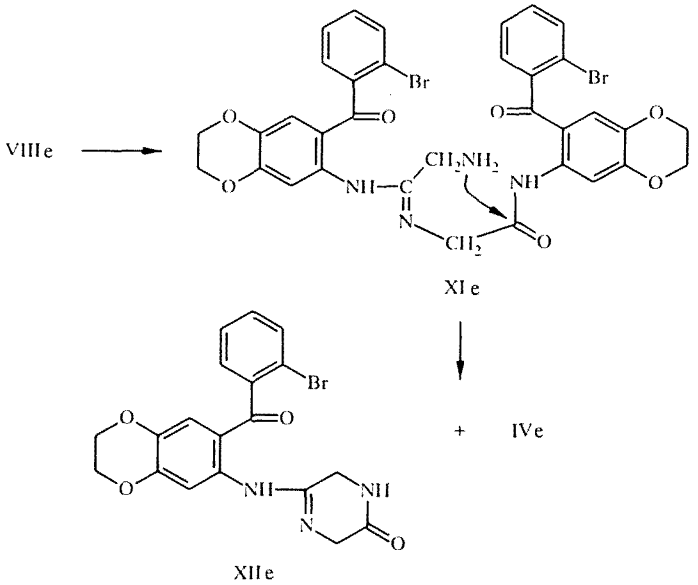
Only in the case of the 2-bromobenzoyl derivative VIIe was a mixture of the expected benzodiazepinone IXe and compounds VIIIe and Xe obtained.

The discovery in these reaction products of aminoacetanilide VIIIe is, in fact, an indirect confirmation that VIIIa-e are involved in the reaction of bromoacetanilides VIIa-e in alcoholic ammonia. This also shows that cyclization of the aminoanilides VIIIa-e to the corresponding diazepinones can be hindered by a steric effect of the substituent R. In fact, cyclization of the known aminoacetanilide VIIIe to diazepinone IXa needs many hours refluxing in alcohol. In addition, the direct reaction of bromo derivative VIIe with ammonia forms the side product Xe. Evidently, when encountering hindrance to intramolecular reaction involving the ortho-acyl substituent, the product of nucleophilic substitution (VIIIe) condenses at the amide carbonyl of bromoacetanilide VIIe further to form Xe. We do not rule out fission of part of the aminoacetanilide VIIIe under the reaction conditions to give amine IVe and ethyl gylcinate. Condensation of the latter at the amide carbonyl of bromoacetanilide VIIe may lead to a compound which can be also be converted to Xe.

TABLE 1. Constants and PMR Spectral Parameters for Compounds Synthesized

Compound	Empirical formula	Mp, °C (crystallization solvent)	Chemical shift, δ, ppm
IVa	$C_{10}H_{11}NO_3$	127...128 (C_2H_5OH)	2,41 (3H, s, CH_3); 4,21 (4H, s, OCH_2CH_2O); 5,89 (2H, br s, NH_2); 6,01 (1H, s, 8-H); 7,11 (1H, s, 5-H)
IVb	$C_{11}H_{13}NO_3$	92 (C_2H_5OH)	1,14 (3H, t, CH_3); 2,92 (2H, q, $\underline{CH_2}CH_3$); 4,24 (4H, s, OCH_2CH_2O); 5,06(2H, br s, NH_2); 6,12 (1H, s, 8-H); 7,29 (1H, s, 5-H)
IVc	$C_{15}H_{13}NO_3$	135 (C_2H_5OH)	4,21 (4H, м, OCH_2CH_2O); 5,93 (2H, br s, NH_2); 6,19 (1H, s, 8-H); 6,96 (1H, s, 5-H); 7,51 (5H, м, ArH)
IVd	$C_{15}H_{12}NClO_3$	161 (C_2H_5OH)	4,12 (4H, м, OCH_2CH_2O); 6,02 (1H, s, 8-H); 6,15 (1H, s, 5-H); 6,23 (2H, br s, NH_2); 7,23 (4H, м, ArH)
IVe	$C_{15}H_{12}NBrO_3$	147...148 (C_2H_5OH)	4,18 (4H, s, OCH_2CH_2O); 6,12 (1H, s, 8-H); 6,19 (2H, br s, NH_2); 6,75 (1H, s, 5-H); 7,34 (4H, м, ArH)
VIIa	$C_{12}H_{12}NBrO_4$	175 (C_2H_5OH)	2,31 (3H, s, CH_3); 3,78 (2H, s, CH_2Br); 4.07 (4H, s, OCH_2CH_2O); 7,19 (1H, s, 8-H); 7,92 (1H, s, 5-H); 11,90 (1H, br s, NH)
VIIb	$C_{13}H_{14}NBrO_4$	138 (C_2H_5OH)	1,12 (3H, t, CH_3); 2,93 (2H, q, $\underline{CH_2}CH_3$); 3,89 (2H, s, CH_2Br); 4,02 (4H, s, OCH_2CH_2O); 7,10 (1H, s, 8-H); 7,88 (1H, s, 5-H); 12,01 (1H, br s, NH)
VIIc	$C_{17}H_{14}NBrO_4$	155 (C_2H_5OH)	4,01 (2H, s, CH_2Br); 4,28 (4H, м, OCH_2CH_2O); 7,11 (1H, s, 8-H); 7,54 (5H, м, ArH); 8,24 (1H, s, 5-H); 11,72 (1H, br s, NH)
VIId	$C_{17}H_{13}NBrClO_4$	161...162 ($CHCl_3$)	3,95 (2H, s, CH_2Br); 4,18 (4H, м, OCH_2CH_2O); 6,90 (1H, s, 8-H); 7,26 (4H, м, ArH); 8,14 (1H, s, 5-H); 12,29 (1H, br s, NH)
VIIe	$C_{17}H_{13}NBr_2O_4$	167 ($CHCl_3$)	4,03 (2H, s, CH_2Br); 4,26 (4H, м, OCH_2CH_2O); 6,92 (1H, s, 8-H); 7,39 (4H, м, ArH); 8,38 (1H, s, 5-H); 11,04 (1H, br s, NH)
VIIIe	$C_{17}H_{15}N_2BrO_4$	191...192 (C_2H_5OH)	1,68 (2H, br s, NH_2); 3,57 (2H, s, $\underline{CH_2}NH_2$); 4,20 (2H, м,) and 4,34 (2H, м) $-OCH_2CH_2O$; 6,85 (1H, s, 8-H); 7,28 (1H, dd, 3'-H); 7,33 (1H, dt, 5'-H); 7,39 (1H, dt, 4'-H); 7,62 (1H, dd, 6'-H); 8,45 (1H, s, 5-H); 11,54 (1H, br s, NH)
IXa	$C_{12}H_{12}N_2O_3$	274...276 (C_2H_5OH)	2,21 (3H, s, CH_3); 4,07 (2H, s, CH_2); 4,32 (4H, s, OCH_2CH_2O); 6,61 (1H, s, 5-H); 7,04 (1H, s, 8-H); 8,58 (1H, br s, NH)
IXb	$C_{13}H_{14}N_2O_3$	220...221 (C_2H_5OH)	1,11 (3H, t, CH_3); 2,74 (2H, q, $\underline{CH_2}CH_3$); 4,04 (2H, s, CH_2CO); 4,19 (4H, s, OCH_2CH_2O); 6,51 (1H, s, 5-H); 6,93 (1H, s, 8-H); 8,72 (1H, br s, NH)
IXc	$C_{17}H_{14}N_2O_3$	278...280 ($CHCl_3$)	4,26 (2H, m) and 4,33 (2H, м) – OCH_2CH_2O; 4,30 (2H, br s, CH_2CO); 6,62 (1H, s, 5-H); 6,81 (1H, s, 8-H); 7,43 (5H, м, ArH); 7,92 (1H, br s, NH)
IXd	$C_{17}H_{13}N_2ClO_3$	299...300 (CH_3NO_2)	4,18 (2H, m), 4,28 (2H, м) and 4,34 (2H, s) – CH_2CO and OCH_2CH_2O; 6,54 (1H, s, 5-H); 6,56 (1H, s, 8-H); 7,39 (4H, m, ArH); 7,86 (1H, br s, NH)
IXe	$C_{17}H_{13}N_2BrO_3$	287...288 (CH_3NO_2)	4,22 (2H, m), 4,30 (2H, m) – OCH_2CH_2O; 4,35 (2H, s, CH_2CO); 6,55 (1H, s, 5-H); 6,60 (1H, s, 8-H); 7,27 (1H, dt, 5'-H); 7,39 (1H, dt, 4'-H); 7,45 (1H, dd, 3'-H); 7,55 (1H, dd, 6'-H); 8,09 (1H, br s, NH)
Xe	$C_{19}H_{15}N_2BrO_5$	272...274 ($PhNO_2$)	3,72 (4H, m, OCH_2CH_2O); 3,79 (2H, m, $\underline{CH_2}NH$); 4,06 (2H, br s, CH_2CO); 5,92 (1H, s, 8-H); 6,26 (1H, s, 5-H); 6,96 (4H, м, ArH); 9,76 (1H, s, NH)

Based on PMR data (Table 1), the primary side product might be assigned the structure XIIe (cf. lactone Xe) with two nitrogen atoms in the ring. Its formation can be readily explained by an analogous intramolecular reaction of the intermolecular condensation product XIe (see Scheme 4).



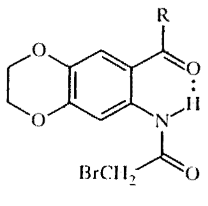
(4)

On the basis of mass spectral data, however, it was unambiguously found that there were two and not three nitrogen atoms in the molecule and that only one occurs in the newly formed heterocycle.

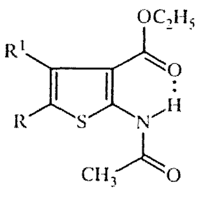
This PMR method of proving the structures of VIIa-e and IXa-e was found to be a suitable test for following the cyclization of the ortho-acylhaloacetanilides (VII) to be corresponding 1,4-benzodiazepinones.

It was found that the PMR spectral signals for the NH group protons in VIIa-e occurred to much lower field (11.04-12.29 ppm) than the analogous signals in the 1,4-benzodiazepinones IXa-e (7.81-8.72 ppm). Because these signals occur in a region not overlapped by others in these compounds, measurement of their PMR integrated intensities provided a method for monitoring the reaction of the haloacetanilide to the corresponding 1,4-benzodiazepinone.

The reason for such a difference in chemical shifts for the NH signals in these compounds ($\Delta\delta$ = 3.18-3.57 ppm) is evidently due to the ability of the amide hydrogen atoms of VIIa-e (in contrast to the atoms of IXa-e) to form intramolecular hydrogen bonds with the ortho-related carbonyl groups. As a consequence, they acquire a markedly acidic character (structure A).



A



B

(5)

Similar behavior has previously been reported for 2-acetamido-3-carbethoxythiophene (structure B, [6]). The amide proton PMR signals occur in virtually the same region (11.29-11.75 ppm) as those of VIIa-e.

EXPERIMENTAL

PMR Spectra were recorded on Varian XL-400 and Tesla BS-467 instruments (CCl_4, $CDCl_3$, CD_2Cl_2) using TMS internal standard. IR Spectra were measured on a UR-20 instrument for Vaseline mulls. Mass spectra were taken on an MK-

1321A instrument with ionization intensity 70 eV. PMR Spectral parameters and constants for the compounds synthesized are given in Table 1.

Elemental analytical data for C, H, and N in the compounds prepared agreed with those calculated.

6-Acetyl-1,4-benzodioxane (IIa) was obtained in 68% yield using the method reported in [7]. mp 85°C (mp [7] 84-85°C). Using the appropriate acyl halide the following were synthesized: 6-propionyl-1,4-benzodioxane (IIb), yield 66%, mp 39-40°C (mp [8] 38°C); 6-benzoyl-1,4-benzodioxane (IIc), $C_{15}H_{12}O_3$, yield 81%, mp. 61-62°C; 6-(2-chlorobenzoyl)-1,4-benzodioxane (IId), $C_{15}H_{11}O_3Cl$, yield 74%, mp 58-59°C; 6-(2-bromobenzoyl)-1,4-benzodioxane (IIe), $C_{15}H_{11}O_3Br$, yield 77%, mp 85°C.

6-Acetyl-7-nitro-1,4-benzodioxane (IIIa). HNO_3 (d 1.51, 3.8 g) was added dropwise with stirring to acetic anhydride (30 ml) at −30°C. 6-Acetyl-1,4-benzodioxane (IIa, 14.5 g, 0.08 mole) in acetic anhydride (70 ml) was added to this solution at the same temperature. The product was stirred for 2 h at −30 to −20°C and poured into water. The precipitated crystals were filtered, washed with water, and recrystallized from alcohol to give IIIa, $C_{10}H_9NO_5$, (14.1 g, 77%) with mp 121°C. PMR Spectrum: 2.41 (3H, s, CH_3); 4.28 (4H, s, OCH_2CH_2O); 6.81 (1H, s, 5-H); 7.59 ppm (1H, s, 8-H).

6-Propionyl-7-nitro-1,4-benzodioxane (IIIb). A. Obtained by nitration of 6-propionyl-1,4-benzodioxane (IIb) as described above to give 64% yield, $C_{11}H_{11}NO_5$, mp 106-107°C. PMR spectrum: 1.4 (3H, t, CH_3); 2.68 (2H, q, CH_2CH_3); 4.31 (4H, s, OCH_2CH_2O); 6.73 (1H, s, 5-H); 7.56 ppm (1H, s, 8-H).

B. 7-Nitroso-6-propionyl-1,4-benzodioxane (VI, for synthesis see [4]) (2.2 g, 0.01 mole) was added portionwise with stirring to nitric acid (d 1.4, 25 ml) at 20°C. The mixture was stirred for 15-20 min and poured into water (200 ml). The reaction product was extracted with either, the extract washed with Na_2CO_3 solution (1 N), and dried ($MgSO_4$). Solvent was evaporated and the residue was recrystallized from alcohol to give IIIb (1.85 g, 78%). A sample mixed with the sample prepared by method A gave no depression of melting point.

6-Benzoyl-7-nitro-1,4-benzodioxane (IIIc). 6-Benzoyl-1,4-benzodioxane (IIc, 21.6 g, 0.09 mole) was added to acetic acid (200 ml). The product was cooled to 0-5°C and a nitrating mixture prepared from H_2SO_4 (d 1.84, 25 ml) and HNO_3 (d 1.51, 5 ml) was added dropwise with stirring at the same temperature. The mixture was stirred for 1 h at 10-20°C and poured into water. The organic products were extracted with $CHCl_3$, the extract washed with 1 N Na_2CO_3, water, and then dried ($MgSO_4$). Solvent was evaporated and the residue recrystallized from alcohol to give IIIc ($C_{15}H_{11}NO_5$, 20.4 g, 80%) with mp 190°C.

By similar means: IId (27.4 g, 0.01 mole) gave **6-(2-chloro-benzoyl)-7-nitro-1,4-benzodioxane (IIId).** (27.5 g 86%), $C_{15}H_{10}NO_5Cl$, mp 158-159°C, PMR spectrum: 4.27, (4H, s, OCH_2CH_2O); 6.90 (1H, s, 5-H); 7.33 (4H, m, ArH); 7.52 ppm (1H, s, 8-H). IR spectrum: 1680 (C = O); 1376, 1530 cm^{-1} (NO_2).

IIe (31.9 g, 0.01 mole) gave **6-(2-bromobenzoyl)-7-nitro-1,4-benzodioxane (IIIe)** (25.8 g, 71%) $C_{15}H_{10}O_5Br$, mp 165°C, PMR spectrum: 4.31 (4H, s, OCH_2CH_2O); 7.09 (1H, s, 5-H), 7.42 (4H, m, ArH); 8.07 ppm (1H, s, 8-H).

7-Amino-6-acetyl-1,4-benzodioxane (IVa). Iron filings (17 g) were added to a suspension of IIIa (22.3 g, 0.1 mole) in ethanol (120 ml). The product was heated 78°C, conc. HCl (1 ml) was added and stirred at this temperature for 6 h with the regular addition of small amounts of conc. HCl (~0.5 ml). The mixture was filtered from iron filings, cooled, and the precipitate separated and recrystallized from alcohol to give amine IVa (14.3 g, 74%).

7-Amino-6-propionyl-1,4-benzodioxane (IVb). A. Obtained in 68% yield by reduction of 6-propionyl-7-nitro-1,4-benzodioxane (IIIb) as described above.

B. Hydrazine hydrate (99%, 1.5 g, 0.03 mole) was added slowly to a solution of 7-nitroso-6-propionyl-1,4-benzodioxane (VI, 4.4 g, 0.02 mole) in absolute alcohol (80 ml) at 50°C. The product was stirred at this temperature for 15 min, the solvent and excess hydrazine reagent distilled off, and the residue recrystallized from aqueous alcohol to give IVb (3.5 g, 84%). A sample mixed with that from method A did not show a depressed melting point.

7-Amino-6-benzoyl-1,4-benzodioxane (IVc) was obtained by reduction of nitro compound IIc as described above. 14.3 g (0.05 mole) gave 9.8 g (77%) of IVc.

Similarly IIId (9.6 g, 0.03 mole) gave **7-amino-6-(2-chlorobenzoyl)-1,4-benzodioxane (IVd)** (6.2 g, 71 g) and the nitrobenzodioxane IIIe (14.5g, 0.04 mole) gave **7-amino-6-(2-bromobenzoyl)-1,4-benzodioxane** (IVe, 9.6 g, 72%).

N-Bromoacetylation of 7-amino-6-acyl-1,4-benzodioxanes (IVa-e). Standard method. Bromoacetyl chloride (0.027 mole) and 3N NaOH solution (9 ml) were added in one portion to a stirred solution of the 7-amino-6-acyl-1,4-benzodioxane (IVa-e, 0.02 mole) in dioxane (80 ml) cooled in ice water. Stirring was continued at 10°C for 2 h and the product poured into water. The organic product was extracted with CH_2Cl_2, the extract washed with water, dried ($CaCl_2$), the solvent evaporated, and the residue recrystallized from a suitable solvent.

IVa (3.85 g) gave **7-bromoacetamide-6-acetyl-1,4-benzodioxane (VIIa, 3.5 g, 56%);**

IVb (4.15 g) gave the **6-propionyl analog** (VIIb, 3.8 g, 58%);

IVc (5.1 g) gave the 6-benzoyl analog (VIIc, 5.1 g, 68%);

IVd (5.8 g) gave the **6-(2-chlorobenzoyl) analog** (VIId, 5.2 g, 64%);

IVe (6.7 g) gave the **6-(2-bromobenzoyl) analog** (VIIe, 5.5 g, 61%);

Synthesis of 1,3-dihydro-5(R)-ethylenedioxy-2H-1,4-benzo-diazepin-2-ones (IXa-e). Standard method. The bromoacetanilide (VIIa-e, 0.01 mole) was added with stirring to methanol (150 ml) saturated with ammonia. The mixture was stirred for 28 h at 20°C, the solvent evaporated, and the residue recrystallized from a suitable solvent.

VIIIa (3.15 g) gave **1,3-dihydro-5-methyl-7,8-ethylenedioxy-2H-1,4-benzodiazepin-2-one (IXa).** Mass spectrum*: 232 (100, M), 217 (3), 204 (68), 203 (64), 176 (3), 148 (5), 119 (3), 89 (4), 68 (4), 52 (6).

Acetanilide VIIb (3.28 g) gave the **5-ethyl analog** (IXb, 1.25 g, 51%). Mass spectrum: 246 (98, M), 245 (100, M-1), 218 (48), 217 (52), 203 (7), 190 (23), 162 (12), 149 (5), 133 (5), 68 (9), 52 (7).

Bromoacetanilide VIIc (3.8 g) gave the **5-phenyl analog** (IXc, 1.83 g, 62%). Mass spectrum: 294 (100, M), 293 (55, M-1), 266 (82), 265 (41), 238 (4), 154 (4), 133 (5) 120 (4), 91 (3), 77 (5), 68 (3).

Compound VIId (4.1 g) gave the **5-(2-chlorophenyl) analog** (IXd, 1.6 g, 48%). Mass spectrum: 328 (100, M**), 327 (48, M-1)**, 300 (69)**, 299 (6)**, 293 (68), 237 (16), 209 (10), 153 (15), 139 (14), 113 (17), 83 (38).

Acetanilide VIIe (4.6 g) gave the **5-(2-bromophenyl) analog** (IXe, 1.2 g, 32%), **7-aminoacetamido-6-(2-bromobenzoyl)-1,4-benzodioxane (VIIIe, 0.55 g, 14%)**, and **6-(3,6-dihydro-2H-1,4-oxazinon-2-yl-5-amino)-7-(2-bromobenzoyl)-1,4-benzodioxane (Xe, 1.17 g, 27%).** Mass spectrum: 430 (20, M)**, 402 (14)** 359 (6)**, 346 (35)**, 333 (100)**, 305 (10), 253 (34), 197 (16), 183 (38)**, 94 (27), 80 (26)**.

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*Values of *m/z* (relative intensity %).

**Mass ions stated for ^{35}Cl and ^{79}Br isotopes.