SYNTHESIS OF 7-ALKYL- AND 7-PHENYLTETRAHYDRO-7H-ISOQUINOLINO[2,1-d][1,4]-BENZDIAZEPIN-6-ONES. III

Ch. Ivanov and M. Levi

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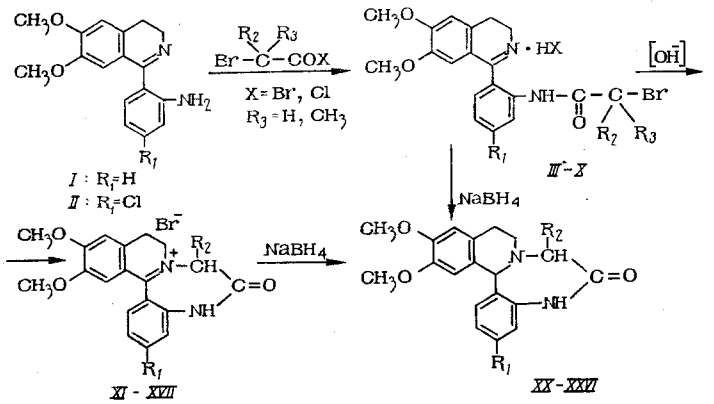
The present investigation is a continuation of a previous paper which described the preparation of tetrahydroisoquinolinobenzdiazepines [1]. In order to study more closely the pharmacology of these compounds, we have synthesized some 7-alkyl and 7-phenyltetrahydroisoquinolinobenzdiazepines by the following route:



The starting materials I and II (1-(2'-aminophenyl)- and 1-(2'-amino- and 4'-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline) were obtained from the corresponding nitro amides by the Bischler–Napieralski reaction, followed by reduction of the nitro group with stannous chloride in hydrochloric acid.

The reaction of α-bromoacetyl bromide with substituted 1-(o-aminophenyl)-3,4-dihydroisoquinolines has been described in the literature [2]. We have applied this reaction to the bromides of higher α-halogenated aliphatic acids in order to prepare 7-alkyl and 7-phenyl-substituted tetrahydroisoquinolinobenzdiazepines (XX-XXVI) for the study of the effects of normal and branched chain alkyl groups on pharmacological activity.

1-[2'-(α-Bromoacetylamino)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochlorides or hydrobromides (Table 1, III-X) were prepared by reaction of I or II with the corresponding α-halogenated aliphatic acid chlorides or bromides.

The following acid chlorides and bromides were employed: α-bromoacetyl bromide, α-bromopropionyl bromide, α-bromobutyryl bromide, α-bromoisobutyryl bromide, α-bromoisovaleryl bromide, α-bromocaproyl bromide, and α-bromophenylacetyl chloride.

The conversion of III-X into the 7-alkyl- and 7-phenyl-12,13-dimethoxy-6,7,9,10-tetrahydro-6-oxo-5H-isoquinolino[2,1-d][1,4]benzdiazepinium bromides (Table 2, XI-XVII) was accomplished by basifying an aqueous solution of III-X with a 2 N sodium hydroxide solution of pH 7.0-7.5 and boiling the free base which separated with 80% aqueous alcohol.

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TABLE 1. 1-[2'-(α-Bromoacylamino)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrobromides and Hydrochlorides

Compound*	R_1	R_2	R_3	Yield, %	mp, °C	Found, %				Molecular formula	Calc., %			
						C	H	Br	N		C	H	Br	N
III	H	H	H	70	204—6	47,40	4,37	33,40	5,55	$C_{19}H_{13}BrN_2O_3$	47,13	4,16	33,00	5,78
IV	H	CH_3	H	70	213—16	48,30	4,70	32,3	5,25	$C_{20}H_{21}BrN_2O_3 \cdot HBr$	48,21	4,44	32,07	5,62
V	H	C_2H_5	H	77	196—8	49,40	4,89	31,45	5,30	$C_{21}H_{23}BrN_2O_3 \cdot HBr$	49,24	4,64	31,20	5,46
VI	H	$CH(CH_3)_2$	H	53	195,5—6,5	50,70	5,35	30,30	5,41	$C_{22}H_{25}BrN_2O_3 \cdot HBr$	50,21	4,97	30,36	5,32
VII	H	$(CH_2)_3CH_3$	H	50	133—5	51,30	5,40	29,50	5,00	$C_{23}H_{27}BrN_2O_3 \cdot HBr$	51,11	5,21	29,39	5,18
VIII	H	CH_3	CH_3	74	206—9	49,0	4,87	31,50	5,53	$C_{21}H_{23}BrN_2O_3 \cdot HBr$	49,24	4,64	31,20	5,46
IX	H	C_6H_5	H	57	205—7,5	56,24	4,74	21,45†	5,24	$C_{25}H_{23}BrN_2O_3 \cdot HCl$	56,46	4,54	21,69†	5,26
X	Cl	H	H	50	203—4	44,20	3,76	37,76†	5,35	$C_{19}H_{18}BrClN_2O_3 \cdot HBr$	44,20	3,67	37,65†	5,40

*Compounds III and IV were recrystallized from aqueous methanol, V to VII from ethanol–ether, and VIII-X from methanol.

†Br + Cl.

TABLE 2. 7-Alkyl- and 7-Phenyl-12,13-dimethoxy-6,7,9,10-tetrahydro-6-oxo-5H-isoquinolino[2,1-d][1,4]benzdiazepinium Bromides

Compound*	R_1	R_2	Yield, %	mp, °C	Found, %				Molecular formula	Calc., %			
					C	H	Br	N		C	H	Br	N
XI	H	H	70	203	53,70	4,35	19,50	6,60	$C_{19}H_{19}BrN_2O_3$	54	4,71	19,80	6,49
XII	Cl	H	72	254	51,70	4,40	—	6,28	$C_{19}H_{18}BrClN_2O_3$	52,11	4,14	—	6,39
XIII	H	CH_3	60	192	57,25	5,60	19,20	7,00	$C_{20}H_{21}BrN_2O_3$	57,55	5,35	19,50	6,71
XIV	H	C_2H_5	60	213	59	5,80	18,24	6,44	$C_{21}H_{23}BrN_2O_3$	58,47	5,37	18,52	6,49
XV	H	$CH(CH_3)_2$	56	204	60,20	6,22	18,27	5,90	$C_{22}H_{25}BrN_2O_3$	59,57	5,67	18,02	6,31
XVI	H	$(CH_2)_3CH_3$	55	196	59,90	6,43	16,83	5,90	$C_{23}H_{27}BrN_2O_3$	60,13	5,92	17,40	6,14
XVII	H	C_6H_5	67	178—180	62,60	4,92	16,83	5,80	$C_{25}H_{23}BrN_2O_3$	62,64	4,83	16,66	5,84

*Compounds XI and XIII were crystallized from methanol, XII from aqueous methanol, XIV from ethanol–methanol, XV from a mixture of absolute ethanol and methanol, XVI and XVII from a mixture of absolute ethanol and ether.

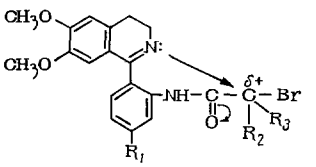
TABLE 3. 7-Alkyl and 7-Phenyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]benzdiazepin-6-ones

Compound	R_1	R_2	Yield, %*	mp, °C	Found, %			Molecular formula	Calc., %		
					C	H	N		C	H	N
XX	H	H	76 (62)	221—3	69,75	6,70	8,65	$C_{19}H_{20}N_2O_3$	70,10	6,40	8,16
XXI	Cl	H	70 (40)	220,5—221,5	60,60	5,59	7,45	$C_{19}H_{19}ClN_2O_3$	60,81	5,33	7,80
XXII	H	CH_3	70	226—9	70,85	6,85	8,65	$C_{20}H_{22}N_2O_3$	71,00	6,50	8,28
XXIII	H	C_2H_5	60	107—9	71,30	6,95	7,80	$C_{21}H_{24}N_2O_3$	71,57	6,86	7,94
XXIV	H	$CH(CH_3)_2$	46	189—190	72,00	7,35	7,35	$C_{22}H_{26}N_2O_3$	72,10	7,11	7,64
XXV	H	$(CH_2)_3CH_3$	20	147—150	72,60	7,84	7,20	$C_{23}H_{28}N_2O_3$	72,60	7,40	7,36
XXVI	H	C_6H_5	52	200—2	74,50	6,08	6,70	$C_{25}H_{24}N_2O_3$	74,98	6,03	6,99

*Yields are given for method A (method B in parentheses).

The structure of the compounds obtained is in good agreement with the results of elemental analyses and the IR and NMR spectra. Thus, the IR spectra of the quaternary salts XI-XVII exhibit absorption bands at 1710 cm^{-1} corresponding to carbonyl group stretching vibrations. The higher frequency of the absorption as compared with the bands of the starting materials III-X (1690 cm^{-1}) is probably the result of electronic factors. The band at 3300-3400 cm^{-1} (NH stretching vibration) is broad, as is usual in quaternary salts.

In the reaction under consideration, the relative rates of formation of the quaternary salts are dependent on the polarity of the medium and on the nature of the substituent on the α-carbon atom.



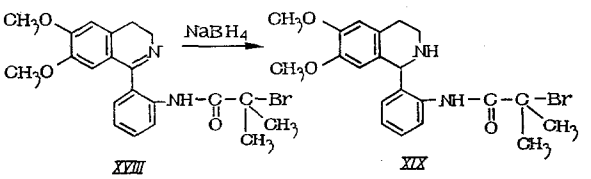
We have shown that the yields of the quaternary salts XI-XVII decrease as the alkyl chain is branched and lengthened (see Table 2). This is due to an increase in the electron density at the α-carbon atom consequent upon the positive inductive effect of the alkyl groups, as well as on steric factors hindering attack of the tertiary nitrogen atom in the isoquinoline ring.

No quaternary salt was formed when two alkyl groups were present on the α-carbon atom of VIII. Instead, 1-[2'-(bromoisobutyrylamino)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline was isolated as the free base (XVIII). This compound was totally insoluble in water, and it gave no reaction for halide ion.

The NMR spectrum of XVIII exhibited a doublet at low field, δ = 8.4 ppm, J_0 = 9 Hz, assigned to the ortho proton (at C_3) in the phenyl ring. It may be assumed that the shift of the signal to low field is due to deshielding of the ortho proton as a result of the spatial orientation of the carbonyl group, the remaining aromatic protons of the phenyl ring appearing as a multiplet at δ = 6.8-7.2 ppm.

No doublet signal due to the ortho proton is observed in the NMR spectra of XI-XVII, and the signals due to the aromatic protons appear as a multiplet. It appears that the carbonyl group of the benzdiazepinium ring is oriented in such a manner that it does not cause deshielding of the ortho proton.

Further proof of the structure of XVII was obtained by reduction with sodium borohydride in aqueous alcohol:



Instead of the expected closure of the benzdiazepine ring, there was formed 1-[2'-(α-bromoisobutyrylamino)phenyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIX). The NMR spectrum of this compound exhibited a singlet at high field (δ = 2.2 ppm) characteristic of the imino group (NH), differing from the amide NH (δ = 10.15 ppm). The doublet at δ = 8.15 ppm, J_0 = 8 Hz, was assigned to the ortho proton. The shift of the signal to low field was due to the same factors as in the spectrum of XVIII.

These facts show that replacement of the two hydrogen atoms on the α-carbon atom by methyl groups results in attack on the tertiary nitrogen atom being subject to considerable steric hindrance, and virtually no formation of the benzdiazepine ring takes place despite the fact that the reaction is carried out in a strongly polar solvent (80% ethanol).

The polarity of the medium is very important in determining the rate of cyclization. We have examined solvents with enhanced solvating abilities such as dioxane, anhydrous ethanol, anhydrous acetone, aqueous ethanol, and aqueous acetone. The greatest yields (56-70%) were obtained by using 80% aqueous ethanol, the yields in less polar solvents such as dioxane being much lower. Reduction of XI-XVII with sodium borohydride gave 7-alkyl- and 7-phenyl-12,13-dimethoxy-5,9,10,14b-tetrahydroisoquinolino-7H-[2,1-d][1,4]benzdiazepin-6-ones (Table 3) (XX-XXVI).

The structures of these compounds were confirmed by their elemental analyses and by their IR and NMR spectra.

The IR spectra of XX-XXVI exhibit bands at 1690 cm^{-1}, characteristic of carbonyl group stretching in secondary amides [3], indicating the absence of strain in the benzdiazepine ring.

Closure of the benzdiazepine ring is also confirmed by the absence in the NMR spectrum of XX-XXVI of a singlet at δ = 2.2 ppm due to the imino group which is characteristic of the tetrahydroisoquinoline ring.

On the basis of the NMR spectral data, some conclusions may be drawn as to the relative effects of the substituents in the 7-position of the benzdiazepine ring on the position of the amide proton signal. In the case of the unsubstituted benzdiazepinones, or in the presence of substituents with short aliphatic chains (XX-XXIV), a shift of the amide proton signal to lower field (δ = 9-10.1 ppm) takes place. The presence of long chain substituents (XXV) results in a shift to higher field (δ = 8.3 ppm), owing to screening of the amide proton resulting from the stronger electron-donating properties of the substitutent. In the spectrum of XXVI also, there is observed a shift of the signal to lower field (δ = 8.3 ppm), probably as a result of screening of the amide proton caused by steric factors.

Compounds XX and XXI were also obtained by reduction of III and X with sodium borohydride, bypassing the preparation of the quaternary salts. The products obtained were identical with those obtained via the quaternary salts. An attempt to convert directly those hydrobromides substituted on the α-carbon atom (1-[2'-(α-bromoacylamino)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinolines) into the corresponding benzdiazepinones was unsuccessful.

All the tetrahydroisoquinolinobenzdiazepinones were obtained as the racemates.

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrophotometer (Nujol mull or chloroform solution). The NMR spectra were recorded on a "Jeol" instrument, having a working frequency of 60 MHz, in deuterated dimethyl sulfoxide (DMSO-d_6) and deuterochloroform ($CDCl_3$), using tetramethylsilane as internal standard. The designations of the NMR spectra are as follows: s (singlet); d (doublet); m (multiplet). The purity of the compounds was established by thin-layer chromatography on silica gel using the solvent system benzene – methanol.

N-[β-(3',4'-Dimethoxyphenyl)ethyl]-2-nitro-4-chlorobenzamide. Homoveratrylamine (10 g) was dissolved in 50 ml of dry benzene, and a solution of 26 g of 2-nitro-4-chlorobenzoyl chloride in 50 ml of dry benzene was added dropwise during 1 h at 5°. To the resulting mixture was added during 1 h 13.2 g of sodium hydroxide in 132 ml of water at a temperature of 8-10°. The reaction was brought to completion by stirring at 30° for 4 h. The resulting precipitate was filtered off, washed with water and 5% hydrochloric acid, then again with water, to give 18.7 g of crude product, which was crystallized from ethanol. Yield of purified product 17 g (86%), pale-yellow needles, m.p. 112-114°.

1-(2'-nitro-4'-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. N-[β-(3',4'-Dimethoxyphenyl)-ethyl]-2-nitro-4-chlorobenzamide (10 g) was dissolved in 80 ml of dry toluene, heated to 90°, and treated dropwise during $1\frac{1}{2}$ h with 30 ml of phosphoryl chloride. The mixture was boiled for 7 h, then cooled, when a pale yellow oil separated. The toluene layer was separated, and the oil was dissolved in 150 ml of hot water. The organic layer was washed with a small amount of water, which was added to the solution first obtained. Basification with ammonia precipitated a pale yellow solid, which was extracted with chloroform. The organic layer was separated, washed with water, dried over sodium sulfate, and the solvent distilled

off, giving 0.1 g of dry residue, which was crystallized from ethanol. Yield of purified product 8.9 g (80%), yellow needles, m.p. 136°. Found, %: C 58.22; H 4.89; Cl 10.20; N 8.30. $C_{17}H_{15}ClN_2O_4$. Calculated, %: C 58.68; H 4.36; Cl 10.20; N 8.07.

1-(2'-Amino-4'-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (II). 1-(2'-Nitro-4'-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (5 g) was dissolved in a mixture of 52 ml of ethanol and 52 ml of concentrated hydrochloric acid. To the solution was added portionwise at room temperature 27 g of crystalline stannous chloride, and the mixture was then heated at the boil for 4 h. After cooling, the mixture was acidified with a solution of 60 g of sodium hydroxide in 240 ml of water. The resulting oily mixture was extracted with chloroform. The organic layer was separated, washed with water, and dried over sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethanol. Yield 3 g (65%), m.p. 136-137°. Found, %: C 64.00; H 5.71; Cl 11.04; N 9.00. $C_{17}H_{17}ClN_2O_2$. Calculated, %: C 64.42; H 5.40; Cl 11.19; N 8.78. Compound I was obtained by the method given in our earlier paper [1].

1-2'-(α-Bromoacetylamino)phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrobromide (III). Compound I (1.5 g) was dissolved in 20 ml of dry chloroform and 20 ml of dry ether, and a solution of 0.5 ml of α-bromoacetyl bromide in 5 ml of dry ether was added dropwise at 0-5°. The mixture was stirred at this temperature for 4 h. The precipitate was filtered off and recrystallized from aqueous methanol to give 1.7 g of yellow needles. IR spectrum (Nujol mull), cm^{-1}: 3180 (NH), 1690 (C=O).

Compounds IV, VII, VIII, and IX were obtained similarly from I and the corresponding α-bromoacid bromide.

1-2'-(α-Bromobutyrylamino)phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrobromide (V). Compound I (1 g) was dissolved in 30 ml of dry benzene, and 0.5 g of α-bromobutyryl bromide in 4 ml of dry benzene was added dropwise at 10°. The mixture was boiled for 5 h. After cooling, the bright yellow needles which separated were filtered off, washed with benzene, and crystallized from a mixture of alcohol and ether to give 1.4 g of V. IR spectrum (Nujol mull), cm^{-1}: 3180 (NH), 1690 (C=O).

Compounds VI and X were obtained similarly from I or II and the appropriate α-bromoacid bromide.

dl-7-Isopropyl-12,13-dimethoxy-6,7,9,10-tetrahydro-6-oxo-5H-isoquinolino-[2,1-d][1,4]benzdiazepinium Bromide (XV). Compound VI (4.9 g) was dissolved in 240 ml of water, and the solution basifed with a 2 N solution of sodium hydroxide to pH 7.5. The bright yellow precipitate was filtered off and dried. The aqueous solution was extracted with chloroform, the organic layer separated, dried over sodium sulfate, and the solvent removed. The residue was added to the precipitate, dissolved in 32 ml of 80% ethanol, and the mixture boiled for 8-10 h. Part of the ethanol was distilled off, and the solution cooled, whereupon bright yellow crystals separated. After recrystallization from a mixture of absolute alcohol and methanol, 2.3 g of XV was obtained. IR spectrum (Nujol mull), cm^{-1}: 1715 (C=O), 3400 (NH).

Compounds XII, XIII, XIV, and XVI were obtained similarly.

12,13-Dimethoxy-6,7,9,10-tetrahydro-6-oxo-5H-isoquinolino[2,1-d][1,4]-benzdiazepinium Bromide (XI). Compound III (2 g) was dissolved in a mixture of 85 ml of water and 25 ml of ethanol at room temperature, basified with 2 N sodium hydroxide to pH 7.3, and evaporated to dryness in vacuo. The residue was dissolved in 40 ml of 80% ethanol and boiled for 2 h. Yellow crystals separated on cooling, and these were filtered off and recrystallized from methanol to give 1.1 g of XI. IR spectrum (Nujol mull), cm^{-1}: 1700 (C=O), 3350 (NH).

Compound XVII was obtained similarly.

1-[2'-(α-Bromoisobutyrylamino)phenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (XVIII). Compound VIII (3 g) was dissolved in a mixture of 120 ml of water and 10 ml of ethanol with gentle warming. The mixture was cooled and neutralized with 5.2 ml of 2 N sodium hydroxide to pH 7.0. The precipitate which separated was filtered off, dissolved in 50 ml of 50% ethanol, and boiled for 10 h. The bright yellow crystals which separated on cooling were filtered off, dried and recrystallized from aqueous acetone to give 2 g (80%) of XVIII, m.p. 121-123°. Found, %: C58.15; H 5.77; Br 18.09; N 6.37. $C_{21}H_{23}BrN_2O_3$. Calculated, %: C 58.47; H 5.37; Br 18.52; N 6.49: IR spectrum (in chloroform), cm^{-1}: 3080 (NH), 1680 (C=O). NMR spectrum (in $CDCl_3$): δ, ppm: 2 (6H, s, 2 CH_3); 2.5-2.9 (2H, m, CH_2–Ar); 3.7-4.2 (2H, m, $-CH_2-N=$); 3.75 (3H, s, CH_3O); 3.95 (3H, s, CH_3O); 6.8 (2H at C_5 and C_8, s, broad); 7-7.6 (3H, m, aromatic protons); 8.4 (1H at C_3 of the benzene ring, d, J_0=9 Hz); 11.2 (1H, s, amide NH).

dl-1-[2'-(α-Bromoisobutyrylamino)phenyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIX). To a solution of 1.2 g of sodium borohydride in 20 ml of a mixture of alcohol and water (2 : 1) was added in

portions at room temperature 2 g of XVIII in 60 ml of a mixture of ethanol and water (2 : 1), and the mixture was stirred for 3 h. When the reaction was complete the mixture became colorless. Hydrochloric acid (10%; 25 ml) was added, then basified with ammonia. The amorphous white precipitate which formed was filtered off and washed with water. Recrystallization from ethanol gave 0.9 g of colorless crystals, m.p. 110-112.5°. Found, %: Br 17.90; N 6.14; $C_{21}H_{25}BrN_2O_3$. Calculated, %: Br 18.43; N 6.46. IR spectrum (in chloroform), cm^{-1}: 3080, 1680. NMR spectrum (in $CDCl_3$), δ, ppm: 1.65 (3H, s, CH_3); 1.9 (3H, s, CH_3); 2.2 (1H, s, imino NH); 2.5-3.2 (4H, m, $-CH_2-N-$); 3.55 (3H, s, CH_3O); 3.8 (3H, s, CH_3O); 5.05 (1H on C_1, s); 6.25 (1H on C_8, s); 6.6 (1H on C_5, s); 10.15 (1H, s, amide NH); 8.15 (1H on C_3 of benzene ring, d, J_0=8 Hz); 6.95-7.5 (3H, m, aromatic protons).

dl-12,13-Dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]-benzdiazepin-6-one (XX). A. To a solution of 1.6 g of sodium borohydride in a mixture of 40 ml of ethanol and 50 ml of water was added during 20 min 3.2 g of XI, and the mixture was stirred at room temperature for 3 h. When the reaction was complete, a colorless crystalline mass separated, which redissolved on adding 55 ml of 10% hydrochloric acid. Basification with 10% sodium hydroxide solution to pH 8.0 precipitated a colorless crystalline solid. Recrystallization from ethanol gave 1.9 g of XX, m.p. 221-223°. IR spectrum (in chloroform), cm^{-1}: 3400 (NH), 1690 (C=O), 1595, 1480, 1340. NMR spectrum (in $CDCl_3$), δ, ppm; 2.2-3.2 (4H, m, $-CH_2-CH_2$); 2.9 (1H, d) and 3.5 (1H, d), J_{AB}=10 Hz ($-CH_2-C=O$); 3.65 (3H, s) and 3.95 (3H, s), $2CH_3O$; 5.3 (1H on C_{14b}, s); 6.3 (1H on C_{14}, s); 6.68 (1H on C_{11}, s); 6.6-7.5 (4H, m, aromatic protons in the benzene ring). B. To a solution of 0.65 g of sodium borohydride in 24 ml of a mixture of ethanol and water was added 1.2 g of III in portions. After addition of each portion the mixture became colorless. The mixture was stirred at room temperature for 4 h, when a white precipitate separated. Acidification with 8 ml of 20% hydrochloric acid gave a clear solution which was basified with ammonia to pH 8.0. The colorless precipitate which resulted (0.8 g) was filtered off and washed with water. Recrystallization from ethanol gave 0.48 g of XX as colorless needles, m.p. 221-223°.

The purity of the products obtained by the two methods was established by thin-layer chromatography, and confirmed by elemental analyses and IR and NMR spectra.

dl-3-Chloro-12,13-dimethoxy-5,9,10-14b-tetrahydro-7H-isoquinolino[2,1-d] [1,4]-benzdiazepin-6-one (XXI). This was obtained similarly to XX by methods A and B. IR spectrum (in chloroform), cm^{-1}: 1690 (C=O), 3400 (NH). NMR spectrum (in $CDCl_3$), δ, ppm; 2.4-3.5 (6H, m, CH_2-CH_2-N- and $CH_2-C=O$); 3.65 (3H, s) and 3.85 (3H, s) (2 CH_3O); 5.3 (1H at C_{14b}, s); 6.3 (1H at C_{14}, s); 6.7 (1H at C_{11}), s; 6.5-7.3 (3H, m, aromatic protons); 10 (1H, s, amide NH).

dl-7-Methyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]-benzdiazepin-6-one (XXII). Obtained similarly to XX by reduction of XIII with sodium borohydride. Crystallized from a mixture of benzene and methanol. NMR spectrum (in $CDCl_3$), δ, ppm: 1.2 (3H, s, CH_3); 3.6 (3H, s, CH_3O); 3.8 (3H, s, CH_3O); 5.15 (1H at C_{14b}, s); 6.4 (1H on C_{14}), 6.82 (1H on C_{11}, s); 6.45-7.5 (4H, m, aromatic protons); 9.1 (1H, s, NH).

dl-7-Ethyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]benzdiazepin-6-one (XXIII). To a solution of 0.9 g of sodium borohydride in a mixture of 34 ml of ethanol and 17 ml of water was added in portions 1.5 g of XIV at room temperature. The mixture was stirred for 2 h. The precipitate was filtered off, and the filtrate diluted with 50 ml of water. The precipitated solid was filtered off and washed with water to give 0.65 g of crude product. After removal of the alcohol from the aqueous–alcoholic filtrate under reduced pressure, the aqueous solution was extracted with chloroform. The organic layer was separated, dried over sodium sulfate and evaporated to dryness, giving 0.5 g of dry residue. Both products were combined and recrystallized from benzene to give 0.7 g of colorless crystals. IR spectrum (in chloroform), cm^{-1}: 2690 (C=O), 3400 (NH). NMR spectrum (in $CDCl_3$), δ, ppm: 0.6-1.2 (3H, triplet); 2.35-3.3 (6H, m, CH_2-CH_2-N and CH_2 of the ethyl group); 3.15 (3H, s) and 3.35 (3H, s), $2CH_3O$; 5.3 (1H on $C_{12}b$, s); 6.3 (1H on C_{14}, s); 6.7 (1H on C_{11}, s); 6.75-7.6 (4H, m, aromatic protons in the benzene ring); 9.1 (1H, s, amide NH)

dl-7-Isopropyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]benzdiazepin-6-one (XXIV). To a solution of 0.65 g of sodium borohydride in 12 ml of ethanol and 12 ml of water was added in portions at room temperature 1.2 g of XV. The mixture was stirred for 3 h. Towards the end of the reaction a colorless precipitate separated. Addition of 10% hydrochloric acid caused the precipitate to dissolve, followed by slow separation of XXIV hydrochloride. The hydrochloride was filtered off, dissolved in a mixture of 20 ml of water and 10 ml of ethanol, and the solution basified with ammonia to pH 8.0. The precipitate was filtered off, dried, and recrystallized from ethanol to give 0.4 g of XXIV as bright yellow crystals. IR spectrum (in chloroform), cm^{-1}: 1690 (C=O), 3400 (NH). NMR spectrum ($CDCl_3$), δ, ppm: 0.8 (6H, s,

$2CH_3$); 2.3-3.4 (6H, m); 3.6 (3H, s) and 3.85 (3H, s), 2 CH_3O; 5.15 (1H on C_{14b}, s); 6.25 (1H on C_{14}, s); 6.6 (1H on C_{11}, s); 6.8-7.5 (4H, m, aromatic protons in the benzene ring); 10.1 (1H, s, amide NH).

dl-7-Butyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]benzdiazepin-6-one (XXV). To a solution of 0.77 g of sodium borohydride in 20 ml of a mixture of ethanol and water (1:1) was added in portions 1.35 g of XVI. The mixture was stirred for 1 h at room temperature, then acidified with dilute hydrochloric acid. The precipitate was filtered off and dissolved in 20 ml of a mixture of ethanol and water. Basification precipitated a white solid. The acid filtrate was basified with ammonia to pH 8.0 and diluted with 10 ml of water, whereupon a colorless solid separated. Both products were combined and recrystallized from benzene to give 0.2 g of XXV. IR spectrum (in chloroform), cm^{-1}: 1690 (C=0), 3400 (NH). NMR spectrum (in $CDCl_3$), δ, ppm: 0.72-0.96 (3H, triplet, CH_3); 1-1.62 (6H, m, $CH_2-CH_2-CH_2-$); 1.68-3.2 (5H, m, CH_2-CH_2 and $-CH$); 3.56 (3H, s),and 3.72 (3H, s) 2 CH_3O; 5.08 (1H on C_{14b}, s); 6.08 (1H on C_{14}, s); 6.52 (1H on C_{11}, s, broad);6.6-7.4 (4H, m, aromatic protons in the benzene ring); 8.32 (1H, s, amide NH).

dl-7-Phenyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-7H-isoquinolino[2,1-d][1,4]benzdiazepin-6-one (XXVI). To a solution of 1.2 g of sodium borohydride in 15 ml of a mixture of ethanol and water (1:1) was added dropwise 1.85 g of XVII in 35 ml of a mixture of ethanol and water (1:1), and the mixture was stirred at room temperature for 3 h. Acidification with 23 ml of 5% hydrochloric acid gave a clear solution which was basified with ammonia to pH 8.0. The precipitate which separated was recrystallized from a mixture of ethanol and methanol to give 0.78 g of XXVI. IR spectrum (in chloroform), cm^{-1}: 1675 (C=0), 3400 (NH). NMR spectrum (in $CDCl_3$), δ, ppm: 2.4-3 (4H, m, CH_2-CH_2-N); 3.56 (3H, s) and 3.8 (3H, s), $2CH_3O$; 4.72 (1H, s, CH-Ph); 5.12 (1H on C_{14b}, s); 6.32 (1H on C_{14}, s) 6.52; (1H on C_{11}, s); 6.6-7.4 (9H, m, aromatic protons in the benzene rings); 8.32 (1H, amide NH).

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