1,4-BENZODIAZEPINES.

IV. 6-PHENYL- AND 6-THIENYL-TETRAHYDROISOQUINOLINO-[2,1-d]-(1,4)-7H-BENZODIAZEPINES

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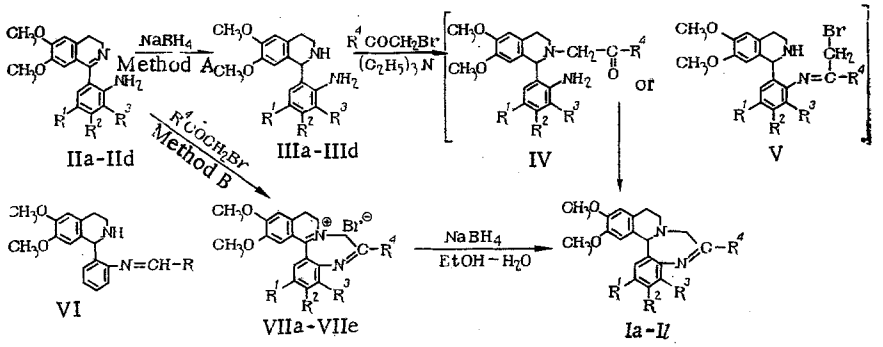
In our previous works [1, 2] we have investigated the reaction of 1-phenyl-substituted di- and tetrahydroisoquinolines with α-halogenated fatty acid chlorides and esters, which resulted in the corresponding tetrahydroisoquinolino[2,1-d]-(1,4)-benzodiazepin-6-ones.

In the present work, we have investigated the reaction of 1-phenyl-substituted di- and tetrahydroisoquinolines with α-halogenated aliphatic aromatic ketones. This reaction results in the formation of 6-phenyl- and 6-thienyl-7,9,10,14b-tetrahydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepines (Ia-Iℓ).



The starting materials for the preparation of I are the 1-(o-aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinolines IIa (R^1 = Cl, R^2 = H, R^3 = H), IIb (R^1 = H, R^2 = Cl, R^3 = H), IIc (R^1 = R^2 = R^3 = H), and IId (R^1 = R^2 = R^3 = OCH_3), which are reduced with sodium borohydride in methanol to give the corresponding 1-(o-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines IIIa-IIId (method A). Reaction of IIIa-IIId with α-halogenated aliphatic aromatic ketones in absolute ethyl alcohol in the presence of triethylamine at the reflux temperature for 10 h gives benzodiazepines Ia-Iℓ (see Table 1).

The following α-halogenated aliphatic aromatic ketones were investigated: ω-bromoacetophenone, 4-bromophenacyl bromide, 4-methoxyphenacyl bromide, 4-nitrophenacyl bromide, α-bromoacetothienone, and α-bromopropiophenone.

There are two possible routes for the formation of the benzodiazepine ring: intramolecular condensation with elimination of water from amino ketones IV formed by alkylation of the NH group in the isoquinoline nucleus; and intramolecular alkylation of the Shiff's bases V formed by reaction of the α-halo ketone with the aromatic ortho amino group.

We were unable to isolate either of the possible intermediates IV or V in the course of the reaction. We assume that the first route for the formation of the benzodiazepine ring is the more probable, since we found in previous investigations [3] that Shiff's bases of type VI formed by reaction of 1-(o-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with aromatic aldehydes are not alkylated by ethyl bromoacetate of α-brominated aliphatic aromatic ketones. This may be explained by a decrease in the electron density and a possible

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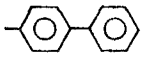
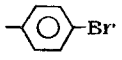
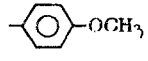
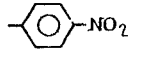
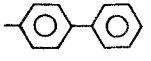
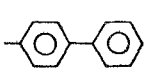
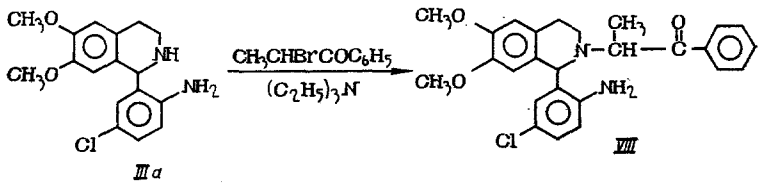
TABLE 1. 6-Phenyl- and 6-Thienyltetrahydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepines (Ia-Il)

Compound (synthesis method)	R_1	R_2	R_3	R_4	Yield (%)	Melting point (deg)	Found (%)					Empirical formula	Calculated (%)				
							C	H	N	Cl Cl+Br	S		C	H	N	Cl Cl+Br	S
Ia (A, B)	Cl	H	H		25	169–71*	71,95	5,40	6,70	8,37	—	$C_{25}H_{23}ClN_2O_2$	71,68	5,53	6,68	8,46	
Ib (A, B)	Cl	H	H		30	193–4*	74,95	5,85	5,54	7,36	—	$C_{31}H_{27}ClN_2O_2$	75,22	5,50	5,68	7,01	—
Ic (A, B)	Cl	H	H		24	178–80†	60,40	4,24	5,65	22,90	—	$C_{26}H_{25}BrClN_2O_2$	60,32	4,45	5,62	23,17	—
Id (A, B)	Cl	H	H		24	180–1†	69,20	5,80	6,65	8,20	—	$C_{26}H_{25}ClN_2O_3$	69,56	5,60	6,23	7,89	—
Ie (B)	Cl	H	H		30	165–8*	64,95	5,10	8,85	8,06	—	$C_{25}H_{22}ClN_3O_4$	64,72	4,77	9,05	7,64	—
If (A)	Cl	H	H		15	162–5*	64,75	5,20	7,01	8,63	7,10	$C_{23}H_{21}N_2O_2S$	65,01	4,95	6,67	8,34	7,54
Ig (A)	H	H	H		30	176–7††	77,82	6,45	7,43	—	—	$C_{25}H_{24}N_2O_2$	78,14	6,29	7,28	—	—
Ih (A)	H	H	H		30	176–80††	80,50	6,52	6,21	—	—	$C_{31}H_{28}N_2O_2$	80,84	6,12	6,08	—	—
Ii (A)	H	H	H		30	193–4‡	70,20	5,99	7,30	—	7,64	$C_{23}H_{22}N_2O_2S$	70,74	5,67	7,17	—	8,20
Ij (A)	H	Cl	H		30	168–9*	71,15	5,90	6,75	8,48	—	$C_{25}H_{23}ClN_2O_2$	71,68	5,53	6,68	8,46	—
Ik (A)	H	Cl	H		33	187–91*	74,58	5,95	5,76	7,22	—	$C_{31}H_{27}ClN_2O_2$	75,22	5,50	5,88	7,01	—
Il (A)	CH_3O	CH_3O	CH_3O		16	158–60**	70,90	6,70	6,21	—	—	$C_{28}H_{30}N_2O_5$	80,84	6,52	6,08	—	—

*From benzene–ethanol.
†From acetone–benzene.
‡From ethanol–acetone.
**From methanol.
†† From benzene–dioxane.

weakening of the nucleophilic character of the nitrogen atom in the isoquinoline system, and also by steric hindrance. Similar results were obtained when the reaction of 2-chloro-7-nitrobenzophenone and 2-chloro-7-trifluoromethylbenzophenone with ethylenediamine was investigated [4]. In this case, the authors concluded that an intermediate amino ketone was formed and underwent intramolecular cyclization to form the corresponding 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine.

Unlike the other α-halo ketones, the reaction of α-bromopropiophenone with 1-(2-amino-5-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIIa) under analogous conditions gives not the expected benzodiazepine ring, but α-[1-(2-amino-5-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl]propiophenone (VIII).



IIIa VIII

In this case, closure of the benzodiazepine ring is sterically hindered by the methyl group in the α position to the ketone carbonyl group in VIII. The steric factor obviously has less effect on the alkylation reaction than on the formation of the C=N double bond, which is in accord with our previous hypotheses concerning the formation of the benzodiazepine system. This result is in agreement with known literature data indicating that the sterically hindered aromatic ketones are practically unreactive toward aromatic amines [5].

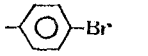
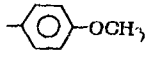
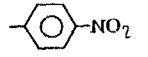
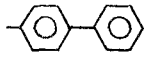
The structure of VIII was confirmed by its IR and NMR spectra. The IR spectrum of VIII has two absorption bands at 3340 and 3450 cm^{-1} corresponding to the stretching vibrations of the aromatic amide group, while the 1690 cm^{-1} absorption band corresponds to the stretching vibrations of the CO group. The NMR spectrum of VIII contains a singlet signal at a field strength of $\delta = 4$ ppm, characteristic of the amino group.

We studied the effect of different factors on the formation of the benzodiazepine ring. It was found that the yield of the compounds decreases with the polarity of the solvent (benzene or toluene). The highest yield (25-30%) was obtained when absolute ethyl alcohol was used as solvent. Increasing the amount of triethylamine and ketone does not lead to any appreciable increase in yield. The reaction goes much more slowly when the triethylamine is replaced by pyridine. The relatively low yield is probably due to the low rate of cyclization of the intermediate ketone IV.

The structure of the tetrahydroisoquinolinobenzodiazepines was confirmed by their IR, UV, and NMR spectra. Thus, the IR spectra of Ia-Iℓ do not contain absorption bands in the 3300-3400 cm^{-1} region, which would be characteristic of the stretching vibrations of and amino groups, or absorption bands in the 1680-1700 cm^{-1} region, characteristic of CO stretching vibrations. Absorption bands are observed in the 1580-1620 cm^{-1} region, which is characteristic of the azomethine group. The NMR spectra contain no strong-field singlet signals characteristic of the starting tetrahydroisoquinolines (imino and amino groups). The UV spectra of Ia and Ij have absorption bands at 268 and 329 nm, and that of Iℓ has bands at 263 and 353 nm. The UV spectra of the starting tetrahydroisoquinolines do not contain absorption bands at 329 or 353 nm.

We also investigated a second scheme (method B) for synthesizing the tetrahydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepines. Starting materials IIa-IId are reacted with the α-halogenated aliphatic aromatic ketones to form the corresponding substituted 6-phenyl-9,10-dihydroisoquinolino[2,1-d]-(1,4)-benzodiazepinium bromides VIIa-VIIe. The reaction is carried out by boiling equimolar amounts of the reactants in absolute ethyl alcohol for 6-8 h. The yield of the compounds obtained is 20-50% (Table 2). The mechanism by which the benzodiazepine ring is formed is analogous to that in method A. The yield of VIIa-VIIe is 20-30% higher than the yield of Ia-Iℓ in method A. This indicates that the reaction between the dihydroisoquinolines and the α-halogenated aliphatic aromatic ketones proceeds at a faster rate than the alkylation of the tetrahydroisoquinolines in method A. The structure of VII was confirmed by the IR and UV spectra and also by elementary analysis. The UV spectrum of VIIa contains absorption bands at 225, 268, and 400 nm, the latter band being absent in the spectrum of the starting dihydroisoquinoline. The spectra of the other compounds VII is similar in character.

TABLE 2. 6-Phenyl-7,9,10,14b-tetrahydroisoquinolino[2,1-d]-(1,4)-benzodiazepinium Bromides (VIIa-VIIe)

Compound	R^1	R^2	R^3	R^4	Yield (%)	Melting point (deg)	Found (%)		Empirical formula	Calculated (%)	
							N	Cl + Br		N	Cl + Br
VIIa	Cl	H	H		50	188—92*	5,60	22,50	$C_{25}H_{22}ClBrN_2O_2$	5,62	23,17
VIIb	Cl	H	H		41	194—7†	4,85	33,41	$C_{25}H_{21}Br_2ClN_2O_2$	4,85	33,85
VIIc	Cl	H	H		35	196—8†	5,33	23,00	$C_{26}H_{24}BrClN_2O_3$	5,30	23,85
VIId	Cl	H	H		23	192—6	7,77	20,80	$C_{25}H_{21}BrClN_3O_4$	7,92	21,23
VIIe	Cl	H	H		50	191—3‡	4,98	19,82	$C_{31}H_{26}BrClN_2O_2$	4,88	20,09

*From absolute ethanol.
†From acetone—methanol.
‡From acetone.

Reduction of VIIa-VIIe with sodium borohydride in 60% ethyl alcohol or a mixture of ethyl alcohol and tetrahydrofuran at room temperature gives the correspondingly substituted tetrahydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepines I, which are completely identical in properties to the compounds obtained by method A. When the reaction is carried out under these conditions, the C=N bond in the isoquinoline ring is selectively reduced while the azomethine group in the benzodiazepine ring is unaffected. This is confirmed by the fact that tetrahydroisoquinolinobenzodiazepines Ia-Iℓ are not reduced by sodium borohydride under these conditions.

The formation of the benzodiazepine ring is also affected by the nature of the substituents in the initial di- and tetrahydroisoquinolines and α-halo ketones. Thus, when IIId ($R^1 = R^2 = R^3 = OCH_3$) is reacted with bromoacetophenone, the yield is approximately 16%. When IIa (R^1 = Cl, R^2 = H, R^3 = H) is reacted with 4-nitrophenacyl bromide, the yield of VIId is 23%, whereas the yield is twice this value when IIa is reacted with α-bromoacetophenone. A similar decrease in yield is observed when IIIa is reacted with α-bromoacetophenone. On the basis of this, we can conclude that electron-accepting substituents in the halogenated ketone inhibit the formation of the benzodiazepine ring. The same goes for electron-donating substituents in the di- and tetrahydroisoquinolines.

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrophotometer (suspensions in mineral oil or chloroform). The NMR spectra were recorded using a Yeol instrument with a working frequency of 100 MHz in chloroform with tetramethylsilane as internal standard. The UV spectra were recorded in methyl alcohol. The purity of the compounds obtained was monitored by thin-layer chromatography on silica gel with benzene–ethanol as solvent.

1-(2-Amino-5-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (IIa). A sample (53 g, 0.1 mole) of 1-(2-nitro-5-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline was dissolved in a mixture of 600 ml ethyl alcohol and 600 ml concentrated hydrochloric acid. The solution was treated portionwise at room temperature with 280 g of stannous chloride. The mixture was boiled for 4 h and then cooled. The precipitated hydrochloride was filtered off, dissolved in a mixture of 170 ml ethyl alcohol and 340 ml water, and the solution made alkaline with 170 ml of 30% sodium hydroxide solution, to give 35.5 g of the base. On standing, a further 7.3 g of the hydrochloride was isolated from the filtrate obtained after the reduction. This was treated as above and the resulting 3 g of base added to the main batch. Recrystallization from ethyl alcohol gave pale-yellow crystals, mp 160-162°. The yield was 67%. Found, %: C 64.55; H 5.73; N 8.85; Cl 11.25. $C_{17}H_{17}ClN_2O_2$. Calculated, %: C 64.45; H 5.47; N 8.84; Cl 11.12.

An analogous method was used to prepare 1-(2-amino-3,4,5-trimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (IId), mp 132-133.5°, in a yield of 60%. Found, %: C 64.10; H 6.85; N 7.33. $C_{20}H_{24}O_5N_2$. Calculated, %: C 64.54; H 6.46; N 7.52.

Compounds IIb and IIc were prepared by the method described in our previous communications [1, 2].

1-(2-Amino-5-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIIa). A solution of 6.9 g (0.025 mole) of IIa in 70 ml methyl alcohol was heated to 50°, treated portionwise at this temperature with 2.6 g sodium borohydride, boiled for 3 h, cooled, and acidified with 90 ml of 10% hydrochloric acid. After stirring for 30 min, the precipitate formed during the reaction redissolved. The resulting solution was alkalized with ammonia to form a white crystalline precipitate. This was recrystallized from ethyl alcohol to give 5.5 g (78%) of IIIa in the form of colorless crystals, mp 166-167°. Found, %: C 60.46; H 6.52; N 8.99; Cl 10.96. $C_{17}H_{19}ClN_2O_2$. Calculated, %: C 60.91; H 6.10; N 8.78; Cl 11.12.

Analogous methods were used to prepare IIIb, mp 144-147°, 75% yield; IIIc, mp 162-164°, 70% yield; and IIId, mp 133-134°, 85% yield.

dl-2-Chloro-6-phenyl-12,13-dimethoxy-7,9,10,14b-tetrahydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepine (Ia). Method A. A mixture of 2 g (0.006 mole) of 1-(2-amino-5-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIIa), 1.25 g (0.006 mole) of phenacyl bromide, and 1.7 ml (0.016 mole) of triethylamine in 20 ml of absolute ethyl alcohol was boiled on a steam bath for 6 h and then cooled. The resulting yellow crystals were filtered off and recrystallized from a mixture of benzene and ethyl alcohol to give 0.65 g (25%) of Ia, mp 166-

167°. Found, %: C 71.25; H 5.40; N 6.70; Cl 8.37. $C_{25}H_{23}ClN_2O_2$. IR spectrum (in chloroform), cm^{-1}: 1620, 1590. UV spectrum, nm: 268, 329. NMR spectrum, ppm: 2.4-3.4 (4H) multiplet (CH_2CH_2N); 2.6 (1H) doublet; 3.95 (1H) doublet, J_{AB} = 10 Hz (CH_2N); 4.82 (1H at C_{14b}) singlet; 3.63 (3H) singlet; 3.84 (3H) singlet ($2CH_3O$); 6.2 (1H at C_{14}) singlet; 6.64 (1H at C_{11}) singlet; 7.2-8.2 (7H) multiplet (aromatic protons).

Compounds Ib-Il were prepared analogously (see Table 1).

2-Chloro-6-phenyl-12,13-dimethoxy-9,10-dihydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepinium Bromide (VIIa). Method B. A mixture of 4 g of IIa and 2.4 g of phenacyl bromide in 40 ml of absolute ethyl alcohol was boiled for 10 h. After cooling and keeping overnight, 3.9 g of pale-yellow crystals were precipitated. These were recrystallized from ethyl alcohol to give 3.2 g of VIIa, mp 188-192°, yield 50%. IR spectrum (in chloroform), cm^{-1}: 1620, 1590. UV spectrum, nm: 225, 268, 400.

Compound VIIb was prepared analogously (see Table 2).

dl-2-Chloro-6-phenyl-12,13-dimethoxy-7,9,10,14b-tetrahydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepine (Ia). Method B. A solution of 2.61 g (0.0053 mole) of 2-chloro-6-phenyl-12,13-dimethoxy-9,10-dihydroisoquinolino[2,1-d]-(1,4)-7H-benzodiazepinium bromide (VIIa) in 50 ml of a 2:1 mixture of ethanol and water was added portionwise to a solution of 0.78 g (0.021 mole) of sodium borohydride in 40 ml ethyl alcohol, to form a yellow precipitate. The mixture was stirred at 20° for 3 h and treated with 25 ml of 10% hydrochloric acid to form a pale-yellow solution, which was adjusted to pH 8.0 with ammonia. The yellow crystalline precipitate was filtered off, dried, and recrystallized from a mixture of benzene and ethyl alcohol to give 1.1 g (50%) of pale-yellow crystals, mp 169-171°.

The identity of the compounds obtained by the two routes was established by thin-layer chromatography, mixed melting point determination, and a comparison of their IR, UV, and NMR spectra. Compounds Ib (50%), Ic (25%), Id (30%), and Ie (30%) were prepared analogously.

α-[1-(2-Amino-5-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]propiophenone (VIII). A mixture of 1.5 g (0.0047 mole) of 1-(2-amino-5-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 1 g (0.0047 mole) of α-bromopropiophenone, and 1.26 g triethylamine in 15 ml absolute alcohol was boiled for 6 h. After concentrating the solution, 0.45 g of colorless crystals were precipitated. These were recrystallized from acetone to give 0.2 g of VIII, mp 155-157°. Found, %: C 69.00; H 6.10; N 6.52; Cl 8.20. $C_{26}H_{27}ClN_2O_3$. Calculated, %: C 69.02; H 6.03; N 6.21; Cl 7.80. IR spectrum (in chloroform), cm^{-1}: 3340, 3460 (NH_2), 1690 (CO), 1620, 1530. NMR spectrum, ppm: 1.26 (3H, doublet, CH_3CH), J = 7.2 Hz; 4.45 (1H, quadruplet, $CHCH_3$), J = 7.2 Hz; 2.6-3.4 (4H, multiplet, CH_2CH_2N); 3.6 (3H) and 3.8 (3H, singlet, $2CH_3O$); 4.05 (2H, singlet, NH_2); 4.8 (1H at C_{14b}, singlet); 6.22 (1H, singlet at C_{14}); 6.56 (1H, singlet at C_{11}); 7-7.8 (8H, multiplet, aromatic protons).

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LITERATURE CITED

1. M. Levi, Ch. Ivanova, and M. Dryanska, Khim. Farmats. Zh., No. 4, 5 (1973).
2. M. Levi, Ch. Ivanov, and M. Dryanska, Khim. Farmats. Zh., No. 12, 12 (1974).
3. M. Levi, Ch. Ivanov, M. Dryanska, et al., Khim. Farmats. Zh., No. 2, 33 (1971).
4. L. H. Sternbach, G. A. Archer, et al., J. Org. Chem., 28, 3013 (1963).
5. H. H. Strain, J. Am. Chem. Soc., 52, 820 (1930).