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Study of Cyclization Mechanism of *N*-Substituted-2-amino--benzophenones into 1,4-Benzodiazepines; β-Participation of an Vinylogous Amide Nitrogen

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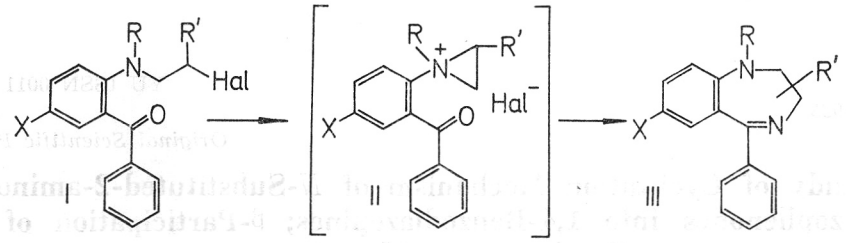
2-(*N*-β-Bromoalkyl)-amino-5-substituted benzophenones **28, 32, 33** and **38** have been induced by treatment in ethanolic solution of hexamethylentetramine or ammonia to ring closure into 1,4-benzodiazepines **39—46.** Deuterium β-labeled compound **28** gave on cyclization two 1,4-benzodiazepines (**39** and **40**) in the ratio 45/55, revealing β-participation of nitrogen atom. The neighbouring group participation was further investigated by determining the ratio and configuration of the 2- and 3-substituted chiral 1,4-benzodiazepines resulting on ring closure: **32** gave (S)-**41** and (S)-**42** (ratio 82/18), **33** gave (S)-**43** and (S)-**44** (ratio 92/8), **38** gave **45** and **46** (ratio 58/42). High regioselectivity was also observed for re-cyclization of aziridines **36** in (S)-**41** and (R)-**42** (ratio 63/37), and **37** in (S)-**43** and (R)-**44** (ratio 76/24), respectively. An opposite stereochemical course of formation of **42** and **44** from **32** and **33,** as from **36** and **37** is observed. Absolute configuration of (—)- and (+)-**42** and **44** was determined by comparison of their CD spectra with those of (S)-**50**, and mechanistic scheme is offered accounting for all experimental results.

INTRODUCTION

During the work on chiral 1,4-benzodiazepines[1,2] it became interesting to undertake a study of the cyclization mechanism of 2-(β--haloethyl)-amino--5-substituted benzophenones (I) into 1,4-benzodiazepines III (Scheme 1). Ammonolysis and spontanous cyclization of the compounds I is a well known[3,4] way for the preparation of various achiral 1,4-benzodiazepines with benefitial CNS-activity[5]. Most reported examples refer to cyclization into 1,4-benzodiazepines with an 2,3-ethylenic group as a part of the heterocyclic ring ($R' = H$ in the scheme 1). We assume β-participation of vinylogous amide nitrogen to occur during ammonolysis of 2-(β-haloethyl)-derivatives I. Intermediate formation of aziridinium derivatives II can not conveniently be proved for the formation of 2,3-unsubstituted benzodiazepines, since the same product would arise either on direct ring-closure into a 7-membered ring or including β-participation. In the preparation of chiral derivatives (for $R' \neq H$ β-C-atom in I is chiral) different structural and stereoisomers should arise, depending on whether β-participation is operative or not.

SCHEME 1



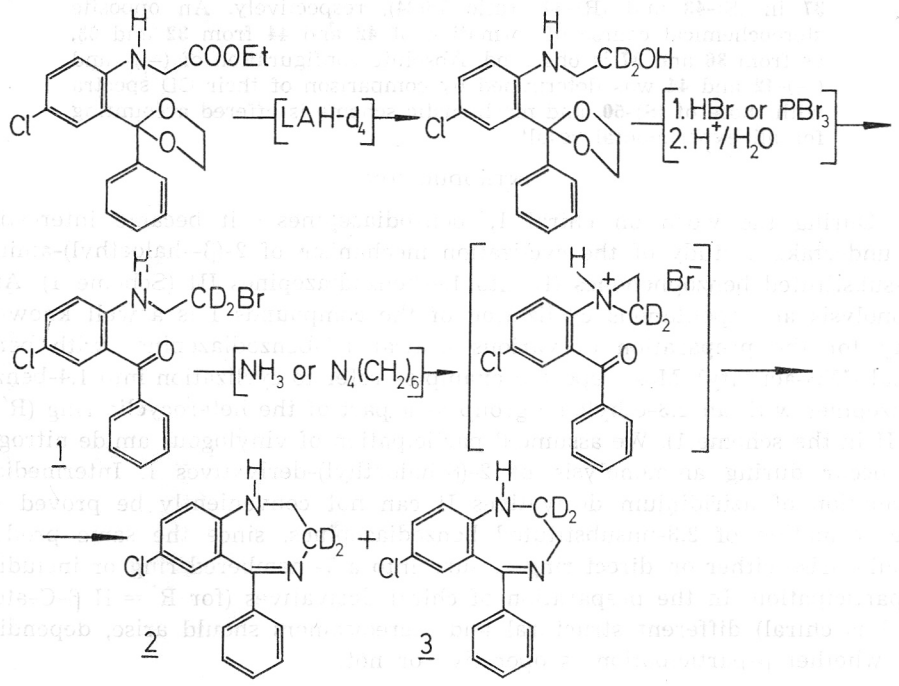
Some results of investigations described herewith have already been reported in a preliminary form[6]; this paper represents a full account of our work.

RESULTS AND DISCUSSION

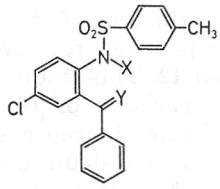
A. *Preparation of 2-(β-haloalkyl)- and 2-aziridino-5-substituted benzophenones.*

The initially attempted synthetic sequence is outlined in the Scheme 2. Compound **1**, deuterium labelled in the β-methylenic group, was envisaged as a convenient model for preliminary confirmation of β-participation. Ketalization of starting 2-amino-5-chlorobenzophenone (ethylenglycole, *p*-TSOH) led to dimer 2,8-dichloro-6,12-diphenyl (b, f) 1,5-dibenzdiazocyne (m. p. 218—

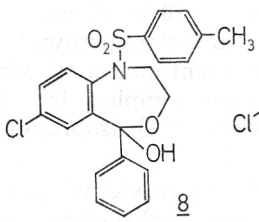
SCHEME 2



220 °C[7]) as the only product. Therefore proceding alkylation of 2-amino group revealed to be necessary. This was performed *via* Na-salt of the *N*-tosyl--derivative **4**, prepared by an improved procedure of Sternbach et al.[8], and its alkylation into **5** (93% yield) using ethyl-α-bromoacetate in dimethylformamide. Ketalization of **5** by standard procedure[9] was unsuccesfull (starting material unchanged). Following the improved procedure by Adachi and Sato[10] slow conversion (after 300 h) led to the dissappearance of starting **5** and the formation of three isolable products **6**, **7** and **8** (22%, 1% and 28%, respectivelly). Ketalization procedure developed for highly unreactive, electronegatively substituted ketones[11], has further been attempted. Transesterification takes place, however, to give **9** as the only product in 61% yield. Its structure was confirmed, and the structure of originally regarded isomer **10** disclosed, by the appearance of two carbonyl bands in ir spectrum at 1660 cm^{-1} (for ketone), and at 1740 cm^{-1} (for ester), and the absence of any hydroxyl absorption.



	X	Y
4	Na	O
5	CH_2COOEt	O
6	p-tosyl	O-CH_2 / O-CH_2
7	H	O-CH_2 / O-CH_2
9	$CH_2COOCH_2CH_2Br$	O
11	CH_2CH_2OH	O



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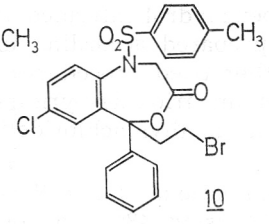
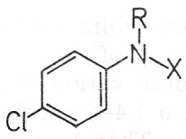


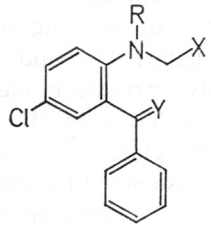
10

After ketalization was found to be unsuccesful, a detour was interposed in the synthetic sequence shown on the Scheme 2. *N*-Tosylation of *p*-chloroaniline, and subsequent alkylation led to **13** (95% yield). On reduction of **13** with lithium aluminium hydride (LAH) into **14** (93% yield), extensive attempts failed to induce it to undergo Friedel-Crafts-type *ortho* benzoylation. Benzoylester **15** could only be isolated; it was hydrolised into **16**, which was identical with an authentic sample.



	X	R
13	CH_2COOEt	p-tosyl
14	CH_2CH_2OH	p-tosyl
15	$CH_2CH_2OOC_6H_5$	H
16	CH_2CH_2OH	H

It was concluded that reduction and reoxydation of ketone karbonyl group cannot properly be avoided, and the preparation of **1** without protection of the ketone carbonyl was started.



	R	X	Y		R	X	Y
12	H	CH_2OH	O	23	H	CH_2OOCMe	O
17	H	COOH	O	24	H	COOEt	H,OH
18	H	COOEt	O	25	CH_3	COOEt	O
19	H	CD_2OH	H,OH	26	CH_3	CD_2OH	H,OH
20	H	CH_2OH	H,OH	27	CH_3	CD_2OH	O
21	H	CD_2OH	O	28	CH_3	CD_2Br	O
22	H	CH_2Br	O	29	CH_3	COOMe	O

Ester **18** was prepared from **5** in two steps *via* compound **17** and in 85% all round yield. Reductions according to Eliel[12] and Vogel[13], using calculated volumes of etheric solution of LAH, led to mixtures of the products **12**, **20**, **24** and of some unreacted **18**, as well. Their separation revealed the formation of only 2.5% of properly regioselective reduced **12**. This finding prompted the use of a great molar excess of LAH-d_4 in preparation of **19**, which resulted in 92.5% yield of pure product. Its NMR spectrum showed a singlet at 3.13 ppm for N—CH_2 methylenic protons, while its non-deuterated counterpart **20** exhibited two triplets at 3.14 and 3.67 ppm. No carbonyl absorption appeared in the infrared spectra of both.

Reoxidation of benzhydrol intermediate **19** in **21** with »active« manganese dioxide in acetone, prepared according to Attenburrow,[14–16] gave the highest yield (48%) of all other tried procedures (chromium trioxide in 50% aqueous acetic acid,[17], chromium trioxide-pyridine complex in methylenchloride[18,19], manganese dioxide in methylenchloride[14], in di-isopropylether, ether, or in chloroform).

Preliminary brominations of the *N*-β-hydroxiethyl group were performed on non-deuterated **12** using 48% aqueous hydrobromic acid at 125—130 °C. Yields of ca. 65% of **22** stimulated the use of the same method for bromination of **21**. NMR spectrum of crude **1** revealed a high degree of deuterium randomisation on α- and β-position. The α/β CD_2 ratio was 40 : 60, as estimated from signal intensities at 3.52 and 3.70 ppm, respectively. This result was the first evidence of β-participation by the nitrogen atom.

Careful treatment of **21** with phosphorus tribromide in nitromethane yielded 45—55% of unrearanged *N*-β-bromoethyl compound **1**, while attempted β-bromination of **12** with 48% hydrobromic acid in glacial acetic acid at ambient temperature led to *O*-acetylation, giving **23** (66% yield) as the only isolable product.

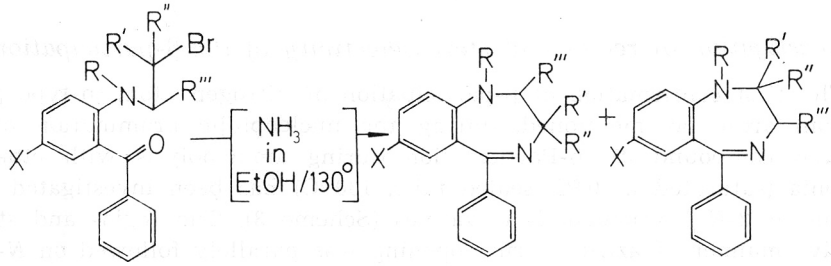
First experiments on cyclization of **1** with ethanolic ammonia or hexamine revealed its limited reactivity and the appearance of numerous side product. This finding was in accordance with earlier observation[4] that cyclization of 2-*N*-alkylated-*N*-(β-haloethyl)-benzophenones into 1,4-benzodiazepines proceeds easier than that of analogous 2-*NH*-derivatives. Therefore preparation of *N*-methyl-derivative **28** from **25** was performed. Starting compound **25** was

obtained by modified Eschweiler-Clarke reductive methylation[20,21] of **18**. Methyliodide-barium oxyde in dimethylformamide[1,4] led to the methyl ester **29** instead of the *N*-methyl derivative when both **17** or **18** have been reacted with.

Compound **25** was reduced with LAH-d_4 (over 80% yield), the benzhydrolic group in **26** reoxidized, and **27** then brominated to give **28**.

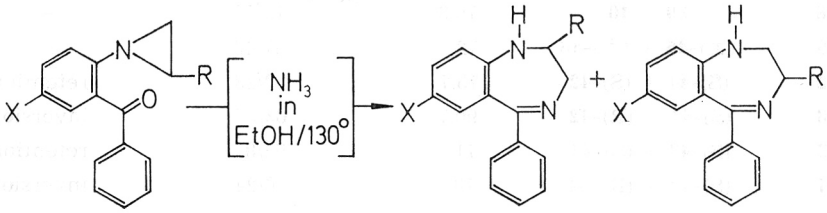
In order to compare stereo- and regioselectivity during recyclization of 2-aziridinoyl-benzophenones *vs.* intermediary postulated aziridinium — ions II (Scheme 1), the compounds **34**—**37** (Scheme 4) have been prepared by two different routes. 5-Chloro-derivative **34** and 5-nitro-derivative **36** were obtained by cyclization of *N*-β-bromoalkyl-derivatives **22** (prepared *via* **12**) and **32** (prepared *via* **30**) with barium oxide in DMF. The 5-nitro-2-ethylaziridino-de-

SCHEME 3



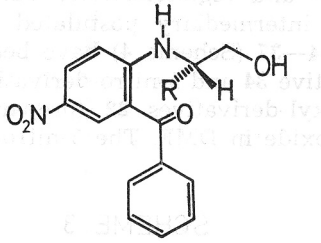
	X	R	R'	R''	R'''		
28	Cl	Me	D	D	H	39	40
32	NO_2	H	H	H	(*S*)-Me	(*S*)-41	(+)-42
33	NO_2	H	H	H	(*S*)-Et	(*S*)-43	(+)-44
38	Cl	Me	H	Me	H	45	46

SCHEME 4



	X	R		
34	Cl	H		47
35	NO_2	H		48
36	NO_2	(*S*)-Me	(*S*)-41	(−)-42
37	NO_2	(*S*)-Et	(*S*)-43	(−)-44

rivative **37** was prepared *via* **31** and **33** and alternativily, from 2-chloro-5--nitrobenzophenone by *N*-arylation of 2-(S)-ethylaziridine[22,23] in 88.6% yield. Compound **35** was prepared only by the second route using ethylenimine (76% yield). 2,5-Dichlorobenzophenone did not arylate aziridines, or other amines, although vinylogous acid chlorides are reported[24] to alkylate aziridines under mild conditions.



	R
(*S*)-30	Me
(*S*)-31	Et

B. *Investigation of regio- and stereoselectivity of the β-participation*

The first confirmation of β-participation of nitrogen atom (n-type participation) arose, as mentioned, during the nucleophilic bromination of the dideutero-compound **21**. β-Participation during ammonolysis with ethanolic ammonia (saturated at 0 °C, sealed tube, 130 °C) has been investigated on a number of 2-*N*-β-bromoalkyl-derivatives (Scheme 3). The regio- and stereoselective manner of aziridine ring opening was parallely followed on *N*-aryl--aziridines (Scheme 4).

Results are summarized in Table 1 and allow the following statements:

TABLE I

Regio- and stereoselectivity in cyclization of 2-(N-β-bromoalkyl)- and 2-aziridinyl-benzophenones into 2H-1,4-benzodiazepines

Starting compound	Products	Total yield %	Regioselectivity[a]	Stereoselectivity[b]
28	**39** + **40**	70.8	45/55	—
38	(±)-**45** + (±)-**46**	72	57/43	—
32	(S)-**41** + (S)-**42**	75.7	82/18	retention
36	(S)-**41** + (R)-**42**	90.1	63/37	inversion
33	(S)-**43** + (S)-**44**	71	92/8	retention
37	(S)-**43** + (R)-**44**	70	76/24	inversion

[a] Ratio of 2- *vs.* 3-substituted 1,4-benzodiazepines. All values have been prooved by glc.
[b] Indicating stereochemical outcome at C-3 in 1,4-benzodiazepines formed.

a) Both, aziridines **34**—**37** and aziridine precursors **28**, **32**, **33** and **38** led to 1,4-benzodiazepines in approximately same yields (70—80%).

b) Both type of substrates opened the aziridine ring regioselectively whereby »normal« ring openings[25–27], *i. e.* those between nitrogen and lower substituted carbon, predominated. Dideutero-derivative **28** exhibited low regioselectivity slightly favouring N—CH_2 over N—CD_2 bond braking (see Figure 1.)

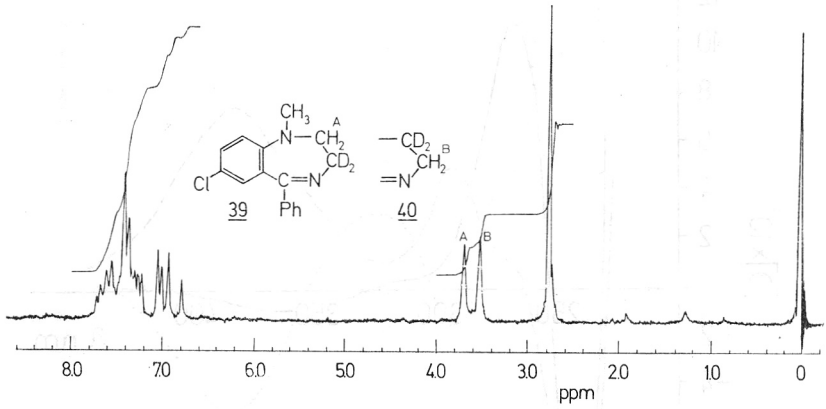
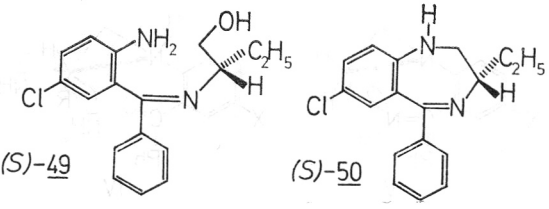


Figure 1. NMR spectrum of the isomeric **39** and **40** in 45/55 mixture as obtained on recyclisation of the compound **28** in ethanolic solution of hexamine.

c) Chiral substrates **32**, **33**, **36** and **37** exhibited high stereoselecitivity. Moreover, depending on the substrate opposite stereochemical course took place. While chiral aziridines **36** and **37** recyclized into 3-chiral-1,4-benzodiazepines under inversion, their »precursors« **32** and **33** gave the same products under high incidence of retention. Absolute configurations of (+)- and (—)-**42** and **44** have been deduced by comparing their CD spectra with those of »standard« **50** (S) (Figure 2). For correlation of configurations short-wave Cotton-effects at 250 nm have been compared, since Cotton-effects at 350—400 nm originated from different chromophores, *i. e.* chloro- and nitro-substituted benzene ring. For the last one it was shown by circular dichroism[28] that it rises an optically active transition near 300 nm.

Model compound **50** for CD-correlation was prepared from S-(+)-2-amino-butanol and 2-amino-5-chlorobenzophenone *via* ketimine **49**. All attempts to prepare analogous 7-nitro-1,4-benzodiazepine by the same procedure failed, since 2-amino-group in 2-amino-5-nitrobenzophenon-β-hydroxy-alkylimine proved to be entirely unreactive in the cyclization step[29].



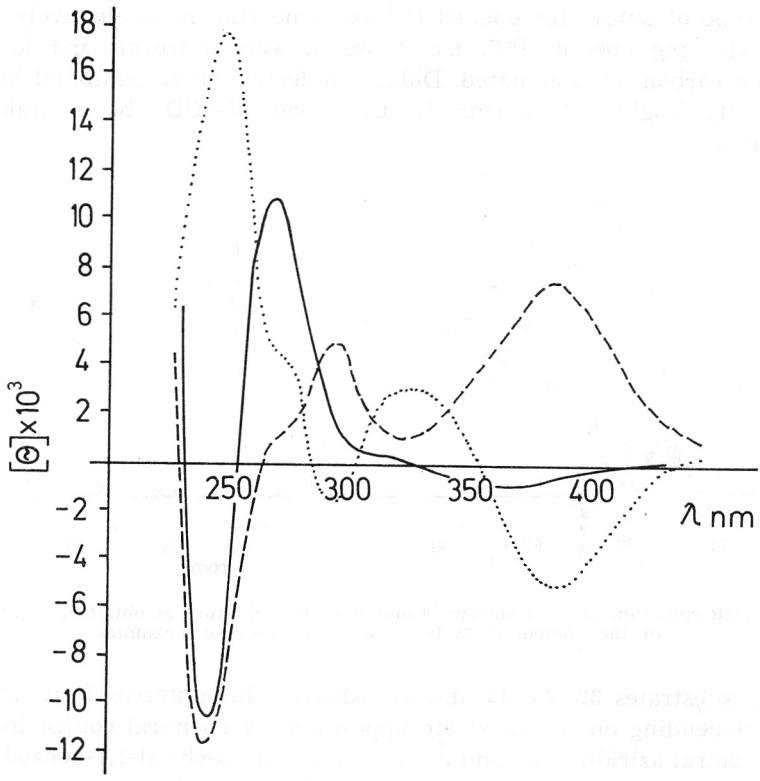


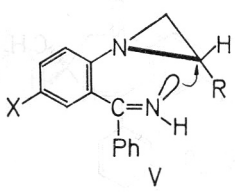
Figure 2. CD spectra of the enantiomeric (+)- and (—)- **44** and the standard curve of **50** (all in abs. ethanol):

——— (S)-(+)-**50**
— — — — (S)-(+)-**44**
. . . . . (R)-(—)-**44**

CONCLUSION

From the results summerized under a—c following conclusions may be drawn:

a) Ammonolysis of aziridines is a S_N2 process, since S_N1-type attack should lead to a higher incidence of »abnormal« ring openings (through the more stable secondary carbonium ion), as was reported for acid-catalyzed aziridine cleveage[30,31]. Highly stereoselective formation of enantiomers of **42** and **44** from **32** and **36** (or from **33** and **37**), instead of racemization, confirms a bimolecular mechanism.



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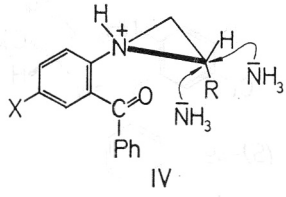

IV

b) Aziridines **34**—**37** or aziridinium intermediates from **28**, **32**, **33**, **38** are intermolecularly attacked by ammonia (IV), and not intramolecularly oppened *via* ketimines (V), which may arise as intermediates under reaction conditions used[32].

Intramolecular mode of ring opening should inevitably occur as a front-side attack of ketimine nitrogen, being a well-established mode of nucleophilic ring opening of aziridines in other intra[33,34] as well as in some intermolecular reactions. Consequently, *retention* of configuration should be expected in ring openings of *both* **32** and **36** or **33** and **37**. Since inversion actually occured in reactions with **36** and **37**, presumably no benzophenone--imine intermediate was involved.*

c) Opposite stereochemical outcome of ammonolysis and cyclization of **32** and **33** in relation to **36** and **37** may be explained as follows (Scheme 5). β-Participation in **32** and **33** leads to tightly bound ion-pair intermediate (S)-VI in which the bromine is placed at the rear side of the aziridinium ring. This intermediate can therefore hardly undergo a back-side attack by ammonia, and must be attacked from the front-side. This results in recyclization *via* nonisolable (S)-VII into (S)-(+)-**42** and (S)-(+)-**44** with retention of configuration. Contrary to the aziridinium ions, aziridines **36** and **37** are open to back-side nucleophilic attack, and inversion of configuration takes place during recyclization *via* nonisolable (R)-VII into (R)-(—)-**42** and (R)--(—)-**44**. There is no bond-braking to the chiral centre in pathways B, so that same intermediate (S)-VIII arises leding to (S)-**41** and (S)-**43**.

EXPERIMENTAL

Melting points were determined on a Kofler-microheating stage and are uncorrected. NMR spectra were obtained on a Varian T-60 spectrometer using TMS as internal reference, shifts are given as δ values in ppm. Ir spectra were run on a Perkin Elmer M 257 spectrophotometer, and are for KBr pellets, unless otherwise stated. Optical rotations were measured with a Perkin Elmer M-141 polarimeter at ambient temperature. Analytical glc. was performed on a Perkin-Elmer F11 gas chromatograph using Carbowax 20M-TFA 2% on Chromosorb W 80—100 mesh; temperature of the column was 250° block 240 °C, and nitrogen was the carrying gas. CD spectra were obtained on a JASCO J-20 spectropolarimeter at ambient temperature, and uv spectra on a Varian-Techtron UV-VIS, M-635 automatic spectrophotometer. Silicagel plates F-254 (Merck) were used for TLC. Column chromatography was run on silicagel 0.05—0.2 mm (Merck), fractions were collected automatically using a LKB 7000 Ultra Rac instrument, and monitored by TLC using an UV-254 nm lamp. Light petroleum refers to that fraction which boils between 30 and 60 °C. All organic solutions were dried over anhydrous sodium suplhate, and evaporated *in vacuo* using a Rotavapor (Büchi).

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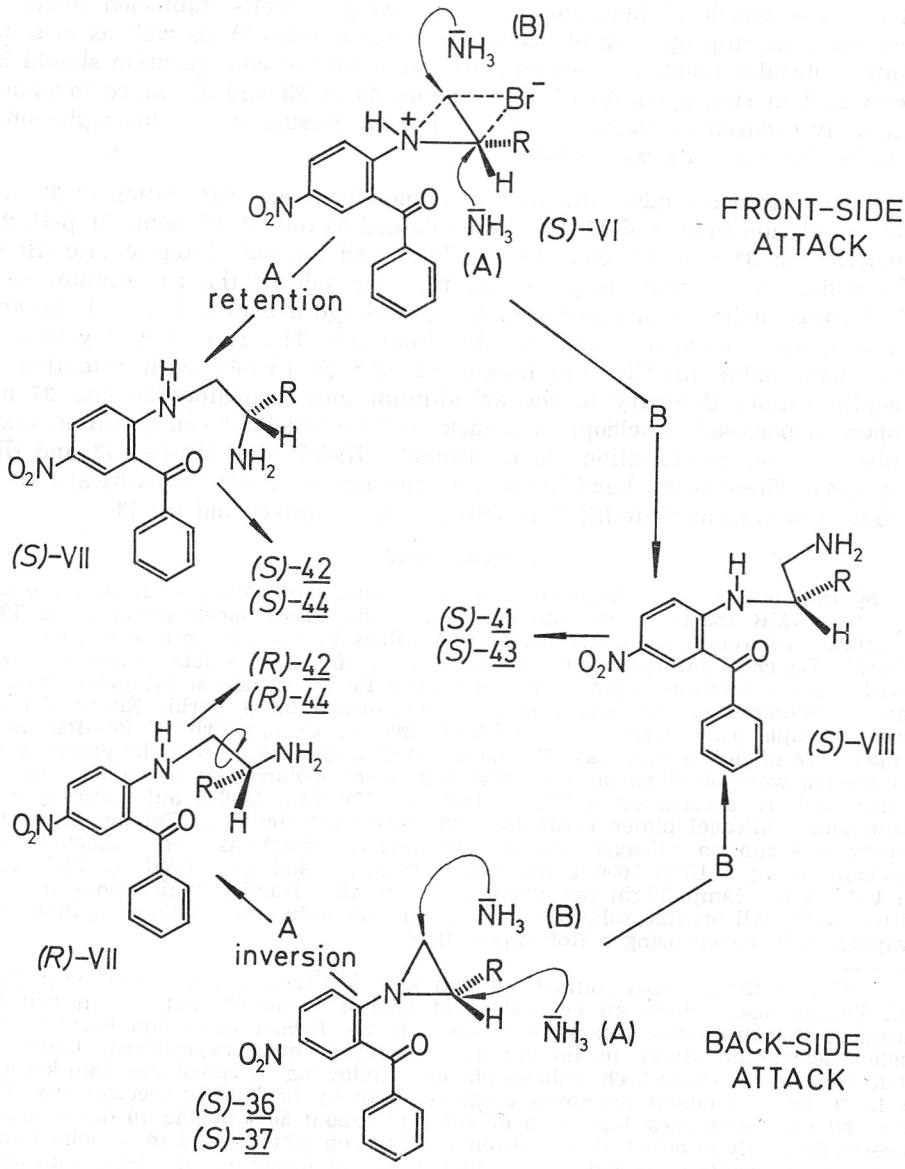
* One of the referees pointed out that ketimine formation could occur in those aziridinium cases where an equivalent of acid is available, but not in aziridine cases, so that front-side attack could occur in the former cases and normal back--side nucleophilic attack in the latter. Therefore control experiments have been undertaken on 2-amino-5-chlorobenzophenone, following its conversion into ketimine at 125 °C (satd. ethanolic ammonia, ampules), both by tlc and uv spectroscopy. They revealed extremely slow formation of ketimine (about 50% during 10 days), and no observable catalytic effect of hydrobromic acid even when added in a molar excess. First kinetic results indicated a much higher rate of formation of 1,4-benzodiazepine **47** from both **22** and **34**, than the above formation of ketimine. Thus, the intramolecular ketimine attack seems not to be operative for the aziridinium cases, as well. Full account of the relevant kinetic studies will be submitted for publication in this journal. The authors are indebted to one of the referees for drawing our attention to the above point.

SCHEME 5


(B)
Br⁻
R
H
(S)-VI
FRONT-SIDE ATTACK
(A)
A
retention
B
(S)-VII
(S)-42
(S)-44
(S)-41
(S)-43
(S)-VIII
(R)-42
(R)-44
(R)-VII
A
inversion
B
(B)
(A)
BACK-SIDE ATTACK
(S)-36
(S)-37

2-(p-Toluensulfonamido)-5-chlorobenzophenone-Na salt (**4**)

2-Amino-5-chlorobenzophenone (20.0 g, 86.4 mmol), and p-TsCl (20.0 g, 105 mmol) were dissolved in dry pyridine (70 ml) and set aside overnight at ambient temperature. Thereafter the mixture was poured on 600 ml of ice-water, the crude product succtioned off, washed with water and recrystallized from 200 ml of EtOH (32.9 g, 98% yield, m. p. 118—120 °C lit.[8] m. p. 120—121 °C). The tosylate (23.1 g, 60 mmol) was slurried in dry ether (300 ml) and NaH (55% suspension in mineral oil, 3.1 g, 70 mmol) was added under stirring and water-cooling. After 3 hr stirring at room temp. 3 ml of EtOH were added, stirred for 15 min, the precipitated **4** filtered off and thoroughly washed with ether. Yield 24.3 g (100%), m. p. 298—302 °C (lit.[8] m. p. 298—299 °C).

2-(N-Tosyl)-amino-5-chlorobenzophenone-ethylenketal (**7**)

Na-salt **4** (16.3 g, 40 mmol) and ethyl-α-bromoacetate (16.7 g, 100 mmol) were dissolved in DMF (60 ml) and stirred at 60—65 °C for 2 hr. The solvent was evaporated, the residual oil was dissolved in $CHCl_3$ (50 ml), washed with water (50 ml) and the aqueous layer extracted with $CHCl_3$ (2 × 30 ml). The organic layers were dried, evaporated, and the residual crude **5** dissolved in ether (50 ml). On slow addition of light petroleum **5** begins to crystallize. After cooling on ice it was collected on filter and recrystallized from EtOH, yield 17.5 g (93%), m. p. 144—146 °C. NMR ($CDCl_3$): δ 1.30 (t, 3H), 2.22 (s, 3H), 4.20 (q, 2H), 4.70 (s, 2H), 6.9—7.9 (m, 12H). Ir: strong carbonyl bands at 1740 cm^{-1} (ester), and 1662 cm^{-1} (ketone).

Anal. for $C_{24}H_{22}ClNO_5S$ (471.95) Calc'd: C 61.07, H 4.70, N 2.97%
Found: C 61.32, H 4.95, N 3.07%.

Attempted ketalization of **5**. — Compound **5** (4.7 g, 10 mmol) was dissolved in dry benzene (100 ml). Ethylenglycol (5 ml) and p-TsOH (0.2 g) were added, and the mixture was heated under reflux in a Soxlet-apparatus containing a capsule filled with $MgSO_4$. Tlc control revealed the virtual dissappearance of starting **5** after 305 hr of heating. During this period ethylenglycol (15 ml) and p-TsOH (0.2 g) were added in small portions. Thereafter the reaction mixture was washed with satd. aqueous solution of sodium bicarbonate, the benzenic layer dried, and evaporated. The remained viscous oil (5.1 g) was passed through a column of silicagel (100 g using chloroform as eluent). The following compounds were isolated:

2-(N,N-Ditosyl)-amino-5-chlorobenzophenone-ethylenketal (**6**)

(**6**) was obtained as a yellow, glassy-oil (1.267 g, 22%), m. p. 64—67 °C, NMR ($CDCl_3$): δ 2.33 (s, 6H), 4.1—4.6 (m, 4H), 7.1—8.1 (m, 16H). Ir: (neat film) no carbonyl absorption.

Anal. for $C_{29}H_{26}ClNO_6S_2$ (584.09) Calc'd: C 59.63, H 4.48, N 2.39%
Found: C 59.39, H 4.41, N 2.67%.

2-(N-Tosyl)-amino-5-chlorobenzophenone-ethylenketal (**7**)

(**7**) was obtained as the second fraction which on crystallization from EtOH gave 0.150 g of pure material with m. p. 154—156 °C. NMR ($CDCl_3$): δ 2.35 (s, 3H), 4.1—4.6 (m, 4H), 7.1—7.9 (m, 12H), 9.33 (broad s, 1H dissapp. on addtn. of D_2O). Ir: no carbonyl absorption.

Anal. for $C_{22}H_{20}ClNO_4S$ (429.91) Calc'd: C 61,46, H 4.69, N 3.26%
Found: C 61.38, H 4.73, N 3.08%.

1-Tosyl-5-phenyl-5-hydroxy-7-chloro-2,3-dihydro-1,4-oxazepin (**8**)

(**8**) was obtained as the last fraction (1.18 g, 28%), and crystallized from ethylacetate-light petroleum, m. p. 167—168 °C. NMR ($CDCl_3$) δ 2.10 (s, 1H — dissapp. on addtn. of D_2O), 2.33 (s, 3H), 3.83 (t, 2H), 4.46 (t, 2H), 7.1—8.2 (m, 12H). Ir: no carbonyl absorption.

Anal. for $C_{22}H_{20}ClNO_4S$ (429.91) Calc'd: C 61.64, H 4.69, N 3.26%
Found: C 61.26, H 4.72, N 3.50%.

2-(N-Tosyl-N-β-bromoethoxycarbonylmethyl)-amino-5-chlorobenzophenone (**9**)

Compound **5** (0.94 g, 2.0 mmol) was dissolved in 1.5 ml of 2-bromoethanol, and heated under stirring at 75—80 °C for 3 hr. After evaporation of the excess of 2-bromoethanol and crystallization from EtOH (20 ml), 0.7 g (61%) of **9** m. p. 138—145 °C were obtained. Recrystallization from EtOH gave pure **9**, m. p. 145—146.5 °C NMR ($CDCl_3$): δ 2.20 (s, 3H), 3.50 (t, 2H), 4.71 (s, 2H), 6.9—7.9 (m, 12H). Ir: 1740, 1660, 1345, 1160 cm^{-1}.

2-(N-Tosyl-N-β-hydroxyethyl)-amino-5-chlorobenzophenone (**11**)

Na-salt **4** (10.2 g, 25 mmol) and 2-bromoethanol (15.6 g, 125 mmol) in DMF (60 ml), were stirred and heated at 60—65 °C for 22 hr. Solvent was evaporated and the residual oil treated in the same manner as described for **5**. On recrystallization from ether and *n*-hexane 7.1 g (67%) of pure **11** was obtained, m. p. 133—136 °C. NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.56 (b, 1H — dissapp. on addtn. of D_2O), 3.66 (m, 4H), 6.9—7.9 (m, 12H). Ir: 3570, 3100, 1650, 1350, 1155 cm^{-1}.

Anal. for $C_{22}H_{20}ClNO_4S$ (429.91) Calc'd: C 61.46, H 4.69, N 3.26%
Found: C 61.32, H 4.85, N 3.48%.

2-(N-β-Hydroxyethyl)-amino-5-chlorobenzophenone (**12**)

Compound **11** (5.0 g, 11.5 mmol) was slurried in 75% H_2SO_4 (80 ml), briefly heated to 140 °C, and thereafter gradually cooled to 60 °C. The reaction mixture was poured on crushed ice (400 g) and the oily precipitate extracted (6 × 100 ml of ether). Etheric extracts were washed with satd. aqueous bicarbonate (100 ml) and dried. After evaporation of ether, a tarry residue crystallizes from aqueous methanol, 1.2 g (39% of yellow needles, m. p. 82—84 °C, NMR ($CDCl_3$): δ 2.34 (broad s, 1H — dissapp. on addtn. of D_2O), 3.37 (q, 2H), 3.84 (t, 2H), 6.7—7.8 (m, 8H), 8.35 (broad s, 1H-anilinic, dissapp. on addtn. of D_2O). Ir: 3650, 3300, 1620, 1220, 1120 cm^{-1}.

Anal. for $C_{15}H_{14}ClNO_2$ (275.73) Calc'd: C 65.34, H 5.12, N 5.09%
Found: C 65.55, H 5.15, N 5.16%.

N-*Tosyl*-N-*ethoxycarbonylmethyl-4-chloroaniline* (**13**)

N-Tosyl-4-chloroaniline (19.7 g, 70 mmol) was dissolved in dry toluene (400 ml) and NaH (55% suspension, 3.45 g, 80 mmol) was added. After 1 hr stirring 2 ml of ethanol was added, stirred for additional 15 min, the precipitated salt separated by sucction and washed with light petroleum yield quantitative (21.2 g), m. p. 356—360 °C Na-salt (21.2 g. 70 mmol) and ethyl-α-bromoacetate (29,2, 19.5 ml, 175 mmol) were dissolved in DMF (100 ml), stirred and heated at 60—65 °C for 3 hr. After the same treatment as described for **5**, crude **13** was purified on the column (120 g of silicagel) using CH_2Cl_2 as eluent. It was obtained 24.5 g (95%) of yellow oil. NMR (CCl_4) δ 1.14 (t, 3H), 2.37 (s, 3H), 4.08 (q, 2H), 4.23 (s, 2H), 7.0—7.6 (m, 8H).

N-*Tosyl*-N-*β-hydroxyethyl-4-chloroaniline* (**14**)

Compound **13** (3.7 g, 10 mmol) was dissolved in dry ether (50 ml), and 6.6 ml of an etheric solution containing 0.228 g (6 mmol) of LAH was added dropwise, maintaining slow boiling of the solution. After 1.5 hr heating under reflux the reaction solution was cooled, water (10 ml) and then 10% H_2SO_4 (15 ml) were added dropwise. The etheric layer was separated and the aqueous phase extracted with ether (2 × 20 ml). The extracts were combined and washed with satd. aqueous bicarbonate. After drying and evaporation, crude **14** was crystallized from benzene-light petroleum to give 3.05 g (93%), m. p. 98—100 °C. NMR ($CDCl_3$): δ 2.43 (s, 3H), 2.56 (s, 1H — dissapp. on addtn. of D_2O), 3.66 (s, 4H), 6.9—7.7 (m, 8H).

Anal. for $C_{15}H_{16}ClNO_3S$ (325.81) Calc'd: C 55.29, H 4.95, N 4.30%
Found: C 55.05, H 5.09, N 4.20%.

N-(β-*Benzoyloxyethyl*)-4-*chloroaniline* (**15**)

Attempted Friedel-Crafts acylation of **14** (1.6 g, 5 mmol) with benzoylchloride (3.5 g, 25 mmol) at 180—200 °C in the presence of $ZnCl_2$ (1.2 g) gave after 1 hr heating and after usual work-up, compound **15** as the only isolable product. On recrystallization from *n*-hexane 0.65 g (49%) were obtained m. p. 83—85 °C. NMR ($CDCl_3$) δ 3.53 (t, 2H), 4.00 (s, 1H — dissapp. on addtn. of D_2O), 4.53 (t, 2H), 6.5—8.2 (m, 9H).

Anal. for $C_{15}H_{14}ClNO_2$ (275.73) Calc'd: C 65.33, H 5.12, N 5.08%
Found: C 65.41, H 5.03, N 5.23%.

N-(β-*Hydroxyethyl*)-4-*chloroaniline* (**16**)

This compound was obtained from **15**, after brief treatment with diluted ethanolic-aqueous NaOH (equimolar, 18 hrs at room temp.). The same compound was obtained from **14** on detosylation with 75% H_2SO_4; m. p. 75—77 °C. NMR ($CDCl_3$): δ 2.58 (s, 1H — dissapp. on addtn. of D_2O), 3.6—3.8 (m, 4H), 6.9—7.7 (m, 4H).

Anal. for $C_8H_{10}ClNO$ (171.62) Calc'd: C 55.98, H 5.87, N 8.16%
Found: C 56.12, H 5.97, N 8.01%.

2-(N-*Carboxymethyl*)-*amino*-5-*chlorobenzophenone* (**17**)

Compound **5** (7.1 g, 15 mmol) was detosylated with 140 ml of 75% sulfuric acid as described for **12**. Crude crystallinic **17** was obtained after pouring the reaction mixture onto 600 g of crushed ice, (4.3 g, quantitative yield, m. p. 183—186 °C). An analytical sample was obtained on recrystallization from ethylacetate-light petroleum, m. p. 187—189 °C. NMR (pyridine-d_5) δ 4.30 (s, 2H), 6.8—7.9 (m, 8H), 9.5 and 10.9 (two broad s, 1H — both dissapp. on addtn. of D_2O). Ir: 3300, 1728, 1630 cm^{-1}.

Anal. for $C_{15}H_{12}ClNO_3$ (289.71) Calc'd: C 62.18, H 4.17, N 4.84%
Found: C 62.38, H 4.17, N 4.75%.

2-(N-*Ethoxycarbonylmethyl*)-*amino*-5-*chlorobenzophenone* (**18**)

Compound **17** (4.2 g, 14.5 mmol) and *p*-TsOH (5 mg) were dissolved in abs. EtOH (22 ml) and heated under reflux for 5 hr. On cooling and addition of 20 ml of MeOH, crude **18** crystallized (4.0 g, 89%, m. p. 101—103 °C. Anal. sample (from MeOH) had m. p. 103—105 °C. NMR (DMSO-d_6) δ 1.27 (t, 3H), 4.24 (m, 4H), 7.3—7.7 (m, 8H), 8.6 (broad s, 1H — dissapp. on addtn. of D_2O). Ir: 3270, 1710, 1622, 1230 cm^{-1}.

Anal. for $C_{17}H_{16}ClNO_3$ (317.76) Calc'd: C 64.25, H 5.07, N 4.41%
Found: C 64.31, H 5.27, N 4.60%.

Attempted selective reduction of **18**. — To the solution of compound **18** (2.54 g, 8 mmol) in anhydrous ether (80 ml), 0.37 g (9 mmol) of LAH in 12 ml of anhydrous ether was added dropwise. The mixture was heated under reflux for 1.5 hrs and then hydrolized as described for **14**. Usual work-up and evaporation of ether yielded 2.33 g of an oily mixture which was separated by chromatography (120 g silicagel) using methylenchloride-ether (98 : 2) as eluent. First fraction contained 12.5% of unreacted **18**. Further eluation gave following pure compounds:

2-(N-β-*Ethoxycarbonylmethyl*)-5-*chlorobenzhydrol* (**24**)

(**24**) was obtained as the second fraction (0.324 g, 21.1%); on crystallization from aqueous methanol it had m. p. 92—94 °C. NMR ($CDCl_3$): δ 1.23 (t, 3H), 3.25 (m, 1H — dissapp. on addtn. of D_2O), 3.80 (d, 2H, J = 9 Hz — on addtn. of D_2O turns over into singlet), 4.20 (q, 2H), 5.21 (m, 1H — dissapp. on addtn. of D_2O), 5.80 (m, 1H), 6.4—7.4 (m, 8H). Ir: 3430, 3350, 1708, 1235, 1180, 1014 cm^{-1}.

Anal. for $C_{17}H_{18}ClNO_3$ (319.78) Calc'd: C 63.85, H 5.67, N 4.38%
Found: C 63.66, H 5.88, N 4.44%.

2-(N-β-Hydroxyethyl)-amino-5-chlorobenzhydrol (**20**) was obtained as the third oily fraction (0.715 g, 26.3%). On crystallization from benzene-light petroleum (5 : 1), colourless crystalls were separated m. p. 92—94 °C. NMR (CD_3OD): δ 3.14 (t, 2H), 3.67 (t, 2H), 3.80 (s, 1H), 6.7—7.6 (m, 8H). Ir: 3405, 3230, 1075, 1028 cm^{-1}.

Anal. for $C_{15}H_{16}ClNO_2$ (277.74) Calc'd: C 64.86, H 5.81, N 5.04%
Found: C 64.62, H 5.98, N 5.14%.

2-(N-β-Hydroxyethyl)-amino-5-chlorobenzophenone (**12**)

Last fraction contained 0.062 g (2.5%) of crude **12**, which was crystallized from aqueous MeOH, m. p. 82—84 °C. NMR ($CDCl_3$): δ 2.34 (broad s, 1H — dissapp. on addtn. of D_2O), 3.37 (q, 2H), 3.84 (t, 2H), 6.7—7.8 (m, 8H), 8.35 (broad s, 1 H — dissapp. on addtn. of D_2O).

2-(N-β-Hydroxyethyl-β-d_2)-amino-5-chlorobenzhydrol-1-d (**19**)

Compound **18** (4.12 g, 13.0 mmol) in 120 ml of ether, was reduced with LAH-d_4 in etheric suspension (1.5 g in 75 ml of ether) using reversal addition of reactants as described for **14** and **20**. The crude product (1.8 g, 50%) was crystallized from benzene-light petroleum, m. p. 90—92 °C. NMR (CD_3OD): δ 3.13 (s, 2H), 6.5—7.5 (m, 8H).

2-(N-β-Hydroxyethyl-β-d_2)-amino-5-chlorobenzophenone (**21**)

To the solution of potassium permanganate (20.2 g, 128 mmol) in hot water (120 ml), solution of manganese sulfate (22.2 g, 131 mmol) in water (15 ml), and 40% sodium hydroxide (23.5 ml) were contemporarely added dropwise, at 80—90 °C during 1 hr. After additional stirring for 1 hr, the precipitate was filtered off, thoroughly washed with water and dried at 120—125 °C for 18 hr. The amorphous oxyde was then ground in a mortar and pulverized, dried further for 24 hr at 120—125 °C yielding 23 g of »active« manganese dioxide. The dioxide was gradually added during 30 hr to a refluxing solution of **19** (2.0 g, 7.1 mmol) into anhydrous acetone (200 ml). The anorganic precipitate was filtered off, washed with acetone, and the filtrate evaporated. The crude product was purified by chromatography (70 g silicagel column) using benzene-ethylacetate (10 : 1) as eluent. The main fraction consisted of 0.941 g (47.8%) of **21**, which crystallizes from methanol, m. p. 80—82 °C. NMR ($CDCl_3$): δ 2.50 and 8.5 (two broad s, 1H — both dissapp. on addtn. of D_2O), 3.40 (s, 2H), 6.7—7.7 (m, 8H).

2-(N-β-Bromoethyl)-amino-5-chlorobenzophenone (**22**)

Compound **20** (550 mg, 2.0 mmol) in 6 ml of 48% aq. HBr was heated under reflux for 30 hr. The reaction mixture was poured on ice, extracted with ether (3 × 20 ml), extracts were dried, evaporated, and the residual oil crystallized from aqueous ethanol. It was obtained 428 mg (63%) of **22**, m. p. 90—91 °C (lit.[4] m. p. 91—92 °C).

2-(N-β-Bromoethyl-β-d_2)-amino-5-chlorobenzophenone (**1**)

Solution of compound **21** (5.5 g, 20 mmole) in nitromethane (100 ml) was ice-cooled and PBr_3 (12 ml, 34.2 g, 120 mmol) was added dropwise over a period of 2 hr. After additional stirring for 8 hr at ambient temperature the reaction mixture was poured on ice and worked-up as described for **22**. Crystallization yielded 1.77 g (25.8%) of **1** with m. p. 92—93 °C. NMR ($CDCl_3$): δ 3.58 (d, 2H, J 6.5 Hz), 6.6—7.7 (m, 8H), 8.6 (t, 1H — dissapp., and d at 3.58 turns over into s, on addtn. of D_2O).

2-(N-β-Acethyloxyethyl)-amino-5-chlorobenzophenone (**23**)

Compound **12** (234 mg, 0.8 mmol) dissolved in 48% HBr in glacial acetic acid (4 ml) was stirred for 2 hr at room temperature. The solution was poured on ice-

-water (50 ml), neutralized and extracted with ether (3 × 20 ml). Dried extracts were evaporated leaving a yellow oil which crystallized from n-hexane; yield 168 mg (66%), m. p. 53—55 °C. NMR ($CDCl_3$): δ 2.06 (s, 3H), 3.51 (q, 2H), 4.33 (t, 2H), 6.7—8.8 (m, 8H), 8.6 (broad s, 1H — dissapp. on addtn. of D_2O). Ir: 3340, 1728, 1620, 1565, 1385, 1230 cm^{-1}.

Anal. for $C_{17}H_{16}ClNO_3$ (317.76) Calc'd: C 64.40, H 5.06, N 4.40%
Found: C 64.16, H 5.35, N 4.51%.

2-(N-Methyl-N-Ethoxycarbonylmethyl)-amino-5-chlorobenzophenone (**25**)

Compound **18** (8.0 g, 25 mmol) dissolved in a mixture of 98—100% formic acid (70 ml) and 35% aqueous formaldehyde (30 ml), was heated at 95—100° for 18 hr. The reaction mixture was then poured in ice-water (600 ml), neutralized with bicarbonate, and extracted with ether (4 × 250 ml). Etheric extracts were dried, evaporated, and the residual oil purified by chromatography (300 g silicagel) using benzene as eluent. The main fraction consisted of 4.99 g (60%) of pure **25**, yellow oil. NMR (CCl_4): δ 1.20 (t, 3H), 2.80 (s, 3H), 3.33 (s, 2H), 4.08 (q, 2H), 6.9—8.0 (m, 8H).

Anal. for $C_{18}H_{18}ClNO_3$ (331.79) Calc'd: C 65.15, H 5.47, N 4.22%
Found: C 65.32, H 5.51, N 4.07%.

2-(N-Methoxycarbonylmethyl)-amino-5-chlorobenzophenone (**29**)

(**29**) has been obtained in 60% yield when **17** (or **18**; 10 mmol) was stirred in DMF (50 ml) with BaO (5 g) and MeJ (5 ml), and the reaction mixture worked-up as described earlier[1]. Crude **29** was purified by recrystallization from methanol, giving a pure sample, m. p. 100—102 °C. NMR ($CDCl_3$): δ 3.76 (s, 3H), 4.03 (d, 2H), 6.6—7.8 (m, 8H), 8.6 (broad s, 1H, dissapp. on addtn. of D_2O).

Anal. for $C_{16}H_{14}ClNO_3$ (303.74) Calc'd: C 63.27, H 4.65, N 4.61%
Found: C 63.21, H 4.57, N 4.50%.

2-(N-Methyl-N-β-hydroxyethyl-β-d_2)-amino-5-chlorobenzhydrole-1-d (**26**) was obtained in 92.4% yield from **25** (13.6 g, 41 mmol) as a colourless oil using the same procedure as described for **19**. NMR ($CDCl_3$): δ 2.46 (s, 3H), 3.00 (s, 2H), 4.23 (broad s, 2H — dissapp. on addtn. of D_2O), 7.0—7.6 (m, 8H).

2-(N-Methyl-N-β-hydroxyethyl-β-d_2)-amino-5-chlorobenzophenone (**27**) was obtained by oxydation of **26** (3.3 g, 11 mmol) with »active« MnO_2 as described for **21**; yield 45%, visc. oil. NMR ($CDCl_3$): δ 2.63 (s, 3H), 2.60 (broad s, 1H — dissapp. on addtn. of D_2O), 3.20 (s, 2H), 7.0—8.0 (m, 8H).

Anal. for $C_{16}H_{14}D_2ClNO_2$ (291.77) Calc'd: C 65.86, H + D 6.22, N 4.80%
Found: C 65.64, H + D 6.45, N 4.58%.

2-(N-Methyl-N-β-bromoethyl-β-d_2)-amino-5-chlorobenzophenone (**28**) was obtained by bromination of **27** (2.88 g, 9.8 mmol) as described for **1**; 78% yield; visc. yellow oil. NMR ($CDCl_3$): δ 2.70 (s, 3H), 3.30 (s, 2H), 6.9—8.0 (m, 8H). Ir (nujol): 2960—2810, 1660, 1595, 1495, 1460, 1450, 1395, 890, 810, 720 cm^{-1}.

Anal. for $C_{16}H_{13}D_2BrClNO$ (354.68) Calc'd: C 54.18, H + D 4.83, N 3.95%
Found: C 54.31, H + D 4.98, N 3.68%.

2-Aziridino-5-chlorobenzophenone (**34**)

Compound **22** (1.0 g, 3 mmol) added to a slurry of BaO (1.0 g) in DMF (20 ml) was stirred and heated at 60—65 °C for 24 hr. The reaction mixture was then filtered, the solvent evaporated and the residual oil crystallized from n-heptane. 711 mg (79.2%) of yellow crystalls were obtained, m. p. 105—106 °C, NMR ($CDCl_3$): δ 1.97 (s, 4H), 6.8—8.0 (m, 8H). Ir: 3060, 2995, 1662, 1290, 1120, 830 cm^{-1}.

Anal. for $C_{15}H_{12}ClNO$ (257.71) Calc'd: C 69.90, H 4.69, N 5.44%
Found: C 70.15, H 4.49, N 5.55%.

2-Aziridino-5-nitrobenzophenone (**35**)

To 2-chloro-5-nitrobenzophenone (10.0 g, 38.3 mmol) dissolved in anhydrous benzene (500 ml), a solution of ethylenimine (10.0 ml, 8.32 g, 190 mmol) in benzene (100 ml) was added dropwise. The reaction mixture was stirred for 16 hr at ambient temperature, then heated under reflux for 16 hr. The cold solution was filtered, the filtrate evaporated to a resinous residue, which was crystallized from hot ethanol on addition of charcoal. Pure **35** (5.5 g, 76%) was obtained, m. p. 135—136 °C. NMR ($CDCl_3$): δ 2.14 (s, 4H), 7.0—8.3 (m, 8H). Ir: 3080, 3000, 1665, 1510, 1370, 1270, 1130, 845 cm^{-1}.

Anal. for $C_{15}H_{12}N_2O_3$ (268.26) Calc'd: C 67.15, H 4.51, N 10.44%
Found: C 67.35, H 4.83, N 9.98%.

2-(N-Methyl-N-β-bromopropyl)-amino-5-chlorobenzophenone (**38**)

Starting from 2-(N-methyl-N-β-hydroxypropyl)-amino-5-chlorobenzophenone (2.47 g, 8.1 mmol) bromination was performed in nitromethane (40 ml) using PBr_3 (4.4 ml, 12.54 g, 4.6 mmol) as described for **1**. The crude product was purified by chromatography on a column (45 g, silicagel) using benzene-ether (5 : 1) as eluent. The main fraction contained 0.96 g (32.5%) of yellow oil. NMR ($CDCl_3$): δ 1.40 (d, 3H, J = 11.5 Hz), 2.73 (s, 3H), 3.1—3.5 (m, 2H), 3.7—4.4 (m, 1H), 6.9—7.9 (m, 8H).

Anal. for $C_{17}H_{17}BrClNO$ (366.69) Calc'd: C 55.68, H 4.67, N 3.82%
Found: C 55.79, H 4.52, N 3.98%.

2-(N-β-Hydroxypropyl)-amino-5-nitrobenzophenone (**30**)

Starting from 2-chloro-5-nitrobenzophenone (10.46 g, 40 mmol) and (S)-(+) L-alaninol (5 g, 66.5 mmol), $[\alpha]_D^{20} = +23\,^{\circ}C$ (c = 2 in EtOH), using BaO (8.5 g) in DMF (120 ml) as described for **34**, crude **30** was obtained (13.4 g brown, glassy oil). It was purified on a column (240 silicagel) using benzene-ether (5 : 1) as eluent. The main fraction consisted of 9.96 g (83%) of a crystallinic product, m. p. 110—112 °C. $[\alpha]_D^{23}$ + 9.5° (c 2.1 in $CHCl_3$). NMR ($CDCl_3$): δ 1.32 (d, 3H, J = 6 Hz), 2.83 (broad t, 1 H, dissapp. on addtn. of D_2O), 3.93 (m, 3H), 6.85 (d, 1H, J = 10 Hz), 7.6—8.4 (m, 8H), 9.07 (broad d, 1H — dissapp. on addtn. of D_2O). Ir: 3590, 3250, 1630, 1566, 1520, 1330, 1300, 1245, 1105 cm^{-1}.

Anal. for $C_{16}H_{16}N_2O_4$ (300.30) Calc'd: C 63.99, H 5.37, N 9.33%
Found: C 64.15, H 5.32, N 9.50%.

2-(N-1′-Hydroxybutyl-2′)-amino-5-nitrobenzophenone (**31**)

Starting from 2-chloro-5-nitrobenzophenone (7.32 g, 28 mmol) and S-(+)-2--aminobutanol $[\alpha]_D^{23}$ + 11.3°, (c 2.5 in EtOH) (7.5 g, 84 mmol) using BaO (8 g) in DMF (140 ml) as described for **30** and **34**, crude **31** was obtained (11 g, brown oil). It was purified on a column (340 g silicagel), using benzene-ether (4 : 1) as eluent. The main fraction consisted of 7.83 g (89%) of a yellow oil, $[\alpha]_D^{20}$ — 54.7° (c 2.1 in $CHCl_3$). NMR ($CDCl_3$): δ 1.00 (t, 3H), 1.67 (m, 2H), 2.40 and 9.5 (two broad s, 1H each — both dissapp. on addtn. of D_2O), 3.77 (m, 3H), 6.9—8.4 (m, 8H). Ir: ($CHCl_3$): 3620, 3280, 1628, 1536, 1330, 1310 cm^{-1}.

Anal. for $C_{17}H_{18}N_2O_4$ (314.33) Calc'd: C 64.96, H 5.77, N 8.91%
Found: C 65.12, H 6.01, N 8.89%.

2-(N-β-Bromopropyl)-amino-5-nitrobenzophenone (**32**)

As described for **1** compound **32** was prepared starting from **30** (9.57 g, 31.9 mmol) in nitromethane (145 ml), using PBr_3 (39.4 g, 145 mmol). The crude product **30** (8.5 g, brown oil) was purified on a column (140 g silicagel) using benzene-ether (5 : 1) as eluent. The main fraction consisted of 2.78 g (24%) **32** a yellow oil, $[\alpha]_D^{24}$ 121.5° (c 2.14 in $CHCl_3$). NMR (CCl_4): δ 1.47 (d, 3H, J = 6 Hz), 3.45 (d, 2H, J = 4 Hz),

3.97 (m, 1H), 6.70—8.3 (m, 8H), 9.4 (broad d, 1H — dissapp. on addtn. of D_2O). Ir (Neat film): 2265, 1630, 1580, 1530, 1330, 1260, 700 cm^{-1}.

Anal. for $C_{16}H_{15}BrN_2O_3$ (363.21) Calc'd: C 52.91, H 4.16, N 7.71%
Found: C 53.19, H 4.41, N 7.49%.

2-(N-1'-Bromobutyl-2')-amino-5-nitrobenzophenone (**33**)

Compound **33** was prepared starting from 6.44 g (20 mmol) of **31**, and using PBr_5 (9 ml, 25.6 g, 94 mmol) in nitromethane (80 ml) as described for **32.** The crude product (7.4 g) was purified on a column (90 g silicagel) using benzene-ether (5 : 1) as eluent. Pure **33** (2.88 g, 42.7%, yellow oil) had $[\alpha]_D^{20}$ + 63° (c 2.04 in $CHCl_3$). NMR ($CDCl_3$): δ 1.03 (t, 3H), 1.6—2.3 (m, 2H), 3.5—4.2 (m, 3H), 6.8—8.4 (m, 8H), 9.3 (broad s, 1H — dissapp. on addtn. of D_2O). Ir (nujol): 3260, 1630, 1530, 1335, 1300 cm^{-1}.

Anal. for $C_{17}H_{17}BrN_2O_3$ (377.24) Calc'd: C 54.12, H 4.54, N 7.43%
Found: C 54.24, H 4.76, N 7.27%.

2-(2'-(S)-Methylaziridino)-5-nitrobenzophenone (**36**)

From **32** (1.57 g, 4.3 mmol) compound **36** was obtained by cyclization with BaO/DMF (1.6/45 ml) at 75°/4 hr as described for **34.** After usual work-up the crude product (1.9 g) was purified on a column (45 g silicagel) using benzene-ether (5 : 1) as eluent. Pure **36**, yellow oil (1.044 g, 86.1%) had $[\alpha]_D^{24}$ + 58.5° (c = 2 in $CHCl_3$). NMR ($CDCl_3$): δ 1.10 (d, 3H, J = 6 Hz), 1.9—2.5 (m, 3H), 7.0—8.4 (m, 8H). Ir (neat film): 3065, 2990, 2930, 1670, 1605, 1580, 1515, 1340, 1270, 802 cm^{-1}.

Anal. for $C_{16}H_{14}N_2O_3$ (282.29) Calc'd: C 68.07, H 5.00, N 9.93%
Found: C 67.87, H 5.01, N 9.85%.

2-(2'-(S)-Ethylaziridino)-5-nitrobenzophenone (**37**)

From **33** (1.77 g, 4.7 mmol) compound **37** was obtained as described for **36**, and was purified on a column (45 g silicagel) using benzene-ether (10 : 1) as eluent. Pure **37**, pale-yellow oil (1.23 g, 88.6%) had $[\alpha]_D^{20}$ + 168.1° (c 2.2 in $CHCl_3$). NMR ($CDCl_3$): δ 0.91 (t, 3H), 1.0—2.0 (m, 2H), 1.9—2.5 (m, 3H), 7.0—8.4 (m, 8H), Ir (nujol): 2965, 2875, 1665, 1510, 1475, 1465, 1330 cm^{-1}.

Anal. for $C_{17}H_{10}N_2O_3$ (296.31) Calc'd: C 68.90, H 5.44, N 9.46%
Found: C 69.02, H 5.57, N 9.60%.

Compound **37** was also more conveniently obtained (82% yield) starting from 2--chloro-5-nitrobenzophenone and 2-S-(—)-ethylaziridine, $[\alpha]_D^{23}$ — 11.9° (for neat liquid), which was prepared according to the procedure for R-(+)- enantiomer[22], using the BaO/DMF condensation method.

2-Amino-5-chlorobenzophenone-1'-hydroxybutyl-2'-imine (**49**)

2-Amino-5-chlorobenzophenone (10.0 g, 43.2 mmol) 2-S-(+)-aminobutanol (40 ml, 37.6 g) and 2 ml of glac. acetic acid were heated under reflux for 6 hrs. The reaction mixture was cooled, poured on 600 ml ice-water, extracted with 2 × 200 ml of ether, organic layers combined, washed with water, dried, evaporated, and the residual oil crystallized from ether-light petroleum to give 8.6 g (65.7%) of **49**, m. p. 113—117 °C. NMR ($CDCl_3$): δ 0.78 (t, 3H), 1.46 (m, 2H), 3.2—3.8 (m, 3H), 6.5—7.8 (m, 8H).

Anal. for $C_{17}H_{19}ClN_2O$ (302.79) Calc'd: C 67.43, H 6.32, N 9.25%
Found: C 67.15, H 6.04, N 9.47%.

1,2-Dihydro-3-(S)-ethyl-5-phenyl-7-chloro-3H-1,4-benzodiazepine (**50**)

Cyclization of **49** (1.00 g, 3.6 mmol) was performed in polyphosphoric ester (PPE, 100 g) by heating at 140°C for 4 hr. The work-up was performed as recently

described[30], and crude product (0.76 g), was purified by crystallization from ether-light petroleum, m. p. 139—141 °C, $[\alpha]_D^{23}$ + 290.5° (c 1.48 in $CHCl_3$). NMR ($CDCl_3$): δ 1.03 (t, 3H), 1.4—2.2 (m, 2H), 3.2—4.1 (m, 4H), 6.4—7.7 (m, 8H). Ir: 3350, 1608, 1595, 1572, 1560, 1500, 890, 815, 705 cm^{-1}.

Anal. for $C_{17}H_{17}ClN_2$ (284.78) Calc'd: C 71.69, H 6.01, N 9.84%
Found: C 71.67, H 6.24, N 9.80%.

Runs of cyclization and recyclization into 1,4-benzodiazepines under β-participation

All experiments with ammonia (ethanolic solution saturated at 0 °C were performed in sealed tubes (20—100 ml), heated in a thermostate at 125—130 °C. Experiments with ethanolic urotropine were performed under reflux. Reactions times required for high conversion of starting matherials were determined in preliminary semi-micro experiments, using tlc-controle. All separations of structural isomers were performed quantitatively by column chromatography on silicagel.

1,2-Dihydro-2-d_2*-(3-*d_2*)-5-phenyl-7-chloro-1-methyl-3*H*-1,4-benzodiazepine* (**39** and **40**)

Compound **28** (0.531 g, 1.5 mmol), and hexamine (0.6 g, 4.3 mmol) in abs. ethanol (10 ml) were heated under reflux for 20 hr. The solvent was then evaporated, the residue dissolved in chloroform (10 ml), and washed with water (10 ml). The aqueous layer was basified (pH 9) and washed (3 × 10 ml of chloroform), the organic layers combined, dried and evaporated. The crude mixture was purified by chromatography (30 g of aluminium oxyde, Fluka) using benzene-acetone (8 : 1) as eluent. A pure mixture of **39** and **40** (45/55 by NMR; 70% total yield) crystallizes from aqueous acetone m. p. 98—100 °C (lit.[36] m. p. for non-deuterated compound: 102—103 °C).

*1,2-Dihydro-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine* (**47**)

Compound **34** (1.03 g, 4.0 mmol) dissolved in 10 ml of ethanolic ammonia, was heated in a sealed tube at 135 °C for 8 hr. After evaporation of solvent the crude product was crystallized from methanol yielding 725 mg (71%) of **47**, m. p. 173—175 °C (lit.[36] m. p. 174—176 °C — for the sample obtained by LAH-reduction of the corresponding 2-one derivative).

*1,2-Dihydro-5-phenyl-7-nitro-3*H*-1,4-benzodiazepine* (**48**)

Starting from **35** (1 g, 3.7 mmol) compound **48** was obtained in the same way as described for **47**. The crude product was crystallized from acetone to give 700 mg (70.5%) of pure substance, m. p. 210—212 °C (lit.[37] m. p. 211—212 °C — for the sample obtained by condensation of 2-chloro-5-nitro-benzophenone with ethylendiamine).

*1,2-Dihydro-1,3-(and 1,2)-dimethyl-5-phenyl-7-chloro-3*H*-1,4-benzodiazepines* (**45** and **46**)

Compound **38** (0.64 g, 1.7 mmol) and hexamine (0.6 g, 4.3 mmol) in abs. ethanol (10 ml) were heated under reflux for 6 hrs. The reaction mixture was treated as described for **39**/**40**. Crude products were purified on a column (30 g silicagel) using benzene-ether (4 : 1) as eluent.

Compound **45** was obtained as the first fraction (145 mg), which gave yellow plates on crystallization from aqueous acetone, m. p. 103—105 °C. NMR ($CDCl_3$): δ 1.40 (d, 3H, J = 6.5 Hz), 2.80 (s, 3H), 3.0—3.9 (m, 3H), 6.7—7.8 (m, 8H).

Anal. for $C_{17}H_{17}ClN_2$ (284.78) Calc'd: C 71.69, H 6.02, N 9.84%
Found: C 72.00, H 6.22, N 9.90%.

Compound **46** was eluated as the second (195 mg), and crystallizes from diisopropyl-ether pale yellow crystalls, m. p. 92—94 °C. NMR ($CDCl_3$): δ 1.17 (d, 3H, J = 6,5 Hz), 2.73 (s, 3H), 3.1—4.2 (m, 3H), 6.7—7.7 (m, 8H).

Anal. for $C_{17}H_{17}ClN_2$ (284.78) Calc'd: C 71.69, H 6.02, N 9.84%
Found: C 71.91, H 6.14, N 10.02%.

Total yield of both **45** and **46** was 71%, and their ratio (**45/46**) was 43 : 57.

Cyclization of **32** was performed with 1.05 g (2.9 mmol) of **32** in **15** ml of ethanolic ammonia. After 36 hrs at 125° (sealed tube) the reaction mixture was evaporated and crude products **41** and **42** were separated on a column (80 g silicagel, ether as eluent) as follows:

1,2-Dihydro-3(+)-methyl-5-phenyl-7-nitro-3H-1,4-benzodiazepine (**42**) was eluated as the first fraction (0.111 g) which crystallized from methylenchloride-light petroleum, m. p. 245—248 °C and had $[\alpha]_D^{24}$ + 114.4° (c 1.04 in $CHCl_3$). NMR (DMF-d_7): δ 1.50 (d, 3H, J = 7 Hz), 3.5—4.2 (m, 3H), 6.9—8.1 (8H), 7.8—8.1 (m, 1H — dissapp. on addtn. of D_2). Ir: 3325, 1620, 1605, 1545, 1306, 700 cm^{-1}.

Anal. for $C_{16}H_{15}N_3O_2$ (281.30) Calc'd: C 68.31, H 5.37, N 14.93%
Found: C 68.06, H 5.64, N 15.00%.

1,2-Dihydro-2(S)-methyl-5-phenyl-7-nitro-3H-1,4-benzodiazepine (**41**) was eluated as the second (0.506 g), amorphous powder m. p. 55—58 °C, $[\alpha]_D^{23}$ + 311.4° (c 1.94 in $CHCl_3$). NMR ($CDCl_3$): δ 1.28 (d, 3H, J = 6 Hz), 3.4—4.3 (m, 3H), 7.00—8.2 (8H), 7.8—8.2 (m, 1 H — dissapp. on addtn. of D_2O). Ir: 3360, 1612, 1535, 1300, 700 cm^{-1}.

Anal. for $C_{16}H_{15}N_3O_2$ (281.30) Calc'd: C 68.31, H 5.37, N 14.93%
Found: C 68.48, H 5.52, N 14.82%.

The total yield on **41** and **42** was 75.7%.

Cyclization of **33** was performed with 1.00 g (2.7 mmol) of **33** in 10 ml of ethanolic ammonia. After 20 hr at 120 °C the reaction mixture was worked-up as described for **39/40**, and the crude product mixture separated on a column (30 g silicagel, cyclohexane-ether-acetone 10 : 10 : 1 as eluent) as follows:

1,2-Dihydro-3(+)-ethyl-5-phenyl-7-nitro-3H-1,4-benzodiazepine (**44**) was obtained as the first fraction (38 mg), which crystallized from ethylacetate-light petroleum, m. p. 233—235 °C. NMR ($CDCl_3$): δ 1.13 (t, 3H), 1.5—2.4 (m, 2H), 3.4—3.8 (m, 3H), 5.05 (broad s, 1H), 6.6—8.2 (m, 8H). Ir: 3350, 3230, 1623, 1545, 1290, 1250 cm^{-1}. $[\alpha]_D^{20}$ + 227° (c 1.64 in $CHCl_3$).

Anal. for $C_{17}H_{17}N_3O_2$ (295.33) Calc'd: C 69.13, H 5.80, N 14.23%
Found: C 68.85, H 5.92, N 14.69%.

1,2-Dihydro-2(S)-ethyl-5-phenyl-7-nitro-3H-1,4-benzodiazepine (**43**) was eluated as the second fraction (508 mg), and crystallized from carbontetrachloride-light petroleum, m. p. 146—148 °C. NMR ($CDCl_3$): δ 1.00 (t, 3H), 1.3—1.9 (m, 2H), 3.5—4.4 (m, 3H), 4.97 (broad s, 1H), 6.5—8.3 (m, 8H). Ir: 3360, 3240, 1620, 1530, 1310, 1256 cm^{-1}. $[\alpha]_D^{20}$ + 279 ° (c 1.808 in $CHCl_3$).

Anal. for $C_{17}H_{17}N_3O_2$ (295.33) Calc'd: C 69.13, H 5.80, N 14.23%
Found: C 69.30, H 5.75, N 14.01%.

The total yield on **43** and **44** was 71%.

Recyclization of **36**

Compound **36** (0.826 g, 2.9 mmol) was treated under the same conditions as described for **32**, except heating was prolonged for 50 hrs. Total yield on **41** and **42** was 90.1%. They were separated as described for **32**, their ratio was 63 : 37. Both compounds exhibited identical m. p., NMR and Ir spectra as for samples obtained from **32**.

Compound **41** had a rotation $[\alpha]_D^{24}$ + 263° (c 1.86 in $CHCl_3$).

Compound **42** had a rotation $[\alpha]_D^{24}$ — 214.5° (c 1.1 in $CHCl_3$).

Recyclization of **37**

This compound was treated under the same conditions as described for **33**, except heating was prolonged for 72 hr. Total yield on **43** and **44** was 70%; they were separated as described before. Separation revealed their ratio as 76 : 24. Both compounds exhibited identical NMR and Ir spectra as samples obtained in a proceding run.

Compound **43** had a rotation: $[\alpha]_D^{20} + 321^0$ (c 2.2 in $CHCl_3$.

Compound **44** had a rotation: $[\alpha]_{20}^{D} -271^0$ (c 1.73 in $CHCl_3$).

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SAŽETAK

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Studij mehanizma ciklizacije *N*-supstituiranih 2-amino-benzofenona u 1,4-benzodiazepine; β-participacija vinilogno-amidnog dušikovog atoma

2-(*N*-β-Bromoalkil)-amino-5-supstituirani benzofenoni **28**, **32**, **33** i **38** ciklizirani su u 1,4-benzodiazepine **39**—**46** u etanolnoj otopini heksametilentetramina ili amonijaka. Deuterijem β-označeni spoj **28** dao je ciklizacijom dva 1,4-benzodiazepina (**39** i **40**) u omjeru 45/55, otkrivajući β-participaciju dušikovog atoma. Participacija susjedne skupine nadalje je istraživana određivanjem omjera i konfiguracije 2- i 3--supstituiranih kiralnih 1,4-benzodiazepina nastalih ciklizacijom: spoj **32** dao je (S)-**41** i (S)-**42** (omjer 82/12), spoj **33** dao je (S)-**43** i (S)-**44** (omjer 92/8), spoj **38** dao je **45** i **46** (omjer 58/42). Visoka regioselektivnost opažena je također za reciklizaciju aziridina **36** u (S)-**41** i (R)-**42** (omjer 63/37) kao i **37** u (S)-**43** i (R)-**44** (omjer 76/24). Stereokemijski ishod ciklizacije u **42** i **44** iz **32** i **33**, obrnut je u odnosu na slučaj kada se polazi od spojeva **37** i **38**. Apsolutna konfiguracija spojeva (—)- i (+)-**42** i **44** određena je usporedbom njihovih CD-spektara s onima spoja (S)-**50**, a i shema mehanizma reakcije koja tumači sve eksperimentalne rezultate.

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