Chiral 1,4-Benzodiazepines. V. (1). Synthesis and Properties of 1,4-Benzodiazepin-2-ones Containing α-Amino Acids as a Part of the 1,4-Diazepine Ring

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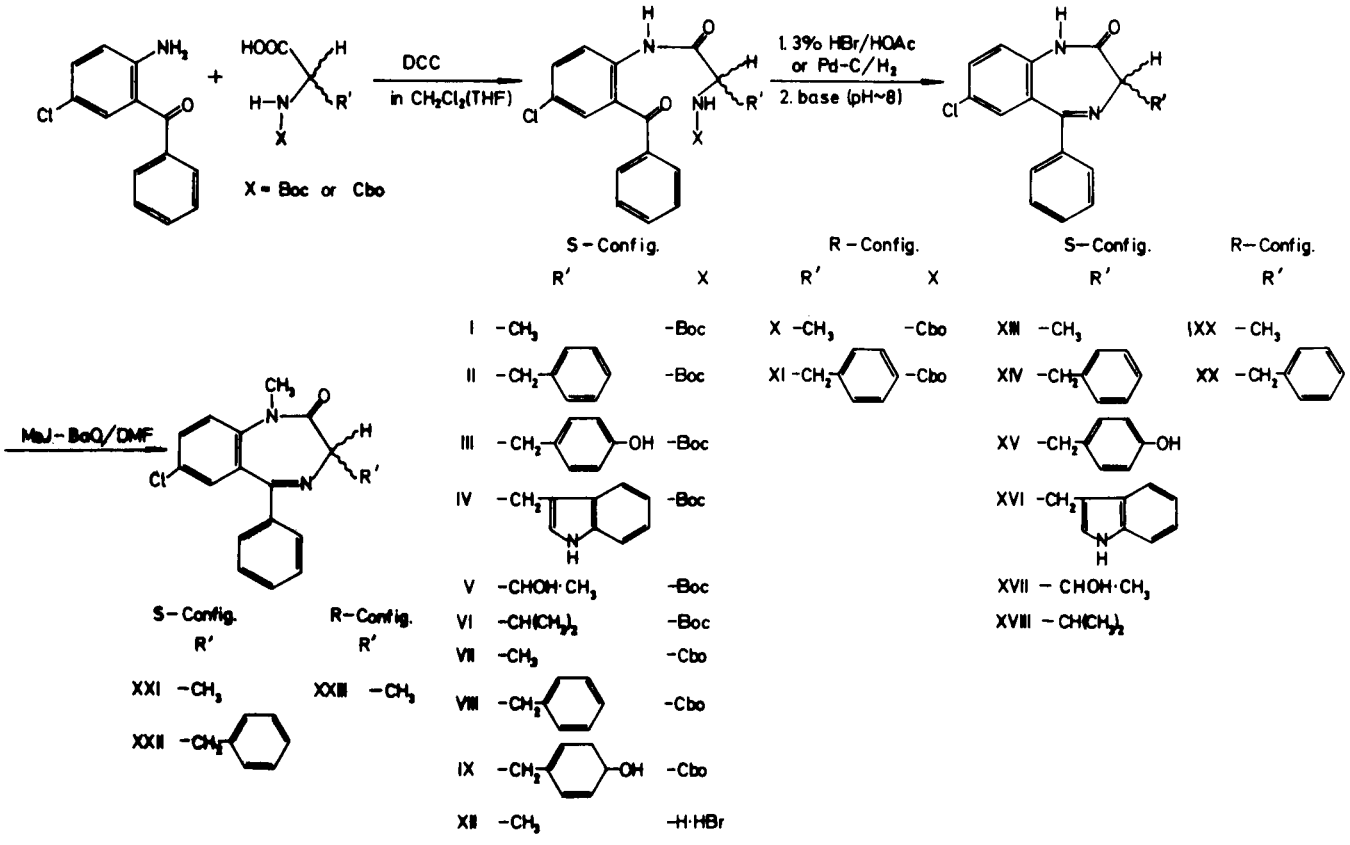
Chiral 1,4-benzodiazepin-2-ones XIII-XXIII (Scheme I) were prepared starting from *N*-protected α-amino acids and 2-amino-5-chlorobenzeophenone; the intermediates I-XII were isolated and identified. Spectroscopic properties of these compounds are discussed (ir, nmr); their optical stability, as well as the cyclization rate for XII-XIII in buffer solution have been determined.

Introduction.

The reasons for our interest in the synthesis of chiral 1,4-benzodiazepin-2-ones have been outlined in a previous paper (1), in which synthesis and resolution of diastereomeric 3-camphoyloxy derivatives were reported. Some additional points, however, prompted the preparation of chiral derivatives XIII-XXIII.

Remarkable activity on the central nervous system (CNS) was expected for the compounds possessing "natural" configuration on the chiral center in the 1,4-diazepine ring, *i.e.* for those prepared from (S)-α-amino acids. Two of these acids, (S)-α-phenylalanine and (S)-α-tyrozine are well known (2) biological precursors in the synthesis of L-Dopa and L-Dopamine, which are important neurotransmitters in CNS. Racemic forms of compounds XIII and XVIII have been prepared earlier (3), and the racemic form of XIII exhibited pronounced tranquillizing activity (4). Furthermore, compounds

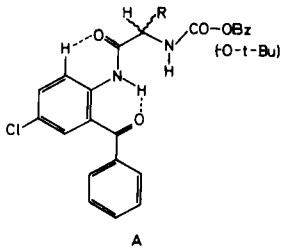


XIII-XX are intended as models for circular dichroism studies, enabling the prediction of the absolute configuration on the C-3 atom in some 1,4-benzodiazepines of unknown configuration (5).

Results and Discussion.

The compounds I-XX have been synthesized according to Scheme I, where Boc and Cbo means *t*-butoxycarbonyl carbobenzoxy protecting groups respectively.

The intermediates I-XI were mainly isolated by column chromatography because of their poor crystallization properties and complexity of the reaction mixture. Some physical data of these compounds are listed in Table I. Their ir spectra exhibited characteristic amide carbonyl bands at 1680-1690 cm^{-1} (Ar-NH-CO-) and at 1635-1640 cm^{-1} (*t*-Bu-O-CONH or Bz-O-CONH). Nmr spectra of these compounds (deuteriochloroform) included a characteristic multiplet at 7.3-7.65 ppm (7*H*-benzophenone moiety), while the signal for the eighth proton was regularly shifted to 8.60 ppm and resolved (see Fig. 1). This signal belongs to the proton on C-3 in the 2-amino-5-chlorobenzophenone moiety, indicating strong intramolecular hydrogen bonding with the amide carbonyl group (7).



A

The sharp singlet at 11.1 ppm caused by Ar-NH-CO- proton indicates another hydrogen bonding, thus confirming the structure A, similarly to those previously observed for some other *ortho*-amidobenzophenone derivatives (8).

Isolation of the compounds I-XII was complicated by the formation of considerable quantities of dicyclohexylurea derivatives XXIV-XXIX of the amino acids used (Table II). These compounds exhibited similar solubility and chromatographic properties as compounds I-XI, so that repeated chromatography was often required for their complete separation. Although such compounds are often mentioned as possible by-products in the course of the formation of the peptide bond (9,10), we were unable to find any physical data for them, even after carefully searching the literature. We are therefore including some data for the compounds XXIV-XXIX (Table II), which have been isolated and purified by chromatography. Their ir spectra included five characteristic bands at 3430-3440, 3220-3280 (both for NH stretching) 1705-1720 1670 and 1625-1630 cm^{-1} for carbonyl stretching vibrations, respectively. After removal of a protecting group (see Experimental) free amines cyclized spontaneously by changing the *p*H to about 7-8. Besides usual methods, we have found that a very fast and clean removal of the *t*-butoxy group can be achieved by dissolving a sample in 3% hydrobromic acid-acetic acid even at 0°. In its usefulness the method seems to equal other standard procedures (11,12). Chiral 1,4-benzodiazepin-2-ones XIII-XXIII exhibited strong optical rotations of the opposite sign as the intermediates I-XI (see Experimental), and strong Cotton effects in CD (5). Since these compounds represent particular cyclic derivatives of α-amino acids, where the amino group is built into an azomethine chromophore, there is additional activity (acidity enhancement) of the proton on the C-3 atom in the 1,4-diazepin-2-one in relation to the simple α-amino acids (13) or peptides. The *p*H-dependent optical stability of these compounds is therefore of real biological importance. An attempt was made to find a K/*p*H plot for the compounds XIII and XIV and two sets of twenty experiments were performed measuring time dependent rotation at *p*H 1.0-12.0 during 72 hours at 23 ± 1°. No observable racemization was observed at *p*H 1.0-9.0 during this period, but rotation was lowered *ca.* 4-5% at *p*H 10, *ca.* 10% at *p*H 11 and *ca.* 26% at *p*H 12 after 72 hours. These results indicate very low k values for this group of compounds so that further kinetic investigations are of no pharmacological interest. The ir spectra of the compounds XIII-XX exhibited a characteristic band at 1605-1615 cm^{-1}, ascribed to the azomethine double bond (14), as well as bands at 1670-1690 (amide carbonyl), 1460-1470, 1445-1450 cm^{-1}. Nmr spectra of these compounds revealed some interesting features caused by diastereotopic, *i.e.* magnetic nonequivalent groups near the center of chirality in the ring. The spectra of the compounds XIII and XXI showed one doublet at 1.76 ppm (CH_3) as well as a quartet at 3.79 ppm (proton on C-3) *i.e.* a simple AX_3 system becuase of the conical symmetry of the methyl group. However, a septet between 3.45-3.90 ppm was observed for the ABC system in the spectra of XIV and XX. On methylation of XIV to XXII this pattern remained practically unchanged (Fig. 2) indicating very small influence of the *N*-methyl group on the conformational mobility of the diazepine ring. For the similar *CH-CH_2- grouping in XV and XVI an unresolved multiplet at 3.40-3.80 ppm was observed. Diastereotopic methyl groups in XVIII gave rise to two superimposed doublets at 0.96 ppm and 1.07 ppm (J = 6.2 Hz, Δ = 6.2 Hz) along with a multiplet centered at 2.79 ppm (1H) and a doublet (1H) at 2.99 ppm (Fig. 3). Magnetic nonequivalence of these groups in the cyclic compound is approximately the same as in the open-

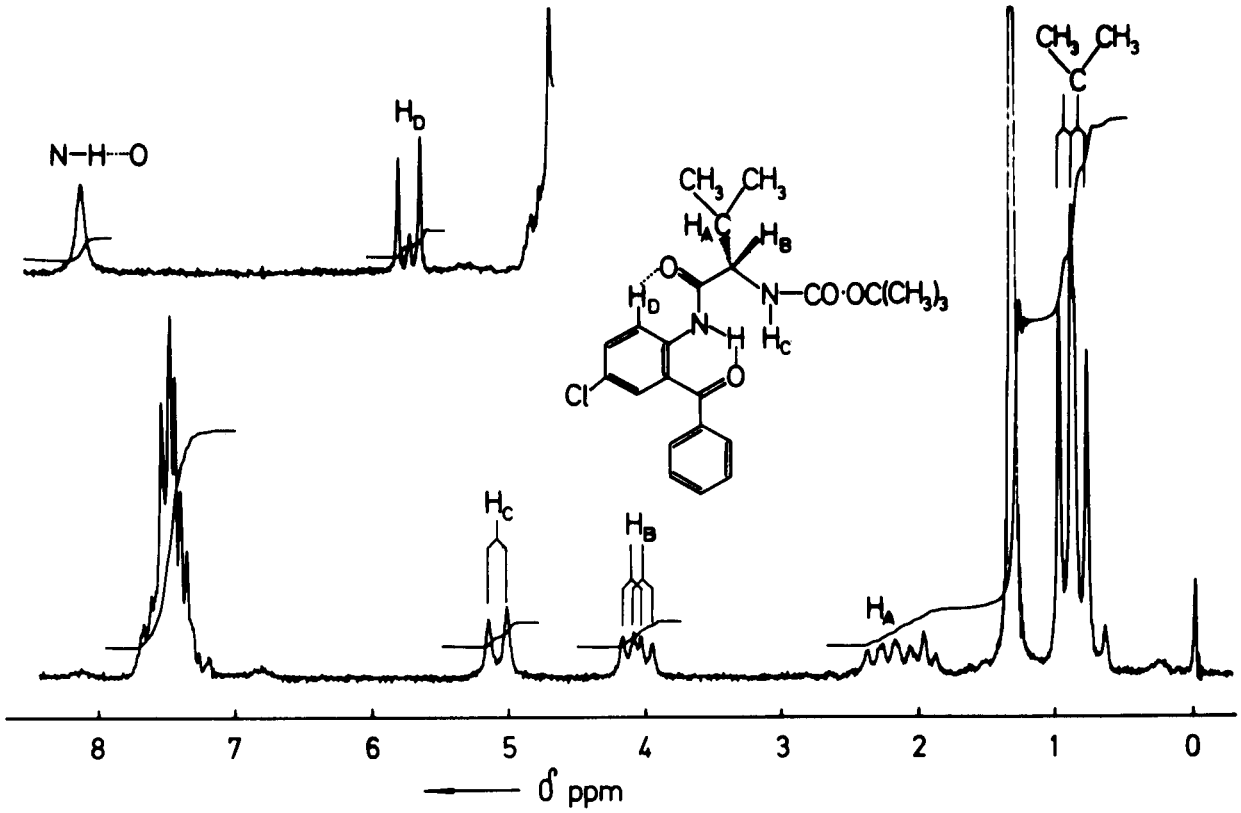


Fig. 1. Nmr spectrum (deuteriochloroform) of the compound VI.

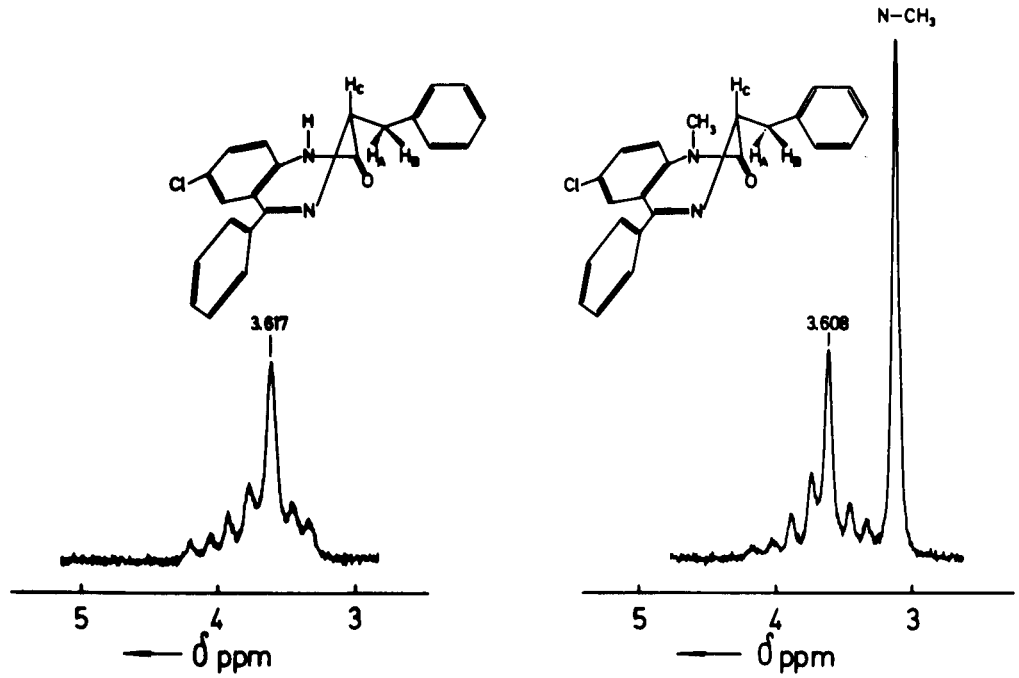


Fig. 2. Part of the ABC system in the nmr spectra (deuteriochloroform) of the compounds XIV and XXII.

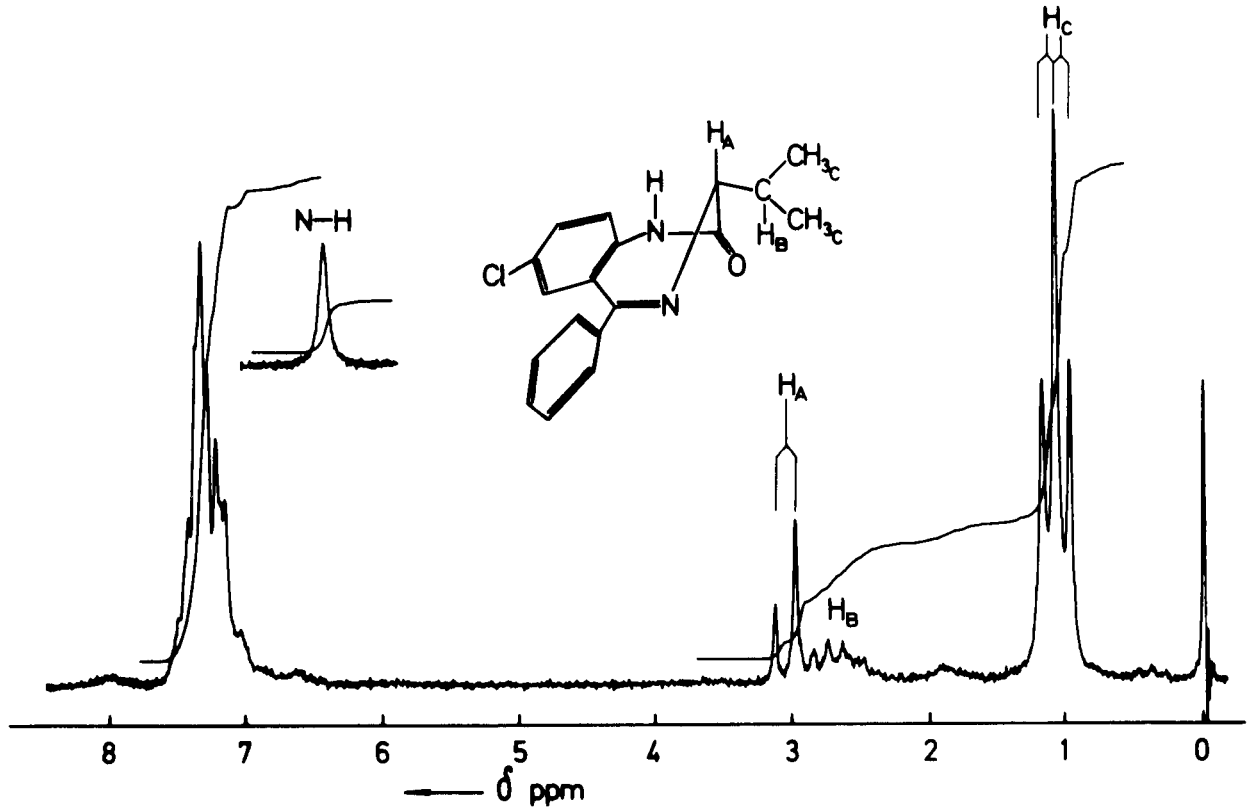
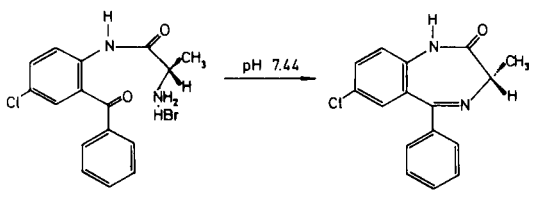


Fig. 3. Nmr spectrum (deuteriochloroform) of the compound XVIII.

chain derivative VI where J for the same double doublet is 5.6 Hz and Δ 6.4 Hz (see Fig. 1).

It was interesting from the pharmacological point of view to prepare some other derivatives of the title compounds. Compounds XIX, XX and XXIII (all of the R-series) have been prepared, enabling parallel pharmacological studies on both enantiomeric derivatives. Compounds XXI-XXIII have been synthesized becuase of their closer structural resemblance to some known N_1-methyl-1,4-benzodiazepin-2-ones of confirmed pharmacological value (15). Compound XII has been isolated as a hydrobromide in order to study, in this example, the *in vitro* cyclization rate of other possible precyclic *in vivo* precursors of 1,4-benzodiazepin-2-ones. On the basis of the uv spectra of XII and XIII (Fig. 4) rate constant measurements were performed at 283 and 361 nm.



The first order rate profile and a good linear plot through four half-lives were obtained at *p*H 7.44 and 37°, *i.e.* under conditions similar to the physiological ones. Following values for k_1 have been determined:

k_1 (283) = 4.335 x 10^{-4} sec^{-1} $t_{1/2}$ = 26.6 min.

k_1 (361) = 4.534 x 10^{-4} sec^{-1}

In view of the known time-dependent activity of some 1,4-benzodiazepines (16), these results indicate potential pharmacodynamic value of the compounds of the type XII as long-acting *in vivo* precursors of chiral 1,4-benzodiazepin-2-ones. Pharmacological investigations in this direction are in progress; many other variants of the chiral compounds presented can be imagined, but we hope to be guided in our further work by the biological results obtained from this first set of analogues. Preliminary results of biotransformations by rat liver homogenate, and anxiolitic behavior of animals, respectively, revealed significant difference in biological responses, both *in vitro* as well as *in vivo* of the enantiomeric compounds tested.

EXPERIMENTAL

All melting points were determined on a Kofler-Mikroheiztisch,

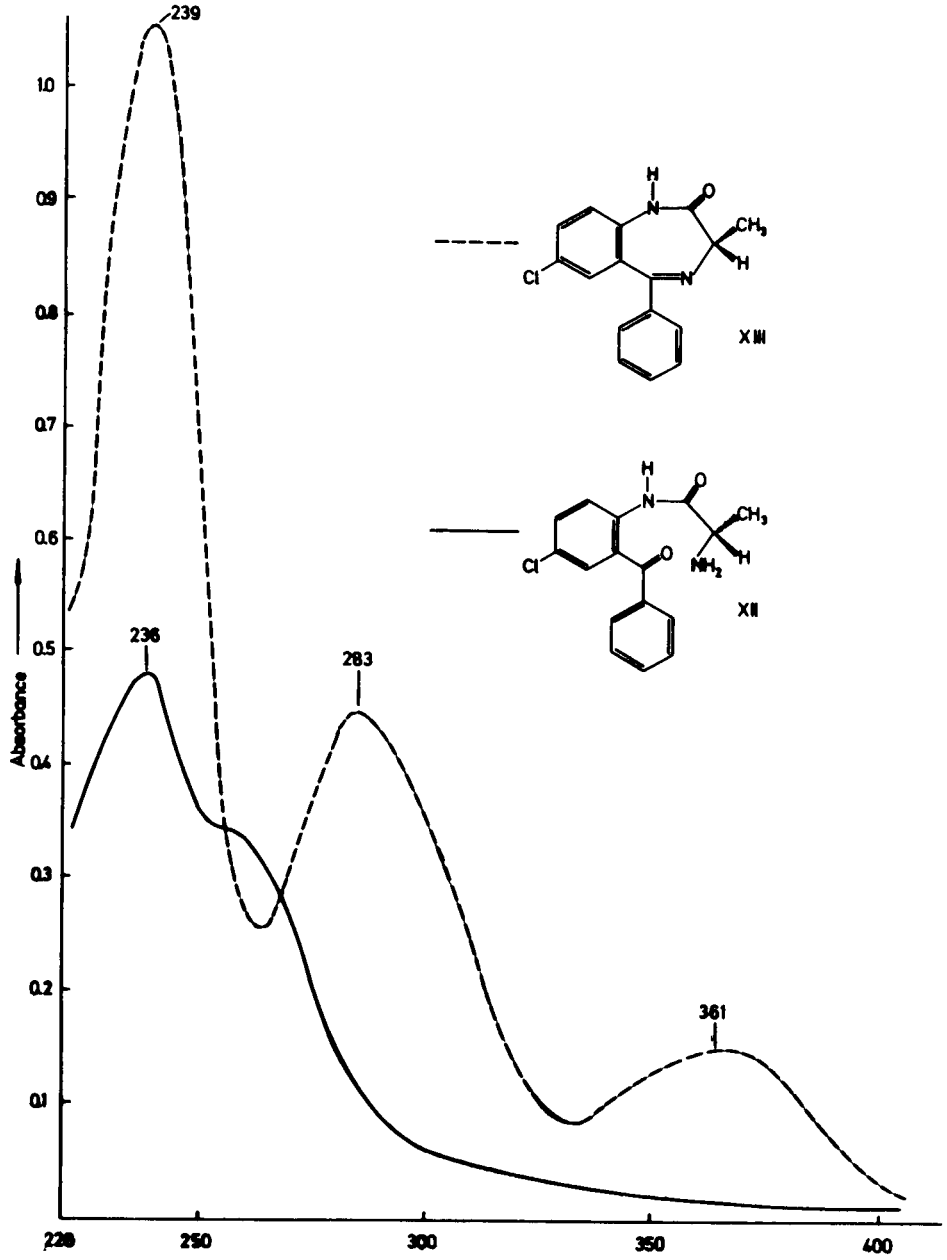


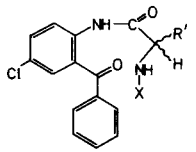
Fig. 4. Absorption spectra of XII (—) and XIII (-----) measured in 0.1 *N* hydrochloric acid ($c = 3.50 \times 10^{-4}$ *M*).

and are uncorrected. Ir spectra were obtained on a Perkin Elmer Model 131 Spectrophotometer; uv spectra and cyclization rate measurements were performed on a Zeiss Opton PMQ II Spectrophotometer; nmr spectra were obtained on a Varian A-60 or Varian T-60 apparatus using TMS (0.00 Hz) or Silicone grease (17) (4.0 Hz) as internal standard. Rotations were measured on a Perkin Elmer Model 141 apparatus, racemization rates were followed on the Opton-Zeiss Polarimeter 0.01°. Thin-layer and column chromatography were performed with the materials and by methods described under reference 1. Light petroleum refers to the fraction b.p. 40-60°. *N*-Boc protected amino acids used (L-Ala, L-Phe, L-Tyr, L-Trypt, L-Threo, L-Val) were puriss grade commerical products (Fluka). *N*-Cbo-protected amino acids (L-Ala, D-Ala, L-Phe, D-Phe, L-Tyr) were prepared in *ca.* 50 g. batches by the procedure already described (18).

General Procedure for the Preparation of the Compounds I-VI.

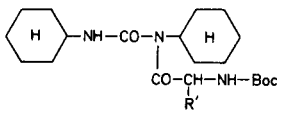
In 20 ml. of methylene chloride, 5.08 g. (22.0 mmoles) of 2-amino-5-chlorbenzophenone and 20.0 mmoles of the particular *N*-Boc-amino acid were dissolved. Because of the low solubility of *N*-Boc-L-tyrosine, *N*-Boc-L-tryptophane and *N*-Boc-L-threonine in methylene chloride, dried tetrahydrofuran (30 ml.) was used. Dicyclohexylcarbodiimide (DCC) (4.49 g., 22.0 mmoles) dissolved in 20 ml. of methylene chloride was added to this solution,

TABLE I



Compd.	R′	X	Yield %	M.p.°	$[\alpha]_{578}$ $[\alpha]_{546}$	Formula	Calcd. % C	H	N	Found % C	H	N
I	$-CH_3$	Boc	86.4	154-155	-58.5° -68.0°	$C_{21}H_{23}ClN_2O_4$	62.61	5.75	6.95	62.48	5.71	6.72
II	$-CH_2-C_6H_5$	Boc	78.5	137.5-139	-72.0° -85.1° 1.196/$CHCl_3$	$C_{27}H_{27}ClN_2O_4$	67.70	5.68	5.85	67.71	5.73	5.85
III	$-CH_2-C_6H_5$-*p*-OH	Boc	61.2	158-160	-66.9° -79.2° 0.688/$CHCl_3$	$C_{27}H_{27}ClN_2O_5$	64.93	5.82	5.24	64.70	5.62	5.41
IV	$-CH_2$-3′-indolyl	Boc	51.5	152-154	-89.5° -106° 1.314/$CHCl_3$	$C_{29}H_{28}ClN_3O_4$	67.24	5.45	8.12	67.30	5.21	7.99
V	$-CHOH-CH_3$	Boc	47.5	79-81	-39.6° -69.0° 1.020/$CHCl_3$	$C_{22}H_{25}ClN_2O_5$	61.05	5.82	6.47	60.94	5.56	6.34
VI	$-CH(CH_3)_2$	Boc	59.0	106-108	-48.3° -57.2° 1.118/$CHCl_3$	$C_{23}H_{27}ClN_2O_4$	64.12	6.30	6.49	63.90	6.60	6.25
VII	$-CH_3$	Cbo	82.5	117-119	-17.8° -22.0° 2.180/$CHCl_3$	$C_{24}H_{21}ClN_2O_4$	65.99	4.84	6.41	66.31	5.14	6.40
VIII	$-CH_2-C_6H_5$	Cbo	66.0	115-116	-48.5° -55.8° 1.200/$CHCl_3$	$C_{30}H_{25}ClN_2O_4$	70.24	4.91	5.46	69.90	4.92	5.24
IX	$-CH_2-C_6H_4$-*p*-OH	Cbo	57.5	117-120	-33.1° -39.3° 0.968/Me_2Co	$C_{30}H_{25}ClN_2O_5$	68.12	4.76	5.30	67.91	4.49	5.17
X	$-CH_3$	Cbo	64.0	118-120	+17.6° +22.2° 2.224/$CHCl_3$	$C_{24}H_{21}ClN_2O_4$	65.99	4.84	6.41	66.25	5.10	6.62
XI	$-CH_2-C_6H_5$	Cbo	78.0	116-117	+47.9° +55.5°	$C_{30}H_{25}ClN_2O_4$	70.24	4.91	5.46	70.11	4.81	5.33

TABLE II



Compd.	-R'	M.p. °C	$[\alpha]_{578}$ (C in $CHCl_3$)	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
XXIV	$-CH_3$	138-140	+51.8° (0.994)	$C_{21}H_{37}N_3O_4$	63.78	9.43	10.62	63.68	9.36	10.89
XXV	$-CH_2-C_6H_5$	130-132	+56.8° (0.618)	$C_{27}H_{41}N_3O_4$	68.78	8.76	8.91	69.06	9.12	9.28
XXVI	$-CH_2-C_6H_4$-*p*-OH	69.72	+51.3° (1.200)	$C_{27}H_{41}N_3O_5$	65.18	8.31	8.44	65.26	8.48	8.91
XXVII	$-CH_3$-3'-indolyl	75-78	+38.7° (1.124)	$C_{29}H_{42}N_4O_4$	68.24	8.29	10.98	68.17	8.01	10.74
XXVIII	$-CHOH-CH_3$	163-165	+46.0 (1.120)	$C_{22}H_{40}N_3O_5$	61.10	9.24	9.88	61.34	8.84	9.89
XXIX	$-CH(CH_3)_2$	165-167	+52.9 (1.218)	$C_{23}H_{41}N_3O_4$	65.21	9.76	9.92	65.13	10.06	10.32

dropwise, during 1 hour at 0° and with stirring. After additional stirring at room temperature for 8 hours, thin-layer control (usually using ether or ether light petroleum 5:1 as eluent) indicated no further formation of the product. The dicyclohexylurea formed was suctioned off and the filtrate evaporated to dryness, the residual crude products were purified as described for each particular compound. Isolation and characteristic constants of the addition products of the relevant Boc-amino-acids on DCC (XXIII-XXIX) are also described.

2-*N*-(*N'*-Boc-alanyl)amino-5-chlorobenzophenone (I).

Recrystallization of the crude product from cyclohexane gave 6.95 g. (86.4%) of I, m.p. 150-154°. Two further recrystallizations from the same solvent gave the analytically pure sample, m.p. 154-155°.

Compound XXIV.

Evaporation of the mother liquors of I and chromatography on a silica gel column (360 g. of silica gel, ether-light petroleum 3:1 as eleutn) gave in fractions 17-28 (5 ml. per fraction) 750 mg. of XIII, m.p. 138-140°; nmr (deuteriochloroform): δ 1.31 ppm (d, 3H), 1.44 (s, 9H), 1.6-1.8 (m, 22H), 4.42 (quint., 1H) 5.12 (d, 1H), 7.42 (d, 1H).

2-*N*-(*N'*-Boc-phenylalanyl)amino-5-chlorobenzophenone (II).

The crude product was purified by column chromatography (320 g. of silica gel, (ether methylene chloride 1:1 as eluent). Fractions 11-27 (10 ml. per fraction) gave 7.50 g. (78.5%) of II, m.p. 132-137°. Recrystallization from cyclohexane gave the analytically pure sample, m.p. 137-139°.

Compound XXV.

After separation of II, fractions 30-48 included a small quantity of XXV; recrystallization from cyclohexane gave the pure compound m.p. 130-132°; nmr (deuteriochloroform): δ 1.42 ppm (s, 9H), *ca.* 1.7-1.85 (m, 22H), 2.95 (d, 2H), 4.63 (m, 1H), 5.10 (1H), 7.23 (s, 5H).

2-*N*-(*N'*-Boc-tyrosyl)amino-5-chlorobenzophenone (III).

The crude product was purified by recrystallization from cyclohexane (900 ml.). The compound III crystallized as a voluminous precipitate which was filtered off with difficulty; m.p. 150-156°, yield 61.2%. The analytically pure sample was obtained by column chromatography (ether as eluent) m.p. 158-160°.

Compound XXVI.

Evaporation of cyclohexane mother liquors after recrystallization of III and chromatographic purification (ether-light petroleum 1:1) gave pure XXVI, m.p. 69-72°.

2-*N*-(*N'*-Boc-tryptophanyl)amino-5-chlorobenzophenone (IV).

The crude product was separated by column chromatography (360 g. of silica gel, methylene chloride-ether 10:1 as eluent). Fractions 24-37 (30 ml. pro fraction) gave 6.52 g. (51%) of chromatographically pure IV. Recrystallization from benzene-light petroleum (1:2) gave the pure sample with m.p. 152-154°.

Compound XXVII.

After separation of IV the column was washed with *ca.* 400 ml. of ether. Evaporation of the eluent gave crude XXVII which was recrystallized twice from ether-light petroleum m.p. 75-78°.

2-*N*-(*N'*-Boc-threnyl)amino-5-chlorobenzophenone (V).

The crude product was obtained by column chromatography on 300 g. of silica gel. Elution with 500 ml. of methylene chloride gave 4.12 g. of starting 2-amino-5-chlorobenzophenone and DCC, thereafter a mixture of methylene chloride-ether 4:1 was used eluting 7.2 g. of crude V. After recrystallization from ether-light petroleum, the pure sample melted at 67-70°.

Compound XXVIII.

This compound was obtained by further eluting with pure ether; *ca.* 400 ml. was used. The crude product melted at 138-163° and after recrystallization from ether-cyclohexane, the m.p. rose to 163-165°.

2-*N*-(*N'*-Boc-valyl)amino-5-chlorobenzophenone (VI).

The crude reaction mixture was applied to a column with 350 g. of silica gel. By elution with methylene chloride (500 ml.), 4.05 g. of a mixture of starting 2-amino-5-chlorobenzophenone

and DCC was separated. Elution with methylene chloride-ether (10:1) gave 6.4 g. of the mixture of crude VI and XXIX. This mixture was separated on a second column (220 g. of silica gel, light petroleum-methylene chloride-ether, 10:5:1, as eluent). There was obtained 5.08 g. (59.0%) of chromatographically pure VI as a viscous oil which, after recrystallization from cyclohexane VI, had m.p. 106-108°.

Compound XXIX.

This compound was eluted with ether (250 ml.) after separation of VI. The crude product (m.p. 155-160°) was twice recrystallized from ether, m.p. 165-167°.

Preparation of the Compounds VII and X (Enantiomers).

Starting with 33.5 g. (0.15 mole) of L- or R-Cbo-alanine, 27.7 g. (0.12 mole) of 2-amino-5-chlorobenzophenone and 30.7 g. (0.15 mole) of DCC and after proceeding in the same way as described for I-VI, the crude product was obtained by crystallization from 210 ml. of hot cyclohexane, yield 78-82%, m.p. 144-117°.

Compounds VIII and X (Enantiomers).

These compounds were prepared in the same way as VII and X starting from 45.0 g. (0.15 mole) of L- or R- Cbo-phenylalanine. Recrystallization from cyclohexane-ether (20:1) gave 64 and 66% yield of VIII and X, respectively.

Compound IX.

This compound was obtained in a 37.5% yield from 31.5 g. (0.10 mole) of *N*-Cbo-tyrozine, 0.10 mole of DCC and 0.09 mole of 2-amino-5-chlorobenzophenone in absolute THF. The isolation was carried out by column chromatography (600 g. of silica gel). By elution with methylene chloride (150 ml.) unconverted amine and DCC were separated. Elution with methylene chloride-ether (5:1) gave crude IX which was recrystallized from cyclohexane-ether (10:1); m.p. 117-120°.

2-*N*-Alanylamino-5-chlorobenzophenon-hydrobromide (XII).

Compound I (1.0 g., 2.48 mmoles) was dissolved at 0° in 8.5 ml. of acetic acid. To this solution 1.5 ml. of hydrogen bromide-acetic acid (4M) was added dropwise. After 2-3 minutes, evolution of gas ceased and thinlayer control after dilution with 10% sodium bicarbonate and extraction with ether indicated that no unreacted I was present. The reaction mixture was evaporated *in vacuo* after addition of 3 x 20 ml. of benzene, and the oily residue was crystallized by addition of light petroleum. The crude product, 0.84 g. (88.5%) was recrysatllized from ether-methanol (12.5:1), giving pure XII with m.p. 129-131°; $[\alpha]_{578}$ -66.7°, $[\alpha]_{546}$ -80.4° (C = 2.364 in water).

Anal. Calcd. for $C_{16}H_{16}BrClN_2O_2$ (383.68): C, 50.09; H, 4.20; N, 7.30. Found: C, 49.78; H, 4.44; N, 7.13.

7-Chloro-1,3-dihydro-3(*S*)methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XIII).

A.) Compound I (8.55 g.) was dissolved in 45 ml. of acetic acid at 0° and 5 ml. of hydrogen bromide-acetic acid (4*M*) was added dropwise. After 5 minutes 50 ml. of benzene was added and the reaction mixture evaporated *in vacuo*. The residual oil was dissolved in 200 ml. of methanol-water (1:1) and the *p*H adjusted to 8.5 by addition of 5% sodium hydroxide. After stirring overnight at room temperature the solution was partially evaporated *in vacuo*, 300 ml. of water was added and the mixture extracted with 3 x 100 ml. of methylene chloride. The organic layer was dried (sodium sulfate), evaporated and the residual oil recrystallized from 150 ml. of acetone-water (1:1). Pure XIII melted at 200-203° after recrystallization at 168-175°; nmr (deuteriochloroform): 1.76 ppm (d, 3H), 3.79 (qv. 1H), 7.3-7.8 (m, 1H), 9.25 (s, 1H); $[\alpha]_{578}$ + 172.5°, $[\alpha]_{546}$ + 210° (c = 2.492 in chloroform).

Anal. Calcd. for $C_{16}H_{13}ClN_2O$ (284.74); C, 67.49; H, 4.61; N, 9.84. Found: C, 67.21; H, 4.88; N, 9.54.

B.) Compound VII (21.75 g. 0.05 mole) was dissolved in 150 ml. of the mixture dioxane-ethane (2:1), and 2.0 g. 10% Pd-C was added. Flow hydrogenation was performed during 6 hours after which time no protected VII was present and thin-layer chromatography indicated that about 80% of the free amine had cyclized into XIII. The catalyst was filtered off, the filtrate evaporated *in vacuo* and the residual oil recrystallized giving 12.8 g. (90%) of XIII possessing the same constants as described under method A.

7-Chloro-1,3-dihydro-3(*R*)methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XIX).

This compound was prepared by the method B as described for XIII, yield 86%, m.p. 200-203°; $[\alpha]_{578}$ -163.8°, $[\alpha]_{546}$ -191.5° (c = 1.09 in chloroform).

Anal. Calcd. for $C_{16}H_{13}ClN_2O$ (284.74): C, 67.49; H, 4.61; N, 9.84. Found: C, 67.34; H, 4.49; N, 9.69.

7-Chloro-1,3-dihydro-3(*S*)-benzyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XIV) and the (3*R*)-Enantiomer (XX).

These compounds were prepared from VIII and XI, respectively by the method B in an 82% yield.

XIV, m.p. 108-110°; nmr (deuteriochloroform): 3.40-3.95 ppm (sept, 3H), 7.1-7.60 (m, 13H), 8.73 (s, 1H); $[\alpha]_{578}$ + 51.8°, $[\alpha]_{546}$ + 58.4° (c = 0.520 in chloroform).

Anal. Calcd. for $C_{22}H_{17}ClN_2O$ (360.84): C, 73.24; H, 4.75; N, 7.77. Found: C, 72.95; H, 4.95; N, 7.79.

XX, m.p. 108-109°, $[\alpha]_{578}$ -50.8°, $[\alpha]_{546}$ -58.6° (c = 0.712 in chloroform).

Anal. Calcd. for $C_{22}H_{17}ClN_2O$ (360.84): C, 73.24; H, 4.75; N, 7.77. Found: C, 73.15; H, 4.49; N, 7.61.

7-Chloro-1,3-dihydro-3(*S*)-*p'*-hydroxybenzyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XV).

This compound was obtained from III in a 76% yield by the method A described for XIII. The crude product was purified by column chromatography (ether-petroleumether, 3:1, as eluent) followed by recrystallization from ether-cyclohexane, m.p. 139-141°; nmr (deuteriochloroform): 3.30-3.75 ppm (broad unres. mult. 3H), 6.69 and 7.13 (dd, 4H), 7.10-7.60 (m, 8H), 8.76 (s, 1H); $[\alpha]_{578}$ + 42.5°, $[\alpha]_{546}$ + 50.2° (c = 0.600 in chloroform).

Anal. Calcd. for $C_{22}H_{17}ClN_2O_2$ (376.84): C, 70.13; H, 4.55; N, 7.44. Found: C, 69.88; H, 4.77; N, 7.57.

7-Chloro-1,3-dihydro-3(*S*)-(3'-indolyl)methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XVI).

Prepared from VI by method A in 75% yield, recrystallized from ether m.p. 149-151°. One mole of ether included in the crystallized product could not be removed even after prolonged drying at 80° and 0.01 mm Hg over phosphorus pentoxide; nmr (deuteriochloroform): 1.18 ppm (t, 6H) 3.45 (quart, 4H), 3.76 (broad s, 3H), 7.0-7.8 (m, 13H), 8.18 (s, 1H), 8.99 (s, 1H).

Anal. Calcd. for $C_{24}H_{18}ClN_3O\cdot(C_2H_5)_2O$ (473.98): C, 70.95; H, 5.95; N, 8.87. Found: C, 70.60; H, 6.02; N, 8.66.

After recrystallization from acetone (m.p. 150-152°) one mole

of solvent proved to be included within the crystals and it was impossible to remove it under the drying conditions mentioned above; nmr (deuteriochloroform): 2.32 ppm (s, 6H), 3.76 (broad s, 3H), 7.0-7.8 (m, 13H), 8.18 (s, 1H), 8.99 (s, 1H); $[\alpha]_{578}$ + 40.4°, $[\alpha]_{546}$ + 48.3° (c = 1.068 in chloroform).

Anal. Calcd. for $C_{24}H_{18}ClN_3O\cdot(CH_3)_2CO$ (457.96): C, 70.82; H, 5.28; N, 9.17. Found: C, 70.86; H, 5.13; N, 9.06.

7-Chloro-1,3-dihydro-3(*S*)-(1′-hydroxy)ethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XVII).

This compound was prepared from V by method A in 80% yield and was purified by column chromatography (ether petroleum-methylene chloride-ether, 1:2:4, as eluent), m.p. 118-121°; nmr (deuteriochloroform); 1.40 ppm (d, 3H), 3.43 (d, 1H), 3.6-3.95 (m, -H), 4.68 (quint, 1H), 7.25-7.70 (m, 8H), 10.14 (s, 1H) $[\alpha]_{578}$ + 154°, $[\alpha]_{546}$ + 179.5° (c = 1.088 in chloroform).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$ (314.77): C, 64.86; H, 4.80; N, 8.89. Found: C, 64.98; H, 4.61; N, 8.98.

7-Chloro-1,3-dihydro-3(*S*)-isopropyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XVIII).

This compound was prepared from VI by method A in 87% yield and was purified by recrystallization from ether petroleum-methylene chloride (40:1), m.p. 192-194°. For nmr see Fig. 1 $[\alpha]_{578}$ + 148°, $[\alpha]_{546}$ + 171° (c = 1.116 in chloroform).

Anal. Calcd. for $C_{18}H_{17}ClN_2O$ (312.79): C, 69.23; H, 5.47; N, 8.95. Found: C, 69.17; H, 5.83; N, 8.92.

General Procedure for the Preparation of the Compounds XXI-XXIII.

Compounds XIII, XIV and XIX, respectively, (10.0 g.) were dissolved in 40 ml. of DMF under nitrogen. Anhydrous barium oxide (2.0 g.) was added and 3 ml. of methyl iodide diluted in 10 ml. of DMF, was added dropwise with stirring during 0.5 hour. After 6 hours stirring the reaction mixture was diluted with 500 ml. of water and extracted with 3 x 200 ml. of methylene chloride; the organic layer was dried (magnesium sulfate) and evaporated. The residual oil was applied to a column (300 g. of silica gel) and eluted with methylene chloride (pure) to remove free 2-amino-5-chlorobenzophenon (yellow zone). Elution with ether-methylene chloride (1:1) gave the corresponding *N*-methylated products in chromatographic purity as viscous oils in 85-90% yields.

Compound XXI.

This compound was crystallized from light petroleum, m.p. 47-50°; nmr (deuteriochloroform): 1.72 ppm (d, 3H), 3.40 (s, 3H), 3.73 (quart., 1H), 7.10-7.75 (m, 8H). $[\alpha]_{578}$ + 212° $[\alpha]_{564}$ + 249° (c = 0.852 in chloroform).

Anal. Calcd. for $C_{17}H_{15}ClN_2O$ (298.77): C, 68.34; H, 5.06; N, 9.38. Found: C, 68.56; H, 5.28; N, 9.65.

Compound XXII.

This compound was crystallized from light petroleum, m.p. 135-137°. For the typical part of nmr spectrum see Fig. 2. $[\alpha]_{578}$ + 98.9°, $[\alpha]_{546}$ + 116 (c = 1,388 in chloroform).

Anal. Calcd. for $C_{13}H_{19}ClN_2O$ (374.87): C, 73.84; H, 5.11; N, 7.47. Found: C, 73.62; H, 5.11; N, 7.48.

Compound XXIII.

This compound was obtained from XIX, m.p. 48-50°; $[\alpha]_{578}$ -213°, $[\alpha]_{546}$ -251.5° (c = 0.796 in chloroform).

Anal. Calcd. for $C_{17}H_{15}ClN_2O$ (298.77): C, 68.34; H, 5.06; N, 9.38. Found: C, 68.16; H, 5.11; N, 9.55.

Rate Constant Measurements.

Twenty five mg. of XII was dissolved in 0.3 ml. of water and the mixture buffer/dioxane (4:1) was added up to 25.0 ml. Sorensen phosphate buffer (*p*H 7.00) and dioxane (4:1) gave a mixture with *p*H 7.44. From the thermostatically heated reaction solution (37.0 ± 0.1°), 1 ml. samples were taken at regular intervals, quanching being achieved by putting the sample in 1.0 ml. of 1.0 *N* hydrochloric acid and diluting to 100.0 ml. Preliminary measurements at 283 and 361 nm revealed that the solution of XII in 0.1 *N* hydrochloric acid showed no formation of XIII within 3-4 hours. Calibration curves were also determined in 0.1 *N* hydrochloric acid solution.

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