Chiral 1,4-Benzodiazepines. IX (1). Attempts at a Preparation of 7-Chloro-5-phenyl-3(*S*)methyl-1,4-benzodiazepin-2-one through C(5)-C(5a) Bond Formation

V. Šunjić, F. Kajfež, N. Blažević, M. Oklobdžija and P. Mildner

CRC, Compagnia di Ricerca Chimica, Chiasso, Switzerland and
Institute of Organic Chemistry and Biochemistry, University of Zagreb, Zagreb, Croatia, Yugoslavia

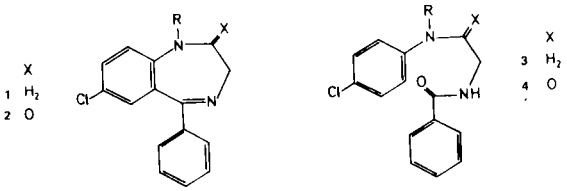
Received March 3, 1975

During attempts at preparation of 7-chloro-5-phenyl-3(*S*)methyl-1,4-benzodiazepin-2-one (**9**) by cyclisation of *N'*-α-chlorobenzylidene-(*S*)alanyl-*p*-chloroaniline (**7**) and the related *o,p*-dichloroaniline derivative (**8**), it was observed that the intermediate products, both *N'*-benzylidene-(*S*)alanyl-*p*-chloroaniline (**5**), as well as the related *o,p*-dichloroaniline derivative (**6**), undergo cyclisation to *N*-(*p*-chlorophenyl)-2-phenyl-4(*S*)methylimidazolidin-5-one (**17**), and *N*-(*o,p*-dichlorophenyl)imidazolidin-5-one (**18**), respectively. Isolation and properties of the side products, *N'*-benzylated-(*S*)alanyl-*p*-chloro-, and *o,p*-dichloroanilines (**15** and **16**), as well as of *N'*-benzoylated-(*S*)alanyl-*p*-chloroanilines (**19** and **20**) are described.

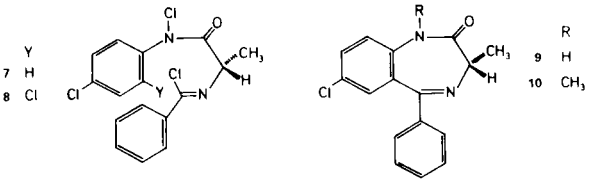
Introduction.

Several syntheses of 1,4-benzodiazepin-2-one (**2**) are based on N(4)-C(5) bond formation in the final step, leading to cyclisation (2,3). Although some other principles have been elaborated for the ring closure in this group of compounds (3), there have, so far, been no attempts at cyclisation by C(5)-C(5a) bond formation. This type of cyclisation, *i.e.* arylation of a reactive methylenic group, has been achieved (4) in preparation of a benzo-3-azepine derivative.

The most efficient synthetic route to 2-deoxo-1,4-benzodiazepines (**1**), on the other hand, involves the C(5)-C(5a) bond formation by a Bischler-Napieralski cyclisation of type **3** precursors (3,5,6). Obviously, a Bischler-Napieralski cyclisation of corresponding oxo-precursors (**4**) must not necessarily give 1,4-benzodiazepin-2-ones, as both amide groups in **4** are reactive and might give rise to imide-halides (7) under Bischler-Napieralski reaction conditions.



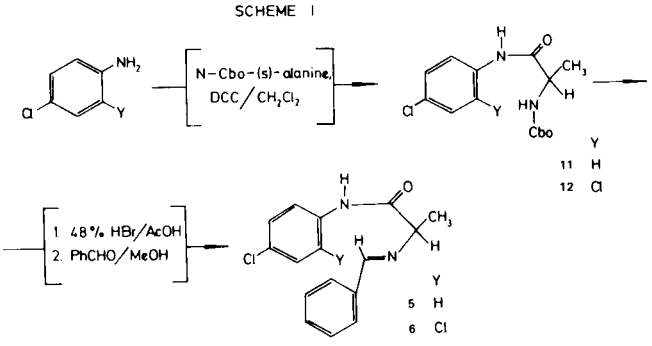
Recent investigations of cyclisation conditions for Schiff-bases and their derivatives (7-9) prompted us to prepare compounds **5-8**, and try to use them as precursors in syntheses of the chiral 1,4-benzodiazepin-2-one (**9**). Compound **9**, as well as its *N*-methyl derivative, **10**, are subjects of our current chemical and pharmacological investigations (10-12).

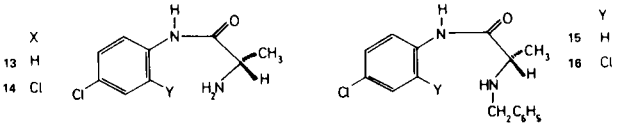


Results and Discussion.

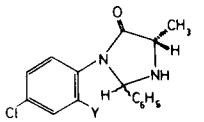
Intermediates **5** and **6** have been prepared as outlined in Scheme I.

SCHEME I



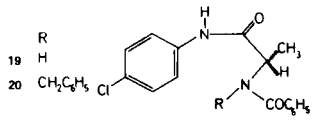


Isolation of the amines **13** and **14** encountered some difficulties caused by formation of side products **15** and **16**. These compounds resulted from benzylation of free amines **13** and **14** by benzyl-bromide formed *in situ*, as recently observed for 2-*N*-(*S*)alanylamino-5-chlorobenzophenone (11). Therefore, a direct acylation of chloro anilides with (*S*)alanylchloride (11) was used in subsequent experiments, giving moderate yields of pure **13** and **14**. Their conversion into **5** and **6** was accompanied by formation of cyclic compounds **17** and **18**. The last were formed in an acid catalysed procedure, thus being dependent on the amounts of benzoic acid, formed *in situ* by air oxidation of benzaldehyde. Compounds **17** and **18** have also been obtained in high yields by hydrochloric acid-catalyzed rearrangement of pure **5** and **6** in methanol. In order to



Y

17 H
18 Cl

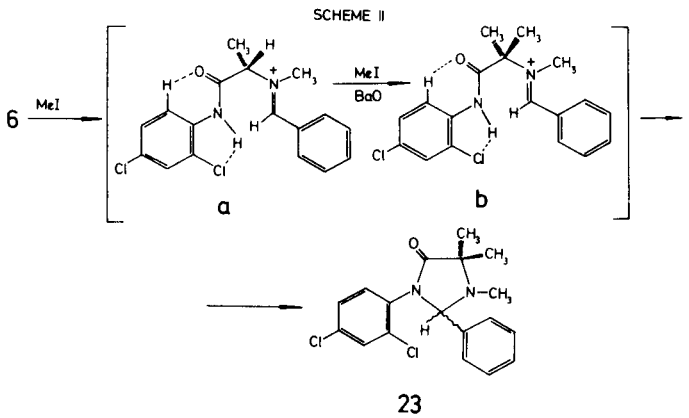


R

19 H
20 $CH_2C_6H_5$

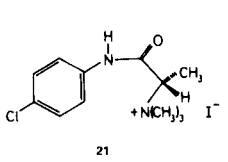
prevent intramolecular addition of the amide -NH group to the azomethine double bond as a side reaction, we tried to methylate compounds **6** and **13** with methyl-iodide-barium oxide in dimethylformamide. Interestingly, both substrates reacted contrary to expectation. Compound **13** gave predominantly the quaternary salt **21**, the structure of which was confirmed by nmr; the three methyl groups on a quaternary nitrogen gave rise to a singlet at 3.30 ppm and the singlet area stood in a ratio of 3:1 to that of the CH_3-CH doublet at 1.66 ppm. Compound **6** gave two cyclic products, **22** and **23**. The cyclisation occured probably after quaternisation of the azomethine nitrogen in either instance. The formation of doubly methylated **23** might be explained in the way

SCHEME II

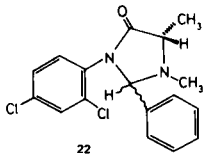


23

shown on Scheme II, where the assumed quaternary aldimine derivative can be seen to possess an acidic proton on carbon C(3). Compound **23** is found to be racemic which indicates that the first chiral center is lost before the second is formed, and this sequence of events precludes any asymmetric induction during the cyclisation into an imidazolidine-5-one ring. The benzylic proton in **23** gives rise to a singlet at 5.23 ppm, whereas the same group in **22** produces two singlets at 5.10 and 5.14 ppm, revealing two external diastereotopic protons. Additions of aniline- or amide nitrogen to a β-azometine double bond, leading to various imidazolidines, were recently observed on similar substrates (14).



21



22

During trials undertaken to prepare aldimine **5**, two further side products, **19** and **20**, were repeatedly isolated. These compounds arose from acylation of the intermediate **13** and its side product **15**, respectively, by benzoic acid present in the reaction mixtures.

Imide-chlorides **7** and **8** were prepared according to the procedure of Exner *et al.* (15), and a cyclization into **9** was attempted *in situ*. It was anticipated that the amidic NH-group may also undergo chlorination under the conditions employed, and therefore a great molar excess of *t*-butyl hypochlorite was used in all experiments. Both procedures tried for ring closure, *i.e.* barium oxide-catalyzed elimination of hydrogen chloride in **7**, and Uhlmann-type (16,17) intramolecular condensation in **8**, were unsuccessful. They gave tarry products and not a trace of the expected product **9** could be identified by tlc.

In conclusion, we found it impossible to cause intermediates **7** and **8**, of the Bischler-Napieralski type to cyclise into a 7-membered benzodiazepine system **9** under the reaction conditions investigated, although similar reactions were recently found (3,6) to proceed readily with other substrates in the synthesis of some benzo-condensed 7-membered heterocycles.

EXPERIMENTAL

Melting points were determined on a Kofler-microheating stage and are uncorrected. Ir spectra were recorded with potassium bromide pellets, unless stated otherwise, on a Perkin-Elmer M 257 instrument. Nmr spectra were obtained with a Varian T60 spectrometer using TMS as internal standard. Optical rotations were measured with a Perkin-Elmer M-141 polarimeter at ambient temperature. Silicagel plates F-258 (Merck) were used for tlc; column chromatography was run on silicagel 0.05-0.2 mm (Merck), fractions being collected by an LKB 7000 Ultra Rac automatic fraction collector, and monitored for products by tlc using an UV-254 lamp.

N'-Carbobenzoxy-(*S*)alanyl-*p*-chloroanilide (**11**).

Starting from 4.04 g. (31.8 mmoles) of *p*-chloroaniline, 6.69 g. (30.0 mmoles) *N*-Cbo-(*S*)alanine (m.p. 82-84°) and 6.48 g. (31.5 mmoles) of dicyclohexylcarbodiimide (DCC) in dichloromethane (70 ml.), compound **11** was prepared according to the standard procedure (10). The crude product (9.2 g., 92.5%) was recrystallized from dichloromethane-light petroleum (b.p. 40-60°); m.p. 166-168°; nmr (deuteriochloroform), ppm: 1.43 (d, J 7,4 Hz, 3H), 4.44 (q, J 7,4 Hz, 1H), 5.10 (s, 2H), 5.76 (d, Cbo-N*H*), 7.22 (AA'BB',) 4H), 7.25 (s, 5H), 8.55 (s, Ar-N*H*); $[\alpha]_{578}$-53.5° (c 1.22, chloroform).

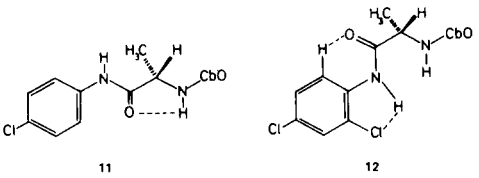
Anal. Calcd. for $C_{17}H_{17}ClN_2O_3$ (332.79): C, 61.36; H, 5.15; N, 8.41. Found: C, 61.33; H, 5.39; N, 8.35.

N'-Carbobenzoxy-(*S*)alanyl-*o,p*-dichloroaniline (**12**).

Compound **12** was prepared in 86% yield by the procedure described for **11** using *o,p*-dichloroaniline, m.p. 148-150° (from chloroform-light petroleum); nmr (deuteriochloroform): ppm, 1.44 (d, J 7.4 Hz, 3H), 4.42 (q, J 7.4 Hz, 1H), 5.12 (s, 2H), 5.48 (d, Cb0-N*H*), 7.1-7.5 (m, 7H), 8.28 (d, 1H), 8.45 (s, Ar-N*H*); $[\alpha]_{578}$-42.1° (c 1.95, chloroform).

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_3$ (367.24): C, 55.61; H, 4.39; N, 7.62. Found: C, 55.84; H, 4.43; N, 7.86.

Nmr data for **11** and **12** indicated two different types of hydrogen bonding in these compounds:



11 12

N-(*S*)Alanyl-*p*-chloroanilide (**13**).

Method A.

Compound **11** (6.64 g., 20.0 mmoles) was dissolved in 48% hydrobromic acid in acetic acid (30 ml.), the solution was stirred for 2 hours, and the solvent evaporated *in vacuo*, all operations being performed at ambient temperature. The residue was redissolved in water (50 ml.), this solution was made alkaline, and then extracted with ether (4 x 50 ml.). The organic layer was dried (sodium sulfate), and the solvent evaporated. The residual oil was crystallized from diisopropyl ether-light petroleum, giving 3.14 g. (79%) of pure **13**, m.p. 79-81°; nmr (DMSO-d_6): ppm: 1.25 (d, J 6.2 Hz, 3H), 3.49 (q, J 6.2 Hz, 1H), 4-5 (broad -NH_2), 7.36 and 7.74 (dd, AA'BB', J 8.8 Hz, 4H); $[\alpha]_{578}$+1.37°, $[\alpha]_{546}$+1.70°, (c 1.46, chloroform).

Anal. Calcd. for $C_9H_{11}ClN_2O$ (198.65): C, 54.41; H, 5.58, N, 14.10. Found: C, 54.60; H, 5.81; N, 14.33.

The oil remaining after evaporation of the mother liquor was purified by column chromatography (50 g. of silicagel, ether as the eluent), giving 450 mg. of *N'*-benzyl-(*S*)alanyl-*p*-chloroanilide (**15**), m.p. 119-120° (from cyclohexane); nmr (deuteriochloroform). ppm: 1.36 (d, J 7.0 Hz, 3H), 1.64 (s, Bz-N*H*), 3.32 (q, J 7.0 Hz, 1H), 3.80 (s, 2H), 7.1-7.7 (m 9H), 9.5 (s, -CON*H*-Ar).

Anal. Calcd. for $C_{16}H_{17}ClN_2O$ (288.77): C, 66.55; H, 5.94; N, 9.72. Found: C, 66.27; H, 5.62; N, 9.96.

N-(*S*)Alanyl-*o,p*-dichloroanilide (**14**).

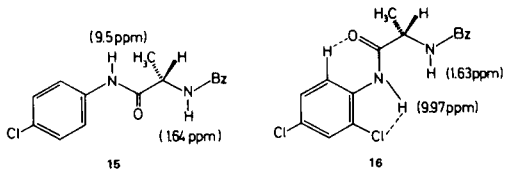
This compound was prepared from **12** (9.5 g.) in 70% yield by the procedure described for **13**. After recrystallization from cyclohexane the pure compound melted at 70-70.5°; nmr (DMSO-d_6) ppm: 1.28 (d, J 6.0 Hz, 3H), 3.56 (q, J 6.0 Hz, 1H), 4-5 (broad s, NH_2), 7.3-8.1 (m, 3H); $[\alpha]_{546}$+5.72° (c 1.40, chloroform).

Anal. Calcd. for $C_9H_{10}Cl_2N_2O$ (233.11): C, 46.38; H, 4.33; N, 12.02. Found: C, 46.54; H, 4.57; N, 12.20.

The oil remaining after evaporation of the mother liquor was applied to a silicagel column (100 g.), and eluted with ethyl acetate; 2.5 g. of an oily liquid was obtained. After distillation (205-210° 0.05 mm Hg) liquid was left to crystallize on ice. From the analytical data (see below), a structure of *N'*-benzyl-(*S*)-alanyl-*o,p*-dichloroaniline was deduced for this substance (**16**); nmr (carbon tetrachloride), ppm: 1.37 (d, J 6.6 Hz, 3H), 1.63 (broad s, Bz-N*H*), 3.27 (q, J 6.6 Hz, 1H), 3.80 (s, 2H), 7.0-7.77 (m, 7H), 8.46 (d, 1H), 9.97 (s, -CON*H*-Ar).

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O$ (323.23): C, 59.46; H, 4.99; N, 8.67. Found: C, 59.54; H, 4.94; N, 8.18.

The nmr spectra of compounds **15** and **16**, again, revealed two different ways of hydrogen bonding.



15 16

N-(*S*)Alanyl-*p*-chloroaniline (**13**).

Method B.

To a suspension of 20.7 g. (0.1 mole) of phosphorus trichloride in 150 ml. of carbon tetrachloride, first stirred for 4 hours at room temperature, (*S*)alanine (4.45 g., 0.05 mole) was added, and the resulting slurry was stirred overnight. The voluminous precipitate was filtered off by suction, washed with carbon tetrachloride (2 x 30 ml.) and immediately added to a solution of *p*-chloroaniline (6.35 g., 0.05 mole) in carbon tetrachloride (100 ml.). The solid dissolved upon stirring and cooling under water, which was continued for 2 hours, followed by further 22 hours stirring at ambient temperature. The reaction mixture was then poured into 200 g. of ice water and adjusted to *p*H 9-10. The organic layer was separated, and the aqueous layer extracted with carbon tetrachloride (2 x 100 ml.). The combined organic extracts were dried (magnesium sulfate), evaporated, and the residual oil diluted with 5 ml. of diisopropyl ether. On standing in a refrigerator, crude **13** crystallized (5.37 g., 54%, m.p. 66-74°) and was further treated as described under Method A.

N'-Benzylidene-(*S*)alanyl-*p*-chloroaniline (**5**).

To the solution of 2.0 g. (10.1 mmoles) of **13** in absolute methanol (40 ml.); freshly distilled benzaldehyde (3.0 ml., 30.0 mmoles) was added, and the resulting mixture was stirred at room temperature, in a nitrogen atmosphere, for 48 hours. At this stage the methanol was removed by evaporation, and the residual oil was taken up into water (30 ml.); after adjustment to *p*H 10, the products were extracted with chloroform (3 x 30 ml.). The organic layer was dried (magnesium sulate), evaporated, and the residual oil was crystallized from hot ether-light petroleum (2:1). After standing in an ice bath for an extended period, 1.48 g. of **5** was obtained, and another 0.36 g. separated after reducing the volume of the mother liquor (69% total yield). An analytically pure sample of **5** was prepared by recrystallizing from cyclohexane. m.p. 97-99°; nmr (deuteriochloroform), ppm: 1.52 (d, J 7.0 Hz, 3H), 4.10 (q, J 7.0 Hz, 1H), 7.0-7.95 (m, 8H), 8.18 (d,

1H), 8.48 (s, 1H), 9.75 (s, 1H); ir, cm^{-1}: 3250, 1695, 1650, 1572, 1600 and 1512; $[\alpha]_{578}$+68.2 (c 1.80, chloroform).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$ (286.76): C, 67.02; H, 5.27; N, 9.77. Found: C, 66.91; H, 5.43; N, 9.54.

The mother liquor from the first crystallization was evaporated, and the residual oil was applied to a column (30 g. of silicagel). Elution was carried out with ether-light petroleum (1:1). The first fraction gave, after recrystallization from ether, 490 mg. of compound **20**, m.p. 115.5-118°; nmr (deuteriochloroform), ppm: 1.56 (d, J 7.0 Hz, 3H), 4.66 (d, J 2.0 Hz, 2H), (diastereotopic benzylic protons), 5.04 (q, J 7.0 Hz, 1H), 7.0-7.6 (m, 12H), 8.03 (d, J 9.0 Hz, 1H), 9.11 (broad s, 1H); ir, cm^{-1}: 3320, 3060, 1688, 1615, 1572, 1520, 1466, 1452, 1430, 1105, 700; $[\alpha]_{574}$ -174° (c 1.04, chloroform).

Anal. Calcd. for $C_{23}H_{20}Cl_2N_2O_2$ (427.34): C, 64.65; H, 4.72; N, 6.56. Found: C, 64.47; H, 4.42; N, 6.80.

The second fraction gave 250 mg. of yellow oil which crystallized from cyclohexane upon chilling, m.p. 84-86°, no mp depression occurred upon admixture of authentic **17**, and ir spectra of analytical and authentic samples were identical.

N-Benzoyl-(*S*)alanyl-*p*-chloroaniline (**19**).

In some preparations where crude **13**, comtaminated with **15**, had been used, compound **19** was obtained as a side product in the last fraction during column chromatography of **5**. Compound **19**, separated by chromatography was further purified by crystallization from chloroform-diisopropyl ether, m.p. 201-202°; nmr (deuteriochloroform). ppm: 1.66 (d, 3H), 5.10 (q, 1H), 7-8 (m, 9H, Ar + 1N*H*), 9.6 (s, 1H; CON*H*); $[\alpha]_{578}$+62.2° (c 2.02, chloroform).

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2$ (302.76): C, 63.50; H, 5.00; N, 9.25. Found: C, 63.76; H, 5.05; N, 9.43.

N'-Benzylidine-(*S*)alanyl-*o,p*-dichloroaniline (**6**).

Using a procedure analogous to that described for preparation of **5**, compound **6** was obtained from 3.5 g. (15.0 mmoles) of **14**, in 58% yield, m.p. 118-119°; nmr (deuteriochloroform), ppm: 1.56 (d, J 7.0 Hz, 3H), 4.14 (q, J 7.0 Hz, 1H), 7.1-8 (m, 7H), 8.35 (s, 1H), 8.50 (d, 1H), 9.8 (s, 1H), ir, cm^{-1}: 3260, 1690, 1650, 1575, 1605 and 1505; $[\alpha]_{578}$+106.5° (c 2.06, chloroform).

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O$ (321.21); C, 59.83; H, 4.39; N, 8.72. Found: C, 59.71; H, 4.66; N, 9.00.

Evaporation of the mother liquor and chromatographic purification of the residue (50 g. of silicagel as support, ether-cyclohexane 3:1 as eluent) yielded 0.48 g. of a compound with m.p. 129-131°, giving an ir spectrum identical with that of an authentic sample of **18**.

N-p-Chlorophenyl-2-phenyl-4(*S*)methylimidazolidin-5-one (**17**).

Compound **5** (1.0 g.) was dissolved in methanol (15 ml.), and 3-4 drops of concentrated aqueous hydrochloric acid was added. This solution was heated under reflux for 6 hours, solvent was removed by evaporation, the residue was dissolved in water (20 ml.), and the solution extracted with ether (3 x 20 ml.). After drying the extract and evaporation of solvent there remained a yellow oil which crystallized slowly on standing at ambient temperature; yield 0.94 g., m.p. 85-86°; nmr (deuteriochloroform), ppm: 1.39 and 1.44 two d, J 7.0 Hz each, 3H (two external diastereotopic methyl groups), 2.1 (broad s, Bz-N*H*), 3.5-4.0 m, 1H- (two quartets superimposed), 5.92 and 5.98 two s, 1H (two diastereotopic benzylic protons), 7.1-7.6 (m, 9H); ir, cm^{-1}: 3350, 3295, 3270, 1705, 1495, 1298, 1110, 830, 765 and 705; $[\alpha]_{546}$+23.8° (c 1.26, chloroform).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$ (286.76): C, 67.02; H, 5.27; N, 9.77. Found: C, 67.12; H, 5.40; N, 9.87.

N-o,p-Dichlorophenyl-2-phenyl-4(*S*)methylimidazolidin-5-one (**18**).

Treatment of compound **6** in the way described for **17** gave an 85% yield of crude **18**. Recrystallization from diisopropyl ether afforded a pure sample, m.p. 130-132°; ir, cm^{-1}: 1697, 1595, 1495, 1380, 1302, 836, 765, 705; $[\alpha]_{578}$+28.5° (c 2.10, chloroform).

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O$ (321.21): C, 59.83; H, 4.39; N, 8.71. Found: C, 59.78; H, 4.02; N, 8.56.

Methylation of *N*-Benxylidine-(*S*)alanyl-*o,p*-dichloroaniline.

A slurry of 1.0 g. of barium oxide in 15 ml. of DMF, to which 10 drops of water were added, was mixed with 1.0 (3.11 mmoles) of aldimine (**6**), then 1.5 ml. (3.42 g.) of methyl iodide was added under water-cooling. The reaction was left to proceed for 12 hours with stirring at ambient temperature in darkness. The resulting mixture was poured into 100 ml. of ice cold 5% aqueous acetic acid. The suspension thus obtained was extracted with chloroform (3 x 50 ml.) and the extract dried (sodium sulfate). After evaporation of the solvent an oily residue remained (830 mg.). This product was chromatographed on a column of 100 g. of silicagel, using ether-light petroleum 1:1 as the eluent, and collecting 5-ml. fractions. The following products were obtained: 290 mg. of crude **22**, from fractions 36-46, a mixture of several (3-4) substances in fractions 47-68, and 190 mg. of crude **23**, from fractions 69-108; The column was then eluted with acetone. A further 60 mg. of mixture was obtained, which was discarded.

N^1-*o,p*-Dichlorophenyl-2-phenyl-N^3-methyl-4(*S*)-methylimidazolidin-5-one (**22**).

The crude product **22**, emerging from the column, was purified by crystallization from light petroleum to which a few drops of ether was added, m.p. 63-67°; nmr (deuteriochloroform), ppm: 1.52 (d, J 6.0 Hz, 3H), 2.44 (s, 3H), 3.32 and 3.35 (double q, J 6.0 Hz, 1H), 5.10 and 5.12 (double s, 1H), 6.65-7.5 (m, 8H); $[\alpha]_{578}$+17.6° (c 0.86, chloroform).

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O$ (335.23): C, 60.92; H, 4.81; N, 8.36. Found: C, 60.71; H, 5.02; N, 8,61.

N^1-*o,p*-Dichlorophenyl-2-phenyl-N^3-methyl-4,4-dimethylimidazolidin-5-one (**23**).

Crude material was purified by distillation in a metallic block. A yellow oil, b.p. 120-125°/0.06 mm Hg, was obtained which crystallized on standing in a refrigerator, m.p. 30-33°; nmr (deuteriochloroform), ppm: 1.33 (s, 3H), 1.46 (c, 3H), 2.19 (s, 3H), 5.23 (s, 1H), 6.6-7.5 (m, 8H); ir (chloroform), cm^{-1}: 2800-2985 (strong multiplet), 1710, 1590, 1568, 1460, 1386 and 1360 (both for $C(CH_3)_2$), 1170, 1140, 890, 833 and 700; $[\alpha]_{578}$0±0.2° (c 1.26, chloroform).

Anal. Calcd. for $C_{18}H_{18}Cl_2N_2O$ (349.26): C, 61.91; H, 5.20; N, 8.03. Found: C, 62.17; H, 5.44; N, 7.76.

Methylation of *N*-(*S*)alanyl-*p*-chloroanilide.

This reaction was carried out with 1.18 g. (5.95 mmoles) of compound **13**, 2 ml. of methyl iodide, and 1.5 g. of pulverized and dried barium oxide, in 20 ml. of DMF to which 5 drops of water were added. Following the same procedure as described for the methylation of **6**, a crude reaction product was obtained, which was recrystallized from 96% ethanol to give 665 mg. of the quaternary salt **21**. After evaporation of the mother liquor a further 320 mg. of **21** was obtained, total yield 45% (m.p. 230-234°); nmr (DMSO-d_6 to which a few drops of trifluoroacetic

acid were added), ppm: 1.66 (d, J 6.4 Hz, 3H), 3.30 (s, 9H), 4.43 (q, J 6.4 Hz, 1H), 7.43 and 7.11 (double d, J 14.0 Hz, each, 2H), 9.2 (s, 1H); ir, cm^{-1}: 3260, 3200, 3130 and 3075 (quartet of medium strong bands), 3005, 1690, 1608, 1345, 1492, 1253 and 830.

Anal. Calcd. for $C_{12}H_{18}ClN_2O$ (368.64): C, 39.10; H, 4.92; N, 7.60. Found: C, 39.34; H, 5.17; N, 7.57.

Attempts at Cyclization of Aldimines to 1,4-Benzodiazepin-2-one (**9**).

A. From Aldimine **5**.

To a solution of *t*-butyl hypochlorite (1.80 g., 22.5 mmoles) in ether (50 ml.) compound **5** (2.15 g., 7.5 mmoles), and 2 drops of methanol were added. This mixture was heated under reflux for 0.5 hours, after which ether was evaporated, and the residue was dissolved in 30 ml. of dry toluene. Dry barium oxide (2 g.) was then added, and the resulting suspension was heated at 50-60° for 6 hours. T.c monitoring (chloroform-acetone 9:1) failed to reveal any trace of compound **9** at the end of this period. Therefore, refluxing was continued overnight. An inorganic precipitate present at this point was filtered off, washed with ether and the combined filtrates were evaporated to a small volume. Now a tlc run indicated the presence of several degradation products with low R_f values, whereas column chromatography (60 g. of silicagel benzene-ethyl acetate 1:2 as the eluent) afforded 650 mg. of starting material as the only defined substance.

B. From Aldimine **7**.

Aldimine **7** (800 mg., 2.49 mmoles) was transformed into the imide-chloride using an etheral solution of *t*-butyl hypochlorite (50 ml., 1.80 g. of *t*-butyl hypochlorite) as described under A. Immediately after evaporation of the solvent, the residual oil was dissolved in 5 ml. of DMF, iodine (0.1 g.) and barium oxide (0.5 g.) were added and the mixture was heated and stirred under nitrogen. After 4 hours of stirring at 60-70°, the temperature was raised to 120-130° and the stirring continued overnight. Examination of the reaction mixture by tlc (after removal of DMF from applied spots by heating the plate in a stream of air at 60° for 4-5 minutes) indicated no trace of compound **9**. On the developed chromatogram all spots were situated within a short distance from the beginning and no attempt was made at separation by column chromatography.

REFERENCES

(1) Part VIII: M. Štromar, V. Šunjić, T. Kovač, L. Klasinc and F. Kajfež, *Croat. Chem. Acta*, **46**, 267 (1974).

(2) L. H. Sternbach, *Angew. Chem., Intern. Edit. Engl.*, **10**, 34 (1971).

(3) K. H. Wünsch, H. Dettmann and S. Schönberg, *Chem. Ber.*, **102**, 3891 (1969).

(4) M. F. Sammelhack, R. D. Stauffer and T. D. Rogerson, *Tetrahedron Letters*, 4519 (1975)

(5) Y. Kanaoka, E. Sato, O. Yanemitsu and Y. Ban, *ibid.*, 2419 (1964).

(6) G. N. Walker, A. R. Engle and R. J. Kempton, *J. Org. Chem.*, **37**, 3755 (1972).

(7) G. Fodor, J. Gal and B. A. Phillips, *Angew. Chem.*, **84**, 947 (1972).

(8) M. R. Falco, J. X. de Vries, E. Marchelli, H. C. de Lorenzo and G. Mann, *Tetrahedron*, **28**, 5999 (1972).

(9) S. V. Kessar and G. S. Joshi, *Tetrahedron*, **29**, 419 (1973).

(10) V. Šunjić, F. Kajfež, I. Štromar, N. Blažević and D. Kolbah, *J. Heterocyclic Chem.*, **10**, 591 (1973).

(11) V. Šunjić, M. Štromar, F. Kajfež, S. Rendić and D. Kolbah, *Acta Pharm. Jug.*, **23**, 213 (1973).

(12) V. Šunjić, J. Kuftinec and F. Kajfež, *Arzneim. Forsch.*, **25**, 340 (1975).

(13) S. J. Benković, T. H. Barrows and P. R. Farnis, *J. Am. Chem. Soc.*, **95**, 8414 (1973).

(14) S. D. Nelson, G. D. Breck and W. F. Trager, *J. Med. Chem.*, **16**, 1106 (1973).

(15) O. Exner and O. Schindler, *Helv. Chim. Acta*, **55**, 1927 (1972).

(16) F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **27**, 3953 (1962).

(17) J. M. F. Gagan and D. Lloyd, *Chem. Commun.*, 1044 (1967).