Comparative Study on the Preparation of *C*(3)-Hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones

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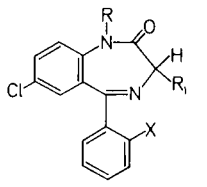
Received April 13, 1979

C(3)-Hydroxy-1,4-benzodiazepin-2-ones **1-3** have been prepared in high yields using a new, two step approach. In the first step, the 3-deoxy-precursors **4-6** were acetylated at *C*(3) using the redox-system lead tetraacetate and iodine, or potassium iodide, in acetic acid. The intermediary acetates **9-11** were quantitatively hydrolyzed into **1-3** in non-aqueous conditions, *i.e.* in a methanol-methylene chloride solvent mixture in the presence of sodium methoxide. Another route to the title compounds has been improved as follows. The yields of *C*(3)-bromination of compounds **4-6** has been significantly augmented in relation to the known methods using the strong trifluoroacetic acid in very dilute carbon tetrachloride solutions as a catalyst for NBS mediated bromination. The intermediary *C*(3)-bromo derivatives have been acetoxylated *in situ*, and compounds **9-11** have been isolated in over 80% yield. These compounds were solvolyzed into **1-3** as described above. The third part of this paper describes the search for feasible reaction conditions in the synthesis of **3** according to a known method (Scheme 1); optimization of the yields in all steps was performed.

J. Heterocyclic Chem., **16**, 1449 (1979).

Introduction.

Among therapeutically valuable 1,4-benzodiazepin-2-ones, the 3-hydroxy derivatives, *e.g.* **1-3**, currently represent one of the most important groups (2-4). This is particularly true since the high anxiolytic and antidepressant activity of these compounds is not accompanied by most of the undesired side-effects observed for some of the earlier synthesized benzodiazepines (5). 3-Hydroxy-1,4-benzodiazepin-2-ones were first isolated as the products of the biotransformation of some 3-deoxy derivatives (6,7). Thereafter they have been synthesized, and found to possess more beneficial therapeutical properties as their *in vivo* precursors. *C*(3)-Oxygenation of some 1,4-benzodiazepin-2-one 4-oxides, using various microbial strains, has recently been described in the literature (8). Consequently, we found a worthwhile working hypothesis to systematically investigate the possibilities for *in vitro* oxygenation of some *C*(3)-deoxy precursors (**4-6**), utilizing diverse hydroxylating (oxygenating) systems, some of them being already applied in bio-mimetic oxygenations (9), and to compare these methods with other synthetic approaches to the title compounds. Similarly, with attempts at direct *C*(3)-oxygenation, certain other *C*(3)-functionalizations have been investigated (halogenation, acetoxylation), having in mind subsequent hydrolysis of the intermediates thus formed to give 3-hydroxy derivatives **1-3**. One high yield approach to the 3-hydroxy-1,4-benzodiazepin-2-ones emerged from this study; however, this paper represents a critical evaluation of all methods investigated.



	X	R	R_1
1	H	H	OH
2	H	CH_3	OH
3	Cl	H	OH
4	H	H	H
5	H	CH_3	H
6	Cl	H	H
9	H	H	$OCOCH_3$
10	H	CH_3	$OCOCH_3$
11	Cl	H	$OCOCH_3$

Results and Discussion.

Various new oxygenating systems, active at saturated or aromatic carbon atoms, are described in the recent literature. Among them we tried the following: cerium (IV) salts and molecular oxygen (10); a ferric chloride-DMF complex (formula $[Fe(DMF)_3Cl_2FeCl_4]$) in a two phase system (water-ether) (11,12); a selenium dioxide-*t*-butylhydroperoxide system (13); triethylphosphine in DMF and molecular oxygen (14); vanadium oxyfluoride in trifluoracetic acid (15); manganese(III) acetate in glacial acetic acid (16); and oxygen in DMF in the presence of copper(II) chloride (17). The results of their application to the oxygenation of **1** are summed up in Table 1.

Direct oxygenating system entirely failed to introduce a *C*(3)-hydroxy group under a variety of conditions investigated. Most of these reagents presumably act as promotors of the oxygen radical chain, and of the subsequent insertion of oxygen into the aromatic, benzylic or allylic C-H bonds of the substrate. Negative results with 1,4-benzodiazepin-2-ones described herewith reveal that the

0022-152X/79/071449-06$02.25

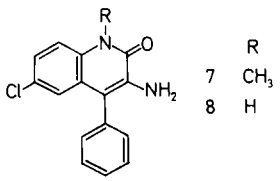
Table 1

Summary of the Attempts at *C*(3)-Oxygenation of Compounds **4** and **5**

Reagents Screened	Solvents	Temperature Interval (°C)	Notes
1) Cerium (IV) Sulfate/Ammonium Sulfate/Molecular Oxygen	Ethanol, Acetonitrile	Room Temperature	No Oxygenation Products
2) Ferric Chloride-DMF Complex	DMF	80-100°	"
3) Selenium Dioxide/*t*-Butylhydroperoxide	Methylene Chloride	Room Temperature	"
4) Triethylphosphite/DMF/Molecular Oxygen	DMF	−15°–Room Temperature	Traces of **2** from **5**
5) Vanadium Oxyfluoride/Trifluoroacetic	Trifluoroacetic Acid	−15°-100°	Formation of **7** and **8**
6) Manganese (II) Acetate/Glacial Acetic Acid	Glacial Acetic Acid	Room Temperature–80°	
7) Copper (II) Chloride/DMF/Molecular Oxygen	DMF	Room Temperature–120°	No Oxygenation Products
8) Palladium on Barium Sulfate/Molecular Oxygen	DMF, Ethanol, Acetonitrile	Room Temperature	"

C(3)-H bond in these compounds does not possess allylic-like, or benzylic-like reactivity. This fact is confirmed by the recent finding that oxygen can be inserted at the C(3) position of some 1,4-benzodiazepin-2-ones, only when the corresponding carbanion was generated by treatment with strong basis under non-aqueous conditions (18).

An interesting reaction was observed, however, when oxygenation with manganese(III) acetate was attempted (16). Compounds **4** and **5** were converted in moderate yield into **7** and **8**, respectively. This conversion of **1** and



2 is in sharp contrast to the reaction of olefins with the same reagent, which affords allylic acetates as the only products (16). The structures of compounds **7** and **8** have been deduced from the following spectral data. In the nmr spectra an AB quartet characteristic of C(3)-H_2 in **4** and **5** was absent, while in the infrared spectra the carbonyl group bands were shifted to shorter wavelengths. Thus, for compound **7** the carbonyl group was shifted from 1685 cm^{-1} in **5** to 1645 cm^{-1}, and for **8** from 1680 cm^{-1} in **4** to 1650 cm^{-1}. At the same time their spectrum of **8** revealed broad NH bonding bands at 3000-3300 cm^{-1}. Mass spectra revealed molecular ion peaks at 284 for **7**, and at 270 for **8**. These molecular weights correspond to those of the starting compounds **4** and **5**, indicating formation of the isomeric structures. This was confirmed by the elemental analysis, so that the structures of the quinolone derivatives could be ascribed to **7** and **8**. Compound **7** has already been prepared in a high yield using our hexamine method (19,20).

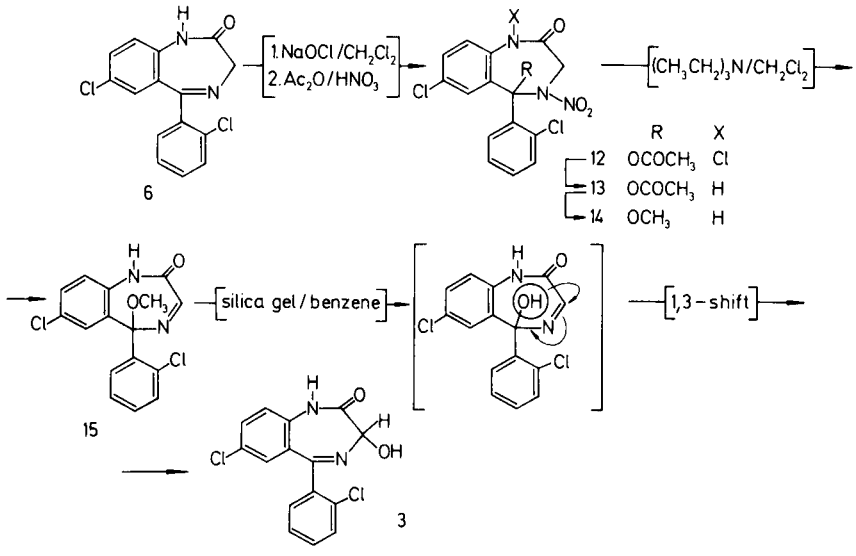
Compounds **1-3** were obtained in greater than 50% yield when *C*(3)-bromination of **4-6** with *N*-bromosuccinimide (NBS) was performed in the presence of α-(poly)-halo-carboxylic acids, particularly in the presence of small amounts of trifluoroacetic acid, followed by hydrolysis of the intermediary 3-bromo-derivatives. The overall yield was increased when acetolysis of the 3-bromo-derivatives was performed, and the 3-acetoxy derivatives **9-11** isolated as described in Experimental. Their subsequent hydrolysis afforded compounds **1-3** in *ca.* 70% overall yields. The most important features of this procedure are the use of highly diluted solutions in carbon tetrachloride, and addition of a strong carboxylic acids in a molar ratio of 1:10. Although it is described in the patent literature (21) that *C*(3)-chlorination of **4**, followed by acetolysis, affords a moderate yield (~35%) of the 3-acetoxy compound **9**, we obtained only unretractable resins on repeated attempts to

follow the reaction conditions described therein. After their hydrolysis and excessive column chromatography we obtained compounds **1-3** in 15-25% only yields. Since activation with azobisisobutyronitrile was required in this procedure (21), the radical chain mechanism of halogenation should be forced. The 1,4-benzodiazepin-2-ones seem not to be substrates prone to *C*(3)-halogenation under such conditions. It is known that bromine represents the dominant radical chain carrier species in NBS bromination reactions, while the succinimidoyl radical usually shares this function at higher concentrations, *i.e.* in solvents other than carbon tetrachloride (22,23). Some ionic-like mechanism of bromination should be taken into account, however, in order to explain the accelerating activity of strong carboxylic acids, particularly that of trifluoroacetic acid. We assume, prompted by the results described in the next paragraph, that N(4) protonated forms of **4-6** may be brominated at C(5) with a concerted double bond shift to the 3,4-position, and that this intermediate subsequently undergoes a 1,3-sigmatropic shift of bromine to the C(3) position.

In the course of these investigations we also found that nearly quantitative yields of the compounds **1-3** could be obtained when hydrolysis of the 3-acetoxy-derivatives was performed in non-aqueous medium, preferentially in a mixture of methylene chloride and methanol, in the presence of sodium methoxide. Here we addopted a method developed in the chemistry of sugars, *i.e.* for the mild hydrolysis of the 1-*O*-acetyl group in peracylated hemiacetals (24,25). This method reveals once again aminal-like reactivity of 3-hydroxy-1,4-benzodiazepines and their *C*(3)-*O*-substituted derivatives, which has already been noticed in our recent work (26,27). This facile and entirely quantitative non-aqueous hydrolysis of the 3-acetoxy derivatives **9-11** into **1-3** prompted us to investigate more thoroughly new possibilities for *C*(3)-acetoxylation of the compounds **4-6**. Limited success with NCS and NBS as *C*(3)-halogenating agents prompted us to investigate the use of elemental iodine as the iodinating agent in the presence of carboxylic acids. High-yield conversion of **4-6** was reached when elad(IV) acetate was used to trap the unstable 3-iodo-intermediates as the 3-acetoxy-derivatives **9-11**. The solvent of choice for both reaction steps proved to be acetic acid, since it both activatives a substrates for iodination and enables use of the otherwise unstable lead(IV) acetate, which is stabilized by the presence of acetic acid. After the first encouraging results with iodine were obtained, we successfully tried potassium iodide in the presence of lead(IV) acetate as the *in situ* origin of the iodine. Elaborating on this procedure we reached over 80% overall yields for **9-11**, while the iodide and lead(II) ions formed in this redox process quantitatively precipitated as the poorly soluble lead(II) iodide. This procedure, according to this comparative study, represents the most efficient approach to the synthesis 1,4-benzodiazepin-2-ones **1-3**.

During this work we attempted the preparation of **3** according to the Scheme 1, *i.e.* according to the method recently developed for preparation of the compounds **1** and **2** (28). To our surprise, however, the preparation of **12** from **6** at room temperature to 40° gave no detectible amount of the product; instead the nitrate of **6** was quantitatively isolated. At -15° to -10° however, compound **12** was obtained in high yield. The second important finding was that conversion of **15** into **3** could be quantitatively performed by silica gel catalysis, *i.e.* on a

SCHEME 1.



silica gel column, or in a batch when an appropriate solvent mixture was used. Conversion of the analogous 5-methoxy-derivative to **1** has been described (28) to take place at room temperature using various acids as the catalyst.

We have strong evidence which indicates that hydrolysis of **15** takes place before sigmatropic migration of the methoxy group on *C*(3), since *C*(3)-methoxy-derivatives, prepared by an independent method (29), do not hydrolyze to the corresponding 3-hydroxy-derivatives under a variety of conditions. Obviously the methoxy group in **15**, being situated on the diphenylmethane-like *C*(5)-carbon, undergoes S*N*1-type hydrolysis faster than a 1,3-sigmatropic shift, or concomitantly with a 1,3-sigmatropic shift, of the entering hydroxy group. Such a rearrangement cannot be excluded *in vivo* as well, so that the observed (28) anxiolytic activities of the 5-methoxy analogous of **15** could at least partially be ascribed to the corresponding 3-hydroxy derivatives formed *in vivo*. A recent attempt at the preparation of a 5-hydroxy isomer of **2**, by ferric chloride hexahydrate catalyzed rearrangement of the *N*(4)-oxide of **5**, failed, and only **2** was isolated (30). We also were not able to identify the *C*(5)-hydroxy intermediate during hydrolysis of **15**, presumably because of the high migratory aptitude of the hydroxy group therein.

EXPERIMENTAL

Melting points were determined on a Mettler FP5 apparatus, and are not corrected. Infrared spectra were obtained on a Perkin-Elmer M 297 spectrometer, and are reported for potassium bromide discs. Nmr spectra were run on a Perkin-Elmer R12 instrument using TMS as internal standard. All reactions were monitored using tlc alumina plates precoated with Merck's silica gel 60F 254. Column chromatographic purifications were carried out with silica gel (0.05-0.2 mm) from Merck. Organic extracts were dried over sodium sulfate and evaporated *in vacuo*. Compounds **4-6** were prepared according to our hexamine procedure described earlier (31,32).

Attempts at Direct *C*(3)-Oxygenation of **6**.

All experiments were performed on a 1.0 mmole basis for the 1,4-benzodiazepines **4-6**. The solvent system for the tlc-monitoring was ether-light petroleum (3:1), while the products were identified under a uv 254 nm lamp. All reactions were carried out at least for 24 hours at the lowest temperature indicated in Table 1, then the temperature was gradually raised every 1-2 hours. The results of these experiments are summed up in Table 1.

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

Method A.

A suspension of the compound **5** (8.0 g., 28.2 mmoles) and NBS (6.1 g., 34.3 mmoles) in carbon tetrachloride (320 ml.) was stirred at ambient temperature for 15 minutes, then trifluoracetic acid (278 mg., 2.44 mmoles) was added. The reaction mixture was vigorously stirred and heated under reflux for 1.5 hours. The hot solution was thereafter separated from the yellow, sticky precipitate by decantation, and the residue washed with hot carbon tetrachloride (2 x 5 ml.). The combined solutions were evaporated to dryness affording 9.84 g. (98%) of an amorphous material (vacuum dried). It was dissolved in a mixture of 5% aqueous sodium acetate (60 ml.) and acetone (80 ml.). The resulting solution (*p*H 6-7) was set aside overnight, thereafter it was evaporated to ca. one fourth of the starting volume. The remaining slurry was further diluted with water (200 ml.), and extracted with chloroform (3 x 50 ml.). The organic extracts were washed with water, dried, evaporated, and the residual oil was brought to crystallization by scratching and addition of ether. Thus, 7.6 g. of crude **2** was obtained, which was purified by slurrying in pyridine (5 ml.), and addition of glacial acetic acid (20 ml.) and acetic anhydride (40 ml.). The crystalline slurry was poured into 300 ml. of ice-water, and after brief stirring, the crystalline product was filtered. Thus, 6.72 g. of pure **10** was obtained, m.p. 255-256° (lit. (33) m.p. 254-256°). This product was dissolved in a mixture of dichloromethane (80 ml.) and methanol (40 ml.), and then 1.5 ml. of a 30% methanolic solution of sodium methylate was added. The reaction mixture was stirred for 10 minutes at room temperature. Water (200 ml.) was then added, the *p*H was adjusted to 3-4, and the solution was extracted with methylene chloride (3 x 30 ml.). The combined extracts were washed with a saturated solution of sodium bicarbonate, washed with water, evaporated and crystallized from ether-light petroleum ether (100:60 ml.) at –15°. Thus, 1.96 g. (65%) of pure **2** was obtained with m.p. 158-160° (lit. (34) m.p. 119-120°). Compounds **1** and **3** have been prepared according to the same procedure in 64% and 70% yield, respectively.

Method B.

Iodine (1.91 g.) was dissolved in glacial acetic acid (40 ml.); at 105°, lead(IV) acetate (3.32 g., 6.55 mmoles) was then added under stirring over a period of 5 minutes. To the resulting suspension, compound **5** (2.84 g., 10.0 mmoles) was added, and the reaction mixture heated at 105° for 1 hour. After cooling to room temperature, methylene chloride was added (40 ml.), the precipitate filtered off, and the filtrate evaporated to dryness. The residue was dissolved in methylene chloride (50 ml.), and sodium thiosulfate were added until the organic phase became colourless. The organic phase was separated and aqueous phase was washed with methylene chloride (3 x 30 ml.). The combined extracts were washed with aqueous bicarbonate, dried, and evaporated to dryness affording 3.22 g. of crude **10**. The crude product was hydrolyzed in a mixture of methylene chloride (40 ml.) and methanol (20 ml.), to which 30% sodium methylate (1.5 ml.) was added, using the same conditions as described in Method A. Thus, 2.35 g. (78.3%) of pure **2** was obtained, m.p. 159-160°. Compounds **1** and **3** were obtained, following Method B in 85% yield. Their spectral data and melting points (196-198° for **1**, and 168-169° for **3**) correspond to those reported in the literature (28,33).

1,7-Dichloro-4-nitro-5-acetoxy-5-(2′-chlorophenyl)-1,2,3,4-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**12**).

To a solution of compound **6** (5.0 g., 16.4 mmoles) in methylene chloride (75 ml.), a 1*M* solution of sodium hypochlorite in 0.1*N* sodium hydroxide (35 ml.) was added at room temperature under vigorous stirring. The reaction proceeded for 40 minutes at ambient temperature. Thereafter, water was added (100 ml.), and the organic layer was separated, dried, and evaporated at room temperature. The residual mass (oil) was cooled to –10°, acetanhydride (75 ml.) was added, and then fuming nitric acid (5.0 ml.) was added dropwise during

20 minutes under vigorous stirring. Stirring was prolonged for 1.5 hours, whereupon a crystalline product separated. It was filtered off, washed with ether and dried affording 6.2 g. (85%) of **12**, m.p. 125-126°; ir: 1760, 1730, 1556, 1290, 1178, 1065, 925, 830, 770, 740; nmr (DMSO-d_6): 1.95 ppm (s, 3H), 4.35 (s, 2H), 7.0-8.0 (m, 7H).

Anal. Calcd. for $C_{17}H_{12}Cl_3N_3O_5$ (444.66): C, 45.91; H, 2.72; N, 9.45. Found: C, 46.07; H, 2.73; N, 9.88.

7-Chloro-4-nitro-5-acetoxy-5-(2′-chlorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**13**).

Freshly prepared compound **12** (5.0 g., 11.2 mmoles) was dissolved in methylene chloride (45 ml.), precooled to –5°, and a saturated solution of methylamine in methylene chloride (4.0 ml.) was added dropwise under stirring and below 0°. After an additional 3 hours of stirring at –5° the reaction mixture was evaporated to dryness, and the residual mass was crystallized from the cold methanol (10 ml.). The crystals were filtered and dried *in vacuo* affording 4.5 g. (97%) of **13**, m.p. 98-100°; ir: 3220, 1765, 1695, 1550, 1295, 1270, 1200, 1085, 988 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}Cl_2N_3O_5$ (410.21): C, 49.77; H, 3.19; N, 10.24. Found: C, 49.52; H, 3.46; N, 10.44.

7-Chloro-4-nitro-5-methoxy-5-(2′-chlorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**14**).

Compound **13** (3.0 g., 7.3 mmoles) was dissolved in 50 ml. of absolute methanol and stirred for 24 hours at 20-22°. The precipitated product was filtered off, washed wiht methanol (20 ml.), and dried *in vacuo*, to afford 2.6 g. (96%) of **14**, m.p. 197-199° dec; ir: 3210, 1695, 1545, 1290, 1270, 1050 cm^{-1}; nmr (DMSO-d_6): 3.39 (s, 3H), 4.7-5.1 (m, 2H), 7.0-8.0 (m, 7H).

Anal. Calcd. for $C_{15}H_{13}Cl_2N_3O_4$ (370.19): C, 48.66; H, 3.54; N, 11.35. Found: C, 50.02; H, 3.24; N, 11.54.

7-Chloro-5-methoxy-5-(2′-chlorophenyl)-1,5-dihydro-2*H*-1,4-benzodiazepin-2-one (**15**).

Compound **14** (1.66 g., 4.5 mmoles) and triethylamine (4.02 g., 8.5 mmoles) were dissolved in methylene chloride (14 ml.), and stirred at ambient temperature for 2.5 hours. Thereafter water was added (200 ml.), and the organic layer was separated, washed with water (3 x 200 ml.), dried and evaporated to dryness. The residue was crystallized from diisopropyl ether affording 1.3 g. (86%) of the vacuum dried **15**, m.p. 169-170°; ir: 3180, 1680, 1635, 1490, 1080; nmr (deuteriochloroform): 3.18 (s, 3H), 6.8-7.7 (m, 7H), 7.9 (s, 1H).

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2O_2$ (335.18): C, 57.33; H, 3.61; N, 8.36. Found: C, 57.27; H, 3.84; N, 8.41.

7-Chloro-5-(2′-chlorophenyl)-3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3**).

Compound **15** (1.0 g., 2.98 mmoles) was dissolved in THF (45 ml.) and 10 ml. of 1*N*) hydrochloric acid was added under vigorous stirring. After 4-5 minutes the reaction was finished, according to tlc. Water (200 ml.) was then added, cooled under stirring for 1 hour and the precipitated crystals were filtered off. After crystallization from acetone-diisopropyl ether 0.885 g. (92%) of pure **3** was obtained, m.p. 167-168° (lit. (34) m.p. 166-168°).

General Procedure for Mananese (II) Acetate Oxidation of **4** and **5**.

Compounds **4** and **5** (10.0 mmoles) were dissolved in glacial acetic acid (40 ml.) and manganese (III) acetate monohydrate (2.5 g., Fluka puriss.) was added under stirring. The resulting slurry was stirred under heating at 105° for 4 hours. A dark-brown solution resulted and white manganese (II) acetate precipitated. The solution was evaporated to dryness, the residue slurried in water (250 ml.), and extracted with chloroform (3 x 40 ml.). The organic extracts were washed with saturated aqueous bicarbonate, dried, and evaporated to afford the crude products.

Crude **7**.

This compound (3.44 g.) was purified on a silica gel column (160 g.), using ether as the eluent, and in fractions 22-36 (5 ml. per fraction), 1.38 g. of pure **7** were obtained. It was crystallized from methylene chloride (5 ml.) and light petroleum (20 ml.) affording 1.32 g. of crystalline **7**, m.p. 139-140° (lit. (19) m.p. 138-140°; ir and nmr spectra superimposable).

Crude **8**.

This compound (3.31 g.) was purified on a silica gel column (150 g.), using the solvent mixture of methylene chloride-acetone (6:1). In the fractions 60-105 (5 ml. per fraction), 1.48 of pure **8** were obtained, which on crystallization from chloroform (25 ml.) and light petroleum (35 ml.) melted at 235-236°; ir: 3450, 3340, 1650, 1675, 1485, 1388, 1290, 1245, 810, 705 cm^{-1}; nmr (deuteriochloroform): 5.05 (s, 2H, disappears on addition of deuterium oxide), 6.82 (d, 1H), 7.35-7.7 (m, 8H); ms: 270 (100), 269 (32), 253 (41), 234 (12), 224 (21), 216 (6), 214 (8), 206 (17), 205 (12), 117.5 (24), 85 (11), 83 (7).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$ (270.72): C, 66.59; H, 4.09; N, 10.35. Found: C, 66.41; H, 4.42; N, 10.03.

Acknowledgement.

The authors are indebted to Prof. L. Klasinc, "Rugjer Bošković" Institute, for providing the mass spectra of compounds **7** and **8**, and to Ing. H. Hofman for hplc data.

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