Quinazolines and 1,4-Benzodiazepines. LXXXV (1) Syntheses of 3-Substituted Imidazo[1,5-*a*][1,4]benzodiazepines

Armin Walser, Thomas Flynn and R. Ian Fryer*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received November 18, 1977

1,4-Benzodiazepines having a leaving group in the 2-position were condensed with carbanions of 1,3-dicarbonyl compounds. The products obtained were converted to the title compounds by a sequence of steps involving hydrolytic decarboxylation, nitrosation, catalytic hydrogenation and condensation with an orthoester or an amide acetal.

Oxidative condensation of the enediamine **12** with a variety of aldehydes also led to imidazobenzodiazepines with various substituents in the 1-position.

J. Heterocyclic Chem., 15, 577 (1978)

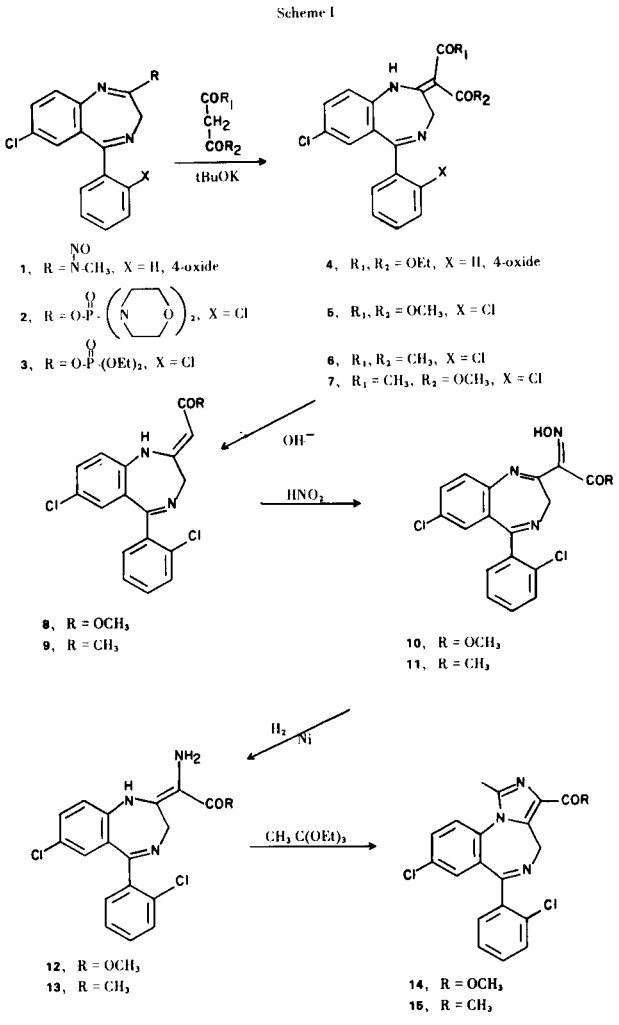
In a previous paper (1) we reported the syntheses of imidazo[1,5-*a*][1,4]benzodiazepines, by a scheme which required the aromatization of an imidazoline ring in the final step. As an alternative approach to these pharmacologically interesting compounds, we now wish to describe methods which led to the title compounds bearing a carboxylic acid function, or an acetyl group in the 3-position and which, in addition, allow for variation of the substituent in the 1-position.

The benzodiazepines **1-3** having a suitable leaving group in the 2-position, were reacted with the anions of 1,3-dicarbonyl compounds to give the condensation products **4-7**. The preparation of the malonic ester derivative **4** by employing the *N*-nitrosomethylamino function of **1** as a leaving group has been described earlier (2). The utilization of the iminophosphate **2** (3a) for the same purpose has also been published (3b) and was extended to the preparation of compounds **5-7**. Compound **5** could also be conveniently prepared from the iminophosphate **3** which in turn was synthesized from the corresponding benzodiazepin-2-one using commercially available diethyl chlorophosphate. The reaction of **2** with the anion of pentane-2,4-dione gave the dione **6**. The formation of the 2′-deschloro analog of **6** by condensation of a 2-aminobenzodiazepine with pentane-2,4-dione has been reported by Szmuskovicz, *et al.*, (4). These authors preferred to represent the analog of **6** in the tautomeric imine-enol structure. However, because of the spectral similarities (uv, ir, nmr) of the compounds **5**, **6** and **7**, we prefer the enamine structures shown. The stereochemistry assigned to **7** is uncertain but is compatible with spectral data.

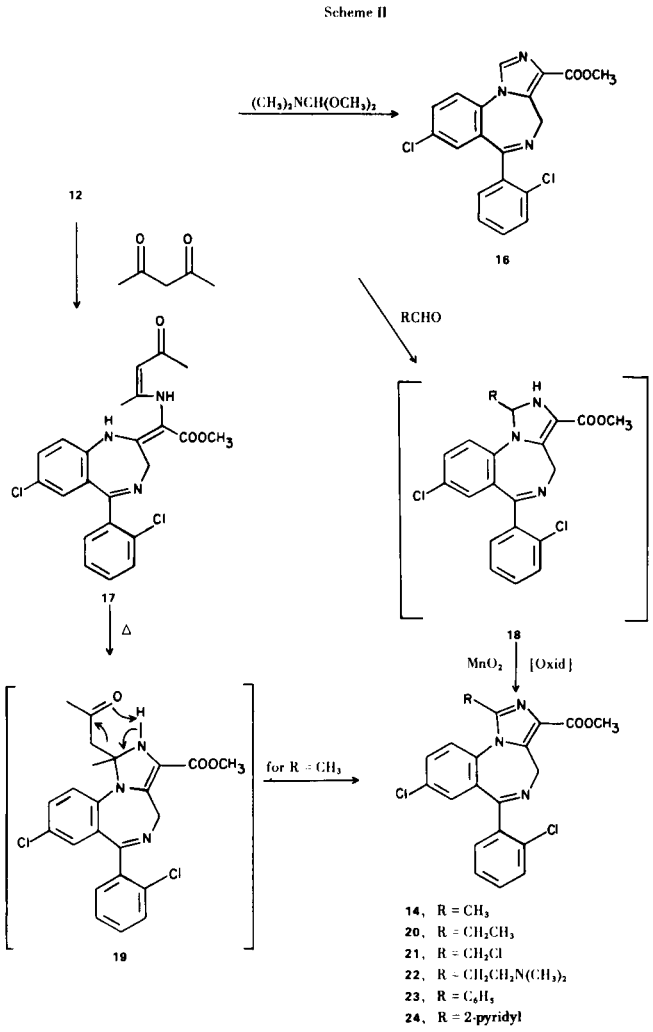
Treatment of **5** with potassium hydroxide in boiling methanol gave the acrylic ester derivative **8** in high yield. The same compound was obtained from the ketoester **7** with cleavage of the acetyl group being preferred. The dione **6** gave under similar conditions the ketone **9**. Compounds **8** and **9** were isolated as single isomers to which we have assigned the *trans*-configuration on the basis of intramolecular hydrogen bonding as evidenced by the low field absorption of the exchangeable protons at δ 10.66 and 12.40 ppm respectively and also by the carbonyl absorption bands in the ir spectra at 1665 and 1633 cm^{-1}, respectively. The tautomeric imine structure with an endocyclic double bond was excluded for the ester **8** by spectral data but has to be considered for the ketone **9**. However the similarity of the spectral data (uv, ir, nmr) of **8** and **9** again led us to prefer the unsaturated ketone structure over the tautomeric enolized form.

The enamine functionality in **8** and **9** was quite reactive towards electrophiles and nitrosation in acetic acid proceeded rapidly at room temperature giving almost quantitative yields of the oximes **10** and **11**. Only one isomer

Scheme I



Scheme II

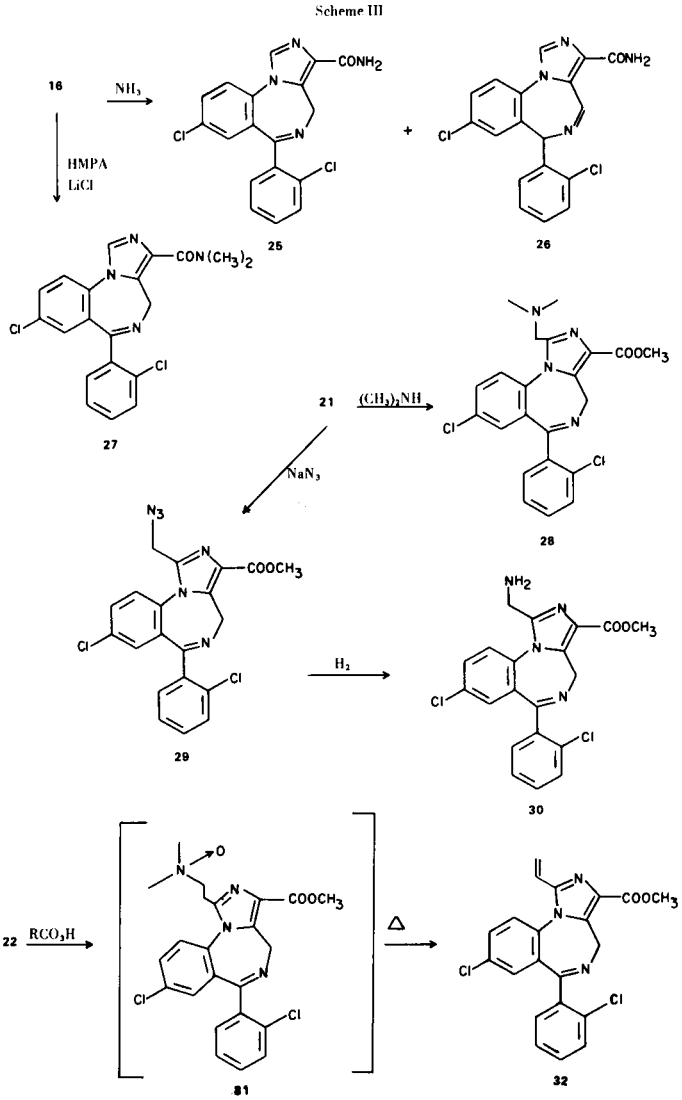


of the oximes was observed. This again may be attributed to a strong hydrogen bonding interaction between the hydroxyl group and the nitrogen in the 1-position. Catalytic hydrogenation of the oximes over Raney nickel led to the enediamines **12** and **13**. Reduction of the ester **10** proceeded particularly well in the presence of ammonia and gave compound **12** as an orange colored, crystalline solvate containing one mole of ethanol. The solvent free form, (yellow needles) was only prepared for the purpose of characterization. The spectral data for **12** are in agreement with the assigned structure and the stereochemistry is supported by the facile conversion to the imidazoles described below. Compound **13** was not characterized but was converted directly to the corresponding imidazobenzodiazepine. The reactions of **12** and **13** with triethyl orthoacetate afforded the imidazo derivatives **14** and **15**, either thermally or by acid catalysis. Condensation of **12** with dimethylformamide dimethylacetal (Scheme II) afforded **16** even at room temperature and in the absence of a catalyst, but brief heating in ethyl acetate was more practical.

The oxidative condensation with aldehydes which has been used for the syntheses of triazolobenzodiazepines (5) proved to be especially useful for the preparation of imidazobenzodiazepines having various substituents in the 1-position. This method was applicable to aliphatic, aromatic and heterocyclic aldehydes as illustrated by the preparation of compounds **20** to **24**.

Thus, for example, reaction of **12** with chloroacetaldehyde followed by treatment with activated manganese dioxide gave the 1-chloromethyl derivative **21**. The 1-methyl analog **14** was found to be a by-product of this reaction and was most likely formed by dehydrohalogenation of the intermediate 1-chloromethylimidazoline **18** (R = CH_2Cl). Since the imidazolines corresponding to **18** appeared to be unstable and quite sensitive to air oxidation, these compounds were not isolated but directly aromatized. For convenience the oxidation was carried out with activated manganese dioxide but other oxidizing agents, including air, could also be used.

Scheme III



The oxidative condensation of **12** with acrolein and manganese dioxide in the presence of dimethylamine led to the basic imidazole **22** in good yield. The 1-methyl derivative **14** was also formed quite efficiently by heating **12** with pentane-2,4-dione in boiling toluene. At lower temperatures (reflux in benzene) it was possible to isolate and characterize the initial adduct **17**. The almost quantitative conversion of **17** to **14** probably involves the elimination of acetone from an intermediate such as **19** by the indicated cyclic mechanism.

Heating the ester **16** with methanolic ammonia in a sealed vessel led to the amide **25** (Scheme III). The double bond isomer **26** was also isolated and was probably formed by abstraction of a proton from the 4-position followed by reprotonation at the 6-position (1). The tertiary amide **27** was prepared by heating the methyl ester **16** with lithium chloride in hexamethyl phosphoric triamide.

The chloromethyl group of **21** could be used for the introduction of other functionalities by displacement of chloride with nucleophiles. Thus, reaction of **21** with dimethylamine gave the dimethylaminomethyl derivative **28** while the corresponding primary amine **30** was obtained by catalytic reduction of the azide **29** prepared in turn by reaction of compound **21** with sodium azide in dimethylformamide.

Treatment of the dimethylaminoethyl analog **22** with *m*-chloroperbenzoic acid under mild conditions gave the *N*-oxide **31**, resulting from a preferential oxidation of the most basic nitrogen. This *N*-oxide was found to undergo a Cope-elimination, even at room temperature, and afforded the vinyl compound **32** after brief heating in benzene.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus or Reichert hot stage microscope. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

7-Chloro-5-(2-chlorophenyl)-2-dimethoxymalonylidene-1,3-dihydro-2*H*-1,4-benzodiazepine (**5**).

A solution of 30.5 g. (0.1 mole) of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (6) in 300 ml. of dry tetrahydrofuran was cooled by an ice-water bath. With stirring, under argon, 13 g. (0.115 mole) of potassium *t*-butoxide was added and 5 minutes later 18 ml. (2.17 g., 0.125 mole) of diethyl chlorophosphate. Stirring and cooling were continued for 10 minutes and a prepared mixture of 23 ml. (26.4 g., 0.2 mole) of dimethyl malonate, 150 ml. of dimethylformamide and 22.4 g. (0.2 mole) of potassium *t*-butoxide was added. The mixture was stirred at room temperature for 2 hours, acidified by addition of 20 ml. of glacial acetic acid, diluted with 500 ml. of saturated aqueous sodium bicarbonate solution and 500 ml. of saturated sodium chloride solution and extracted 3 times with toluene. The extracts were washed with water, dried and evaporated. Crystallization of the residue from 2-propanol yielded 23.5 g. (56%) of product with m.p. 202-205°. The analytical sample was recrystallized from ethyl acetate, m.p. 205-207°; uv: λ sh 214 (ε = 33,700), inflection 240 (17,000), λ max 271 (8,350), 313 (31,500), inflection 355 nm (4,200); ir (chloroform): 3150 (NH), 1720, 1665 ($COOCH_3$) cm^{-1}; nmr (deuteriochloroform): δ 3.76 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 4.53 (s, 2, C_3-H), 6.98 (d, 1, J = 2 Hz, C_6-H), 7.06 (d, 1, J = 8 Hz, C_9-H), 7.2-7.6 (m, 5, aromatic H), 11.6 ppm (broad s, 1, NH).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O_4$: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.37; H, 3.83; N, 6.84.

3-[7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]-2,4-pentadione (**6**).

A mixture of 73 g. (.139 mole) of 7-chloro-5-(2-chlorophenyl)-2-[bis-(morpholine)phosphinyloxy]-3*H*-1,4-benzodiazepine (**2**) (3a), 47 g. (0.418 mole) of potassium *t*-butoxide, 115 ml. of 2,4-pentanedione and 450 ml. of dimethylformamide was stirred at room temperature under an argon atmosphere for 15 minutes and then heated on a steam bath for 1.5 hours. The mixture was cooled, acidified with glacial acetic acid, diluted with 1.5 liter of water and extracted twice with 750 ml. of dichloromethane. The dichloromethane extracts were washed with saturated sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from isopropanol yielded 14.8 g. (27.5%) of product with m.p. 198-202°. The analytical sample was recrystallized from dichloromethane–2-propanol to give colorless crystals with m.p. 205-207°; uv: λ max 217 (ε = 33,200), inflection 270 (8,300), 345 nm (23,800); ir (chloroform): 1680, 1620 (CO) cm^{-1}; nmr (deuteriochloroform): δ 2.28 (s, 3, $COCH_3$), 2.62 (s, 3, $COCH_3$), 4.35 (s, 2, C_3-H), 7-7.7 (m, 7, aromatic H), 13.8 ppm (broad s, 1, NH).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O$: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.10; H, 4.17; N, 7.11.

α-Acetyl-[7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]acetic Acid Methyl Ester (**7**).

A mixture of 2.24 g. (0.02 mole) of potassium *t*-butoxide, 10 ml. of methyl acetoacetate and 30 ml. of dimethylformamide was stirred at room temperature under a nitrogen atmosphere for 15 minutes. To this mixture was then added 5.23 g. (0.01 mole) of 7-chloro-5-(2-chlorophenyl)-1-[bis-(morpholino)phosphinyloxy]-3*H*-1,4-benzodiazepine (**2**) (3a) and the stirring was continued for 2.25 hours. After addition of 1.12 g. (0.01 mole) of additional potassium *t*-butoxide the mixture was heated for 10 minutes on a steam bath, cooled, acidified with glacial acetic acid, diluted with 100 ml. of water and extracted with two 50 ml. portions of dichloromethane. The extracts were combined, washed with saturated sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from 2-propanol/hexane yielded 1.0 g. (25%) of product with m.p. 140-142°. Recrystallization for analysis from 2-propanol gave colorless crystals with m.p. 142-144°; uv: λ max 217 (ε = 33,400), inflection 245 (17,200), 331 nm (24,900); ir (chloroform): 1707 ($COOCH_3$), 1617 (CO); nmr (deuteriochloroform): δ 2.36 (s, 3, $COCH_3$), 3.90 (s, 3, $COOCH_3$), 4.60 (s, 2, C_3-H), 7.0-7.8 (m, 7, aromatic H), 14.1 ppm (broad s, 1, NH).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O_3$: C, 59.57; H, 4.00; N, 6.95. Found: C, 59.95; H, 4.26; N, 7.04.

7-Chloro-5-(2-chlorophenyl)-2,3-dihydro-2-[(methoxycarbonyl)-methylene]-1*H*-1,4-benzodiazepine (**8**).

A) A mixture of 84 g. (0.2 mole) of **5**, 1.5 liter of methanol

and 14 g. (0.25 mole) of potassium hydroxide was heated to reflux for 4.5 hours. The solvent was distilled down to about 400 ml. The product started to crystallize during the concentration and was further precipitated by addition of 300 ml. of water. After cooling, the crystals were filtered off and dried to yield 65 g. (90%) of product with m.p. 156-158°. The analytical sample was recrystallized from dichloromethane/methanol, m.p. 158-159°; uv: λ sh 215 (ε = 34,700), sh 237 (16,300), λ max 273 (31,400), sh 350 nm (3,500); ir (chloroform): 3225, 3275 (NH), 1665 (CO), 1620 cm^{-1}; nmr (deuteriochloroform): δ 3.73 (s, 3, OCH_3), 4.37 (s, 2, C_3-H), 4.92 (s, 1, -CH=), 6.98 (d, 1, J = 2 Hz, C_6-H), 7.02 (d, 1, J = 8 Hz, C_9-H), 7.2-7.6 (m, 5, aromatic H), 10.66 ppm (broad s, 1, NH).

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_2$: C, 59.85; H, 3.91; N, 7.76. Found: C, 59.89; H, 3.85; N, 7.88.

B) A mixture of 0.5 g. (1.24 mmole) of **7**, 0.208 g. (3.72 mmoles) of potassium hydroxide and 50 ml. of methanol was stirred and refluxed for 45 mintues. Half of the methanol was evaporated off and the mixture was diluted with 50 ml. of water. The precipitated product was collected, washed with water and sucked dry to yield 0.43 g. (96%) of crystals with m.p. 154-158°. This material was identical in every respect with the above compound.

1-[7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]-2-propanone (**9**).

A mixture fo 5.8 g. (0.015 mole) of **6**, 2.52 g. (0.045 mole) of potassium hydroxide and 250 ml. of methanol was stirred and refluxed for 2 hours. The solution was then acidified with glacial acetic acid and evaporated. The residue was dissolved in 400 ml. of dichloromethane. The solution was washed with saturated sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from ether/hexane yielded 3.2 g. (61.8%) with m.p. 143-145°. A lower melting modification with m.p. 118-120° was also observed; uv: λ max 216 (ε = 29,450), inflection 240 (14,000), 285 (4,500), 330 nm (25,000); ir (chloroform): 3200, 3250 (NH), 1633 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.17 (s, 3, $COCH_3$), 4.33 (s, 2, $-CH_2-$), 5.4 (s, 1, -CH=), 6.9-7.6 (m, 7, aromatic H), 12.4 ppm (broad s, 1, NH).

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O$: C, 62.62; H, 4.09; N, 8.11. Found: C, 62.66; H, 4.28; N, 8.09.

7-Chloro-5-(2-chlorophenyl)-α-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid Methyl Ester (**10**).

Sodium nitrite, 20.7 g. (0.3 mole), was added in portions over a period of 10 minutes to a solution of 72.2 g. (0.2 mole) of **8** in 600 ml. of glacial acetic acid. Following the addition, the mixture was stirred under nitrogen for 15 minutes longer during which time the product crystallized partially. It was precipitated by addition of 1 liter of water, filtered, washed with water and dried in vacuum. The dry material was recrystallized from tetrahydrofuran/hexane to give 76 g. (97%) of product in two crops. The analytical sample was recrystallized from methanol/tetrahydrofuran and had m.p. 223-225° (dec.); uv: λ max 242 (ε = 32,700), sh 275 (12,500), max 323 (5,280), sh 337 nm (5,170); ir (potassium bromide): 1740 cm^{-1} (COOMe); nmr (deuteriochloroform): δ 3.83 (s, 3, OCH_3), 4.67 (broad s, 2, C_3-H), 7.0-7.7 (m, 7, aromatic H), 13.2 ppm (s, 1, OH); nmr (DMSO-d_6): δ 3.85 (s, 3, OCH_3), 4.4 (broad s, 2, C_3-H), 7.06 (d, 1, J = 2 Hz, C_6-H), 7.3-7.8 (m, 6, aromatic H), *ca.* 13.0 ppm (very broad, s, 1, OH).

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_3$: C, 55.40; H, 3.36; N, 10.77. Found: C, 55.43; H, 3.33; N, 10.72.

1-[7-Chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]-1-hydroxyimino-2-propanone (**11**).

A stirred solution of 2.5 g. (7.54 mmoles) of **9** in 15 ml. of glacial acetic acid was treated with 0.67 g. (9.8 mmoles) of sodium nitrite. The mixture was stirred for 15 minutes, during which time the product precipitated out. The mixture was diluted with 30 ml. of water, the solids were collected, washed with water and sucked dry. Recrystallization from dichloromethane/hexane yielded 2.5 g. (88.6%) of product. The analytical sample was recrystallized from dichloromethane/hexane to give light yellow crystals with m.p. 189-192°; uv: λ max 241 (ε = 31,220) sh 310/20 nm (6,040); ir (chloroform): 3140 (OH), 1720 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.3 (s, 3, $COCH_3$), *ca.* 4.5 (broad s, 2, $-CH_2-$), 7-7.6 (m, 7, aromatic H), 12.8 ppm (s, 1, OH).

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C, 57.78; H, 3.50; N, 11.23. Found: C, 57.61; H, 3.43; N, 11.37.

2-[(Amino)methoxycarbonylmethylene]-7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine (**12**).

A mixture of 50 g. of **10**, 600 ml. of tetrahydrofuran, 300 ml. of ethanol, 50 g. of Raney nickel and 10 ml. of methanol containing 10% of ammonia was hydrogenated at atmospheric pressure for 4 hours when hydrogen consumption ceased. The catalyst was separated by filtration and the filtrate was evaporated under reduced pressure down to a small volume. The orange crystals separated during the evaporation were collected, washed with ethanol and dried to leave 39.3 g. (72.5%) of product solvated with 1 mole of ethanol with m.p. 119-121°; nmr (DMSO-d_6): δ 1.07 (t, 3, J = 6.5 Hz, CH_3, ethanol), 3.5 (m, 2, J = 6.5 Hz, O-CH_2-, ethanol), 3.72 (s, 3, OCH_3), 5.0 (s, 2, C_3-H), 3.0-6.0 (broad, exchangeable signals, 4, NH_2, NH, OH), 6.72 (d, 1, J = 2 Hz, C_6-H), 7.25 (d, 1, J = 8 Hz, C_9-H), 7.4 (dd, 1, J_{AB} = 8 Hz, J_{AX} = 2 Hz, C_8-H), 7.48 ppm (s, 4, aromatic H).

Anal. Calcd. for $C_{18}H_{15}Cl_2N_3O_2 \cdot C_2H_5OH$: C, 56.88; H, 5.01; N, 9.95. Found: C, 56.80; H, 4.95; N, 9.84.

Crystallization of this solvate from ether yielded yellow needles with m.p. 145-150° (dec.); uv: λ sh 217 (ε = 31,200), inflection 280 (7,500) λ max 327 (26,300), inflection 400 nm (1,920); ir (chloroform): 3380, 3320 (NH, NH_2), 1680 ($COOCH_3$), 1630 cm^{-1}; nmr (deuteriochloroform): δ *ca.* 3.8 (broad s, 2, NH_2), 3.76 (s, 3, OCH_3), 5.08 (s, 2, C_3-H), 6.86 (d, 1, J = 8 Hz, C_9-H), 6.88 (d, 1, J = 2 Hz, C_6-H), 7.1-7.7 ppm (m, 5, aromatic H), NH appears as a very broad signal in the region of the aromatic protons.

Anal. Calcd. for $C_{18}H_{15}Cl_2N_3O_2$: C, 57.46; H, 4.02; N, 11.17. Found: C, 57.78; H, 3.98; N, 11.42.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**14**).

A) A mixture of 20 g. of the ethanolate of **12**, 300 ml. of toluene and 20 ml. of triethyl orthoacetate was heated to reflux for 30 minutes. The solvent was evaporated under reduced pressure and the crystalline residue was stirred in ethyl acetate/hexane and filtered off to yield 17.8 g. (93%) of tan product. For analysis it was recrystallized from ethyl acetate to leave off-white crystals with m.p. 228-230°; nmr (deuteriochloroform): δ 2.55 (s, 3, CH_3), 3.9 (s, 3, OCH_3), 3.97 (d, 1) and 5.97 (d, 1) (AB-system, J = 12 Hz, C_4-H), 7.0-7.7 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O_2$: C, 60.01; H, 3.78; N, 10.50. Found: C, 59.80; H, 3.86; N, 10.55.

B) A solution of 0.14 g. (0.3 mmole) of **17** in 10 ml. of toluene was heated to reflux for 1.5 hours. The solvent was evaporated and the residue was crystallized from ether to give 0.12 g. (98%) of the product with m.p. 228-230°.

C) A mixture of 5 g. (0.0116 mole) of the ethanolate of **12**, 5 ml. of pentan-2,4-dione and 50 ml. of toluene was heated to reflux for 1 hour. The solvent was evaporated and the residue was crystallized from ethyl acetate/ether to yield 3.4 g. (75%) of product with m.p. 228-230°.

3-Acetyl-8-chloro-5-(2-chlorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*]-[1,4]benzodiazepine (**15**).

A solution of 1 g. (2.67 mmoles) of **11** in 15 ml. of tetrahydrofuran and 15 ml. of ethanol was hydrogenated over Raney nickel at atmospheric pressure for 1.25 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 50 ml. of methanol. After the addition of 3 ml. of triethylorthoacetate and 0.5 ml. of glacial acetic acid, the mixture was heated to reflux for 2 minutes and then evaporated. The residue was dissolved in 50 ml. of methylene chloride and the solution was washed with saturated sodium bicarbonate, dried and evaporated. Crystallization from ether yielded 0.25 g. (24.3%) with m.p. 220-225°. The analytical sample was recrystallized twice from ethyl acetate/hexane to yield colorless crystals with m.p. 234-236°: nmr (deuteriochloroform): δ 2.56 (s, 3) and 2.60 (s, 3) (CH_3, $COCH_3$), 3.96 (d, 1) and 6.13 (d, 1) (AB-system, J = 12 Hz, C_4-H), 7.1-7.8 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O$: C, 62.51; H, 3.93; N, 10.93. Found: C, 62.61; H, 4.06; N, 10.84.

8-Chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**16**).

A mixture of 42.2 g. (0.1 mole) of the ethanolate of **12**, 14.3 g. (0.12 mole) of dimethylformamide dimethylacetal and 150 ml. of ethyl acetate was heated to reflux for 5 minutes. The product started to crystallize from the hot reaction mixture and was further precipitated by addition of hexane. The crystals were collected after cooling to yield 35.2 g. (91%) of tan product, which was recrystallized from dichloromethane/ethyl acetate for analysis to leave colorless product with m.p. 206-208°; nmr (deuteriochloroform): δ 3.94 (s, 3, OCH_3), 5.1 (broad s, 2, C_4-H), 7.1-7.8 (m, 7, aromatic H), 7.92 ppm (s, 1, C_1-H).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O_2$: C, 59.09; H, 3.39; N, 10.88. Found: 59.27; H, 3.48; N, 10.79.

[7-Chloro-5-(2-chlorophenyl)-2,3-dihydro-1*H*-[1,4]benzodiazepin-2-ylidene]-4-oxopent-2-ene-2-ylaminoacetic Acid Methyl Ester (**17**).

A mixture of 5 g. (0.0116 mole) of the ethanolate of **12**, 12 ml. of pentan-2,4-dione and 100 ml. of benzene was heated to reflux with separation of water for 30 minutes. The solvent and excess reagent were evaporated under reduced pressure and the residue was crystallized from ethyl acetate to yield 3.3 g. (62%) of product which was recrystallized from dichloromethane/ethyl acetate for analysis, m.p. 218-220° (dec.); uv: λ max 324 nm (ε = 39,000); ir (chloroform): 3250, 3200 (NH), 1663 ($COOCH_3$), 1613 (CO), 1570 cm^{-1}; nmr (deuteriochloroform): δ 1.75 (s, 3, CH_3), 1.88 (s, 3, $COCH_3$), 3.73 (s, 3, OCH_3), 4.2 (broad s, 1) and 4.83 (broad s, 1) (-CH_2-), 5.15 (s, 1, -CH=), 6.9-7.6 (m, 7, aromatic H), 11.1 ppm (broad s, 2, NH).

Anal. Calcd. for $C_{23}H_{21}Cl_2N_3O_3$: C, 60.27; H, 4.62; N, 9.17. Found: C, 60.47; H, 4.65; N, 9.26.

8-Chloro-6-(2-chlorophenyl)-1-ethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**20**).

A mixture of 8.5 g. (0.02 mole) of the ethanolate of **12**, 200 ml. of dichloromethane, 4 ml. of propionaldehyde and 10 g. of molecular sieves (5H) was stirred at room temperature for 30 minutes. After addition of 20 g. of activated maganese dioxide, stirring was continued for 15 minutes. The mixture was filtered over Celite and the filtrate was evaporated. Crystallization of the residue from ethyl acetate yielded 4.9 g. (59%) of product which was recrystallized from methanol/ethyl acetate for analysis to give colorless crystals with m.p. 208-210°; nmr (deuteriochloroform): δ 1.3 (t, 3, J = 7 Hz, CH_3), 2.94 (m, 2, -CH_2-), 3.9 (s, 3, OCH_3), 4.0 (d, 1) and 6.03 (d, 1) (AB-system, J = 12 Hz, C_4-H), 7.1-7.8 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O_2$: C, 60.88; H, 4.14; N, 10.14. Found: C, 60.80; H, 4.20; N, 10.04.

8-Chloro-1-chloromethyl-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*]-[1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**21**).

A solution of chloroacetaldehyde, 5 ml., which was prepared by heating a mixture of 50 ml. of 2*N* hydrochloric acid and 50 ml. of chloroacetaldhyde dimethylacetal for 30 minutes to reflux, was added to a solution of 4.5 g. (0.0107 mole) of the ethanolate of **12** in 200 ml. of dichloromethane. After stirring for 15 minutes, the reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic phase was dried and treated with 12 g. of activated manganese dioxide. After stirring for 15 minutes at room temperature, the MnO_2 was separated by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from dichloromethane/ether yielded 2.5 g. (54%) of product contaminated with a small amount of the 1-methyl derivative **14**. The analytical sample was purified by chromatography over a 30 fold amount of silica gel using dichloromethane/ethyl acetate 7:3 (v/v). The pure product was crystallized from ether, m.p. 237-239° (dec.); nmr (deuteriochloroform): δ 3.94 (s, 3, OCH_3), 4.03 (d, 1) and 6.05 (d, 1) (AB-system, J = 12 Hz, C_4-H), 4.5 (d, 1) and 4.98 (d, 1) (AB-system, J = 12.5 Hz, -CH_2Cl), 7.1-8.0 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{20}H_{14}Cl_3N_3O_2$: C, 55.26; H, 3.25; N, 9.67. Found: C, 55.48; H, 3.24; N, 9.59.

8-Chloro-6-(2-chlorophenyl)-1-(2-dimethylaminoethyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**22**).

Dimethylamine, 5 ml., and 2 ml. of acrolein were added to a solution of 4.5 g. (0.0107 mole) of the ethanolate of **12** in 100 ml. of dichloromethane. After stirring for 10 minutes at room temperature, 12 g. of activated manganese dioxide was added and stirring was continued for 15 minutes. The MnO_2 was removed by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from ethanol/ether yielded 3.7 g. (75%) of product which was recrystallized from ethyl acetate/methanol/hexane for analysis, m.p. 203-204°; nmr (deuteriochloroform): δ 2.24 (s, 6, $N(CH_3)_2$), 2.4-3.3 (m, 4, -CH_2-CH_2-), 3.92 (s, 3, OCH_3), 3.97 (d, 1) and 6.0 (d, 1) (AB-system, J = 12 Hz, C_4-H), 7.0-7.9 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{23}H_{22}Cl_2N_4O_2$: C, 60.40; H, 4.84; N, 12.25. Found: C, 60.54; H, 4.95; N, 12.16.

8-Chloro-6-(2-chlorophenyl)-1-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**23**).

A mixture of 0.42 g. of the ethanolate of **12**, 20 ml. of toluene, 0.5 ml. of benzaldehyde and 1 g. of molecular sieves (5A) was heated to reflux for 10 minutes. Following the addition of 1 g. of activated manganese dioxide refluxing was continued for another 10 minutes. The usual workup, crystallization from ether and recrystallization from ethyl acetate/hexane yielded 0.25 g. (54%) of off-white crystals with m.p. 272-275°; nmr (dueteriochloroform): δ 3.95 (s, 3, OCH_3), 4.06 (d, 1) and 6.12 (d, 1) (AB-system, J = 12.5 Hz, C_4-H), 6.8-7.8 ppm (m, 12, aromatic H).

Anal. Calcd. for $C_{25}H_{17}Cl_2N_3O_2$: C, 64.95; H, 3.71; N, 9.09. Found: C, 65.13; H, 3.55; N, 9.21.

8-Chloro-6-(2-chlorophenyl)-1-(2-pyridyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine-3-carboxylic Acid Methyl Ester (**24**).

A mixture of 8.5 g. (0.02 mole) of the ethanolate of **12**, 200

ml. of toluene, 4 ml. of pyridine-2-carboxaldehyde and 15 g. of molecular sieves (4A) was heated to reflux for 10 minutes. Following addition of 20 g. of activated manganese dioxide heating and stirring was continued for another 10 minutes. The usual workup and crystallization from ethyl acetate/ether yielded 7.5 g. (81%) of off-white crystals with m.p. 282-285°. The analytical sample was recrystallized from dichloromethane/ethyl acetate, m.p. 283-285°; nmr (deuteriochloroform): δ 4.0 (s, 3, OCH_3), 4.47 (d, 1) and 6.1 (d, 1) (AB-system, J = 12.5 Hz, C_4-H), 6.9-8.5 ppm (m, 11, aromatic H).

Anal. Calcd. for $C_{24}H_{16}Cl_2N_4O_2$: C, 62.22; H, 3.48; N, 12.09. Found: C, 62.47; H, 3.39; N, 12.26.

8-Chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (**25**) and 8-Chloro-6-(2-chlorophenyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (**26**).

A suspension of 7.7 g. (0.02 mole) of **16** in 75 ml. of methanol containing 20% (v/v) of ammonia was heated at 125° for 16 hours in an autoclave. The precipitated product was collected and washed with methanol to leave 6.6 g. (89%) of crude product. This material was dissolved in 35 ml. of glacial acetic acid by boiling and 2 ml. of *ca.* 3.5*N* ethanolic hydrogen chloride was added. The crystalline salt which precipitated upon cooling was filtered off and washed with a little 2-propanol and ether to leave 6.1 g. of hydrochloride. This salt was slurried in 50 ml. of hot methanol and treated with 4 ml. of concentrated ammonia. After dilution with water the colorless crystalline base was filtered off and washed with methanol and ether to yield 4.6 g. (62%) of **25** which was recrystallized from dichloromethane/ethanol for analysis, m.p. 325-328°; nmr (DMSO-d_6): δ *ca.* 5.0 (very broad s, 2, C_4-H), 6.8-8.0 (m, 9, aromatic H, NH_2), 8.3 ppm (s, 1, C_1-H).

Anal. Calcd. for $C_{18}H_{12}Cl_2N_4O$: C, 58.14; H, 3.26; N, 15.09. Found: C, 58.17; H, 3.45; N, 15.04.

The acetic acid filtrate of the hydrochloride was evaporated and the residue was treated with methanol and aqueous ammonia. The precipitated base (1.7 g.) was chromatographed over 100 g. of silica gel using 3% of ethanol in dichloromethane. The combined fractions containing the less polar component yielded 0.25 g. (3.3%) of **26** which was recrystallized from dimethylformamide for analysis to give colorless needles with m.p. 325-328° (needles transformed to prisms at 270-290°). Tlc after melting indicates conversion to **25**; uv (2-propanol + 2.5% dimethylformamide): λ max 270 (ε = 13,400), sh 290 nm (10,500); ir (potassium bromide) 3330, 3170 (NH_2), 1672 (CON), 1620 cm^{-1} (C=N); nmr (DMSO-d_6): δ 5.62 (d, 1, J = 2 Hz, C_6-H), 6.48 (d, 1, J = 2 Hz, C_7-H), 7.4-8.6 (m, 8, aromatic H and NH_2), 8.74 (s, 1, C_1-H), 8.93 ppm (d, 1, J = 2 Hz, C_4-H).

Anal. Calcd. for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.24; N, 15.09. Found: C, 58.39; H, 3.22; N, 15.00.

8-Chloro-6-(2-chlorophenyl)-*N*,*N*-dimethyl-4*H*-imidazo[1,4-*a*][1,4]benzodiazepine-3-carboxamide (**27**).

A mixture of 2 g. of **16**, 15 ml. of hexamethyl phosphoric triamide and 1.5 g. of lithium chloride was heated to 225°. The cooled reaction mixture was partitioned between water and dichloromethane ether. The organic phase was washed with aqueous bicarbonate solution, dried and evaporated. Crystallization from ether yielded 1.2 g. (58%) of product which was recrystallized from ethyl acetate/methanol for analysis, m.p. 240-242°; nmr (deuteriochloroform): δ 3.22 (broad s, 6, $N(CH_3)_2$), 4.97 (broad s, 2, C_4-H), 7.1-7.7 (m, 7, aromatic H), 7.85 ppm (s, 1, C_1-H).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_4O$: C, 60.16; H, 4.04; N, 14.03. Found: C, 60.19; H, 4.21; N, 14.05.

8-Chloro-6-(2-chlorophenyl)-1-dimethylaminomethyl-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**28**).

A mixture of 0.435 g. (1 mmole) of **21**, 15 ml. of tetrahydrofuran and 1.5 ml. of dimethylamine was heated in a sealed tube at 100° for 3 hours. The solvent was evaporated and the residue was partitioned between dichloromethane and aqueous sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ether to yield o.35 g. (79%) of product. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 181-183°; nmr (deuteriochloroform): δ 2.33 (s, 6, $N(CH_3)_2$), 3.45 (s, 2, $-CH_2-$), 4.0 (d, 1) and 6.05 (d, 1) (AB-system, J = 12 Hz, C_4-H), 7.1 (d, 1, J = 2 Hz, C_7-H), 7.2-7.7 (m, 5, aromatic H), 8.42 ppm (d, 1, J = 8 Hz, C_{10}-H).

Anal. Calcd. for $C_{22}H_{20}Cl_2N_4O_2$: C, 59.60; H, 4.55; N, 12.64. Found: C, 60.09; H, 4.83; N, 12.65.

1-Azidomethyl-8-chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**29**).

A mixture of 2.18 g. (5 mmoles) of **21**, 0.65 g. (10 mmoles) of sodium azide and 30 ml. of dimethylformamide was heated to reflux for 5 minutes. The product was precipitated by addition of water, collected and dissolved in dichloromethane. The solution was dried and evaporated. Crystallization from ethyl acetate/ether yielded 1.7 g. of colorless crystals with m.p. 187-189°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 188-190°; nmr (deuteriochloroform): δ 3.93 (s, 3, OCH_3), 4.02 (d, 1) and 6.03 (d, 1) (AB-system, J = 12 Hz, C_4-H), 4.13 (d, 1) and 4.8 (d, 1) (AB-system, J = 14 Hz, $-CH_2N_3$), 7.1-8 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{20}H_{14}Cl_2N_6O_2$: C, 54.44; H, 3.20; N, 19.05. Found: C, 54.59; H, 3.28; N, 19.03.

1-Aminomethyl-8-chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**30**).

A solution of 2.4 g. (5.4 mmoles) of **29** in 50 ml. of tetrahydrofuran and 50 ml. of ethanol was hydrogenated for 2 hours at atmospheric pressure with Raney nickel as catalyst. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 2-propanol and the solution was treated with 5 mmoles of ethanolic hydrogen chloride. The precipitated hydrochloride was collected and recrystallized from 2-propanol/methanol to yield 1.9 g. (77%) with m.p. 265-270° dec. The analytical sample was recrystallized from the same solvents, m.p. 270-275° (dec.).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_4O_2 \cdot HCl$: C, 53.18; H, 3.78; N, 12.40; Cl, 23.54. Found: C, 53.02; H, 3.98; N, 12.22; Cl, 23.86.

8-Chloro-5-(2-chlorophenyl-1-vinyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**32**).

A solution of 1.9 g. (4.15 mmoles) of **22** in 50 ml. of dichloromethane was cooled to 10° in an ice bath. Following the addition of 1.4 g. (8.1 mmoles) of *m*-chloroperbenzoic acid, the mixture was stirred for 15 minutes at 5° to 10°, then diluted with ether and extracted with 2*N* hydrochloric acid. The extracts were washed with ether, made alkaline with solid sodium carbonate, saturated with sodium chloride and extracted with dichloromethane containing 5% (v/v) of ethanol. The extracts were combined, dried over sodium sulfate and evaporated. The residue which consisted mainly of the *N*-oxide was dissolved in benzene and heated to reflux for 10 minutes. The benzene was evaporated and crystallization of the residue from ether yielded 1.05 g. (61%) of product with m.p. 168-171°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 170-172°; nmr (deuteriochloroform): δ 3.94 ppm (s, 3, OCH_3), 4.0 (d, 1) and 6.05 (d, 1) (AB-system, J = 12 Hz, C_4-H), 5.55 (m, 1) and 6.5 (m, 2) (vinyl-protons), 7-7.8 ppm (m, 7, aromatic H).

Anal. Calcd. for $C_{21}H_{15}Cl_2N_3O_2$: C, 61.18; H, 3.67; N,

10.19. Found: C, 61.38; H, 3.68; N, 10.19.

Acknowledgment.

The authors are grateful to members of our Physical Chemistry Department directed by Dr. R. P. W. Scott and in particular, Dr. F. Scheidl for microanalyses, Dr. V. Toome for uv spectra and Mr. S. Traiman for ir spectra.

REFERENCES AND NOTES

(1) Part LXXXIV: A. Walser, T. Flynn, C. Mason, R. Schwartz, L. Benjamin, R. Ian Fryer, *J. Org. Chem.*, **43**, 936 (1978).

(2) A. Walser and R. Ian Fryer, *ibid.*, **40**, 153 (1975).

(3a) R. Y. Ning, R. Ian Fryer, P. B. Madan and B. C. Sluboski, *ibid.*, **41**, 2720 (1976); (b) R. Y. Ning, R. Ian Fryer, P. B. Mandan and B. C. Sluboski, *ibid.*, **41**, 2724 (1976).

(4) J. Szmuszkovicz, L. Baczyuskyi, C. C. Chidester and D. J. Duchamp, *ibid.*, **41**, 1743 (1976).

(5) A. Walser and G. Zenchoff, *J. Med. Chem.*, **20**, 1694 (1977).

(6) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).