Attempted Synthesis of 1,4-Benzodiazepine Comprising an Additional Ring at the 1-3 Position

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Two possible synthetic routes leading to 1,4-benzodiazepine derivatives comprising an additional heterocyclic ring at position 1-3 have been studied. The first approach (scheme 1) consisted in subjecting intermediates VII and XII to the Bischler-Napieralski reaction while the second one (scheme 2) was based on intramolecular dehydration of amino ketone (XIX); both routes did however fail to yield the expected product XIII.

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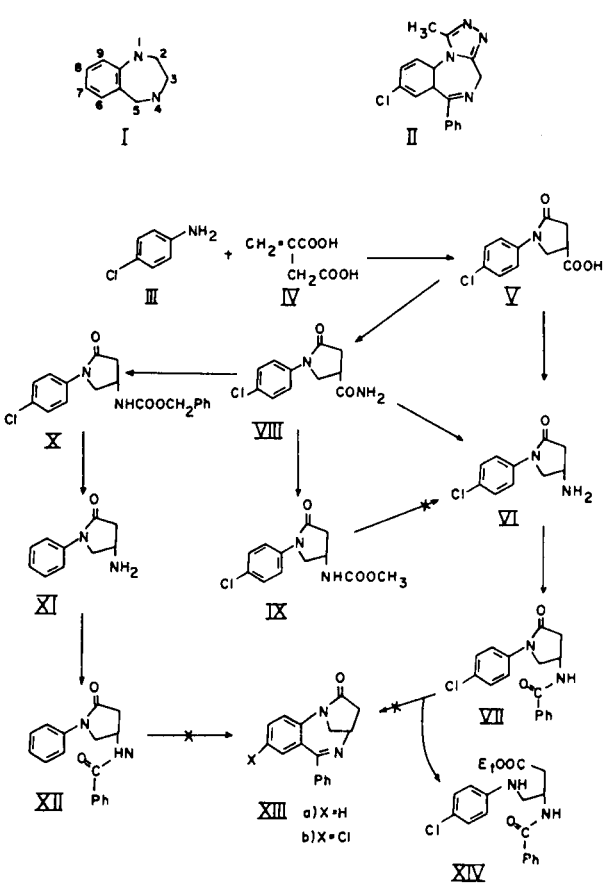
The impressive physiological properties of 1,4-benzodiazepinones have greatly stimulated synthetic work in this series of heterocyclic compounds (2-3). In order to develop drugs showing the highest possible specific activity, the benzodiazepine system (I) was made to undergo certain changes by placing various substituents upon their aromatic moiety, or altering the position of the nitrogen atoms within the seven-membered ring. Recently it has been reported (4) that by fusing additional heterocycles on one of the four open faces of the diazepine ring, preferably at position 1-2 or 4-5 potent C.N.S. drugs as for instance Alprazolan (II) were obtained (5). No attempts have so far been published describing the addition of a third ring at position 1-3 of the 1,4-benzodiazepine system (XIII) in order to study the pharmacodynamic properties of such a tricyclic structure. A rather different synthetic approach has now been devised (scheme 1) involving the use of itaconic acid (IV) as starting material. The well known reaction of this dibasic acid with primary amines (6) leads to the formation of *N*-substituted-4-carboxy-2-pyrrolidones, which in turn can be transformed into cyclic system (XIII) in which the nitrogen atom occupies a bridgehead position a rather interesting lactam bond (7).

Thus, the addition of *p*-chloroaniline (III) to itaconic acid afforded *N*-(*p*-chlorophenyl)-2-pyrrolidone-4-carboxylic acid (V) (6). In order to transform the carboxyl function at position 4 into a primary amine it (V) was submitted to the Schmidt reaction (8), which led to the formation of the benzoylated amine (VII) in poor yield. Therefore, it seemed preferable to try the Hoffman rearrangement (9) upon the amide (VIII) which was prepared from V using conventional methods. However, the desired rearrangement did not take place when the reaction was carried out in aqueous solution, because of

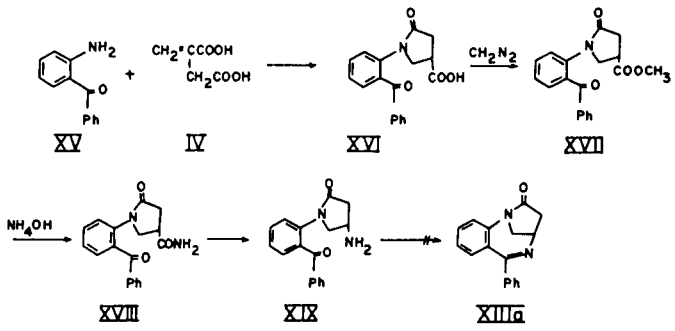
SCHEME 1



poor solubility of VIII in water. When methanol (10) was added to the reaction mixture methyl carbamate (IX) was isolated, however; it proved impossible to hydrolize it in order to isolate the free amine (VI). Replacing methanol by benzyl alcohol yielded the benzyl carbamate (X) in 50% as well as the free crude amine (VI) in 32%. Hydrogenolysis of X at room temperature and atmospheric pressure using palladium/carbon 5% as catalyst and ethanol as solvent, removed at the same time both the benzyl group and the chlorine atom and yielded XI which was identified by its benzoyl derivative (XII) in 92% overall yield. It should be emphasized that when ethylacetate was used as solvent, no reaction occurred. The chlorine atom being essential for the desired C.N.S. activity with the 1,4-benzodiazepinone series (11), more suitable reaction conditions had to be devised in order to apply the Hoffman reaction. When it was carried out in dioxan solution (10), it finally afforded VI which was isolated in the form of its benzoyl derivative (VII) in 70% yield. Attempts to form the seven-membered ring system (XIII) from the intermediates (VII and XII) by applying variations of the Bischler-Napieralski reaction (12,13) were of no avail: the expected products (XIIIa,b) could not be isolated. Similar difficulties were recently encountered by us in the 2,4-benzodiazepinone series (14). The only well defined compound isolated from the reaction mixture when P.P.E. was used to eliminate water happened to be the ester (XIV), a rather surprising result in view of the general reaction scheme governing the formation of adducts from itaconic esters and primary amines (7, 15).

The synthetic route had to be changed accordingly. Instead of establishing the C-C bond at position 5 and the aromatic moiety during the last step of the reaction sequence, the formation of C=N bond at position 4-5 now seemed the preferred procedure (scheme 2).

SCHEME 2



2-Aminobenzophenone (XV) adds to itaconic acid (IV) under more drastic condtion; the reaction mixture is to be heated to 190-200° for approximately 4 hours with effective stirring until no more water is being formed. The crude reaction product (XVI) was esterified by means of diazomethane. The methyl ester (XVII) was purified by chromatography and subsequently transformed into the amide (XVIII) by leaving it with an excess of concentrated alcoholic ammonia solution for 20 hours. It should be emphasized that 2-aminobenzophenone (XV) does not add dimethyl itaconate to yield the pyrrolidone system (XVII) in the same reaction condition applied for the itaconic acid.

The amide (XVIII) was subjected to the Hoffman reaction (10) yielding the amine (XIX) which was purified by means of chromatography. Prospects for the final dehydration step seemed favorable in view of the previously reported ring closure experiments leading to the smooth formation of benzodiazepine systems (14,16) examining the Dreiding model of XIX leads to a similar conclusion. However, when the amino ketone (XIX) was refluxed in various aromatic solvents, no dehydration occurred; the starting material was fully recovered. Direct heating of the amino ketone (XIX) at 190° did not generate any identifiable product.

EXPERIMENTAL

All melting points are uncorrected. H^1-nmr spectra were recorded on a Varian 60 or on HFX-10 Bruker 90 instrument using TMS as internal standard. Chemical shifts are given in δ (ppm) and J in Hz. Ir spectra were recorded on a Perkin-Elmer 237B spectrophotometer. Silica gel HF_{254} was used for chromatography.

Hypochlorite Standard Solution.

A solution of sodium hydroxide (8 g., 0.2 mole) in water (80 ml.) was cooled below 0°. Chlorine gas was bubbled through the solution until neutralization was reached; 45 ml. of sodium hydroxide (0.2 mole) were added so that the solution (125 ml.) contained 0.1 mole of sodium hypochlorite and 0.2 mole of sodium hydroxide.

N-(*p*-Chlorophenyl)-4-amino-2-pyrrolidone (VI) from *N*-(*p*-Chlorophenyl)-2-pyrrolidone-4-Carboxylic Acid (V) (6).

To a well stirred mixture of V (6) (2.38 g., 0.01 mole), 33 ml. of chloroform, and 17 ml. of concentrated sulphuric acid, 0.88 g. (0.0135 mole) of sodium azide were added in portions during 1/2 hour. The reaction mixture was kept at 50° overnight. It was allowed to cool to room temperature and was poured on ice. The acidic solution was made alkaline with 3*N* sodium hydroxide and extracted with ethyl acetate. The organic layer was dried and evaporated to yield 0.4 g. (14%) of an oily product which was identified in the form of its benzoyl derivative (VII).

N-(*p*-Chlorophenyl)-4-benzoylamino-2-pyrrolidone (VII).

A mixture of VIII (4.76 g., 0.02 mole), 37 ml. of the standard hypochlorite solution and 80 ml. of dioxane was kept at 85° for 4 hours. The solvents were evaporated under reduced pressure and the residue was treated with a mixture of ethyl acetate/water. The ethyl acetate layer was washed, dried and evaporated to give the crude product which was then benzoylated using the Schotten

Baumann's method and recrystallized twice from ethanol/water to yield 4.5 g. (72%) m.p. 185-186° of VII; H^1-nmr (DMSO-d_6): δ = 8.98 (d, 1H from -NH-, J = 6.5, disappears with deuterium oxide), 8.08-7.4 (m, 9H aromatic), 5.08-2.78 (m, hydrogens of the pyrrolidone ring); ir (potassium bromide): 3257, 3040 (NH); 1684, 1650 (CO); Mass: m/e 314 (M^+).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.86; H, 4.80; Cl, 11.26. Found: C, 64.69; H, 4.72; Cl, 11.46.

N-(*p*-Chlorophenyl)-2-pyrrolidone-4-carboxamide (VIII).

To a stirred mixture of V (6) (24 g., 0.1 mole) in 1 l. of dry benzene, 10 ml. of thionyl chloride were added dropwise. The solution was refluxed until all the acid dissolved. The benzene was evaporated and the residue was added in portions to a vigorously stirred cold aqueous ammonia solution (25%). The stirring was continued for 20 hours at room temperature. The amide was filtered off and recrystallized from ethyl acetate to yield 18 g. (75%), m.p. 200-201°; H^1-nmr (DMSO-d_6): δ = 7.60 (AB pattern, 4H aromatic, J = 9), 7.2 (broad s, 2H from -$CONH_2$, disappears with deuterium oxide), 4.2-2.43 (m, hydrogens from the pyrrolidone ring); ir (potossium bromide): 3367, 3161 (NH_2); 1700-1625 (two CO bands); Mass: m/e 238 (M^+).

Anal. Calcd. for $C_{11}H_{11}ClO_2N_2$: C, 55.35; H, 4.65; Cl, 14.86; N, 11.74. Found: C, 55.55; H, 4.56; Cl, 14.64; N, 11.65.

N-(*p*-Chlorophenyl)-4-methoxycarbonylamino-2-pyrrolidone (IX).

To a stirred suspension of 7.14 g. (0.03 mole) of VIII and 60 ml. of methanol, 40 ml. of the standard hypochlorite solution were added. The amide dissolved as soon as the hypochlorite solution was added. The solution was refluxed for 1 hour during which crystals of sodium chloride precipitated. It was cooled and the solvents were evaporated *in vacuo*. The residue was treated with a mixture of chloroform and water. The organic layer was dried and evaporated to yield 10 g. of an oily residue which solidified upon treatment with methylcyclohexane. It was then recrystallized twice from benzene/methylcyclohexane to yield 4 g. (50%) of pure product (IX), m.p. 127-129°; H^1-nmr (deuteriochloroform): δ = 7.45 (AB pattern, 4H aromatic, J = 9), 6.08 (d, 1H from -NH-, J = 7, does not disappear with deuterium oxide and with deuterium oxide/hydrochloric acid) 4.83-3.6 (m, 3H from -OCH_3, 3H from the pyrrolidone ring), 3.2-2.3 (m, 2H from the pyrrolidone ring; ir (chloroform): 3430, 3310 (NH); 1740-1680 (CO); Mass: m/e 268 (M^+).

Anal. Calcd. for $C_{12}H_{13}ClN_2O_3$: C, 53.64; H, 4.88; Cl, 13.20; N, 10.43. Found: C, 53.70; H, 4.94; Cl, 13.25; N, 10.42.

N-(*p*-Chlorophenyl)-4-benzyloxycarbonylamino-2-pyrrolidone (X).

A mixture of VIII (10.6 g., 0.0445 mole), standard hypochlorite solution (58 ml.) and benzyl alcohol (122 ml.) was heated to 85° for 3 hours. The organic layer was separated from the aqueous phase and the benzyl alcohol was distilled *in vacuo*. The resulting solid residue was treated with a mixture of benzene/methylcyclohexane (1:10), filtered off and recrystallized from benzene/methylcyclohexane to yield 6.7 g. (44%), m.p. 152-153°; H^1-nmr (deuteriochloroform): δ = 7.58-7.17 (m, 9H aromatic), 5.7 (d, 1H from -NH-, J = 6), 5.08 (s, 2H from benzylic -CH_2-), 4.75-3.53 (m, 3H from the pyrrolidone ring), 3.13-2.21 (m, 2H from the pyrrolidone ring); ir (chloroform): 3440 (NH), 3300 (broad NH); 1725-1675 (CO); Mass: m/e 344 (M^+).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; Cl, 10.28; N, 8.13. Found: C, 62.76; H, 4.86; Cl, 10.12; N, 8.23.

The mother liquid was evaporated. The resulting residue was dissolved in ethyl acetate and extracted with 3*N* hydrochloric acid. From the organic layer another crop (0.7 g., 4.6%) of the carbamate (X) was obtained. The acidic layer was made alkaline with 3*N* sodium hydroxide, extracted with ethyl acetate. Evaporation of the solvent yielded 3.92 g. (32%) of crude amine (VI).

N-Phenyl-4-benzoylamino-2-pyrrolidone (XII).

A solution of X (3.7 g., 0.0107 mole) in ethanol (220 ml.) was hydrogenated at atmospheric pressure in the presence of palladium/carbon 5% (0.36 g.) at room temperature for 3 hours. The catalyst was filtered off and the ethanol was evaporated under reduced pressure.

The crude product was benzoylated using Schotten Baumann's method and the benzoyl derivative was recrystallized from ethanol/water to yield 2.6 g. (92%); m.p. 182-183°; H^1-nmr (DMSO-d_6): δ = 8.91 (d, 1H from -NH-, J = 6.5, disappears with deuterium oxide), 8.1-7.03 (m, 10H aromatic), 5.0-4.47 (m, 1H from the pyrrolidone ring), 4.4-2.7 (m, hydrogens from the pyrrolidone ring); ir (potassium bromide): 3280, 3070 (NH); 1690, 1625 (CO), 1540; Mass: m/e 280 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.92; H, 5.79; N, 10.08.

Ethyl 4-(*p*-Chlorophenylamino)-3-benzoylaminobutyrate (XIV).

A solution of 0.33 g. (0.00105 mole) of VII and 20 ml. of PPE in 80 ml. of dry chloroform was refluxed overnight. The solvent was evaporated under reduced pressure, ice was added under stirring and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated. The residue was chromatographed on a silica gel column (20 g.) using chloroform/ethyl acetate (1:1) as eluant. The major part of the product appeared in the first two fractions (100 ml. per fraction), which yielded 0.05 g. (13%) of XIV after recrystallization (from methylcyclohexane); m.p. 100-101°. No attempt was made to improve the yield; H^1-nmr (deuteriochloroform): δ = 7.88-7.25 (m, 6H aromatic + NH), 6.83 (AB pattern, 4H aromatic, J = 9.5), 4.90-4.45 (m, 1H from -CH-), 4.18 (q, 3H, 2H from -CH_2-CH_3, J = 7, 1H from NH which disappears with deuterium oxide), 3.35 (d, 2H from -CH_2-, J = 7), 2.71 (d, 2H from -CH_2-, J = 5), 1.31 (t, 3H from -CH_3, J = 7); ir (potassium bromide): 3350, 3300 (NH); 1725, 1644 (CO); 1550; Mass: m/e 360 (M^+).

Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$: C, 63.24; H, 5.87; Cl, 9.83. Found: C, 63.38; H, 6.00; Cl, 10.08.

N-(2'-Benzoylphenyl)-2-pyrrolidone-4-carboxylic Acid (XVI).

A well stirred mixture of 2-aminobenzophenone (XV) (2.8 g., 0.0142 mole) and itaconic acid (2 g., 0.0154 mole) was fused at 190° under argon for 3 hours. The reaciton mixture was cooled, dissolved in ethyl acetate and extracted with 3*N* sodium hydroxide. The alkaline solution was neutralized with 3*N* hydrochloric acid and extracted with ethyl acetate. This operation was repeated in order to remove unreacted 2-aminobenzophenone. The resulting ethyl acetate fraction was dried and evaporated to yield 2.3 g. (52%) of an oily yellowish crude product, which was used without further purification in the following reaction.

Methyl *N*-(2'-Benzoylphenyl)-2-pyrrolidone-4-carboxylate (XVII).

To a cold solution of XVI in ethyl acetate (24 g., 0.0772 mole) a small excess of a cold solution of diazomethane in ether was added in small portions. Excess diazomethane was decomposed by the addition of acetic acid. The solvents were evaporated and the crude product was chromatographed on a silica gel column (240 g.) using benzene as the first eluent. After washing the

column with 2 l. of benzene (fractions 1, 2, 3) the eluent was changed gradually from benzene to ethyl acetate. The product (15 g.) was collected from fraction 4 (10% ethyl acetate) to fraction 8 (50% ethyl acetate, 250 ml. per fraction). Attempts to distill the product *in vacuo* resulted in decomposition. The nmr showed absorption at δ = 3.75 indicating the presence of a methyl ester.

N-(2′-Benzoylphenyl)-2-pyrrolidone-4-carboxamide (XVIII).

A solution of 15 g. (0.046 mole) of crude XVII, 50 ml. of ethanol and 50 ml. of concentrated aqueous ammonia (25%) were stirred vigorously overnight. The solvent was evaporated under reduced pressure to yield a yellow crystalline product. The crude product was treated with ethyl acetate and the amide filtered off, and was recrystallized in water to yield 6 g. (42%) of amide, m.p. 183-186°; H^1-nmr (DMSO-d_6): δ = 7.90-7.33 (m, 9H aromatic), 7.1 (broad s, 2H from -NH_2, disappears with deuterium oxide/-hydrochloric acid), 4.18-3.67, 3.04-2.02 (m, hydrogens from the pyrrolidone ring); ir (potassium bromide): 3464, 3360-3100 (several, NH_2); 1720, 1710, 1667, 1655, 1640 (CO); Mass: m/e 308 (M^+).

N-(2′-Benzoylphenyl)-4-amino-2-pyrrolidone (XIX).

A mixture of XVIII (1 g., 0.00357 mole), 6 ml. of the standard hypochlorite solution and 13 ml. of dioxane was kept at 85° for 3 hours. The solvents were evaporated and the residue was dissolved in ethyl acetate. The ethyl acetate fraction was washed with water, dried and evaporated to yield 200 mg. of an oily residue which was chromatographed on silica gel column (15 g.) using ethanol as eluant. The product XIX (70 mg.) was collected from fractions 5, 6 (fractions 1, 2, 3 -10 ml. per fraction; fraction 4 -50 ml.; fractions 5, 6 -100 ml. per fraction).

Since during working up the ethyl acetate solution most of the product had apparently passed into the aqueous layer, the latter was evaporated under reduced pressure and the resulting residue was chromatographed on a silica gel column (30 g.) using ethyl acetate as first eluant. The eluant was changed gradually to ethanol. The product was collected from fraction 6-9 (fraction 1 -100 ml. of ethyl acetate; fraction 2, 3, 4, 5 -100 ml. of ethyl acetate/ethanol (7:3) per fraction; fractions 6, 9 -100 ml. of ethyl acetate/ethanol (1:1) per fraction), overall yield, after crystallization from benzene/methylcyclohexane, 600 mg. (65%); m.p. 132-133°. H^1-nmr (deuteriochloroform): δ = 8.15-7.07 2.70-1.77 (m, 2H from the pyrrolidone ring), 1.5 (s, 2H from -NH_2, disappears with deuterium oxide); ir (chloroform): 3367, 3299 (NH); 1690, 1660 (CO).

The benzoyl derivative of XIX was prepared by using Schotten Baumann's method. The product was recrystallized from 2-propanol/water, m.p. 189-190°; H^1-nmr (DMSO-d_6): δ = 8.67 (d, 1H from -NH-, J = 6), 8.08-7.17 (m, 14H aromatic), 5,58-3.75 (m, 3H from the pyrrolidone ring), 2.67-2.17 (m, hydrogens from the pyrrolidone ring); ir (potassium bromide): 3356 (broad NH); 1690, 1670, 1650 (CO); Mass: m/e 385 (M^+ deuterated).

Anal. Calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.88; H, 5.25; N, 7.21.

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