Attempted Synthesis of 2,4- and 1,3-Benzodiazepinones

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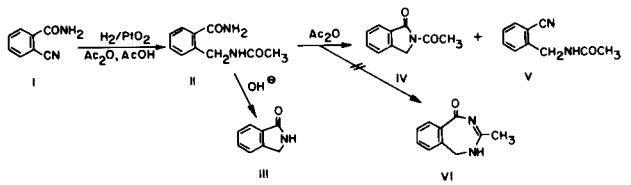
The cyclodehydration reaction performed upon α-acylamino carboxamides is known to constitute a facile synthetic approach to five-membered heterocyclic systems. Attempts to prepare 2,4- and 1,3-benzodiazepinone derivatives (VI, XIX) of potential C.N.S. Activity using such methods, proved unsuccessful. A new triazine system (X) which was prepared did not exhibit any C.N.S. activity.

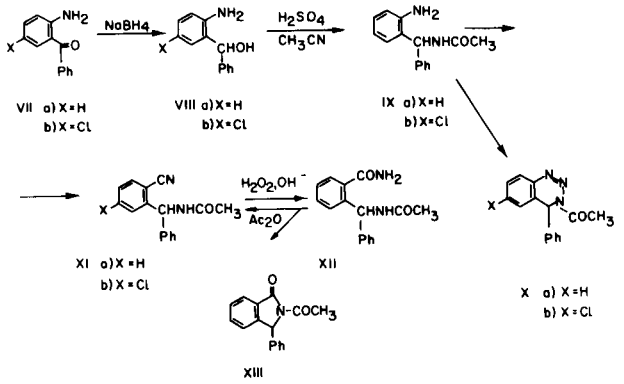
The well known C.N.S. activity of 1,4-benzodiazepinones has inspired a host of medicinal chemists to look for structurally similar bicyclic "lactams" of the benzodiazepinone type (1). It has been found recently that 2,4-benzodiazepinones possess C.N.S. activity of the same order of 1,4-benzodiazepinone (2), these findings encouraged further investigation in this type of benzodiazepinones.

The cyclodehydration reaction performed upon α-acylaminocarboxamides is known to constitute a facile synthetic approach to imidazolones (3). It seemed, therefore, an attractive route towards the formation of seven membered ring systems. *o*-Cyanobenzamide (I) (4) was hydrogenated catalytically in the presence of an anhydride. This implies that the amine while being formed will react immediately with the anhydride to form the acylaminocarboxamide (II), rather than to cyclize to the isoxindole (III) *via* internal transamidation. Thus the acylaminocarboxamide (II) was made to undergo cyclodehydration conditions in the presence of an organic anhydride. Two products were isolated from the reaction mixture; *N*-acetylisoxindole (IV) which is formed by intramolecular elimination of ammonia, and a compound to which in view of its nmr spectrum the structure of benzodiazepinone (VI) was assigned. The location of the double bond seems to be at position 2-3 (a doublet of the methylene group which turns to a singlet when treated with deuterium oxide), which indicates an acylimine structure. This structure is known to be very reactive (5) unless the neighboring nitrogen atom participates with its lone pair of electrons in the stabilization of the acylimine bond (6). In order to confirm this rather interesting structure the ir spectra was carefully studied. A very small peak was observed at 2230 cm^{-1} (3% chloroform) which turned to a significant one at higher concentration (6% chloroform) suggesting the presence of a nitrile group. Interpretation of its mass spectra indicated the presence of a $-NHCOCH_3$ group: m/e 174 (M), 131 (M-$COCH_3$), 116 (M-$NHCOCH_3$). These findings clearly indicated the structure of the cyano derivative (V), which is formed by straight dehydration of the primary amide. The reaction of α-acylaminocarboxamides with base leads to heterocyclic systems (3). However, when II reacted with base the expected hydrolysis (7) took place and isoxindole (8) (III) was isolated.

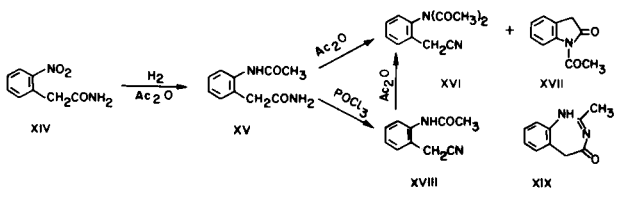


Although this method did not yield the desired benzodiazepinones it seemed worthwhile to apply it to similar systems. Since a phenyl group at position five at the benzodiazepinone ring is thought to be essential for the desired C.N.S. activity (9) a sequence of reactions leading to this compound was selected. 2-Aminobenzophenone (VIII) was reduced by means of sodium borohydride to yield the aminoalcohol (VIII). This was in turn subjected to a Ritter reaction (10) affording the acylamino derivative (IX). Its amino group was then exchanged against a cyano group using Sandmeyer reaction for this purpose. Subsequent hydrolysis of XI by means of hydrogen peroxide in basic media produced the acylaminocarboxamide derivative (XII). However when XI was reacted with an anhydride again the isoxindole (XIII) was obtained by the above mentioned deamination reaction with concurrent formation of the cyano derivative (XI) *via* simple dehydration of the primary amide. In this instance the identification of

the nitrile (XI) offered no difficulty since it had served as starting material for the preparation of the acylamino carboxamide (XII). The Sandmeyer reaction afforded as a by product a triazine derivative (X) (11), which became the major reaction product when the diazonium salt of IX was treated with sodium carbonate. Although the triazine system (X) bears some structural resemblance to 1,4-benzodiazepinones, methaqualone and other C.N.S. active triazine system (12) it did not exhibit any C.N.S. activity.



Attempts to synthesize 1,3-benzodiazepinone (XIX) by the same method were also undertaken. *o*-Acetylaminophenylacetamide (XV) obtained by catalytic hydrogenation of *o*-nitrophenylacetamide (XIV) in the presence of acetic anhydride was submitted to cyclodehydrating conditions. When acetic anhydride was used as dehydrating agent *N*-acetyloxindole (XVII) and *o*-diacetylaminophenylacetonitrile were the only reaction products to be isolated. By substituting phosphorus oxychloride as a dehydrating agent *o*-acetylaminophenylacetonitrile (XVIII) was obtained. It was subsequently acetylated by means of acetic anhydride to form XVI.



It thus appears that the cyclodehydration reaction is of immediate value for the preparation of five-membered heterocyclic systems only, while the formation of similar six (13) or seven membered rings has not been observed so far.

EXPERIMENTAL

All melting points are uncorrected. H^1-nmr spectra were recorded on a Varian 60 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 137 spectrophotometer. Silica gel HF_{254} was used for cheomatography.

o-Acetylaminomethylbenzamide (II).

o-Cyanobenzamide (I) (4) (10.2 g., 0.07 mole) was treated with 70 ml. of acetic acid and 50 ml. of acetic anhydride and hydrogenated (60 psi) during 24 hours using platinum oxide (1 g.) as catalyst. The catalyst was filtered off through celite and the solvents were removed by evaporation under reduced pressure. The solid residue was treated with ethyl acetate and ether filtered and recrystallized from ethanol to yield 6 g. (45%) of II, m.p. 215-216°; H^1-nmr (d_6-DMSO): δ = 8.21 (t, J = 6 1H -NH-disappears when treated with deuterium oxide + hydrochloric acid), 7.90 (broad s, 1H from $-CONH_2$ disappears with deuterium oxide + hydrochloric acid), 7.58-7.22 (m, 5H 4 aromatic and 1H from $-CONH_2$ which disappears with deuterium oxide + hydrochloric acid), 4.41 (d, J = 6 $-CH_2-$ turns to s with deuterium oxide + hydrochloric acid), 1.85 (s, 3H $-COCH_3$).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.57; H, 6.42; N, 14.50.

o-Cyano(*N*-acetyl)benzylamine (V).

o-Acetylaminomethylbenzamide (II) (5 g., 0.026 mole) was refluxed in 50 ml. of acetic anhydride for 20 minutes until all the solid dissolved. The solvent was removed by evaporation under reduced pressure and the semi-solid residue was treated with methylcyclohexane and benzene, filtered and the crystalline compound was recrystallized twice from isopropanol to yield 0.4 g. (10%) of IV, m.p. 154-155°; H^1 nmr (deuteriochloroform): δ = 8.00-7.40 (m, 4H aromatic), 4.79 (s, 2H-CH_2-), 2.65 (s, 3H $-COCH_3$), no change in the spectra when treated with deuterium oxide + hydrochloric acid. The mother liquor was concentrated and the semi-solid residue was treated with a very little 2-propanol and methylcyclohexane, filtered, and recrystallized from methylcyclohexane and benzene to yield 0.7 g. (18%) of V, m.p. 124-125°; H^1 nmr (deuteriochloroform): δ = 7.80-7.32 (m, 4H aromatic) 6.55-6.10 (broad m, 1H NH disappears with deuterium oxide), 4.62 (d, 2H-CH_2- turn to s with deuterium oxide), 2.02 (s, 3H-$COCH_3$); ir (6% chloroform) 2230 cm^{-1} (-CN), 1675 cm^{-1} (amide). No attempt was made to isolate additional amounts of both compounds from the mother liquor.

Anal. Calcd. for (IV) $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.77; H, 5.01; N, 7.80.

Anal. Calcd. for (V) $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.87; H, 5.79; N, 16.12.

Isoxindole (III).

A mixture of II (0.96 g., 5 mmoles) and 1*N* sodium hydroxide (25 ml.) were refluxed for 1.5 hours. It was then cooled, acidified with acetic acid and extracted with ethylacetate. The extract was dried and evaporated to yield 0.5 g. (75%) of product III m.p. 150° (8) (from water).

o-Aminobenzhydryl Alcohol (VIIIa).

To a cooled and stirred mixture of 2-aminobenzophenone (VIIa) (30 g. 0.151 mole) in 300 ml. of methanol, sodium borohydride (8 g.) was added in portions. The cooling bath was removed and the stirring was continued at room temperature until a clear solution resulted. Acetic acid (12 ml.) was added dropwise and the reaction mixture was evaporated under reduced pressure. The residue was treated with ethyl acetate and water, the organic layer was dried, evaporated and the residue was recrystallized from methylcyclohexane to yield 25 g. (83%) of VIIIa, m.p. 113-114°;

H^1-nmr (deuteriochloroform): δ = 7.32-6.42 (m, 9H aromatic), 5.65 (s, 1H-CH-), 3.62 (broad s, 3H $-NH_2$ and -OH disappear with deuterium oxide).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.60; N, 6.58; N, 6.77.

2-Amino-5-chlorobenzhydryl Alcohol (VIIIb).

This compound was prepared in 87% yield by the procedure described for VIIIa, m.p. 105° (from carbon tetrachloride); H^1-nmr (deuteriochloroform): δ 7.40-6.45 (m, 8H aromatic), 5.75 (s, 1H-CH-), 3.42 (s, 3H $-NH_2$ and -OH disappear with deuterium oxide).

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 67.10; H, 4.77; N, 6.02; Cl, 15.24. Found: C, 67.23; H, 4.76; N, 6.10; Cl, 15.02.

N-Acetyl-*o*-aminobenzylhydrylamine (IXa).

Concentrated sulfuric acid (30 ml.) was added dropwise to a cold, stirred solution of VIIIa (20 g., 0.101 mole) in acetonitrile (50 ml.). The cooling bath was removed and the reaction mixture was stirred overnight. It was poured on iced water, ethyl acetate was added and then the whole mixture made basic. The organic layer was washed well dried and evaporated. The residue was treated with benzene filtered and recrystallized from benzene to yield 18.5 g. (77% of IXa) m.p. 176-177°; H^1-nmr (deuteriochloroform): δ = 7.86-6.22 (m, to aromatic H -CH- and -CONH-), 3.92-3.55 (broad s, 2H $-NH_2$ disappears with deuterium oxide), 2.02 3H $-COCH_3$).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.77; H, 6.40; N, 11.44.

N-Acetyl-2-amino-5-chlorobenzhydrylamine (IXb).

This compound was prepared in 73% yield by the procedure described for IXa, m.p. 192° (from methyl cyclohexane); H^1-nmr (deuteriochloroform): δ = 7.40-6.25 (m, aromatic H, -CH and -NHCO), 3.97-3.70 (broad s, 2H-NH_2 disappears with deuterium oxide), 2.07 (s, 3H $-COCH_3$).

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20; Cl, 12.90. Found: C, 65.79; H, 5.48; N, 10.13; Cl, 12.95.

N-Acetyl-*o*-cyanobenzhydrylamine (XIa).

A mixture of the amine (IXa) (4 g., 0.0165 mole) 6*N* hydrochloric acid (9 ml.) was stirred well at 0-5° and a cold solution of sodium nitrite (1.5 g.) in water (2.5 ml.) was added dropwise. The reaction mixture was stirred at that temperature for one half hour, ethyl acetate was added, and then cold mixture of cuprous cyanide (4 g.), sodium cyanide in water (12.5 ml.) was added in portions. Temperature was kept at 5° for one half hour, then it was allowed to rise to 20° (1 hour); then it was warmed at 60° for another 2 hours. It was filtered from insoluble material and the organic layer was dried, evaporated and treated with benzene. The crystalline product was filtered and recrystallized from benzene to yield 1.4 g. (32%) of XIa, m.p. 177-178°. H^1-nmr (deuteriochloroform): δ = 7.70-7.03 (m, 9H aromatic), 6.85-6.52 (broad AB pattern NH disappears with deuterium oxide + hydrochloric acid), 6.36 (AB pattern J = 7 turn to s with deuterium oxide + hydrochloric acid), 1.96 (s, 3H $-COCH_3$); ir (chloroform): 2270 cm^{-1} (CN), 1700 cm^{-1} (amide).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.83; H, 5.58; N, 10.95.

3-Acetyl-4-phenyl-3,4-dihydro-1,2,3-benzotriazine (Xa).

The diazotized amine (IXa) (the procedure is described in the preparation of XIa) was treated with a portion of solid sodium carbonate at 0-5° in the presence of ethyl acetate until the *p*H reached 8. It was then stirred well for 2 hours and the organic layer was collected, washed well with water, dried, and evaporated. The residue was treated with hexane, filtered, and recrystallized from hexane to yield 78% of X, m.p. 96-97°; H^1-nmr (deuteriochloroform): δ = 7.92-6.96 (m, 9H aromatic), 6.55 (s, 1H -CH-), 2.54 (s, 3H-$COCH_3$).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.72; H, 5.28; N, 16.84.

N-Acetyl-2-cyano-5-chlorobenzhydrylamine (XIb).

The procedure described for the preparation of XIa was applied here. The crude reaction mixture was chromatographed on a silica gel column using chloroform as the eluant. Flasks 1-2 (50 ml. per flask) yielded after recrystallization from methylcyclohexane, the triazine derivative (Xb) in 15% yield, m.p. 157°; H^1-nmr (deuteriochloroform): δ = 7.90-7.08 (m, 8H aromatic), 6.50 (2, 1H-CH-), 2.57 (s, 3H, $-COCH_3$). Flasks 5-6 yielded after recrystallization from methylcyclohexane and benzene the cyano product (XIb) in 15% m.p. 182-183°; H^1-nmr (deuteriochloroform): δ = 7.70-7.10 (m, 8H aromatic), 6.65-6.20 (m, 2H-CH- and -NHCO-), 2.10 (s, 3H $-COCH_3$); ir (chloroform): 2220 cm^{-1} (CN), 1670 cm^{-1} (amide).

Anal. Calcd. for (Xb) $C_{15}H_{11}ClN_3O$: C, 63.27; H, 3.89; N, 14.76. Found: C, 63.10; H, 4.09; N, 14.92.

Anal. Calcd. for (XIb) $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.75; H, 4.44; N, 9.71.

N-Acetyl-*o*-carboxamidobenzhydrylamine (XII).

A mixture of the nitrile (XIa) (1 g., 0.004 mole), 6*N* sodium hydroxide (0.25 ml.), 30% hydrogen peroxide (7 ml.) and ethanol (10 ml.) was stirred at 50° for 1 hour (14). It was neutralized, evaporated at reduced pressure, extracted with hot ethyl acetate and evaporated. The residue was separated on a silica gel column (20 g.) using equal parts of chloroform and ethyl acetate as eluant. In the first four flasks (50 ml. per flask), some starting material was recovered (0.2 g.). In the next few flasks only 0.15 g. (18%) of the product (XII) was obtained (recrystallized from ethyl acetate), m.p. 180-182°. H^1-nmr (DMSO-d_6): δ = 8.48 (d, J = 8, 1H -NH- disappears slowly with deuterium oxide), 7.38 and 7.23 (2s, 9H aromatic), 6.69 (d, J = 8, 1H -CH- turns slowly to s with deuterium oxide), 1.90 (s, 3H-$COCH_3$).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.44; H, 6.14; N, 10.30.

Reaction of XII with Acetic Anhydride.

Compound XII (0.45 g., 1.68 mmoles) was refluxed with acetic anhydride (5 ml.) for one half hour. The solvent was removed by evaporation and the semi solid residue was treated with methyl cyclohexane and ethyl acetate and filtered. The solid (0.17 g.) was separated by chromatography on a silica gel column (15 g.) using equal parts of chloroform and ethyl acetate as the eluant. From the first four flasks (30 ml. per flask) the cyano derivative (XIa) was obtained (80 mg.) m.p. 178-179°, and from the next few flasks the starting material (40 mg.) was recovered. The mother liquor evaporated leaving 0.25 g. of material which was separated by chromatography on a silica gel column (20 g.) using chloroform as the eluant. *N*-Acetylisoxindole derivative (XIII) was collected first from the column (0.11 g., m.p. 153-154° from methylcyclohexane), then another portion of the cyano derivative (XIa), 30 mg. was isolated (overall yield 27%); H^1 nmr of XIII (deuteriochloroform): δ = 8.09-7.86 (m, 1H aromatic), 7.67-7.06 (m, 8H aromatic), 6.13 (s, 1H -CH-), 2.66 (s, 3H $-COCH_3$).

o-Nitrophenylacetamide (XIV).

The methyl ester of *o*-nitrophenylacetic acid was prepared first

by treatment of the free acid (9 g., 0.054 mole) which was dissolved in 100 ml. of ethylacetate with a small excess of diazomethane. The solvent was removed by evaporation and the residue was distilled at a b.p. of 105-107° (0.2 mm Hg) to yield 8.8 g. (90%); H^1 nmr (carbon tetrachloride): δ = 8.07-7.86 (m, 1H aromatic), 7.64-7.14 (m, 3H aromatic), 3.91 (s, 2H-CH_2-), 3.59 (s, 3H-OCH_3).

The ester (8.5 g., 0.045 mole) was stirred well with concentrated ammonium hydroxide (50 ml.) in a closed flask for 20 hours. The product was filtered off and recrystallized twice from dilute ethanol to yield 6 g. (73%) of XIV, m.p. 161-162°; H^1 nmr (DMSO-d_6): δ = 8.12-7.92 (m, 1H aromatic), 7.85-7.32 (m, 4H 3 aromatic and 1 NH), 7.98 (broad s, 1H NH), 3.96 (s, 2H -CH_2-).

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.10; H, 4.47; N, 15.11.

o-Acetylaminophenylacetamide (XV).

A solution of *o*-nitrophenylacetamide (XIV) (3.96 g., 0.022 mole) in 30 ml. of acetic anhydride was hydrogenated (40 psi) during 1 hour using 5% palladium/carbon (0.5 g.) as the catalyst. Acetic acid was added to dissolve the insoluble product and then it was filtered from the catalyst, and evaporated from the solvents at reduced pressure. The solid residue was treated with ethyl acetate and ether, filtered and recrystallized from ethyl acetate and ethanol to yield 3.8 g. (90%) of XV, m.p. 212°; H^1 nmr (DMSO-d_6): δ = 10.00 (broad s 1H NH disappears with deuterium oxide) 7.78-7.00 (m, 6H 4 aromatic and 2 NH which disappear with deuterium oxide), 3.47 (s, 2H -CH_2-), 2.05 (s, 3H -$COCH_3$).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.28; H, 6.58; N, 14.24.

o-Diacetylaminophenylacetonitrile (XVI).

In an attempt to prepare the 1,3-benzodiazepinone derivative (XIX) *o*-acetylaminophenylacetamide (XV) (3.6 g., 0.019 mole) was refluxed in 30 ml. of acetic anhydride for 2 hours until all the starting material was dissolved. It was cooled, filtered from some impurities and evaporated. The residue was chromatographed on a silica column (100 g.) using first benzene as an eluant and then a mixture of benzene and ethyl acetate (3:1). *N*-Acetyloxindole (XVII) (15) was collected first from the column and it was recrystallized from 2-propanol to yield 0.3 g. (10%), m.p. 130°; H^1 nmr (carbon tetrachloride): δ = 8.30-8.02 (m, 1H aromatic), 7.42-7.07 (m, 3H aromatic), 3.63 (s, 2H -CH_2-), 2.60 (s, 3H -$COCH_3$), no change with deuterium oxide. The product XVI was next collected from the column to yield after recrystallization from benzene and methylcyclohexane, 1.2 g. (30%) m.p. 77-78°; H^1-nmr (deuteriochloroform): δ = 7.58-7.07 (m, 4H aromatic), 3.54 (s, 2H -CH_2-), 2.27 (s, 6H 2 -$COCH_3$); ir (6% chloroform): 2240 cm^{-1} (-CN), 1680 cm^{-1} (C=O).

Anal. Calcd. for (XVI) $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.81; H, 5.50; N, 12.80.

o-Acetylaminophenylacetonitrile (XVIII).

A mixture of *o*-acetylaminophenylacetamide (XV) (3 g., 0.0156 mole) and 2 ml. of phosphorus oxychloride was refluxed in 50 ml. of dry benzene for 1.5 hours. The solvent was decantated from tar into ice water, extracted with ethylacetate, washed well with water, dried and evaporated. The solid residue was treated with benzene, filtered and recrystallized from benzene to yield 0.5 g. of XVIII m.p. 120°. The tar was extracted twice with ethyl acetate and was chromatographed on an aluminum oxide (grade III) column (30 g.) elution with benzene, an additional 0.5 g. (overall yield 40%) of XVIII was obtained; H^1 nmr (deuteriochloroform): δ = 8.00-7.70 (broad s, 1H -NHCO- disappears slowly with deuterium oxide) 7.45-7.12 (m, 4H aromatic) 3.65 (s, 2H -CH_2-) 2.10 (s, 3H-$COCH_3$); ir (6% chloroform): 2250 cm^{-1} (-CN), 1670 cm^{-1} (amide). When it was refluxed for 2 hours in acetic anhydride, an almost quantitative yield of XVI was obtained.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.89; H, 5.87; N, 15.80.

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