The Synthesis of some 2,4-Benzodiazepin-1-ones, Potent C.N.S. Agents (1)

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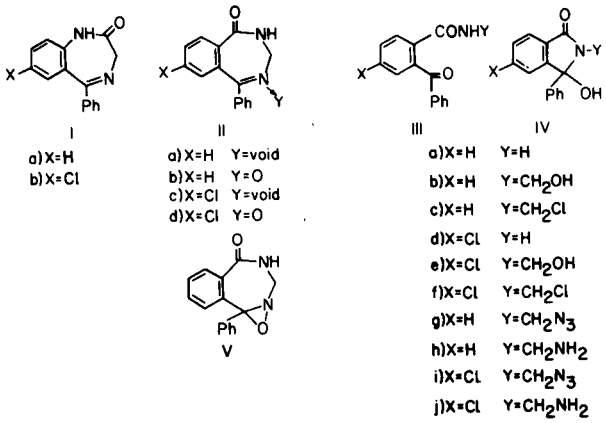
The synthesis of 2,4-benzodiazepin-1-ones (II, V) has been accomplished. Their C.N.S. properties are of the same order of the well known 1,4-benzodiazepins (Valium).

The impressive physiological properties of 1,4-benzodiazepinone derivatives (I) have greatly stimulated synthetic work in this series of heterocyclic compounds over the last two decades (2-3). The structure-activity relationship within this new class of highly active C.N.S. drugs and manifold structural variations of benzodiazepinone systems have been extensively studied (3-5).

It seems therefore rather surprising that no attempts of synthesizing the last remaining isomer, namely 2,4-benzodiazepin-1-one (II) have been reported so far. We are now describing a novel method of preparing these rather elusive compounds.

O-Benzoylbenzamide (IIIa) (6) adds formaldehyde in basic media (7) to form *N*-hydroxymethyl-(2-benzoyl)-benzamide (IIIb). Since *O*-benzoylbenzamide is equally being assigned the isoxindole structure IVa (8), the formaldehyde adduct could as well be represented by formula IVb. Two reasons seem to support our contention that we are here in the presence of the open chain form. Firstly methylol derivatives of primary amides are formed much easier than those of secondary amides, (7) secondly the smooth proceeding of the sequence of reactions leading to the formation of 2,4-benzodiazepinones (II) from the formaldehyde adduct (IIIb) stresses the open chain character of the intermediate.

When treated with thionyl chloride the methylol derivative (IIIb) affords crude chloromethyl derivative IIIc in high yield. Without further purification IIIc is reacted with aqueous ammonia in dioxan. Pure 2,4-benzodiazepinone IIa is obtained by chromatography of the crude reaction product under carefully controlled conditions, the yield being rather poor (12%). Oxidation of IIa by means of *m*-chloroperbenzoic acid yielded 40% of the *N*-oxide derivative (IIb), and 12% of the oxaziridine derivative (V) which was identified by its oxidizing properties (9).

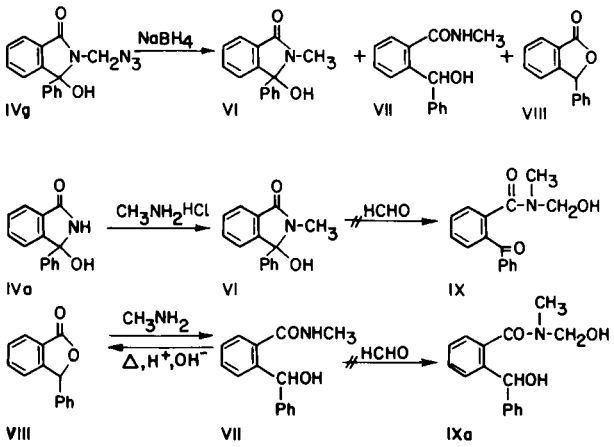


Preliminary pharmacological assays revealed that the new benzodiazepinones (IIa, IIb) do exhibit marked C.N.S. activity especially in the antimetrazol test where they show ED_{50} values of 24, 28 mg./kg. respectively when administered per os. These figures come very close to those shown by 1,4-benzodiazepinone unsubstituted at the seven position (Ib) when submitted to this particular test (4). In view of these rather encouraging findings the synthesis of the 7-chloro derivative seemed indicated. It was finally possible to prepare this benzodiazepinone (IIc) by using our newly established route, but quite unexpectedly more serious experimental difficulties were encountered. Pharmacological screening of IIc showed the expected higher C.N.S. activity with ED_{50} at 1.5 mg./kg. per os in the antimetrazole test putting it clearly in the range of Valium activity (4).

These pharmacological findings stimulated further work in this series. The need of preparing larger amounts of new compounds for more extensive pharmacological testing induced renewed efforts to improve the synthetic procedure. The reaction of the chloromethyl compounds IIIc,f with aqueous ammonia being the weak point of this route.

The possible use of a suitable precursor of a primary amino group was investigated. Reacting IIIc with sodium azide leads to the formation of IIIg with a 65% yield. Catalytic hydrogenolysis of the azide furnished the free amine IIIh in almost quantitative yield. It needs however refluxing in benzene in the presence of an acidic catalyst to form the 2,4-benzodiazepinone IIa in 60% yield. When the same sequence of reaction was applied to the chloro derivative (IIIf) experimental difficulties similar to those in the former route had to be overcome and lower yields were obtained. It looks rather surprising that in this case the formation of the seven membered ring apparently does not occur as smoothly as in the previous instance. One possible reason could be that the azide derivative appears in the isoxindole (VIg) structure. Its reduction leads to the free amine (VIh) which isomerizes in acidic media to the benzamide derivative (IIIh). Only then cyclization to the benzodiazepinone (IIa, IIc) is likely to occur. This assumption can be confirmed unambigously by C^{13} nmr, in which the chemical shift of C_3 of isoxindole (VIg) isomer will be in the aliphatic region whereas that of the benzamide isomer (IIIg) appears in the aromatic one. In the C^{13} nmr spectra of the two azides (IVg, IVi) no chemical shift was observed near δ = 195.6 ppm (the chemical shift of the ketone of benzophenone) but in δ = 89.6 ppm which clearly confirms the isoxindole structure. These rather surprising findings stimulate further investigation of C^{13} nmr spectra of some more compounds so that it will be possible to decide between the open chain (III) and the isoxindole (IV) structures. It turned out that all compounds which were examined are isoxindole derivatives (IV) (Table I).

The fact that the dibenzyl carbynol bond remained intact after the catalytic reduction of the azides (IVg,i) to the amines (IVh,j) should be emphasized. The chemical reduction of the azide (IVg) by means of sodium borohydride was also investigated. In two of the reaction products (VI, VII) which were isolated the azido group was cleaved altogether with formation of a methyl group, a rather unusual feature in this type of reduction. These two compounds may constitute potential starting materials for the synthesis of *N*-substituted-2,4-benzodiazepinones (XIII). They were also prepared using an alternative way.



Compound VI did however not add formaldehyde *via* the postulated isoxindole ring opening in basic or acidic media to form IX. Compound VII when heated with aqueous formaldehyde recyclized to the lacton VIII.

Efforts have been made to synthesize *N*-substituted-2,4-benzodiazepines (VIII) *via* a completely different route which had proved successful in the case of 1,4-benzodiazepine derivatives (10). The suitable starting materials XI and XII were prepared. Attempts to form the seven membered ring by using variations of the Bischler-Napieralski reaction were of no avail. Degradation products of the starting materials such as benzonitriles *N*-methylbenzamides and *N*-methylbenzylamine were the only well definded compounds isolated.

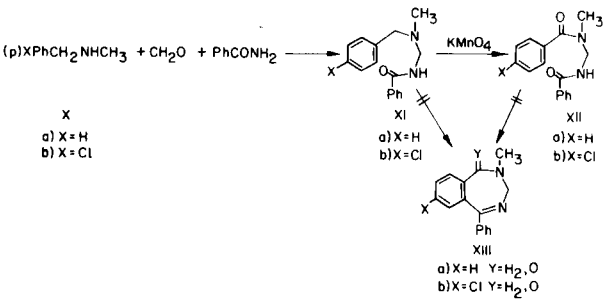


Table I

δ (ppm) of aliphatic carbons (C^{13}-nmr)

Compound	Solvent	-CO-NH-	Ph-C-OH	$-NCH_2-$
IVa	DMSO	168.4	87.3	---
IVb	DMSO	166.2	90.4	62.2
IVe	DMSO	166.3	90.1	62.4
IVc	DMSO	166.7	90.4	50.3
IVg	Deuteriochloroform	167.0	89.6	53.4
IVi	Acetone	166.8	89.6	55.3

EXPERIMENTAL

All melting points are uncorrected. H^1-nmr spectra were recorded on a Varian A-60 instrument, C^{13}-nmr spectra on a Bruker HFX-10 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 and 137 spectrophotometers. Silica gel HF_{254} was used for chromatography.

1-Oxo-2-hydroxymethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVb).

A mixture of 22.5 g. (0.1 mole) of IVa (6), 40 ml. of aqueous formaldehyde solution (38%), 40 ml. of ethanol and 40 ml. of a solution of 1 g. of potassium carbonate in 35 ml. of water was refluxed for 3 hours. Water was added to the hot mixture until crystals were formed. It was then allowed to cool and the product was filtered off and washed with 30% ethanol to yield 22.1 g. (85%) of product, m.p. 168-169°; H^1-nmr (d_6 DMSO): δ = 7.95-7.20 (m, 9H aromatic), 7.13 (s, 1H OH disappears with deuterium oxide), 5.62 (t, J = 7 1H OH disappears with deuterium oxide), 5.10-4.67 (m, 2H $-CH_2-$ turn to double d at 4.82 J = 11 when treated with deuterium oxide).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.80; H, 5.28; N, 5.57.

1-Oxo-2-chloromethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVc).

To a stirred mixture of 1.27 g. (0.005 mole) of IVb and 8 ml. of dry chloroform, 0.36 ml. (0.005 mole) of thionyl chloride was added dropwise while external cooling was applied. The crystalline starting material dissolved within few minutes and after a short while the product started to crystallize out. It was left overnight under stirring and then 10 ml. of methylcyclohexane were added dropwise, the crystals were filtered off and washed with methylcyclohexane to yield 1.15 g. (85%) of the product (IVc), m.p. 136-138° dec. Its reactivity did not afford further purification which seemed unnecessary after obtaining the analytical data; H^1-nmr (deuteriochloroform): 8.00-7.20 (m, aromatic H), 5.23 (double d J = 11 $-CH_2-$) 3.75-3.50 (broad s OH disappears with deuterium oxide); mass spectrum: m/e 255 (M^+).

Anal. Calcd. for $C_{15}H_{12}NO_2Cl$: C, 65.82; H, 4.42; N, 5.11; Cl, 12.95. Found: C, 65.67; H, 4.55; N, 5.28; Cl, 12.72.

5-Phenyl-2,3-dihydro-1*H*-2,4-benzediazepin-1-one (IIa).

To a cooled and stirred solution of 20 g. (0.073 mole) of IVc in 300 ml. of dioxane, 400 ml. of 25% aqueous ammonia were added dropwise. The mixture was stirred at room temperature for two days and the solvents evaporated under reduced pressure. The resulting oily residue was dissolved in ethylacetate and washed with water, the organic layer was dried and the solvent then removed under reduced pressure. The resulting oil was taken up in little chloroform and chromatographed on a silica gel column (200 g.) using chloroform as eluant. The major quantities of the product were in fractions 9, 10 and 11 (150 ml. per fraction). Evaporation of the solvents under reduced pressure yielded a solid which on recrystallization (ethylacetate of dioxan) yielded 2.05 g. (12%) of IIa, m.p. 214°; H^1-nmr (d_6-DMSO): δ = 9.17 (t, J = 6 NH disappears with deuterium oxide), 8.10-7.17 (m, 9H aromatic), 4.75-4.10 (broad s, CH_2); C^{13}-nmr of aliphatic carbons (d_6-DMSO): δ = 171.5 (C=N), 168.6 (C=O), 56.3 ($-CH_2-$); mass: m/e 236 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.97; H, 5.20; N, 11.80.

5-Phenyl-2,3-dihydro-1*H*-2,4-benzodiazepin-1-one 4-Oxide (IIb).

To a stirred solution of 0.84 g. (0.004 mole) of IIa in 50 ml. of dry chloroform, 0.85 g. of *m*-chloroperbenzoic acid was added. The reaction mixture was stirred 20 hours and then it was successively washed with 20 ml. of 5% potassium carbonate solution and water, dried over magnesium sulfate and evaporated to dryness at reduced pressure. The yellowish oily residue was chromatographed on a silica gel column (30 g.) to yield 0.1 g. (10%) of the oxaziridine derivative (V) using a mixture of equal parts of chloroform and benzene as eluant. Compound V was isolated from fractions 4-7 (75 ml. per fraction), m.p. 180° (from benzene); H^1-nmr (deuteriochloroform): δ = 8.20-7.00 (m, 9H aromatic and NH), 5.10-4.60 (m, 1H from $-CH_2-$) 4.05-3.75 (m, 1H from $-CH_2-$); mass: m/e 252 (M^+). On elution with ethyl acetate 0.4 g. (40%) of the *N*-oxide (IIb) was obtained (from ethyl acetate with little chloroform) m.p. 215°. H^1-nmr (deuteriochloroform): δ = 8.88 (t, J = 7 NH, disappears with deuterium oxide) 8.20-8.00 (m, 1H aromatic), 7.72-7.75 (m, 7H aromatic), 7.17-6.90 (m, 1H aromatic), 5.15 (d, J = 7 $-CH_2-$ turns to s with deuterium oxide). Recrystallization from benzene affords other crystalline form of m.p. 102-103° which contains 2 moles of benzene.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found for (V): C, 71.44; H, 4.95; N, 11.35; for (IIb): C, 71.45; H, 4.93; N, 11.29.

6-Chloro-1-oxo-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVd).

First the starting material 2-cyano-5-chlorobenzophenone was prepared. To a cooled (0-5°) and stirred solution of 115.7 g. (0.5 mole) of 2-amino-5-chlorobenzophenone in 140 ml. of concentrated hydrochloric acid and 200 ml. of methanol, a solution of 36 g. of sodium nitrite in 100 ml. of water was added dropwise at such a rate that the temperature was kept under 5°. The reaction mixture was stirred at 0-5° for 1 hour and then it was cooled to -15°. A cold solution of 80 g. of cuprous cyanide and 100 g. of sodium cyanide in 500 ml. of water was added dropwise to the reaction mixture at such a rate that inner temperature was kept below -5°. The cooling bath was removed and the reaction mixture was kept at room temperature for 2 hours and then at 40-50° for 1 hour. It was then extracted with ethyl acetate, washed well with water, dried and evaporated. Upon distillation the fraction which was collected at b.p. 160-190° (0.4 mm) afforded 40 g. (33% yield) of the nitrile, m.p. 85° (from *n*-hexane).

Anal. Calcd. for $C_{14}H_8ClNO$: C, 69.57; H, 3.34; N, 5.80; Cl, 14.67. Found: C, 69.70; H, 3.50; N, 5.62; Cl, 14.50.

A mixture of 29 g. (0.12 mole) of the nitrile and 80 ml. of concentrated sulfuric acid was stirred 3 hours. It was then poured slowly on iced water (750 ml.) and stirred overnight. The crystals were filtered off and washed with water until neutral to yield 28 g. (90%), m.p. 188-190°. It can be recrystallized from dilute ethanol to reach a m.p. of 209° but only 19 g. (61%) were regained. Since the analytical data of both is correct it is quite safe to use the crude product in the next step.

Anal. Calcd. for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39; Cl, 13.65. Found: (m.p. 209°): C, 64.96; H, 3.84; N, 5.09; Cl, 13.55; (m.p. 190°): C, 64.60; H, 4.10; N, 5.50; Cl, 13.53.

6-Chloro-1-oxo-2-hydroxymethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVe).

This compound was prepared in 90% yield according to the procedure described for IVb, m.p. 206-210° (crude). Recrystallization from ethyl acetate and a little ethanol affords m.p. 214° but

the yield drops to 60%; H^1-nmr (d_6-DMSO): δ = 7.89-7.28 (m, 8H aromatic and OH at 7.28 s which disappears with deuterium oxide), 5.74 (t, J = 7, 1H OH disappears with deuterium oxide), 4.75 (dd, J = 7, 2H -CH_2- turn to dd J = 11 with deuterium oxide).

Anal. Calcd. for $C_{15}H_{12}ClNO_3$: C, 62.18; H, 4.18; N, 4.84; Cl, 12.24. Found: C, 62.40; H, 4.04; N, 5.06; Cl, 12.18. Mass: m/e 289 (M^+).

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

The *N*-chloromethyl derivative (IVf) was prepared according to the procedure described for IVc. It was impossible to isolate a crystalline product so the crude oil which was obtained after removal of the solvent was taken to the next step as described for IIa. The isolation of the product was carried out as follows: the crude reaction mixture was chromatographed on a silica gel column (250 g.) using equal parts of chloroform and ethyl acetate and all fractions which contained the product (tlc, ethyl acetate Rf = 0.5, H^1-nmr broad s at about δ = 4.80-4.30) were rechromatographed on silica gel column (100 g.) using first chloroform as eluant (until fraction 20, 60 ml. in each one) and then chloroform and ethyl acetate in equal parts. The pure product (IIc) was in fraction 30-32 (8% yield). It was very difficult to recrystallize it and only after dissolving in methylcyclohexane and allowing to stand for ten days, a crystalline product m.p. 139° was isolated; H^1-nmr (deuteriochloroform): δ = 8.52 (t, J = 6 NH), 8.12-7.18 (m, 8H aromatic), 4.80-4.30 (broad s, -CH_2-); mass: m/e 270 (M^+).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Cl, 13.10. Found: C, 66.48; H, 3.92; N, 10.69; Cl, 13.05.

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

It was prepared from 0.56 g. (0.002 mole) of crude starting material (IIc) by the same method described for IIb. The purification was done by means of preparative chromatography (ethyl acetate used as eluant), it yielded only 0.025 g. (5%) of pure product (IId) m.p. 232-233° (from carbon tetrachloride and little chloroform); H^1-nmr (deuteriochloroform): δ = 8.80 (t, J = 7 NH), 8.10-7.04 (m, 8H aromatic) 5.15 (d, J = 7 -CH_2-); mass: m/e 286 (M^+), 270 (M^+-16).

1-Oxo-2-azidomethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVg).

To a stirred and chilled solution of 1.35 g. (0.005 mole) of *N*-chloromethyl derivative (IVc) in 50 ml. of dioxane, a cold solution of sodium azide (1.3 g., 0.02 mole) in 6 ml. of water was added at once and then it was stirred overnight. The solvents were removed under reduced pressure and the residue was treated with water and ethyl acetate. The organic layer was collected, dried and evaporated, and the oily residue was chromatographed on silica gel column (60 g.) using chloroform as eluant. The product was collected in fractions 6-11 (60 ml. per fraction), and the methylol derivative (IVb) was obtained as a byproduct (0.3 g., 25%), when the solvent was changed to ethyl acetate. Recrystallization (benzene and hexane) afforded a pure product 0.87 g. (63%), m.p. 137-138°; H^1-nmr (deuteriochloroform): δ = 7.85-7.25 (m, 9H aromatic) 4.65 (AB pattern J = 12.5 -CH_2-); ir (chloroform): 3580 cm^{-1} (OH); 2140-2110 cm^{-1} (N_3); 1720 cm^{-1} (lactam).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.34; H, 4.35; N, 20.01.

1-Oxo-2-aminomethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVh).

A solution of 2.8 g. (0.01 mole) of the azide derivative (IVg) in 50 ml. of ethyl acetate was hydrogenated (45 psi) in the presence of 10% palladium-carbon (0.25 g.) for 4 hours. The catalyst was removed by filtration through celite, the solvent was evaporated and the solid residue was treated with methylcyclohexane and filtered off. The product (IVh) was recrystallize from benzene and methylchlorohexane to give 2.5 g. (98%) m.p. 126-128° dec; H^1-nmr (deuteriochloroform): δ = 7.75-7.15 (m, 9H aromatic) 4.50-3.50 (broad m, 5H CH_2, OH, NH_2 it turns to broad AB q when treated with deuterium oxide).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.96; H, 5.60; N, 10.83.

5-Phenyl-2,3-dihydro-1*H*-2,4-benzodiazepin-1-one (IIa).

A solution of 0.54 g. (0.0021 mole) of IVh and few crystals of *p*-toluene sulphonic acid in 30 ml. of dry benzene was refluxed for 6 hours using Stark-Dean receiver to collect water which was formed during the cyclization. The solvent was removed by evaporation and the solid residue was treated with little ether acetate filtered off and recrystallized from ethyl acetate to yield 0.3 g. (60%) of the benzodiazepinone (IIa), m.p. 214°. It is identical to the one obtained from the reaction of IVc with ammonia.

6-Chloro-1-oxo-2-azidomethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVi).

It was prepared according to the procedure described for IVg. Isolation of the product (IVi) from the reaction mixture was accomplished by means of chromatography on silica gel column using equal parts of benzene and chloroform as eluant. When the product started to come from the column (flask 6) the eluant was changed to chloroform, from all the fractions the azide (IVi) was obtained in 36% yield after recrystallization from methylcyclohexane, m.p. 148-150° (the methylol derivative (IVe) was obtained as a byproduct 15% yield, when the chromatography was continued with ethyl acetate); H^1-nmr (deuteriochloroform): δ = 7.70-7.20 (m, 8H aromatic), 4.68 (AB pattern J = 12.5, 3H of CH_2 and OH at about δ = 4.77 which disappears with deuterium oxide); ir (chloroform): 3580 cm^{-1} (OH); 2140-2110 cm^{-1}; (-N_3); 1720 cm^{-1} (lactam).

Anal. Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80; Cl, 11.26. Found: C, 57.12; H, 3.52; N, 17.97; Cl, 10.95.

6-Chloro-1-oxo-2-aminomethyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (IVj).

A solution of 1.15 g. (0.0037 mole) of the azide derivative (IVi) in 200 ml. of ethyl acetate was hydrogenated (60 psi) in the presence of 10% palladium-carbon (0.2 g.) overnight. The catalyst was removed by filtration through celite, the solvent was evaporated and the solid residue was treated with methylcyclohexane and filtered off to yield 0.9 g. (95%) m.p. 135°. A small sample was recrystallized from benzene and methylcyclohexane to raise m.p. to 146-147° with loss of more than half of the product.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.54; N, 9.70; Cl, 12.28. Found: C, 62.20; H, 4.55; N, 9.77; Cl, 12.14.

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

A solution of 0.6 g. (0.0022 mole) of IVj and a few crystals of *p*-toluene sulphonic acid in 40 ml. of dry benzene was refluxed for 3 hours using Stark-Dean receiver to collect water which was formed during the cyclization. The solvent was evaporated and the residue was purified by means of preparative chromatography using ethyl acetate as eluant. The fraction containing the benzo-

diazepinone (IIc) Rf 0.3-0.6 was collected (0.3 g., 55%) and its nmr spectra was identical to the benzodiazepinone which was prepared from the reaction of IVf with ammonia.

Reduction of IVg with Sodium Borohydride.

To a stirred solution of 0.56 g. (0.002 mole) of IVg in 20 ml. of 2-propanol, 0.25 g. of sodium borohydride was added in portions during 1 hour and it was then stirred overnight. The solvent was evaporated and the residue was treated with water and ethyl acetate, the organic layer was dried and evaporated. The residue was purified by preparative chromatography using equal parts of ethyl acetate and chloroform as eluant. Three compounds were isolated: VIII, 0.1 g. (25%) Rf 0.9, m.p. 118-119°; VI, 0.15 g. (30%) Rf 0.6, m.p. 189-190°; VII, 0.08 g. (15%) Rf 0.4, m.p. 123-124°. Their synthesis is described in the following procedures.

1-Oxo-2-methyl-3-phenyl-3-hydroxy-2,3-dihydro-1*H*-isoindole (VI).

A mixture of 16.15 g. (0.072 mole) of IVa and 10 g. (0.15 mole) of methylamine hydrochloride were stirred and heated at 200-210° for 1 hour. The reaction mixture was allowed to cool and when temperature reached 150° dilute ethanol was added and the crystalline product which was formed was filtered off. The product was recrystallized by dissolving it in hot ethanol, filtering from impurities then adding hot water until crystals started to form to yield 14 g. (82%), m.p. 188-189°. H^1-nmr (deuteriochloroform): δ = 7.52-7.12 (m, 9H aromatic), 5.03 (broad s, 1H OH disappears with deuterium oxide), 2.53 (s, 3H $-CH_3$).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.11; H, 5.55; N, 5.96.

o-(Phenylhydroxymethyl)-*N*-methylbenzenecarboxamide (VII).

The lactone VIII was first prepared as follows: 10.16 g. (0.04 mole) of 2-carboethoxy benzophenone was stirred well in 50 ml. of 2-propanol and sodium borohydride (1.4 g.) was added in portions and then it was stirred overnight. A few drops of acetic acid were added and the reaction mixture was evaporated treated with ethyl acetate and water, the organic layer was dried, evaporated and the residue was recrystallized from methyl cyclohexane to yield 5.3 g. (62%), m.p. 117-118°. H^1-nmr (deuteriochloroform): δ = 8.05-7.15 (m, 9H aromatic), 6.40 (s, 1H aliphatic).

The lactone VIII (30 g., 0.014 mole) was added to a stirred solution of 4 g. of methylamine in 35 ml. of ethanol and stirred overnight. The reaction mixture was evaporated, treated with methylcyclohexane and the solid was filtered off to yield 3.3 g. (95%) of the product (VII), m.p. 123-124°. When it was recrystallized from benzene and methyl cyclohexane the m.p. dropped to 121-122° and the yield to 66%. The lactone (VIII) which was formed during this process was isolated from the solvent. The lactone (VIII) was also formed when the amide (VII) was treated in a reaction in basic or acidic media. H^1-nmr (deuteriochloroform): δ = 7.50-7.20 (m, 9H aromatic), 6.80-6.35 (broad s, 2H OH and NH disappear with deuterium oxide), 5.86 (s, 1H -CH-), 2.68 (d, J = 5 $-CH_3$ turns to s when treated with deuterium oxide); mass: m/e 241 (M^+).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.38. Found: C, 74.83; H, 6.38.

N-Benzamidomethyl-*N*-methylbenzylamine (XIa).

A mixture of benzamide (36.3 g., 0.3 mole), *N*-methylbenzylamine (36 ml. 0.3 mole), 35 ml. of 38% aqueous formaldehyde solution and 100 ml. of ethanol was refluxed for 1 hour. It was allowed to cool very slowly during which crystals were formed and then it was left for two days. The crystalline product was filtered off and recrystallized twice from benzene and methylcyclohexane to yield 36 g. (48%), m.p. 108-109°; H^1-nmr (deuteriochloroform): δ = 7.90-7.68 (m, 2H aromatic), 7.55-7.05 (m, 8H aromatic and NH which starts to disappear when treated with deuterium oxide), 4.33 (d, J = 6, 2H $-CH_2$-NHCO turns slowly to s when treated with deuterium oxide), 4.52 (s, 2H $-CH_2-NR_2$), 2.25 (s, 3H $-CH_3$).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.40; H, 7.20; N, 11.21.

N-Methyl-bis-benzamidomethylene (XIIa).

A solution of 7.62 g. (0.03 mole) of XIa in 100 ml. of acetone was added to a stirred solution of 3.14 g. (0.02 mole) in 300 ml. of acetone. Portions of 6.3 g. (0.04 mole) of potassium permanganate were added during 5 hours, and then it was stirred overnight. A solution of sodium hydrosulfite was added until the pink colour of the solution disappeared. It was then filtered off and evaporated to dryness. The residue was treated with chloroform and 3*N* hydrochloric acid and the organic layer was washed well with water, dried and evaporated. The residue was purified by preparative chromatography using chloroform as eluant and the fraction of Rf 0.2 was collected and yielded 1.4 g. (20%) of XIIa, m.p. 75-85° (successive recrystallization from dilute ethanol or benzene and hexane did not improve the m.p.); H^1-nmr (deuteriochloroform): δ = 8.20-7.70 (m, 2H aromatic and 1H NH which disappears slowly when treated with deuterium oxide), 7.55-7.20 (m, 8H aromatic), 5.13 (d, J = 6.5, 2H $-CH_2$- which turns slowly to s on treatment with deuterium oxide), 3.11 (s, 3H $-NCH_3$); mass: m/e 268 (M^+).

N-Benzamidomethylene-*N*-methyl(*p*-chloro)benzylamine (XIb).

This compound was prepared according to the procedure described for XIa in 40% yield, m.p. 108-110° (from benzene and *n*-hexane); H^1-nmr (deuteriochloroform): δ = 7.88-7.20 (m, 9H aromatic), 6.90 (broad t, 1H NH disappears slowly with deuterium oxide), 4.32 (d, J = 6, 2H $-CH_2$-NHCO- turns slowly to s with deuterium oxide), 3.60 (s, 2H $-CH_2$-), 2.25 (s, 3H $-NCH_3$); mass: m/e 288 (M^+).

N-Benzamidomethylene-*N*-methyl(*p*-chloro)benzamide (XIIb).

It was prepared according to the procedure described for XIIa in 20% yield, m.p. 142-143° (from carbon tetrachloride) (it was purified by column chromatography using equal parts of chloroform and ethyl acetate as eluant - the product collected in flasks 8-11, 60 ml. per fraction), H^1-nmr (deuteriochloroform): δ = 8.02-7.75 (m, 2H aromatic and , H NH which disappears with acidic deuterium oxide), 7.50-7.25 (m, 7H aromatic), 5.12 (d, J-6.5 $-CH_2$-NHCO - turns to s with acidic deuterium oxide), 3.14 (s, 3H-NCH_3); mass: m/e 302 (M^+).

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; Cl, 11.71. Found: C, 63.15; H, 5.18; Cl, 11.62.

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