New Synthesis of Substituted 3,5-Dihydro-4*H*-2,3-benzodiazepin-4-ones (1)

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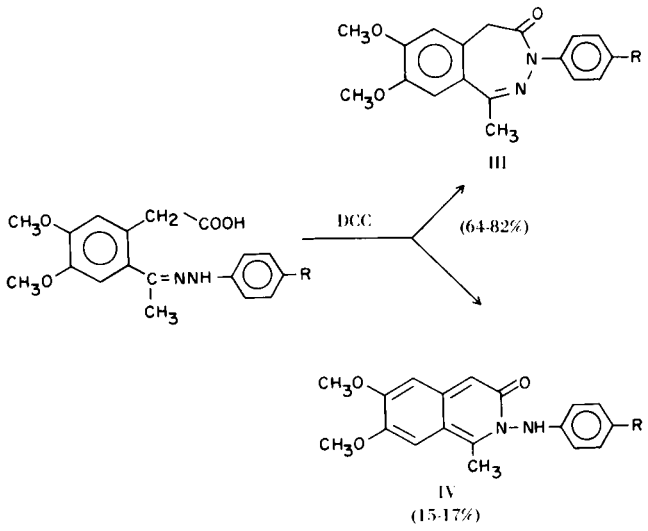
Synthetic routes for the preparation of 2,3-benzodiazepin-4-one derivatives have been described (4-6), but alternate methods are desirable.

A new synthesis of 3,5-dihydro-4*H*-2,3-benzodiazepin-4-one derivatives has now been accomplished by the reaction of 2-acetyl-4,5-dimethoxyphenylacetic acid phenylhydrazones (Table II) with *N,N'*-dicyclohexylcarbodiimide (7,8), as the cyclizing agent.

This rather convenient procedure leads to desired products (Table III) in high yields, along with concominant 2-amino-3-isoquinolone formation (Table IV). Facile removal of isomeric isoquinolones was effected by silica gel column chromatography.



Attempts to cyclise IIa by pyrolytic dehydration (4) at 190°/0.1 mm Hg did not lead to satisfactory results. Thus IIIa and IVa were obtained in 32% and 20% yields respectively. Using phosphorus pentachloride, as the cyclizing agent of IIa in boiling anhydrous benzene, the process yielded 75% of IVa and only 5% of IIIa. It is interesting to note that treatment of ethyl 2-acetyl-4,5-dimethoxyphenylacetate (9) with phenylhydrazine in boiling acetic acid produced compound IVa in 55% yield, while traces of IIIa were detected by thin layer chromatography. These observations are consistent with the predominant isoquinolone formation in acidic medium (4).

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and have not been corrected. Infrared spectra were recorded on a Perkin-Elmer Grating Infrared Spectrophotometer and nmr spectra on a Varian A-60 nmr spectrometer. Microanalyses are by the Laboratories of Nuclear Research Center "Democritos" and National Research Foundation.

Preparation of 2-Acetyl-4,5-dimethoxyphenylacetic Acid Hydrazones (IIa, IIb, and IIc).

Solutions prepared from 0.01 mole quantity of ethyl 2-acetyl-4,5-dimethoxyphenylacetate (8) and 0.01 mole of the appropriate phenylhydrazine in 75 ml. of 1-butanol were heated under reflux for 24 hours. After removal of the solvent *in vacuo* the remaining residues were recrystallized from ethanol. The yields and melting points are recorded in Table I.

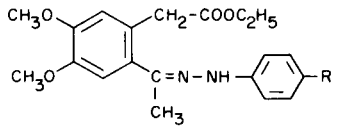
Saponification of 0.005 mole of ethyl 2-acetyl-4,5-dimethoxyphenylacetate phenylhydrazones was effected in 75% aqueous ethanol containing the equimolar amount of potassium hydroxide and reflux for 2 hours. After cooling the resulting derivatives were precipitated by dropwise addition of dilute acetic acid to *p*H 5-6, collected by filtration and were washed with water several times. After drying over phosphorus pentoxide *in vacuo* the desired products were recrystallized from ethanol. The yields, melting points, and microanalytical data are given in Table II.

3,5-Dihydro-4*H*-2,3-benzodiazepin-4-ones (IIIa, IIIb, IIIc).

To solutions of 0.0025 mole quantity of 2-acetyl-4,5-dimethoxyphenylacetic acid phenylhydrazones (IIa, IIb, IIc) in 30 ml. of methylene chloride (or dioxane), was added 0.0025 mole of *N,N'*-dicyclohexylcarbodiimide (DCC) with stirring for 2 hours at room temperature. The precipitated *N,N'*-dicyclohexyurea was removed by filtration and the organic layer (10) was washed with dilute bicarbonate solution, water, dried over anhydrous sodium sulphate and was concentrated to dryness under reduced pressure. The remaining crude reaction mixture was passed through a 25 x 500 cm^3 column packed with 50 g. of silica gel (70-230 mesh, ASTM, Merck) with first a mixture of 1:1 (v:v) benzene-ethyl acetate (eluate 1) and later with 1:1 (v:v)

TABLE I

Ethyl 2-Acetyl-4,5-dimethoxyphenylacetate Phenylhydrazone Derivatives



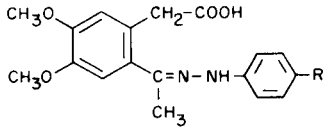
Ia, R = H
Ib, R = Cl
Ic, R = Br

Compound	Yield %	Molecular Formula	M.p., °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	65	$C_{20}H_{24}N_2O_4$	113	67.41	6.74	7.86	67.35	6.70	7.81
Ib	72	$C_{20}H_{23}ClN_2O_4$	120	61.45	5.88	7.17	61.30	5.73	7.03
Ic	67	$C_{20}H_{23}BrN_2O_4$	124	55.17	5.28	6.43	55.02	5.18	6.33

(a) Ir 3325 cm^{-1} (NH), 1720 (C=O), 1600 (C=N). (b) Ir 3300 cm^{-1} (NH), 1720 (C=O), 1590 (C=N). (c) Ir 3300 cm^{-1} (NH), 1720 (C=O), 1590 (C=N).

TABLE II

2-Acetyl-4,5-dimethoxyphenylacetic Acid Phenylhydrazone Derivatives



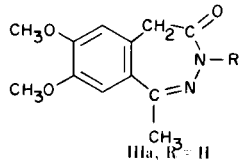
IIa, R = H
IIb, R = Cl
IIc, R = Br

Compound	Yield %	Molecular Formula	M.p., °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	93	$C_{18}H_{20}N_2O_4$	157	65.85	6.09	8.53	65.80	5.95	8.41
IIb	94	$C_{18}H_{19}ClN_2O_4$	177	59.58	5.24	7.72	59.35	5.14	7.65
IIc	93	$C_{18}H_{19}BrN_2O_4$	164	53.07	4.66	6.87	52.92	4.50	6.68

(a) Ir 3325 cm^{-1} (NH), 1700 (C=O), 1600 (C=N). (b) Ir 3300 cm^{-1} (NH), 1700 (C=O), 1590 (C=N). (c) Ir 3300 cm^{-1} (NH), 1700 (C=O), 1590 (C=N).

TABLE III

3,5-Dihydro-4*H*-2,3-benzodiazepin-4-one Derivatives



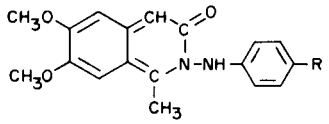
IIIa, R = H
IIIb, R = Cl
IIIc, R = Br

Compound	Yield %	Molecular Formula	M.p., °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	82	$C_{18}H_{18}N_2O_3$	194	69.67	5.80	9.03	69.47	5.78	9.00
IIIb	64	$C_{18}H_{17}ClN_2O_3$	185	62.69	4.93	8.41	62.75	4.85	8.30
IIIc	72	$C_{18}H_{17}BrN_2O_3$	189	55.52	4.37	7.19	55.36	4.21	7.08

(a) Ir 1650 cm^{-1} (C=O), 1600 (C=N), nmr (deuteriochloroform): τ 293 (C_6-H), 3.05 (C_9-H), 6.4 (CH_2). (b) Ir 1660 cm^{-1} (C=O), 1600 (C=N), nmr (deuteriochloroform): τ 292 (C_6-H), 3.05 (C_9-H), 5.98 (C_7-H), 6.00 (C_8-H), 6.42 (CH_2), 7.42 (C_1-H). (c) Ir 1660 cm^{-1} (C=O), 1600 (C=N), nmr (deuteriochloroform): τ 292 (C_6-H), 3.05 (C_9-H), 5.98 (C_7-H), 6.00 (C_8-H), 6.42 (CH_2), 7.42 (C_1-H).

TABLE IV

1-Methyl-2-phenylamino-2,3-dihydro-3-oxo-6,7-dimethoxyisoquinolines



IVa, R = H
IVb, R = Cl
IVc, R = Br

Compound	Yield %	Molecular Formula	M.p., °C	Analysis Calcd. C	H	N	Found C	H	N
IVa	15	$C_{18}H_{18}N_2O_3$	244	69.67	5.80	9.03	69.60	5.70	8.98
IVb	17	$C_{18}H_{17}ClN_2O_3$	267	62.69	4.93	8.41	62.55	4.90	8.35
IVc	16	$C_{18}H_{17}BrN_2O_3$	276	55.52	4.37	7.19	55.38	4.26	7.09

(a) Ir 3220 cm^{-1} (NH), 1630 (C=O), nmr (deuteriochloroform): τ 3.2 (C_5-H), 3.32 (C_8-H), 3.15 (C_4-H), 1.5 (NH). (b) Ir 3320 cm^{-1} (NH), 1625 (C=O).

benzene-methanol (eluate 2) as developers for 3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones (Table III) and isomeric isoquinolones (Table IV) respectively. A total volume of about 200 ml. was used for the elution of each isomer. Eluted 1 and 2, on removal of the solvent systems under high vacuum and at 30-35° gave the desired products, which were recrystallized from ethanol (Table III) and from mixture of chloroform-ethanol (Table IV).

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REFERENCES

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(3) To whom any correspondence concerning this paper should be addressed.

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(10) In case of dioxane as the solvent for compounds IIb and IIc, it was removed in vacuum at this stage and was replaced with methylene dichloride or chloroform for further treatment.