Synthesis of Some Amides and Amines Containing the 1,4-Benzodioxan Nucleus as Potential Adrenolytic Agents

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Ten substituted 1,4-benzodioxan carboxamides and five substituted aminomethyl-1,4-benzodioxans have been synthesized for evaluation as potential adrenolytic agents.

NUMEROUS COMPOUNDS containing the 1,4-benzodioxan nucleus have been synthesized and pharmacological evaluation of a number of these compounds has revealed a variety of pharmacological activities (1). Most of the active adrenolytic agents contain a mono- or disubstituted aminomethyl group in the 2 position of the benzodioxan nucleus. The substituents on the nitrogen and position of the nitrogen have been shown to affect the activity of the benzodioxans as adrenergic blocking agents (2–4). Very few examples of 2-arylaminomethyl-1,4-benzodioxans have been reported. Therefore, the synthesis of some 2-arylaminomethyl-1,4-benzodioxans was undertaken to explore the effect of this type of substitution upon pharmacological activity. In addition to the variation in the substituent attached to the nitrogen, this series will produce a decrease in the basicity of the compounds as compared to previously prepared aliphatic derivatives of the benzodioxan nucleus. Because of the potent adrenolytic activity of several bis-benzodioxan derivatives (5, 6) some compounds of this type were also synthesized.

The preparation of these derivatives was first attempted by the reaction of 2-chloromethyl-1,4-benzodioxan with the appropriate amine, a procedure commonly used for the synthesis of this type of compound. Because this route required large amounts of 2-chloromethyl-1,4-benzodioxan, a modified synthesis was initially developed for the chloro compound. This material had been reported previously to have been prepared from the reaction of 2-hydroxymethyl-1,4-benzodioxan with thionyl chloride and an organic base in the presence of an inert solvent (7). A more convenient route for the preparation of 2-chloromethyl-1,4-benzodioxan involved the reaction of excess thionyl chloride with the alcohol in the absence of an acid acceptor. The product obtained in this manner was identical in all respects to the product obtained utilizing the older procedure. The reaction of aniline with 2-chloromethyl-1,4-benzodioxan produced the desired amine in moderate yield. However, when the latter reaction was carried out using *p*-phenylenediamine no desirable product was isolated. A variety of reaction conditions and isolation procedures was attempted with no success.

An alternate procedure for the synthesis of substituted aminomethyl-1,4-benzodioxans has been reported by Koo (8). In this method the appropriate amine is reacted with 1,4-benzodioxan-2-carbonyl chloride to produce the amide which upon reduction with lithium aluminum hydride produced the desired amine. This method proved to be more successful and resulted in the synthesis of the compounds shown in Tables I and II. Attempts to reduce several of the compounds failed to result in the isolation of identifiable products. Since certain benzodioxancarboxamides have been reported to show an effect on the central nervous system (9), the intermediate carboxamides in this study are also of pharmacological interest. The compounds synthesized have been submitted for a general pharmacological screening and the results obtained will be the subject of a subsequent communication.

The general procedure for the synthesis is given below and the specific properties and analytical data are cited in Tables I and II.

2-Chloromethyl-1,4-benzodioxan.—Twenty-five grams (0.15 mole) of 2-hydroxymethyl-1,4-benzodioxan (10) in a 500-ml., two-neck flask equipped with magnetic stirrer, dropping funnel, and reflux condenser was reacted with 36 Gm. (0.30 mole) of thionyl chloride at room temperature. The reaction mixture was refluxed for 30 minutes and excess thionyl chloride removed by distillation at atmospheric pressure. The crude product was distilled and the 2-chloromethyl-1,4-benzodioxan collected at 110–112° (5 mm.), n_D^{25} 1.5510, yield 83% [reported b.p. 132° (14 mm.) (10)]. The product thus obtained had an infrared spectrum compatible with its structure, was light yellow, and was pure enough for subsequent reactions. The yellow color may be removed by washing the thionyl chloride stripped product with water and drying prior to vacuum distillation. A preparation was carried out with a fourfold quantity of reactants and gave an over-all yield of 77%.

2-Phenylaminomethyl-1,4-benzodioxan.—To a 100-ml. three-neck flask was added 10 Gm. (0.054 mole) of 2-chloromethyl-1,4-benzodioxan and 25 ml. (0.27 mole) of aniline. The mixture was refluxed under nitrogen for 2 hours, and the excess aniline removed by rendering the mixture basic with aqueous sodium hydroxide and steam distilling. The residue remaining was extracted twice with ether. The ethereal extracts were combined, dried over anhydrous sodium sulfate, and evaporated to yield a brownish colored oil. Aqueous hydrochloric acid (5 *M*) was added to the oil, producing a solid material. The solid material was recrystallized twice from propyl alcohol and was identical with the material formed by the alternate procedure.

1,4-Benzodioxan-2-carboxamide.—Koo's method (8) was used to obtain the 1,4-benzodioxan-2-carbonyl chloride used in the following reaction. 1,4-Benzodioxan-2-carbonyl chloride in 50 ml. of benzene was added dropwise with stirring over a period of 1 hour to a solution of the appropriate amine in 150 ml. of boiling benzene. The mixture was stirred and refluxed for an additional 2 hours. A 2:1 molar ratio of the appropriate amine to acid chloride was used when the amine had one reactive amino group. When the amine had two reactive

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TABLE I.—AMIDES OF 1,4-BENZODIOXAN-2-CARBOXYLIC ACID

Amine Used	M.p.,[b] °C.	Molecular Formula	Analysis[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Yield, %	Recrystallization Solvent
Aniline	116–118	$C_{15}H_{13}NO_3$	70.57	70.76	5.19	5.09	78	Ligroin
1-Phenylpiperazine	138–139	$C_{19}H_{20}N_2O_3$	70.35	70.62	6.22	6.35	73	Methylcyclohexane
2-Amino-4-methylpyridine	109	$C_{15}H_{14}N_2O_3$	66.65	66.57	5.22	5.33	67	Ethanol and Water
p-Dimethylaminoaniline	127–128	$C_{17}H_{18}N_2O_3$	68.44	68.23	6.08	5.90	62	Methylcyclohexane
p-Phenylenediamine	271–275 dec.	$C_{24}H_{20}N_2O_6$	66.66	66.41	4.66	4.61	63	Dioxane and Water
trans-1,4-Aminomethylcyclohexane	209–210	$C_{26}H_{30}N_2O_6$	66.93	67.02	6.48	6.30	63	Ethanol
cis-1,4-Aminomethylcyclohexane	124–125	$C_{26}H_{30}N_2O_6$	66.93	66.80	6.48	6.36	77	Ethanol and Water
Diphenylamine	127–128	$C_{21}H_{17}NO_3$	76.12	76.09	5.17	5.28	89	Ethanol and Water
Phenothiazine	138–140	$C_{21}H_{15}NO_3S$	69.91	69.91	4.18	4.29	Quant.	Ethanol and Water
p-Nitroaniline	179	$C_{15}H_{12}N_2O_5$	60.05	60.15	4.03	4.09	Quant.	Benzene

[a] Elemental analysis was performed by Alfred Bernhardt Microanalytical Laboratories, 433 Mülheim (Ruhr), Höhenweg 17, Germany. [b] Melting points reported here are uncorrected.

TABLE II.—(1,4-BENZODIOXAN-2-YLMETHYL) AMINES

Amine Used	M.p.[b] of Salt, °C.	Molecular Formula	Analysis[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Yield, %	Recrystallization Solvent
Aniline	191–192	$C_{15}H_{16}ClNO_2$	65.10	64.85	5.82	5.90	60	Isopropanol
1-Phenylpiperazine	240–244	$C_{19}H_{24}Cl_2N_2O_2$	59.53	59.42	6.31	6.31	37	Ether and Ethanol
p-Dimethylaminoaniline	195–199	$C_{17}H_{21}ClN_2O_2$	57.15	57.29	6.21	6.38	43	Ether and Ethanol
p-Phenylenediamine	234–236	$C_{24}H_{26}Cl_2N_2O_4$	60.38	60.23	5.49	5.38	64	Ether, Ethanol, and HCl
1,4-Aminomethylcyclohexane	261–265	$C_{26}H_{36}Cl_2N_2O_4$	61.05	61.37	7.10	6.97	40	Ether and Ethanol

[a] Elemental analysis was performed by Alfred Bernhardt Microanalytical Laboratories, 433 Mülheim (Ruhr), Höhenweg 17, Germany. [b] Melting points reported here are uncorrected.

amino groups, a one to one ratio of the amine to acid chloride was employed. Here, the addition of the last half of the amine was delayed until the reaction had been refluxed for 1 hour, and it was added to the reaction mixture over a period of 1.5 hours; the mixture was refluxed for 2 additional hours. In either of the above cases, after standing overnight, the resultant mixture was treated with cold water to dissolve the precipitated amine salt. The benzene layer was washed with 10% aqueous potassium hydroxide, with 2.5 *N* aqueous hydrochloric acid, and finally twice with water. It was dried with anhydrous sodium sulfate and evaporated. If the amine had a second nonreactive nitrogen or the amide formed was only slightly soluble in cold benzene, modified techniques for obtaining the product were employed. If the amide was only slightly soluble in benzene, cold water was added and the product removed by filtration. If the amine had a second nonreactive nitrogen, cool water was added and the benzene layer separated. The benzene was washed once with potassium hydroxide solution and twice with water. In this latter technique most of the amine was separated from the amide in the benzene layer which was dried over anhydrous sodium sulfate and evaporated leaving the product which was purified by recrystallization from the appropriate solvent. The solvents of recrystallization, analysis and physical properties are listed in Table I.

Substituted Aminomethyl-1,4-benzodioxans.—2-Carboxamides were added in a 1:4 molar ratio to lithium aluminum hydride suspended in anhydrous ether and the reaction mixture was stirred and refluxed for a period of 8 hours. Ethyl acetate (20 ml.) was added dropwise to decompose the lithium aluminum hydride and 200 ml. of 20% potassium sodium tartrate in water was added to the reaction mixture. The ether layer was separated and the water layer extracted twice with ether. The ethereal extracts were combined, washed twice with water, and dried over anhydrous sodium sulfate. Evaporation of the ether yielded an oil or solid material which was dissolved in absolute ether to which was added hydrogen chloride to form the appropriate amine salt. When the compound reduced had two carboxamide groups, a 1:8 ratio of amide to lithium aluminum hydride was employed. The properties of the compounds prepared are listed in Table II.

SUMMARY

A number of previously unreported substituted aminomethyl-1,4-benzodioxans have been synthesized. A general method for the synthesis of 2-aminomethyl-1,4-benzodioxans containing an aryl or heteroaryl substituent on the nitrogen has been developed.

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