was removed under reduced pressure, and the residue was dissolved in chloroform, washed with base and then water, and chromatographed; the position of the oxazole band could be determined by its fluorescence under ultraviolet light. No marked differences in yields of oxazole were found; the reproducibility was not of a high order, however. Complete details of these runs are to be found in the thesis of C. M. S.[1]

Acknowledgment.—The authors wish to thank Research Corporation for a grant in support of this work and Messrs. Ralph Denham and Jacob Cholak of the Kettering Laboratory for determining the infrared spectra.

NEW YORK 16, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE NATIONAL DRUG COMPANY]

Derivatives of 1,4-Benzodioxan. I. 1,4-Benzodioxan-2-carboxamides

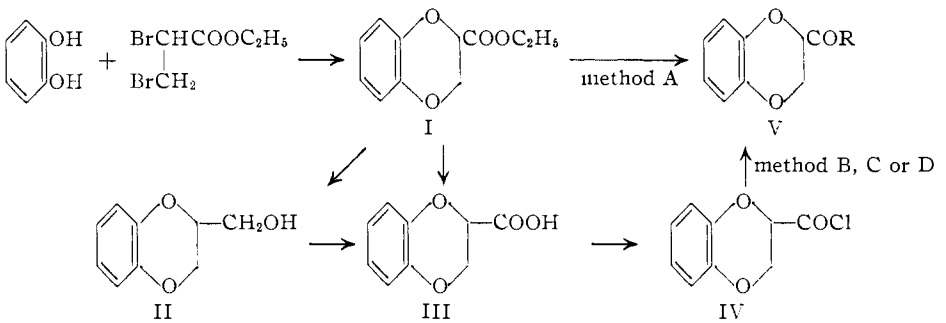
BY JOHN KOO, SOUREN AVAKIAN AND GUSTAV J. MARTIN

RECEIVED MARCH 21, 1955

A number of 1,4-benzodioxan-2-carboxamides were synthesized by reaction of ethyl 1,4-benzodioxan-2-carboxylate (I) with primary aliphatic amines or of the corresponding acid chloride IV with secondary, aromatic or heterocyclic amines. The structure of I was proved by reduction to the known 2-hydroxymethyl-1,4-benzodioxan (II), which in turn was oxidized to the acid *III*.

Relatively little is known about the chemistry and pharmacology of 1,4-benzodioxan derivatives. However, a few N-substituted-2-aminomethyl-1,4-benzodioxans have been used as adrenergic blocking agents,[1] and it was therefore believed desirable to prepare analogous compounds for pharmacological evaluation. This paper describes the synthesis of a number of N-substituted 1,4-benzodioxan-2-carboxamides; they are listed in Table I.

The previously unknown ethyl 1,4-benzodioxan-2-carboxylate (I), considered as a required intermediate, was obtained in good yield by condensation of catechol with ethyl α,β-dibromopropionate in the presence of potassium carbonate. Its structure was proved by lithium aluminum hydride reduction to the known[2] 2-hydroxymethyl-1,4-benzodioxan (II). Permanganate oxidation of II or saponification of I produced the same carboxylic acid III.



R = aliphatic, aromatic or heterocyclic amine

In both instances, the yield of the acid was greatly decreased by employment of slightly stronger conditions such as prolonged heating or more concentrated alkaline solution. It is believed, therefore, that the cyclic ether linkage is more readily cleaved by alkaline reagents in 1,4-benzodioxane than in the somewhat analogous methylenedioxybenzene.

Ammonolysis of the ester I with ammonia, hydrazine or primary aliphatic amines (method A) at room temperature or with slight heating provided the corresponding amides in excellent yield. This method failed, however, with other classes of amines. Secondary amines yielded the desired amides by reaction with the acid chloride IV in boiling methylene chloride (method B). The less reactive aromatic and heterocyclic amines were acylated only in the higher boiling benzene (method C). Finally, 2-aminobenzimidazole was converted to the amide by acylation in pyridine (method D). The reaction product of the ester with 2-amino-1-propanol was acetylated, and the two diastereoisomeric acetyl derivatives were separated.

Experimental[3]

Ethyl 1,4-Benzodioxan-2-carboxylate (I).—To a solution of 77 g. of catechol in 500 ml. of dry acetone was added 70 g. of anhydrous potassium carbonate, then dropwise, with stirring and gentle refluxing, 50 g. of ethyl α,β-dibromopropionate. Another 70 g. of potassium carbonate and 50 g. of dibromo ester was added similarly and this was repeated twice more using altogether 280 g. of potassium carbonate and 200 g. of ester. Stirring and refluxing were continued for another 18 hours, adding periodically dry acetone to keep the reaction mixture fluid enough for stirring. It was then filtered and the residue washed with acetone. Concentrating the filtrate to about 200 ml. and diluting with 300 ml. of cold water precipitated an oil, which was extracted repeatedly with ether. The extracts were washed with water, dried over magnesium sulfate and evaporated. The ester distilled at 105–107° (0.15 mm.) and formed a colorless oil, $n^{25}D$ 1.5214; yield 110 g. (76%).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.58.

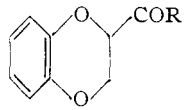
2-Hydroxymethyl-1,4-benzodioxane (II).—To a stirred suspension of 1 g. of lithium aluminum hydride in 100 ml. of anhydrous ether was added 2.0 g. of the ester I in 20 ml. of ether. The mixture was stirred and refluxed for three hours, cooled and decomposed by adding dropwise ice-water, then rapidly 60 ml. of 20% sodium potassium tartrate solution.

(1) E. Fourneau and D. Bovet, *Arch. Intern. pharmacodynamie*, **46**, 178 (1933); M. Goldenberg, C. H. Snyder and H. Aranow, *J. Am. Med. Assoc.*, **135**, 971 (1947).

(2) A. Grun, U. S. Patent 2,366,102 (1944); *C. A.*, **40**, 2271 (1946).

(3) All melting and boiling points are uncorrected. Microanalyses were performed by Mr. S. Alpert and Mr. E. P. McGrady of our Analytical Department.

TABLE I

1,4-BENZODIOXAN-2-CARBOXAMIDES, 

Cmpd.	R	Method	M.p. or b.p. (mm.), °C.	Yield, %	Recryst. from	Formula	Nitrogen, % Calcd.	Found
1	Amino	A	142–144	94	Ethanol–water	$C_9H_9O_3N$	7.82	7.76
2	Hydrazino	A	113–115	86	Ethanol–water	$C_9H_{10}O_3N_2$	14.43	14.50
3	Methylamino	A	111–112	96	(Not recrystd.)	$C_{10}H_{11}O_3N$	7.25	7.23
4	Ethylamino	A	71–73	86	Ethanol–water	$C_{11}H_{13}O_3N$	6.76	6.69
5	Allylamino	A	59–61	90	Benzene–ligroin	$C_{12}H_{13}O_3N$	6.39	6.26
6	3-Dimethylaminopropylamino	A	151 (0.1)	79	.....	$C_{14}H_{20}O_3N_2$	10.60	10.36
7	3-Isopropylaminopropylamino hydrochloride	A	165–166	78	Ethanol–ether	$C_{15}H_{23}O_3N_2Cl$	8.90	8.85
8	2-Acetoxyisopropylamino (high melting isomer)	A	105–106	24	Benzene–ligroin	$C_{14}H_{17}O_5N$	5.02	4.93[a]
9	2-Acetoxyisopropylamino (low melting isomer)	A	78–79	18	Benzene–ligroin	$C_{14}H_{17}O_5N$	5.02	4.98[b]
10	Furfurylamino	A	80–82	83	Toluene–ligroin	$C_{14}H_{13}O_4N$	5.40	5.21
11	2-(4-Morpholinyl)-ethylamino hydrochloride	A	179–181	71	Ethanol–ether	$C_{15}H_{21}O_4N_2Cl$	8.52	8.53
12	N-(2-Diethylcarbamylethyl)-N-ethylamino	B	190–192 (0.3)	65	.....	$C_{18}H_{26}O_4N_2$	8.38	8.16
13	N-Diethylcarbamylmethyl-N-ethylamino	B	190–192 (0.5)	85	.....	$C_{17}H_{24}O_4N_2$	8.74	8.53
14	Diethylamino	B	140–142 (0.25)	95	.....	$C_{13}H_{17}O_3N$	5.95	5.87
15	Diallylamino	B	160–162 (0.2)	92	.....	$C_{15}H_{17}O_3N$	5.40	5.15
16	4-Morpholinyl	B	139–140	93	Ethanol–water	$C_{13}H_{15}O_4N$	5.62	5.65
17	1-Piperidyl	B	69–70	86	Ether	$C_{14}H_{17}O_3N$	5.66	5.47
18	1-Pyrrolidyl	B	66–67	85	Ether–ligroin	$C_{13}H_{15}O_3N$	6.01	5.98
19	4-(1,4-Benzodioxan-2-carbonyl)-1-piperazinyl	B	185–186	75	Ethanol–water	$C_{22}H_{22}O_6N_2$	6.83	6.89
20	2-Pyridylamino	C	84–86	72	Ethanol–water	$C_{14}H_{12}O_3N_2$	10.93	10.76
21	*p*-Methoxyphenylamino	C	102–104	70	Ethanol–water	$C_{16}H_{15}O_4N$	4.91	4.89[c]
22	3,4,5-Trimethoxyphenylamino	C	115–117	94	Benzene–Skellysolve B	$C_{18}H_{19}O_6N$	4.06	3.89[d]
23	1,2,3,4-Tetrahydro-1-quinolyl	C	78–80	76	Ether	$C_{18}H_{17}O_3N$	4.74	4.81[e]
24	2-Thiazolylamino	C	203–205	72	Toluene	$C_{12}H_{11}O_3N_2S$	10.68	10.96
25	2-Benzthiazolylamino	C	154–156	96	Benzene–ligroin	$C_{16}H_{12}O_3N_2S$	8.97	8.76
26	2-Benzimidazolylamino	D	224–225	91	Pyridine–water	$C_{16}H_{13}O_3N_3$	14.23	14.20

[a] Calcd.: C, 60.20; H, 6.14. Found: C, 60.46; H, 5.84. [b] Calcd.: C, 60.20; H, 6.14. Found: C, 60.37; H, 6.03. [c] Calcd.: C, 67.36; H, 5.30. Found: C, 67.60; H, 5.48. [d] Calcd.: C, 62.78; H, 5.27. Found: C, 62.76; H, 5.35. [e] Calcd.: C, 73.20; H, 5.80. Found: C, 73.42; G, 5.67.

The ether layer was separated and the aqueous solution extracted twice with ether. The combined extracts were washed with 5% sodium bicarbonate solution, then with water, dried over magnesium sulfate and evaporated. The residual oil (1.44 g., 90%) solidified on standing; m.p. 83–85°. Recrystallization from dilute ethanol afforded a colorless product, m.p. 85–86° (lit.[2] 86°), which did not depress the m.p. of an authentic sample.[2]

1,4-Benzodioxan-2-carboxylic Acid (III). (a) **By Saponification of the Ester I.**—A mixture of 6.2 g. of I and 40 ml. of 10% aqueous sodium hydroxide was gently heated on the steam-bath for 30 minutes, and the clear solution acidified with hydrochloric acid. Colorless crystalline material separated on chilling; it was collected, washed with a little cold water and dried; yield 4.9 g. (91%), m.p. 116–118°. The acid, which was rather soluble in water, crystallized from benzene–ligroin in colorless needles, m.p. 119–120°. When a more concentrated alkaline solution was used or when heating was vigorous and prolonged, the yield of acid was greatly decreased.

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.21; H, 4.50.

(b) **By Oxidation of 2-Hydroxymethyl-1,4-benzodioxan** (II).—To a stirred suspension of 160 g. of II in 1.5 l. of water containing 52 g. of potassium hydroxide cooled to 5° was added 200 g. of potassium permanganate in small portions at such a rate that the temperature did not exceed 15°. This required two to three hours, and stirring at 10–15° was continued for another six hours. The mixture was then filtered, acidified with hydrochloric acid and placed in the ice-box overnight. The product was collected and recrystallized from benzene–ligroin to yield 95 g. (55%) of acid, m.p. 118–119°, no depression with a sample prepared by procedure (a).

1,4-Benzodioxan-2-carbonyl Chloride (IV).—A mixture of 32 g. of thionyl chloride and 50 ml. of benzene was added slowly with stirring to a solution of 40 g. of the acid III in 150 ml. of benzene. Ten minutes later, the mixture was refluxed for 0.5 hour, then concentrated under reduced pressure. The residue was added to 400 ml. of hot Skellysolve B and the solution filtered at once, then cooled to yield 35 g. (79%) of colorless needles, m.p. 56–57°, unchanged after recrystallization.

Anal. Calcd. for $C_9H_7O_3Cl$: Cl, 17.85. Found: Cl, 17.83, 17.82.

Preparation of 1,4-Benzodioxan-2-carboxamides (Table I). **Method A.**—Ammonolysis of ethyl 1,4-benzodioxan-2-carboxylate is illustrated by the preparation of **1,4-benzodioxan-2-carboxamide** (compd. 1). A solution of 10 g. of the ester I in 25 ml. of ethanol was treated in a glass-stoppered 200-ml. erlenmeyer flask with 75 ml. of concd. aqueous ammonia. The flask was shaken vigorously for several minutes, then allowed to stand at room temperature for two days with occasional shaking. The heavy crystalline precipitate was collected; yield 5.5 g., m.p. 142–144°. Concentration of the filtrate gave another 2.6 g. of slightly im-

pure product; m.p. 140–142°. The combined yield was 8.1 g. (94%). Recrystallization from 30% ethanol provided small colorless needles, m.p. 142–144°.

In some of the other preparations, the ester dissolved readily in the amine and no additional solvent was used. Heating on the steam-bath was employed with higher boiling and less reactive amines. These modifications are illustrated by the preparation of two diastereoisomers of **N-(2-acetoxyisopropyl)-1,4-benzodioxan-2-carboxamide** (compds. 8 and 9). A solution of 15 g. of I in 50 ml. of 2-amino-1-propanol was heated on the steam-bath for 2.5 hours, then allowed to stand at room temperature for five days. Excess aminopropanol was evaporated under reduced pressure. The thick oily residue, which could not be distilled without decomposition, was dissolved in 150 ml. of pyridine. The solution was treated with 80 ml. of acetic anhydride, gently heated on the steam-bath for 1.5 hours, cooled and poured into 500 ml. of ice-water. The mixture of diastereoisomers separated as a colorless crystalline solid; yield 15 g., m.p. 90–96°. It was recrystallized twice from benzene–ligroin, then once from aqueous ethanol to yield 4.8 g. (24%) of colorless short needles, m.p. 105–106°. Evaporation of the first benzene–ligroin mother liquor left a colorless solid melting at *ca.* 75°, which was recrystallized once from aqueous ethanol, then once from benzene–ligroin, providing 3.7 g. (18%) of the second isomer as colorless clusters of needles, m.p. 78–79°.

Compound 6 could not be crystallized and was purified by vacuum distillation. Some of the basic acids (compd. 7 and 11) were isolated as the hydrochlorides by saturating their solutions in anhydrous ether with dry hydrogen chloride and recrystallizing the salts from absolute ethanol–ether.

Method B.—The preparation of **N-ethyl-N-(β-diethylcarbamyl)-ethyl-1,4-benzodioxan-2-carboxamide** (compd. 12) serves to illustrate the acylation of secondary amines. Ten grams of 1,4-benzodioxan-2-carbonyl chloride (IV) in 50 ml. of methylene chloride was added slowly with stirring to 20 g. of N,N-diethyl-β-ethylaminopropionamide in 50 ml. of methylene chloride. The mixture was refluxed for two hours, evaporated under reduced pressure, and the residue added to dilute hydrochloric acid. The oil was extracted with ether, which was then washed with water and sodium bicarbonate solution, dried and evaporated. The oily product distilled at 190–192° (0.3 mm.); yield 11 g. (65%).

Method C.—This modification of method B was employed with aromatic and heterocyclic amines. It is illustrated by the preparation of **N-(2-pyridyl)-1,4-benzodioxan-2-carboxamide** (compd. 20). To a stirred solution of 12 g. of 2-aminopyridine in 150 ml. of boiling dry benzene was added 11.8 g. of IV in 50 ml. of benzene dropwise over one hour. The mixture was stirred and refluxed for another two hours, allowed to stand overnight and treated with cold water to dissolve the precipitated amine salt. The benzene layer was separated, washed with 50 ml. of 5% sodium bicarbonate solution, then with 50 ml. of 5% hydrochloric acid, and finally with 50 ml. of water, dried over magnesium sulfate and evaporated. The yield of pale yellow solid residue, m.p. 80–83°, was 11 g. (72%). Recrystallization from benzene–ligroin then 60% ethanol afforded small colorless needles, m.p. 84–86°.

Method D.—None of the preceding methods was successful in attempted preparations of **N-(2-benzimidazolyl)-1,4-benzodioxan-2-carboxamide** (compd. 26), which was therefore synthesized as follows: To a solution of 5.32 g. of 2-aminobenzimidazole in 80 ml. of dry pyridine was added with stirring and cooling in ice 8 g. of the acid chloride IV in small portions over one hour. The ice-bath was removed and stirring continued at room temperature for one hour, then with gentle heating on the steam-bath for 0.5 hour. The mixture was kept overnight, poured into 250 ml. of ice-water, and the colorless precipitate collected, washed with small portions of ice-water and dried at 60°; yield 10.7 g. (91%), m.p. 222–224°. Recrystallization from aqueous pyridine provided the analytical sample, m.p. 224–225°.

PHILADELPHIA 44, PA.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

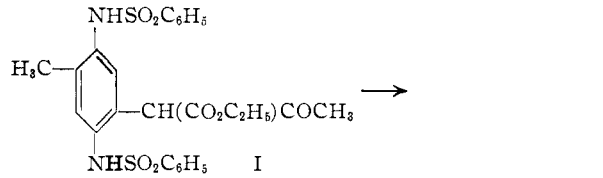
Quinone Imides. XXXVII. Conversion of *p*-Quinone Diimides to Indoles

BY ROGER ADAMS AND WILLIAM P. SAMUELS, JR.[1]

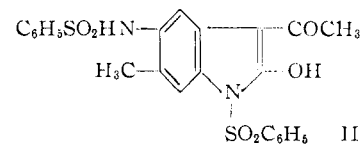
RECEIVED APRIL 13, 1955

Active methylene compounds have been added to several *p*-quinonebis-(dimethylsulfamimides) and 1,4-naphthoquinonebis-(dimethylsulfamimide). Treatment of the resulting substituted diamides with 48% hydrobromic or 22% hydrochloric acid under reflux or cold concentrated sulfuric acid converts them to indoles.

The addition of active methylene compounds and in particular of β-diketones and β-ketoesters to quinone diimides has been studied previously.[2] However, the only reported cyclization of a compound of this type is the conversion of ethyl α-[2,5-dibenzenesulfonamido-4(?)-methylphenyl]-acetoacetate (I) to 3-acetyl-5-benzenesulfonamido-6(?)-methyloxindole (II) by heating it above its melting point; ring closure occurred with the loss of a molecule of ethanol.[2c] Examination of an active methylene adduct such as III reveals that by elimination of a molecule of water an indole derivative might result. If the 1-sulfonamido group of III were hydrolyzed to the amino group, the resulting aromatic amine would be of the type that previously has been demonstrated to cyclize readily to an indole.

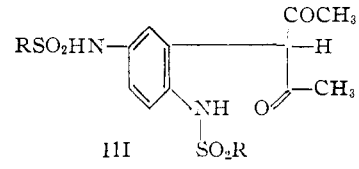


I



II

This communication describes the results of experiments on the formation of indoles from such diamides.



III

(1) An abstract of a thesis submitted by William P. Samuels, Jr., to the Graduate College of the University of Illinois, 1955, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy; Standard Oil of California Fellow, 1952–1954.

(2) (a) R. Adams and W. Moje, THIS JOURNAL, **74**, 5557 (1952); (b) R. Adams and D. S. Acker, *ibid*, **74**, 5872 (1952); (c) R. Adams and D. C. Blomstrom, *ibid.*, **75**, 3403 (1953).