below 20° during the 1-hr. addition period. The solution was stirred overnight at 25°, neutralized with 20% HCl, diluted with water, and extracted with two 200-ml. portions of ether, which were combined, dried (Na_2SO_4), and evaporated. Distillation provided 25.8 g. of product; λ_{max}^{EtOH} 270 mμ (ε 1490), 264 (1530), 258 (1020), and a shoulder at 253 (580). Infrared bands appeared at 4.46, 4.48, and 10.03 μ (CCl_4).

A mixture of the dinitrile IX (1.8 g., 0.01 mole) and 25 ml. of concentrated HCl was stirred vigorously at 25°; complete solution occurred within 30 min. After 20 min. of additional stirring, the yellow solution was poured onto ice, and the deposited solid was filtered, washed with water, and dried. The diamide X weighed 1.4 g. and was recrystallized from ethanol; λ_{max}^{Nujol} 6.05, 6.14, and 10.03 μ.

A mixture of the dinitrile IX (3.6 g., 0.02 mole) and 60 ml. of concentrated HCl was refluxed for 4 hr. The solution was cooled, and the precipitated solid was filtered, washed with water, and dried. Recrystallization from water afforded 3.55 g. of the diacid XI as a white, crystalline powder; λ_{max}^{Nujol} 5.80 and a shoulder at 10.07 μ.

The diacid XI (4.4 g., 0.02 mole) and 4.1 g. (0.04 mole) of acetic anhydride were heated at an oil bath temperature of 130° for 2 hr. The resulting solution was refrigerated for 24 hr., and the precipitated material was filtered with the aid of a minimum amount of benzene. Recrystallization from benzene yielded 2.2 g. of **1-(2-carboxyethyl)benzocyclobutene-1-carboxylic acid anhydride (XII)** as a white, crystalline powder; λ_{max}^{Nujol} 5.53, 5.70, and 10.07 μ.

Spiro[benzocyclobutene-1,3′-(2′,6′-dioxopiperidine)] (XIII).—A solution of 5.6 g. (0.03 mole) of the dinitrile IX in 10 ml. of glacial acetic acid and 4 ml. of concentrated H_2SO_4 was heated at an oil bath temperature of 120° for 10 min.[9] The warm solution was poured onto ice and immediately neutralized ($NaHCO_3$). The precipitated material was taken up in two 100-ml. portions of chloroform, which were combined, washed with saturated brine solution, dried (Na_2SO_4), and evaporated. The remaining solid was recrystallized from ethyl acetate–Skelly B to afford 3.1 g. of a white powder; λ_{max}^{EtOH} 272 mμ (ε 1590), 265 (1810), 259 (1400), 253 (1130), 245 (1110), and 238 (1120). Infrared bands appeared at 6.02, 6.12, and 10.01 μ (Nujol).

N-Phthalyl-O-(1-benzocyclobutenyl)hydroxylamine (XIV).—A solution of 1-bromobenzocyclobutene[8,10] (1.83 g., 0.01 mole), prepared in 31% yield from benzocyclobutene-1-carboxylic acid by a modified[11] Hunsdiecker reaction, N-hydroxyphthalimide (1.63 g., 0.01 mole), and triethylamine (1 g., 0.01 mole) in 35 ml. of acetonitrile was refluxed for 24 hr. The solvent was evaporated; the residual solid was washed repeatedly with water and dried. Recrystallization from aqueous ethanol provided 1.5 g. of pale tan needles; λ_{max}^{Nujol} 5.59 and 5.80 μ.

O-(1-Benzocyclobutenyl)hydroxylamine Hydrochloride (XV).—The imide XIV (4 g., 0.015 mole) and 0.9 g. (0.015 mole) of 85% aqueous hydrazine hydrate in 60 ml. of methanol was refluxed with stirring for 3 hr. The methanol was removed under vacuum, and the residue was treated with 40 ml. of 10% HCl and 10 ml. of water. The mixture was stirred overnight at 25°, filtered, and evaporated to dryness. Recrystallization of the residue from ethanol–ether provided 2.3 g. of white flakes; λ_{max}^{EtOH} 273 mμ (ε 1680), 267 (1720), 261 (1120), and a shoulder at 254 (614). An infrared band appeared at 10.05 μ as a shoulder (Nujol).

1-Benzocyclobutenylglycine (XVI).—To a solution of 1.73 g. (0.075 g.-atom) of sodium in 100 ml. of absolute ethanol under nitrogen was added 12.8 g. (0.075 mole) of ethyl acetamidocyanoacetate. The pale yellow solution was stirred for 30 min. and then was treated with 13.8 g. (0.075 mole) of 1-bromobenzocyclobutene. The darkened reaction mixture was refluxed for 40 hr., cooled, and filtered. The filtrate was evaporated to near dryness, and the residue was diluted with water. The organic layer was taken up in 150 ml. of ethyl acetate, which was washed with saturated brine and dried (Na_2SO_4). Solvent evaporation afforded 16.6 g. of a brown oil which was put on a column of 450 g. of alumina. Elution with chloroform afforded 9.55 g. (47%) of ethyl 1-benzocyclobutenylacetamidocyanoacetate as a viscous liquid. A 9-g. sample of this material was refluxed in a solution of methanol (75 ml.) and 10% NaOH (75 ml.) for 2 days. The amber solution was concentrated under vacuum, diluted with water, and extracted with ethyl acetate. Neutralization with 4 *N* HCl caused the immediate precipitation of a pale tan flocculent solid. Recrystallization was effected by addition of 500 ml. of ethanol to a cold, aqueous (450 ml.) solution of the material. The white flakes weighed 2.2 g. Thin layer chromatography on silica gel G with *n*-butyl alcohol–acetic acid–water (7:1:2) gave a single spot (ninhydrin), R_f 0.43. An infrared band appeared at 10.07 μ (Nujol).

(9) E. Tagmann, E. Surry, and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).

(10) L. Horner, A. Kirmse, and K. Muth, *Chem. Ber.*, **91**, 430 (1958).

(11) F. W. Baker, H. D. Holtz, and L. M. Stock, *J. Org. Chem.*, **28**, 514 (1963).

Some N-Substituted Dimethoxyphenylacetamides and Dimethoxyphenylethylamines

C. G. STUCKWISCH[1] AND JANICE S. HILLIARD

Department of Chemistry, New Mexico Highlands University, Las Vegas, New Mexico

Received June 7, 1965

In connection with a study of compounds related to sympathomimetic amines, a number of N-substituted dimethoxyphenylethylamines were prepared by the reduction of the corresponding amides with $LiAlH_4$.

Experimental[2]

Ethyl 3,4-dimethoxyphenylacetate[3] [b.p. 143° (2.5 mm.)] and ethyl 2,5-dimethoxyphenylacetate[4] [b.p. 139–140° (2.5 mm.)] were prepared in 65 and 82% yields, respectively, by Fisher esterification of the corresponding acids. 2-Amino-6-chlorobenzothiazole[5] and 2-amino-6-methoxybenzothiazole[6] were prepared by published procedures.

Preparation of the Amides (Table I).—Fifty milliliters of a 0.213 *M* solution of ethylmagnesium bromide in tetrahydrofuran was added dropwise to 10.7 mmoles of amine in 20 ml. of tetrahydrofuran cooled in an ice bath. The cooling bath was removed and the mixture was stirred until the initially formed precipitate dissolved. To the stirred solution was added 10.7 mmoles of ester in 20 ml. of tetrahydrofuran. After 2 hr. the solvent was removed at the water pump. The residue was stirred with 40 ml. of 5% NH_4Cl solution; the mixture was cooled in an ice bath, and the amide was then collected on a filter and crystallized from hot aqueous ethanol subsequent to decolorization with Norit. The results are summarized in Table I.

Preparation of the Amines (Table II).—A solution of 1.1 g. of $LiAlH_4$ in 100 ml. of diethyl ether was added to 4 mmoles of amide dissolved in 80 ml. of hot benzene. The mixture was refluxed for 72 hr. The solution was then cooled and cautiously heated with 25 ml. of water followed by 25 ml. of 10% H_2SO_4. The aqueous phase was separated, brought to pH 5 by addition of solid Li_2CO_3, and filtered. The filtrate, heated to 70°, was treated with 1.2 g. of picric acid. The picrate which separated was filtered from the cooled solution, and crystallized from aqueous ethanol. The purified picrate was suspended in 10% aqueous NaOH and the liberated amine was extracted from the mixture with ether. The ether extract was evaporated and the residual amine crystallized from the solvent indicated in Table II.

(1) Chemistry Department, State University of New York at Buffalo, Buffalo, N. Y. 14214.

(2) All melting points were determined on a hot stage apparatus and are uncorrected.

(3) J. G. Watkinson, W. Watson, and B. L. Yates, *J. Chem. Soc.*, 5437 (1963); R. Quelet and J. Gavavett, *Compt. rend.*, **230**, 394 (1950); C. Schoepf, G. Goettmann, E. Meisel, and L. Neuroth, *Ann.*, **563**, 86 (1949).

(4) G. Leaf and A. Neuberger, *Biochem. J.*, **43**, 606 (1948).

(5) G. M. Dyson, R. F. Hunter, and R. W. Morris, *J. Chem. Soc.*, 1186 (1927).

(6) C. G. Stuckwisch, *J. Am. Chem. Soc.*, **71**, 3417 (1949).

TABLE I

N-SUBSTITUTED DIMETHOXYPHENYLACETAMIDES

$(CH_3O)_2C_6H_4CH_2COR$

Compd.	$(CH_3O)_2$ position	R	M.p., °C.	Yield, %	Formula	% calcd. C	% calcd. H	% found C	% found H
I	3,4	NHC:NCH:CHS	166–167	80	$C_{13}H_{14}N_2O_3S$	56.09	5.07	56.27	5.21
II	3,4	NHC:$NC_6H_3(CH_3O)$S	189–190	75	$C_{18}H_{18}N_2O_4S$	60.35	5.06	60.61	5.18
III	3,4	NHC:NC_6H_3(Cl)S	153–154	73	$C_{17}H_{15}ClN_2O_3S$	56.21	4.16	56.54	4.20
IV	2,5	NHC:NCH:CHS	199–200	60	$C_{13}H_{14}N_2O_3S$	56.09	5.07	56.55	5.17
V	2,5	NHC:$NC_6H_3(CH_3O)$S	156–157	60	$C_{18}H_{18}N_2O_4S$	60.35	5.06	59.99	5.01
VI	2,5	NHC:NC_6H_3(Cl)S	168–170	58	$C_{17}H_{15}ClN_2O_3S$	56.21	4.16	56.44	4.27

TABLE II

N-SUBSTITUTED DIMETHOXYPHENYLETHYLAMINES AND THEIR PICRATES

$(CH_3O)_2C_6H_4CH_2CH_2R$

Compd.	$(CH_3O)_2$ position	R	M.p., °C.	Yield, %	Formula	% calcd. C	% calcd. H	% found C	% found H	Picrate m.p., °C.
I	3,4	NHC:NCH:CHS	106–107[a]	35	$C_{13}H_{16}N_2O_2S$	59.09	6.06	58.76	6.23	177–178
II	3,4	NHC:$NC_6H_3(CH_3O)$S	107–108[a]	20	$C_{18}H_{20}N_2O_3S$	62.79	5.81	62.51	5.79	189–190
III	3,4	NHC:NC_6H_3(Cl)S	180–180.5[b]	27	$C_{17}H_{17}ClN_2O_2S$	58.53	4.88	58.61	4.67	197–198
IV	2,5	NHC:NCH:CHS	99–100[a]	35	$C_{13}H_{16}N_2O_2S$	59.09	6.06	59.11	6.13	182–184
V	2,5	NHC:$NC_6H_3(CH_3O)$S	166–167[a]	21	$C_{18}H_{20}N_2O_3S$	62.79	5.81	62.51	5.89	204–205
VI	2,5	NHC:NC_6H_3(Cl)S	171–172.5[b]	50	$C_{17}H_{17}ClN_2O_2S$	58.53	4.88	48.39	4.75	235–236

[a] Crystallized from water. [b] Crystallized from aqueous methanol.

Book Reviews

Drugs of Choice 1964-1965. Edited by W. MODELL with 47 Contributors. C. V. Mosby Co., St. Louis, Mo. 1964. xli + 1018 pp. 18 × 25 cm. $16.75.

The fourth revision of this guide to medicinal therapy, like its predecessors, establishes its worth to the reader on the basis of broad coverage, up-to-date information, authoritative opinion, and a well-organized format.

On the first count, the 1964–1965 revision fares well indeed, with a total of 41 chapters by 47 authors, ranging in size from the short chapter, "The Choice of Stimulants to the Medulla," to Modell's chapter, "Drugs for Diseases of the Heart." The introductory chapters on principles of choice, applications of clinical pharmacology, physical and clinical considerations, and adverse drug reactions are full of wisdom as well as information. The last six chapters cover drugs used in the various specialties and in the treatment of poisoning, topics which could not well be fitted into other pigeon holes.

Perhaps "1964–1965" in the title is ambiguous; a book published in January 1964 can only contain knowledge derived up through 1963 at the latest. Even after this short interval, it is hard to remember how much each author could have known and written on his own topic at that time. The chapters on antimicrobials seem quite up to the minute, for example, while the oral contraceptives are described and dismissed in half a page, without naming or comparing any of the preparations then available. Similar examples of either tendency can be found in other chapters; on balance, the book succeeds much more often than it fails.

What has been difficult for many authors is to give a clear yet concise idea of the subvarieties of clinical disease, and, thus, how best to choose the proper drugs for each. Perhaps most of them would conclude that the physician had best learn this elsewhere before attempting to use this book. The chapter on antidiabetic agents is short, extremely general, and lacks any discussion of how one evaluates results of treatment and control of diabetes in general. The next author, in the chapter on endocrine dysfunction, succumbs to the temptation to write a textbook of endocrinology, but does a much better job of adapting the treatment of the patient to the problems he presents.

Each chapter is headed by a short table of contents which usually includes an introduction, discussion of the clinical and pharmacological considerations involved, describes the several drugs in use, discusses a rational plan for therapy, and ends with a prospective analysis of how newer or yet undeveloped drugs might be even more effective. Selected references, apropos and up to date, follow each chapter. There is a Drug Index (on green paper) giving a capsule listing of all commercial drugs worthy of note and a very good general index of the book itself.

This is a well-organized and useful comparison of drugs available in the treatment of human disease. No book can tell a specific physician what his specific patient needs for a specific complaint, but this one is a good point of departure on the road to self-education.

UNIVERSITY OF VIRGINIA HOSPITAL
CHARLOTTESVILLE, VIRGINIA
JOHN A. OWEN, JR.

The National Formulary, Twelfth Edition. Prepared by THE COMMITTEE ON NATIONAL FORMULARY under the supervision of the Council, by authority of the American Pharmaceutical Association. Published by the American Pharmaceutical Association, Washington, D. C. 1965. Distributed by Mack Publishing Co., Easton, Pa. xliv + 618 pp. 15 × 23 cm. $10.00

This new edition becomes official on September 1, 1965, and represents a rather drastically revised book in comparison with the last edition. Extent of use has been eliminated as a criterion for selection and monograph admission is based solely on therapeutic value. Monographs are given for 783 drugs, 248 of which are new to this edition, while 280 drugs from the eleventh edition