Boos and associates for microanalytical data, to Messrs. A. B. White and R. W. Walker for phase solubility analysis and infrared spectra, respectively, and to Drs. C. C. Porter and J. J. Wittick for pharmacological testing and optical rotatory measurements, respectively.

New Compounds

Some Substituted γ,γ-Pentamethyleneparaconamides

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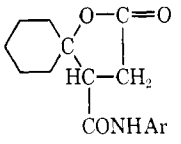
Received October 27, 1970

In connection with our interest in pharmacological properties of paraconamide derivatives, we have synthesized some derivatives of γ,γ-pentamethyleneparaconamide. However, none of the compounds described here (Table I) was active when screened for insecticide, fungicide, and herbicide activity. The methods of preparation are adaptations of known procedures.

TABLE I

N-ARYLPARACONAMIDE



No.	Ar	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
1	C_6H_5	195–197	MeOH–H_2O	87.6	$C_{16}H_{19}NO_3$
2	2-ClC_6H_4	118–120	EtOH–H_2O	79.6	$C_{16}H_{18}ClNO_3$
3	4-ClC_6H_4	207–210	MeOH	74.5	$C_{16}H_{18}ClNO_3$
4	α-$C_{10}H_7$	210–211	MeOH	92.9	$C_{20}H_{21}NO_3$
5	β-$C_{10}H_7$	175–176	EtOH	91.6	$C_{20}H_{21}NO_3$

[a] All compds were analyzed for C, H, N.

Experimental Section[1]

γ,γ-Pentamethyleneparaconyl Chloride.—A mixture of 9.9 g (0.05 mole) of γ,γ-pentamethyleneparaconic acid[2] and 10 ml of $SOCl_2$ was refluxed for 6 hr. Excess $SOCl_2$ was removed under diminished pressure, then PhH was added and evapd to dryness. Recrystn of the residue from hexane gave 10.1 g (93.5%) of product, mp 86–87°. *Anal.* ($C_{10}H_{13}ClO_3$) C, H.

General Procedure for Compounds Listed in Table I.—To a soln of the appropriate amine in 10–40 ml of PhH was added a soln of 0.05 mole of acid chloride in 90 ml of PhH at room temp and stirred for an additional hr. The sepd cryst were collected, washed with H_2O, and recrystd to give the pure paraconamides listed in Table I.

(1) All melting points are uncorrected. Microanalyses were performed by Miss Teruko Nisi. The analytical results obtained for the indicated elements are within ±0.3% of the theoretical values.

(2) W. S. Johnson, C. E. Davis, R. H. Hunt, and G. Stork, *J. Amer. Chem. Soc.*, **70**, 3021 (1948).

Synthesis of 2,3,6-Trimethoxy-β-phenethylamine

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Received September 21, 1970

In a recent paper, Matsuhiro and Furst[1] have questioned the identity of 2,3,6-trimethoxy-β-phenethylamine, which was first reported by Merchant and Mountwalla[2] and later by us.[3] The present paper concerns an unequivocal synthesis of this amine which had not previously been reported by us in our investigation of the deamination of polymethoxy-β-phenethylamines by liver monamine oxidase.[3,4]

Experimental Section

2,3,6-Trimethoxyphenylacetonitrile.—A slurry of 100 g (0.47 mole) of 2,3,6-trimethoxybenzoic acid, mp 148–149° (reported,[5] 148–149°), obtained in 61% yield from 1,2,4-trimethoxybenzene by the procedure of Gilman and Thirtle,[5] in 1 l. of dry C_6H_6 was added gradually to a stirred mixt of 38 g (1 mole) of LAH in 1 l. of anhyd Et_2O. The mixt was stirred and heated under reflux for 4 hr, cooled, and decompd with H_2O and dil H_2SO_4. The Et_2O–C_6H_6 layer was sepd, washed with H_2O, dil Na_2CO_3, and H_2O, dried ($MgSO_4$), and filtered. The filtrate was treated with 5 ml of pyridine and 75 ml of $SOCl_2$ was added slowly. The mixt was stirred at room temp for 2 hr and poured into ice–H_2O; the org layer was sepd, washed (H_2O, dil Na_2CO_3, H_2O), dried ($MgSO_4$), and filtered and the solvents were evapd. The residual oily crude chloride was dissolved in 700 ml of Me_2CO and stirred for 28 hr with a soln of KCN in 300 ml of H_2O. The Me_2CO was evapd, and the residue was extd with Et_2O; this ext was washed (H_2O) and dried ($MgSO_4$), the Et_2O was evapd, and the residue distd; bp 128–133° (0.25 mm); yield, 24 g (25%). *Anal.* ($C_{11}H_{13}NO_3$) C, H, N.

2,3,6-Trimethoxy-β-phenethylamine.—A soln of 16 g (0.077 mole) of 2,3,6-trimethoxyphenylacetonitrile in 60 ml of MeOH contg 8.3 g of NH_3 and 10 ml of Raney Ni catalyst slurry were placed in a 300-ml stirring autoclave, which was sealed and pressured to 105 kg/cm² with H_2. The mixt was stirred and heated at 125° for 2 hr and filtered, the MeOH was evapd, and the residue was distd; bp 110–115° (0.4 mm); yield, 13.9 g (86%). A soln of the free base in Et_2O treated with dry HCl gave the HCl salt, mp 122–123° (reported[1] 134–135°), after one crystn from EtOH–EtOAc–Et_2O. After 2 more recrystns from *i*-PrOH–EtOAc (1:3), the HCl salt melted at 131–132° (Fisher block). The tlc (on silica gel (Chroma-Plate 7 G), developed with 1-Bu-

(1) B. Matsuhiro and A. Furst, *J. Med. Chem.*, **13**, 973 (1970).

(2) J. R. Merchant and A. J. Mountwalla, *J. Org. Chem.*, **23**, 1774 (1958).

(3) L. C. Clark, F. Benington, and R. D. Morin, *J. Med. Chem.*, **8**, 353 (1965).

(4) L. C. Clark, F. Benington, and R. D. Morin, *Alabama J. Med. Sci.*, **1**, 417 (1964).

(5) H. Gilman and J. R. Thirtle, *J. Amer. Chem. Soc.*, **66**, 858 (1944).

OH–AcOH–H_2O, 4:1:1, visualized with ninhydrin spray) gave R_f 0.72 (reported[1] 0.65). *Anal.* ($C_{11}H_{17}NO_3 \cdot HCl$) C, H, N, Cl.

The picrate, prepared from a small sample of the crude amine and picric acid in hot EtOH, melted at 175–177° (Fisher block), unchanged after recrystn from EtOH (reported[1] 176°; reported[2] 166–167°).

Had metallation of 1,2,4-trimethoxybenzene taken place at either positions 5 or 6, the final amines would have had substituent orientations at 2,3,5 or 2,4,5, resp. Both of these amine hydrochlorides have been prepd in this laboratory[3] in accordance with previously reported procedures[2,6] and differ considerably from the properties of 2,3,6-trimethoxy-β-phenethylamine·HCl.

Acknowledgment.—This work was supported by National Institute of Mental Health Grant 5 RO1 MH 11588-04 and by Public Health Service Grant M-1588.

(6) M. P. J. Jansen, *Recl. Trav. Chim. Pays-Bas*, **50**, 291 (1931).

Book Reviews

Topics in Medicinal Chemistry. Edited by JOSEPH L. RABINOWITZ and RALPH M. MYERSON, with 16 contributors. Wiley-Interscience, New York, N.Y. 1970. xi + 427 pp. 15.3 × 23.4 cm. $25.00.

The title of this series can cover a multitude of subjects and approaches, some appropriate to the title, some inappropriate. The editors are not chemists, and their inclination is slanted toward biological and clinical problems. Maybe they should even be excused on this basis for allowing statements such as this to get into print (p 363): "The antihistaminics are compounds with chemical structures similar to that of quinidine, having tertiary N atoms with various side chains." Such gross slips make one wish for differently oriented editors, or a different title for these books. But there are other chapters, written by chemists, which are executed superbly, especially one by H. J. Schaeffer who reviewed his own studies on adenosine deaminase inhibitors just before he changed from academia to industry. Gaining significance are the clinical applications of isoenzymes (J. H. Wilkinson); these subtle enzymatic differences have found uses in the diagnosis of myocardial infarction, megaloblastic anemia, muscular dystrophy, liver and renal dysfunction, and cancers. The multitude of actions of the phenothiazine drugs inevitably points to their involvement at many active sites of many enzymes; S. Gabay and S. R. Harris have surveyed this facet well. Leslie M. Werbel has written very capably on the chemotherapy of schistosomiasis, and an organophosphate anthelmintic, dichlorvos, has been accorded a whole chapter by R. K. Hass. A discussion of gout and hyperuricemia does not quite measure up to other reviews on this subject. The clinical, diagnostic, and pharmacological description of cardiac arrythmias by T. Lawrence is one of the clearest this reviewer has found anywhere, but the discussion of antiarrhytmic drugs lags far behind in quality.

On the whole, this volume is a considerable improvement over the first two of this series, and one will look forward to future issues with more emphasis on chemistry.

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Two Books on Molecular Pharmacology

I. Essentials of Molecular Pharmacology: Background for Drug Design. By ANDREJUS KOROLKOVAS. Wiley-Interscience, New York, N. Y. 1970. xv + 339 pp. 16 × 23.5 cm. $16.50

The principal aim of pharmacology is the understanding of the mode of action of chemicals in biochemical and biological systems. Molecular pharmacology and medicinal chemistry try to answer questions of drug action in chemical and physical terms. The greatest puzzle in experimental studies in molecular pharmacology is the very existence and nature of drug receptors and their topography which must be, in some way, complementary to agonist and antagonist molecules.

Reviews of such studies have been scattered widely as chapters of many texts and symposia volumes. To my knowledge, only one previous book, "Principles of Drug Action" by A. Goldstein, L. Aronow, and S. M. Kalman (1968), has surveyed the whole field, mainly from a pharmacological viewpoint, under one cover. The present book, more compact and terse, approaches the subject from a chemist's point of view, and will therefore be particularly welcomed by medicinal chemists. The whole field of drug action is covered thoroughly, in good English, up-to-date, and critically. Among the chapter headings are influence of physicochemical, stereochemical, and structurally specific properties; drug receptors (their nature, topography, and structure); bonding interactions between drugs and receptors; and theories and mechanisms of drug action. Many of the more widely studied receptors are discussed in great detail. There are numerous illustrations, unfortunately often placed on remote pages by the printer so that one has to thumb one's way from text to figures. But as a readable, carefully prepared, and well-documented book, this volume will provide a landmark in the description of the background to drug research that no medicinal chemist can afford to miss.

II. Chemical Mechanisms of Drug Action. By CURT C. PORTER. Charles C Thomas, Springfield, Illinois. xi + 165 pp. 23.5 × 16 cm. $11.0

This small book seeks to single out a few facets of the mechanisms of drug action based on alterations of membrane permeability, inhibition of protein and NA synthesis, and the effects of cyclic AMP and metal ions. Cholinergic and adrenergic mechanisms are discussed at some length. The author apologizes for restrictions imposed on the material but wanted to set forth fundamentals only. Everyone admits the obscurity of receptors and receptor mechanisms but the claim on p 4 that enzymes are not homogeneous entities takes us back to concepts that were in fashion quite a few years ago. This reviewer found many pertinent data in this book, but their arrangement and connection were confusing more than once. It is almost as if an adequate literature search had not been followed by a period of gestation and critical appraisal. Since other much better books on the subject are available (see above), the professional medicinal chemist and pharmacologist should be advised to consult them first.

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