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PHARMACEUTICAL CHEMISTRY of ADRENERGIC and CHOLINERGIC DRUGS

György Szász

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Pharmaceutical Chemistry of Adrenergic and Cholinergic Drugs

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PREFACE

The term pharmaceutical chemistry is not treated uniformly either in the literature or as far as the programs of higher education are concerned. Works under the title pharmaceutical chemistry in most cases cover problems of chemical structure — biological activity relationships, therapeutical applications, and the methods of synthesis. These are obviously the important features of pharmaceutical (medicinal) chemistry.

However, one can rarely encounter a treatment of the subject where pharmaceutical chemistry is introduced in a complex manner, i.e., all the pharmaceutically important properties are interpreted in the light of the chemical structure.

It is evident here that the term *pharmaceutically important properties* needs to be defined. These are the group of properties which are involved.

1. In the biological (therapeutic) activity; also the metabolic behavior
2. In the drug formulation, i.e., the preparation of dosage forms; also in the stability and degradation properties
3. In the physical and chemical methods of analysis; also quality control and analysis for diagnostic, toxicologic, etc. purposes

In other words, pharmaceutical chemistry is a complex science covering the chemical knowledge needed by all experts working with drug substances.

The above-mentioned general treatment of the structure-property relationships could help to make those employed in the various branches of the pharmaceutical profession, i.e., drug formulation, dispensing pharmacy, information service for patients and physicians, drug quality control, competent experts in a wide range of work relating to drugs.

This book is to be considered an attempt to introduce the application of the above concepts.

THE AUTHOR

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Dr. Szász was born in 1927 and received his pharmaceutical training at the Semmelweis Medical University between 1947 and 1952. In 1953 he joined the staff of the Department of Pharmaceutical Chemistry. He defended his thesis on the field of pharmaceutical analysis of amines and alkaloids and obtained his C.Sc. (1968) and D.Sc. (1980) scientific degrees. He is a member of the Committee of the Hungarian Academy of Sciences on Analytical Chemistry.

His major research interest is the structure-property relationship study among nitrogen-bridged compounds.

Dr. Szász published over 120 papers, several of them in western periodicals. He is also the Editor of the *Textbook of Pharmaceutical Chemistry* (Volumes 1 and 2, 3rd ed., Medicina, Budapest, 1983).

TABLE OF CONTENTS

Chapter 1

ADRENERGIC AGONISTS

I. BIOGENIC CATECHOLAMINES

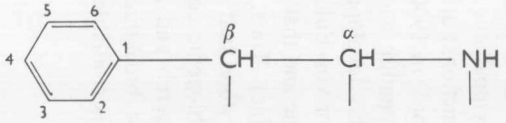
A. History

The hypertensive effect of an intravenous injection of a suprarenal gland extract was first described in 1895 by Oliver and Schäfer.[1] The proof that this action is due to the suprarenal medulla and not the whole suprarenal gland was provided by Langley[2] who demonstrated that the effect of the medulla extract was equivalent to that of electric stimulation of the sympathetic nerve. The synthetic adrenaline exhibits the same effect.[3] The name adrenaline was given by Takamine,[4] while earlier the same substance was named by Abel[5] as epinephrine. Takamine isolated this compound in pure form from a suprarenal extract and established its molecular formula in 1901. The synthesis of adrenaline (epinephrine) was achieved by Stolz.[6] Its correct structural formula was published simultaneously by several scientists.[7,8] Cushny[9] recognized that the effect of synthetic epinephrine is only 50% of that of the natural substance. This drew attention to the stereochemistry of epinephrine and first demonstrated the importance of stereoselectivity in the interactions between drug molecules and receptors. In 1909, Flächer[10] succeeded in resolving the racemate components of synthetic epinephrine in the form of bitartrate salts. After the medium had been made alkaline with ammonia, the bases proved to be equipotent with natural epinephrine. These successes in chemical drug research encouraged further investigations in the field of physiology and new impetus was provided in the results of Loewy.[11] One of the most exciting principles leading to further development was undoubtedly the idea that sympathetic neurotransmission takes place chemically (i.e., by the mediation of chemical reactions) at the nerve endings (1921). The neurotransmitter was named sympathin by Cannon[12] in 1930. Due to the lack of versatile and sufficiently sensitive analytical methods, sympathin was believed to be a homogeneous single compound, for more than 10 years. The development in analytical methods and particularly chromatography, made it possible for von Euler[13,14] to show that sympathin is actually a mixture of adrenaline and noradrenaline and that the main factor in sympathetic neurotransmission is noradrenaline (norepinephrine). Thus, the physiological role and importance of this substance became properly understood half a century after its synthesis. That isopropyladrenaline (isoproterenol) is also a biogenic compound was recognized and experimentally verified only in 1957. The research and results relating to epinephrine and its congeners may be considered the major breakthrough in molecular biochemistry and pharmacology. The historical background is available in a much more detailed form in several monographs.[15-18]

B. Biosynthesis

The center of catecholamine biosynthesis is the medulla of the suprarenal gland. The pair of suprarenal glands is located at the height of thoracic vertebrae 11 and 12. They are orange organs, enclosed in the capsule of the kidneys and are pressed mildly to the upper pole of the kidney.[19] The weight of each of the human suprarenal glands is about 11 to 18 g. The suprarenal gland consists of two portions. The outer (yellow) is the cortex, which occupies the greater part of the organ, and the inner part (dark-red or brown) is the medulla. The catecholamines are concentrated in the medullary part of the glands (see Figure 1) in an amount of 0.5 to 0.7 mg/g, and comprise 90% epinephrine and 10% norepinephrine; isoproterenol is also produced, but only in a quantity of 0.1% (relative). The main particles within the medulla are the large chromaffine cells, arranged in a network. Epinephrine and

Table 1
ADRENERGIC AGONIST (SYMPATHOMIMETIC) AGENTS

Generic name	Phenylalkylamine type				Proprietary name Synonyms	Therapeutic use	Doses
							
Dihydroxyphenylalkylamines							
Dopamine	3-OH,4-OH	H	H	H	Intropin	α-Receptor stimulator, vasopressor, important in the treatment of some types of shock and of chronic refractory congestive heart failure	I.v. 1-5 μg/kg/min; increased gradually to 20-50 μg/kg/min
Norepinephrine bitartrate (USP)	3-OH,4-OH	OH	H	H	Arterenol, Noradrenalin, Levophedbitartrate, Sympathin	α-Receptor stimulator; vasopressor with little action on β_2-receptor; of therapeutic value in hypotension due to shock	I.v. 0.5-1 mg (strong diluted) with 0.2-0.5 μg/kg/min velocity; checking blood pressure!
Epinephrine bitartrate (USP) Epinephrine (USP)	3-OH,4-OH	OH	H	CH_3	Adrenalin, Suprarenin, Tonogen, Suprel, Vasotonin	α- and β-receptor stimulator with main actions on blood vessels, heart and bronchial muscle; used in collapse, in shock, in allergic reactives in nasal decongestions, bronchial asthma and as a topical hemostatic (nasal, stomach, uterus bleeding)	I.m. s.c. 0.1-0.5 mg, 3 × I.v. 0.2 mg, 3 × (diluted and very slow!) Orally 1-2 mg, 3 ×
Nordefrin	3-OH,4-OH	OH	CH_3	H	Cobefrin, Corbadrin, Isoadrenalin, Levonordefrin, Vasofren, Corbazil	α-Receptor stimulator, local vasoconstrictor in local anesthesia	
Epinine	3-OH,4-OH	H	H	CH_3	Dezoxyepinephrin		
Ethylnorepinephrine hydrochloride (USP)	3-OH,4-OH	OH	CH_2-CH_3	H	Bronkephrine, Butanefrine, Ethylnoradrenaline	Adrenergic agonist, bronchodilator, used in the treatment of asthma	I.m. s.c. 1-2 mg 3 × daily

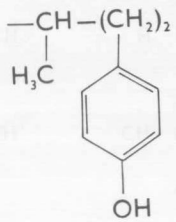
Isoproterenol hydrochloride (USP)	3-OH,4-OH	OH	H	$CH(CH_3)_2$	Isoprenalin	β-Receptor stimulator; no action on α-receptors; relaxes the bronchial (β_2-receptor) and gastrointestinal smooth muscle; used as a cardiac stimulant too	I.v. 10-60 mg (repeatable) Oral inhalation 80-160 mg
Isoetharine hydrochloride	3-OH,4-OH	OH	C_2H_5	$CH(CH_3)_2$	Asthmalitan Neoisuprel Dilabron	β_2-Agonist for the treatment of bronchospasm with fewer cardiac side effects than isoproterenol	
Dobutamine	3-OH,4-OH	H	H		Dobutrex	Selective β_1-agonist acting directly on the receptors; cardiotonic effect based on inotropic activity	2.5-10 μg/kg/min I.v. infusion
Metaproterenol	3-OH,5-OH	OH	H	$-CH(CH_3)_2$	Orciprenalin Alupent Metaprel	β_2-Adrenergic agonist; resistant to COMT therefore effective orally (different from isoproterenol); used in treatment of bronchial asthma	Simple dose 0.65 mg for inhalation Orally 20 mg 3-4 × daily
Terbutaline sulfate (USP)	3-OH,5-OH	OH	H	$C(CH_3)_3$	Bricanyl Brethine	Selective β_2-stimulator; like metaproterenol, is resistant to COMT; used in bronchial asthma	S.c. 0.25 mg repeated max 1 × within 4 hr Orally 5 mg 3 × daily
Monohydroxyphenylalkylamines							
Phenylephrine hydrochloride (USP)	3-OH		OH	H	CH_3	Isonefrine Mesaton Meta-Synephrine Neo-Synephrine m-Sympatol	α- Receptor agonist; causes a rise in blood pressure; is a nasal decongestant and a pressor agent; also used in paroxysmal tachycardia and in ophthalmology as a mydriatic drug	I.m., S.c. 1-10 mg I.v. 100-500 μg

Table 1 (continued)
ADRENERGIC AGONIST (SYMPATHOMIMETIC) AGENTS

Generic name	Phenylalkylamine type				Proprietary name Synonyms	Therapeutic use	Doses
Metaraminol bitartrate (USP)	3-OH	OH	CH_3	H	Aminocardiol Isophenylephrine Pressorol Aramine	α-Receptor stimulator used mainly as a pressor agent against hypotension	I.m. 2-10 mg
Hydroxyamphetamine hydrochloride (USP)	4-OH	H	CH_3	H	Paredrine, Methyltyramin, Norpholedrin, Oxamphetamine	α-Receptor agonist, nasal decongestant and mydriatic	
Salbutamol	4-OH, 5-CH_2OH	OH	H	$C(CH_3)_3$	Albuterol Vertilan	β_2-Receptor agonist, bronchodilator and myorelaxant	Orally 2-4 mg 3-4 × daily
Methoxyphenylalkylamines							
Methoxamine hydrochloride (USP)	2-OCH_3, 4-OCH_3	OH	CH_3	H	Methoxamedrine hydrochloride Mexan, Vasoxine	α-Receptor stimulator; has no stimulant action on the heart; used mainly as pressor agent in hypotensive states	I.m. 10-20 mg daily
Methoxyphenamine hydrochloride (USP)	2-OCH_3	H	CH_3	CH_3	Euspirol Ortoxin	β_2-Receptor agonist, bronchodilator; used mainly in mild cases of asthma	Orally 50-100 mg every 3-4 hr if necessary
Phenylalkylamines							
Amphetamine sulfate (USP)		H	CH_3	H	Benzedrine Aktedron	Although it has peripheral α and β action, its powerful CNS stimulating action is used in therapy	
Methamphetamine hydrochloride (USP)		H	CH_3	CH_3	Dezoxin Pervitin Oxydrin Desoxyephedrin	Similar to amphetamine it has a CNS action, but in larger doses produces cardiac stimulation; mainly used for its central effect	
Mephentermine sulfate (USP)		H	$C(CH_3)_2$	CH_3	Wyamine Angiofen	It is a vasopressor also used topically as nasal decongestant	I.m. 10-30 mg Orally 12.5-25 mg repeated max 1 × daily

Ephedrine hydrochloride (USP)	OH CH$_3$ [R-(R^x,S^x)]	CH$_3$	Ephedrol Fedrin	It has an α and a β-receptor stimulating effect; applicable orally and has a rather long duration action; CNS effects of ephedrine much weaker than those of amphetamine; main clinical applications as bronchodilator, nasal decongestant and mydriatic	Orally 25-50 mg every 2-3 hr
Pseudoephedrine hydrochloride (USP)	OH CH$_3$ [S-(R^x,R^x)]	CH$_3$	Dofedrin Isofedrin Ro-Fedrin	Like ephedrine, is a bronchodilator but is much less active in increasing blood pressure; also used as a decongestant	
Phenylpropanolamine hydrochloride (USP)	OH CH$_3$	H	Propadrine hydrochloride Midriatin Norephedrin	Its pharmacological effect is like that of ephedrine and it is approximately equal in potency except that it causes less CNS stimulation; mainly used as a nasal decongestant	

Imidazoline Derivatives

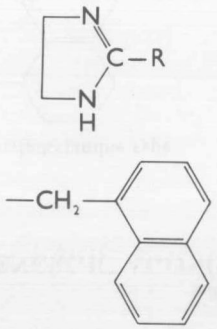
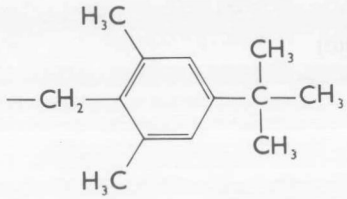
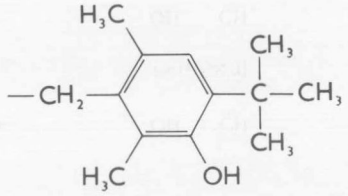
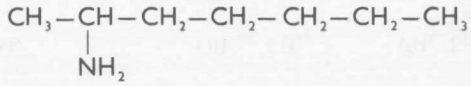
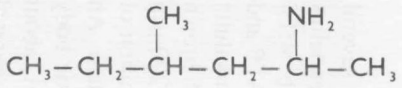
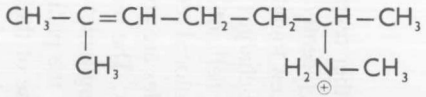
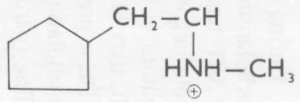
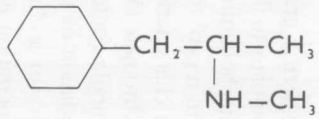
Generic name	Chemical structure	Proprietary name Synonyms	Therapeutic use	Doses
Naphasoline hydrochloride (USP)		Naphazolin Pentazoline	Sympathomimetic; vasoconstrictor, similar to ephedrine in action; used as a nasal decongestant	Intranasal in 0.1% soln

Table 1 (continued)
ADRENERGIC AGONIST (SYMPATHOMIMETIC) AGENTS

Generic name	Phenylalkylamine type	Proprietary name Synonyms	Therapeutic use	Doses
Tetrahydrozoline hydrochloride (USP)		Tyzine hydrochloride Visine, Nasin	Sympathomimetic, similar to naphasoline	
Xylomethazoline hydrochloride		Novorin, Otrivin	Sympathomimetic, similar to naphasoline	
Oxymethazoline hydrochloride		Afrin hydrochloride Nasofarma	Sympathomimetic, similar to naphasoline	
	Aliphatic Amines			
Tuaminoheptane (USP)		Heptilamine sulfate Rhinitryl Tonadrin	Nasal decongestant, the duration of its effect is greater than that of ephedrine	Intranasal in 1% soln

Methylhexamine		Forthane		
Isometheptane hydrochloride		Octin hydrochloride	Although it has moderate general sympathomimetic activity it is mainly used as an antispasmodic and a vasoconstrictor	I.m. 50-100 mg Orally 75-100 mg 4 × daily
Cyclopentamine hydrochloride		Clopane hydrochloride Cyclosan	Its effects are similar to those of ephedrine, but it produces only slight cerebral excitation; orally it is more effective than ephedrine; mainly used as a nasal decongestant	2 drops, 3-4 × daily (1% soln)
Propylhexedrine		Benzedrex Benhaler	Sympathomimetic; has vasoconstrictive and a decongestant effect on the nasal membranes and produces scarcely any effect on the nervous system	

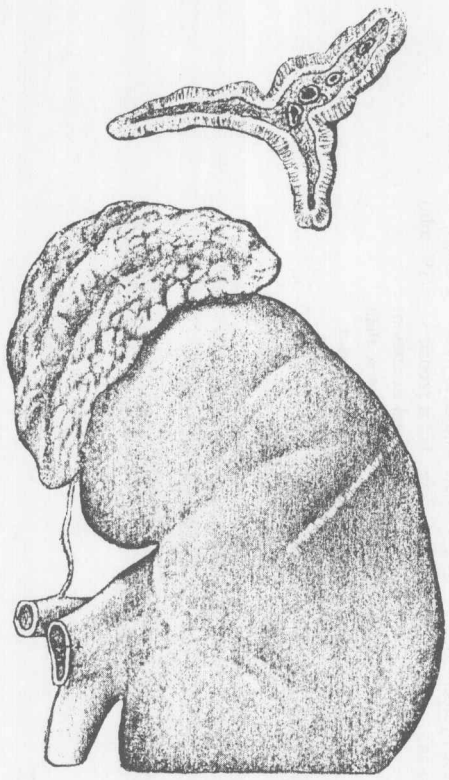


FIGURE 1. The left kidney with the suprarenal gland. Cross section of the suprarenal gland.

norepinephrine are found stored in these specific granules. During further research several other components have been shown to accompany to the catecholamines; recently enkephalins were identified.[20,21] The molar ratio of catecholamine and ATP has been found to be 4:1[22] and 4.5:1,[23] which is nearly equivalent with regard to the four negative charges of ATP and the one of catecholamine molecules. One characteristic feature of the cells of the medulla is that after treatment with a solution of a chromate (VI) salt, they are colored reddish brown due to the reaction of their chromaffine granule content.[24] These granules are about 200 μm in size. This reaction is based on the oxidation of the catecholamines. The recognition of this chromium affinity led to the discovery of a chromaffine (paraganglionic) system. An interesting fact which awaits proper interpretation is that in neonates, the para-aortic body (a chromaffine group of cells at the crosspoint of the aorta and the base of the heart, about 1 cm in length) has a relatively high epinephrine content, many times that of the suprarenal glands.[25] Thanks to the rapid development in modern chromatographic and other separatory methods, all of the enzymes involved in the biosynthesis of catecholamines have been discovered and the biosynthetic pathways have also been elucidated. The key substance in the biosynthesis of catecholamines is L-tyrosine, (2) which is formed from the corresponding essential amino acid, L-phenylalanine (1) on the action of phenylalanine hydroxylase. This enzyme is located mostly in the liver and requires dihydrobiopterine (1a) as cofactor.[26] L-tyrosine is oxidized further to L-dihydroxyphenylalanine (3) by tyrosine hydroxylase (TH). The tissue distribution of this enzyme coincides with that of the catecholamines (adrenal medulla, brain, heart, etc.), indicating that the physiological role of this enzyme is mainly its contribution to the biosynthesis of catecholamines; the reaction involving the enzyme is found to be the rate-limiting factor.[27] This enzyme needs tetrahydropteridine (2a) as cofactor.

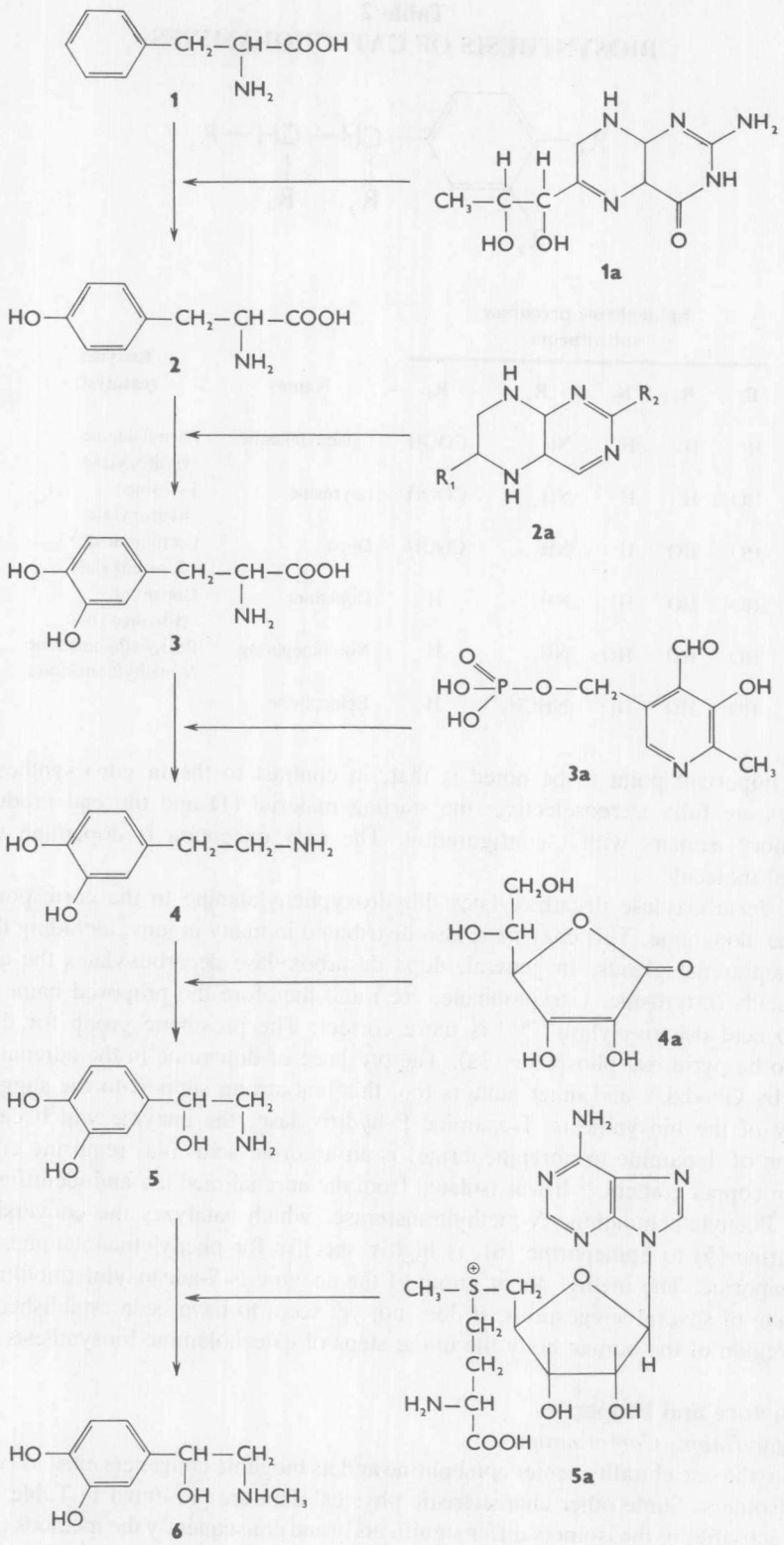


FIGURE 2. Biosynthesis of catecholamines.