New Compounds

Peptides with Terminal Tyrosyl and Phenylalanyl Groups

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Since tyrosine and phenylalanine are two of the most important components of the vasopressor octapeptide, angiotensin II,[1] three tripeptides and a pentapeptide (**5a–5d**, Table II) containing both N-terminal L-tyrosyl and C-terminal L-phenylalanyl groups were prepared for general cardiovascular evaluation. To link the end groups, 4-aminobutyric, *m*-aminobenzoic, and 1-aminocyclopentane-1-carboxylic acids and triglycine were used.

Peptides **5a–5d** were administered iv to anesthetized dogs. Only the cyclopentane derivative **5c**, which caused a marked, transient decrease in blood pressure at 1 mg/kg, displayed activity. This compound at concentrations up to 10 μg/ml did not inhibit angiotensin-induced contractions of the isolated rat uterus.

Experimental Section

Melting points, taken with a Thomas-Hoover capillary apparatus, are uncorrected. Analyses were performed in our laboratories and by Drs. G. Weiler and F. B. Strauss, Oxford, England. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analytical tlc was carried out on silica gel G (Brinkman) with *tert*-BuOCl–KI spray for the intermediate compds and ninhydrin for the final peptides.

TABLE I
INTERMEDIATE PEPTIDES OF L-PHENYLALANINE METHYL ESTER

$C_6H_5CH_2CHCO_2CH_3$
|
RNH-Z-CONH

Compd	R	Z	Mp, °C	Crystn solvent[a]	$[\alpha]^{25}D$, deg[b]	Yield, %	Formula[c]
1a	Cbz[d]	$(CH_2)_3$	101–103	A–B	−10.8 (1)	90	$C_{22}H_{26}N_2O_5$
1b	Cbz	C_6H_4[e]	154–156	A–B	−55.9 (1)	75	$C_{25}H_{24}N_2O_5$
1c	Cbz	C_5H_8[f]	141–143	A–B	−5.8 (1)	77	$C_{24}H_{28}N_2O_5$
1d	Cbz	$CH_2CONHCH_2CONHCH_2$	98–103	A–B	+7.2 (2)	61	$C_{24}H_{28}N_4O_7$
2a	H·HOAc	$(CH_2)_3$	100–102	C–D	+2.4 (3)	87	$C_{14}H_{20}N_2O_3 \cdot C_2H_4O_2$
2b	H	C_6H_4[e]	122–124	A–B	−77.1 (1)	60	$C_{17}H_{18}N_2O_3$
2c	H·HBr	C_5H_8[f]	181–183	D–E	−31.1 (4)	89	$C_{16}H_{22}N_2O_3 \cdot HBr$
2d	H·HOAc	$CH_2CONHCH_2CONHCH_2$	146–147	D–F	+4.2 (4)	78	$C_{16}H_{22}N_4O_5 \cdot C_2H_4O_2$

[a] A = $CHCl_3$, B = Skellysolve B, C = EtOAc, D = Et_2O, E = EtOH, F = MeOH. [b] (1) *c* 2, DMF; (2) *c* 5, DMF; (3) *c* 2, MeOH; (4) *c* 2, H_2O. [c] All compds were analyzed for C, H, N. [d] Cbz = carbobenzoxy. [e] Meta-substituted. [f] 1,1-Disubstituted.

TABLE II
PEPTIDES CONTAINING L-TYROSINE AND L-PHENYLALANINE

$4\text{-}ROC_6H_4CH_2CHCONH\text{-}Z\text{-}CONHCHCH_2C_6H_5$
| |
NHR' CO_2R''

Compd	R	R′	R″	Z	Mp, °C	Crystn solvent[a]	$[\alpha]^{25}D$, deg[b]	Yield, %	Formula[c]
3a	Cbz[d]	Cbz	CH_3	$(CH_2)_3$	174–177	A–B	−18.5 (1)	73	$C_{39}H_{41}N_3O_9$
3b	Cbz	Cbz	CH_3	C_6H_4[f]	118–122	C–D	−15.4 (1)	27	$C_{42}H_{39}N_3O_9$
3c	Cbz	Cbz	CH_3	C_5H_8[g]	165–168	B–E	−12.4 (1)	13	$C_{41}H_{43}N_3O_9$
3d	Cbz	Cbz	CH_3	$CH_2CONHCH_2CONHCH_2$	125–130[e]	C–F–D	−10.9 (1)	57	$C_{41}H_{43}N_5O_{11}$
4a	H	Cbz	H	$(CH_2)_3$	191–193	B–F	−15.4 (1)	89	$C_{30}H_{33}N_3O_7$
4b	H	Cbz	H·H_2O	C_6H_4[f]	78–85[e]	D–G	+3.7 (2)	83	$C_{33}H_{31}N_3O_7 \cdot H_2O$
4c	H	Cbz	H·H_2O	C_5H_8[g]	115–118	B–F	+7.6 (2)	86	$C_{32}H_{35}N_3O_7 \cdot H_2O$
4d	H	Cbz	H·3H_2O	$CH_2CONHCH_2CONHCH_2$	75–81[e]	H–F–D	+11.9 (2)	47	$C_{32}H_{35}N_5O_9 \cdot 3H_2O$
5a	H	H·HOAc	H	$(CH_2)_3$	134–141[e]	F–I	+35.1 (2)	79	$C_{22}H_{27}N_3O_5 \cdot C_2H_4O_2$
5b	H	H·HOAc	H	C_6H_4[f]	175–180[e]	F–I	+88.4 (2)	84	$C_{25}H_{25}N_3O_5 \cdot C_2H_4O_2$
5c	H	H·HOAc	H·H_2O	C_5H_8[g]	214–217	B–F	+25.8 (3)	88	$C_{24}H_{29}N_3O_5 \cdot C_2H_4O_2 \cdot H_2O$
5d	H	H·HOAc	H	$CH_2CONHCH_2CONHCH_2$	130–180[e]	F–I	+34.4 (2)	85	$C_{24}H_{29}N_5O_7 \cdot C_2H_4O_2$

[a] A = acetone, B = H_2O, C = $CHCl_3$, D = Skellysolve B, E = EtOH, F = MeOH, G = EtOAc, H = dioxane, I = Et_2O. [b] (1) *c* 2, DMF; (2) *c* 2, MeOH; (3) *c* 2, HOAc. [c] All compds were analyzed for C, H, N. [d] Cbz = carbobenzoxy. [e] As a foam. [f] Meta-substituted. [g] 1,1-Disubstituted.

Typical procedures are given for the preparation of the intermediate compds in Table I and the final peptides in Table II.

Carbobenzoxy-4-aminobutyryl-L-phenylalanine Methyl Ester (1a).—A soln of carbobenzoxy-4-aminobutyric acid[2] (11.9 g, 0.05 mole) and Et_3N (5 g, 0.05 mole) in 100 ml of DMF at −15° was treated with 6.8 g (0.05 mole) of isobutyl chloroformate, and the mixt was stirred for 15 min at near −15°. A precooled soln of L-PheOMe from 10.8 g (0.05 mole) of the ester·HCl and an equiv amt of Et_3N in 50 ml of DMF was added in one portion, and the mixt was stirred at 5° for 3 days. H_2O (500 ml) was

(1) E. Schröder and K. Lübke, *Peptides*, **2**, 60 (1966).

(2) Except for carbobenzoxy-*m*-aminobenzoic acid, mp 219–220°, these were known compds.

added; the mixt was extd with 3 portions of EtOAc, which were combined, washed with 2 *N* HCl, H_2O, satd $NaHCO_3$ soln (twice), and again with H_2O. Evapn of the dried (Na_2SO_4) solvent afforded a colorless gum which was dissolved in $CHCl_3$ and pptd as a white powder (17.9 g) with Skellysolve B.

4-Aminobutyryl-L-phenylalanine Methyl Ester Acetate (2a).—A soln of **1a** (15.2 g, 0.038 mole) in MeOH (150 ml)–HOAc (100 ml) was hydrogenated[3] at 1.5 kg/cm² and 25° using 10% Pd/C as catalyst. Filtration and evapn of the solvent afforded an oil which was covered with Et_2O and refrigerated. Recrystn of the resulting semisolid provided 10.75 g of white flakes.

Dicarbobenzoxy-L-tyrosyl-4-aminobutyryl-L-phenylalanine Methyl Ester (3a).—A soln of **2a** (13 g, 0.04 mole) and 4 g (0.04 mole) of Et_3N in 40 ml of DMF was allowed to react with a soln of the mixed anhydride from 18 g (0.04 mole) of diCbz-L-Tyr, 4 g (0.04 mole) of Et_3N, and 5.5 g (0.04 mole) of isobutyl chloroformate in 150 ml of DMF at −15°. Following the isolation procedure described for **1a** and recrystn, 20.4 g of a white powder was obtained in two crops.

***N*-Carbobenzoxy-L-tyrosyl-4-aminobutyryl-L-phenylalanine (4a).**—A soln of **3a** (4.7 g, 0.0067 mole) and 7.5 ml (0.015 mole) of 2 *N* NaOH in dioxane (50 ml)–MeOH (50 ml) was stirred at 25° for 2 hr.[4] After solvent evapn, the residue was dissolved in H_2O, and the soln was extd with EtOAc (discarded), acidified with 4 *N* HCl, and reextd with EtOAc. Evapn of the dried (Na_2SO_4) solvent and recrystn of the solid residue provided 3.3 g of a white powder.

L-Tyrosyl-4-aminobutyryl-L-phenylalanine Acetate (5a).—A 5.5-g sample (0.01 mole) of **4a** was treated with H_2 in MeOH–HOAc as outlined for **2a**. Two recrystns of the resulting crude product afforded 3.75 g of a white powder.

(3) The carbobenzoxy group of **1c** was removed with HBr in HOAc since hydrogenolysis gave 1,4-diazo-4-benzylspiro[4.5]decane-2,5-dione (62%) as the only identifiable product. This cyclization has been described by P. Tailleur and L. Berlinguet, *Can. J. Chem.*, **40**, 2214 (1962).

(4) For another example of the selective removal, under alkaline conditions, of an *O*-carbobenzoxy group from an *N,O*-dicarbobenzoxytyrosyl peptide see H. Determann, O. Zipp, and T. Wieland, *Justus Liebigs Ann. Chem.*, **651**, 172 (1962).

Book Reviews

An Introduction to Psychopharmacology. Edited by RICHARD H. RECH and KENNETH E. MOORE, with 10 contributors. Raven Press, New York, N.Y. 1971. xii + 353 pp. 16 × 23 cm. $9.75.

There are many symposium volumes available on psychopharmacology, but they presume some knowledge of the field and are supposed to bring one up to date. The present monograph is a textbook in the best sense of the word. The reader is not expected to have a knowledge even of general pharmacology or anatomy. He is introduced to these sciences gingerly and in an orderly fashion, and every chemist whose crowded chemical curriculum precluded courses in biology will be able to follow the text easily. In fact, he will feel at home quickly after the two introductory general chapters since the remaining 7 sections reflect the chemical theoretical background of psychopharmacology, and the decisive role of drugs in the study of normal and abnormal psychopharmacological systems and conditions. The investigation of general and localized metabolism of brain tissues stands and falls with the refinement of methods able to detect infinitesimally small amounts of neurohormones and cofactors. The extent and limitations of these methods are discussed ably. The present interest in agents affecting learning, memory, and retention of conditioned behavior is given broad and authoritative coverage. One of the most valuable chapters describes animal testing and screening procedures in evaluating psychotropic drugs. This chapter alone would justify acquisition of the book by the experimentalist who wishes to refer to a highly practical discussion of such procedures. The practising psychiatrist will find two clinical chapters on the drug treatment of excited and depressed mental states. These sections on the therapy of mental illnesses offer thoughtful descriptions of the background of drug treatment, give virtually all the latest drugs and methods, and critically evaluate the merits and disadvantages of each procedure.

This textbook should become a classic in drawing novices into the field of psychopharmacology, and in consolidating the knowledge of the expert in this fascinating working area.

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Biochemistry, Schizophrenias and Affective Illnesses. Edited by HAROLD E. HIMWICH, with 23 contributors. Williams and Wilkins Co., Baltimore, Md., 1970. xiv + 500 pp. 16 × 23 cm. $18.75.

As pointed out in a preface by Irving H. Page, brain chemistry made its debut in Tudichum's writings in 1884, and today's generation finds it laughable that anyone ever doubted that the brain operated by chemical reactions. However, the first observations to give these beliefs experimental support were not made until the late 1950's, if one discounts the fundamental discoveries of the role and metabolism of norepinephrine, dopamine, serotonin, ACh, and some lesser compounds in neurotransmission 15 years earlier. The explosive growth of brain biochemistry and central neuropharmacology in the last decade has led to the publication of many compendia, of which the present multiauthored volume is one of the latest. The first chapter defines and describes the schizophrenias, setting the stage for two chapters containing arguments for the chemical causation of psychoses. These three chapters transmit a feeling that psychiatrists still need to be convinced of biochemical aberrations as the basis of what they see in the mental ward. Then follows an array of surveys, some of them excellent, on indoleamines, catecholamines, α-2-globulin, electrolytes, steroids, carbohydrates, and amino acids in brain metabolism and in psychoses. A chapter entitled "Psychotomimetic compounds in man and animals" should have been called "The behavior of psychotomimetics in man and animals" since it deals with such behavior. In this chapter, the old and now abandoned adrenochrome and homoveratrylamine hypotheses of psychoses are still discussed, though critically, but Snyder's erroneous comparison of phenethylamines with indoles is given as a truism. The editor could have vetoed the repeated broad introduction to various chapters in which the same description of different types of psychoses is reiterated. But apart from such minor points, this monograph paints a diversified, critical, and readable picture of normal and abnormal brain chemistry and will serve well as a text and reference book in this multidisciplinary area.

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