of the branching Dab residue, a possibility already envisaged by HAUSMANN and CRAIG[2] and also favoured by us on biogenetic considerations[7]. We have now synthesized the substance possessing this revised structure (7α, all L-Dab, Figure 2 [IV]) according to the following scheme.

Removal of the tert. butyloxycarbonyl group in I by trifluoroacetic acid and coupling with the azide of II led to the protected octapeptide. This was transformed into the corresponding hydrazide and condensed with III by means of the azide procedure. After removal of the C- and N-protecting groups the decapeptide was submitted to cyclization and was then reduced and purified in the way previously described[1]. The end product (Figure 2 [IV]) was isolated as pentahydrochloride and carefully compared with the pentahydrochloride of natural polymyxin B_1.

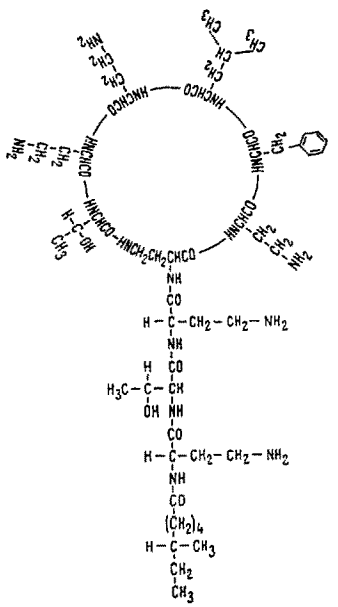


Fig. 2. Polymyxin B_1 (IV).

Both conformed in thin-layer chromatography, amino acid content, $[\alpha]_D^{25}$ and optical rotatory dispersion of the nickel-complex[8] especially sensitive to isomeric structures[1d]. The microbiological activity against *Klebsiella pneumoniae* ATCC 100 131 agreed with that of the natural antibiotic[1d].

The synthetic product could be crystallized as the pentaphosphate[9].

Full details will be given in Helvetica chimica Acta.

Zusammenfassung. Es wird über die Synthese des cyclo-Decapeptides 7α, in welchem alle Dab-Reste die L-Konfiguration aufweisen, berichtet. Dieses erwies sich als identisch mit natürlichem Polymyxin B_1 (Figur 2).

K. VOGLER, R. O. STUDER, P. LANZ, W. LERGIER, and ERIKA BÖHNI

Forschungsabteilung der F. Hoffmann-La Roche & Cie., AG, Basel (Switzerland), June 1, 1964.

[7] R. O. STUDER and K. VOGLER, Helv. chim. Acta *45*, 819 (1962).
[8] H. BRINTZINGER, Helv. chim. Acta *44*, 744 (1961).
[9] We are very much indebted to Dr. S. WILKINSON, Wellcome Research Laboratories, Langley Court, Beckenham, Kent (England), for informing us of the method of crystallizing the natural antibiotic.

Psychotomimetic Amphetamines: Methoxy 3,4-Dialkoxyamphetamines[1]

Both 3,4,5-trimethoxyamphetamine (I, TMA)[2] and 3-methoxy-4,5-methylenedioxyamphetamine (II, MMDA)[3] have exhibited psychotropic potencies greater than that of mescaline. Both the lengthening of the aliphatic chain of I[4] and the enlargement of the heterocyclic ring in II[3] have resulted in a decreased human effectiveness. On the contrary, it has been found that the repositioning of the *meta*-methoxy group, in either of these compounds, to an available *ortho*-location, can result in an appreciable increase in potency. The syntheses and preliminary pharmacological evaluation of these positional isomers are described.

Two methods of synthesis were employed. With the two bases possessing the 2,4,5-alkoxy orientation, the appropriately substituted propenylbenzene was oxidized with tetranitromethane to the corresponding β-nitropropene. $LiAlH_4$ reduction of these nitrostyrenes to the amphetamines was performed as previously described[5]. The propene required for III, asarone, was obtained by the fractional distillation of oil of Parsley. The necessary precursor of IV, 2-methoxy-4,5-methylenedioxy propenylbenzene was obtained by conventional steps from sesamol. The Claisen rearrangement of allyl sesamyl ether occurred predominantly to the unhindered side; O-methylation and base-catalyzed isomerization yielded the requisite propenylbenzene.

The vicinal analogs V and VI were both prepared from the corresponding benzaldehydes by condensation with nitroethane followed by reduction of the resulting nitrostyrene as described above. The properties of these products, together with those of the 3,4,5-analogs for comparison, are listed in the Table.

Behavioral and toxicological studies were performed on male Swiss white mice, and these results are also recorded in the Table. All four isomers were found to be somewhat

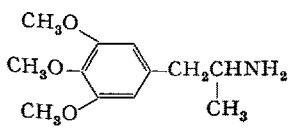
[1] Psychotomimetic Amphetamines, part II; for part I see [3].
[2] D. I. PERETZ, J. R. SMYTHIES, and W. C. GIBSON, J. mental Sci. *101*, 317 (1955). – A. T. SHULGIN, S. BUNNELL, and T. SARGENT III, Nature *189*, 1011 (1961).
[3] A. T. SHULGIN, Nature, *201*, 1120 (1964). (To be considered paper I of this series.)
[4] A. T. SHULGIN, Exper. *19*, 127 (1963).
[5] F. A. RAMIREZ and A. BURGER, J. Am. chem. Soc. *72*, 2781 (1950).

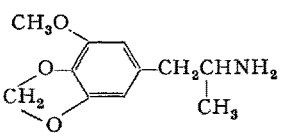
Physical and pharmacological properties

Compound	Nitrostyrene m.p.	Base·HCl m.p.	ED[a] (mice) mg/kg	LD_{50} (mice) mg/kg	ED[b] (human) µg/kg	M.U.[c] (human)
(I) TMA[d]	94	209	20	260	1700	2.2
(II) MMDA	110	191	35	150	1400	2.7
(III) TMA-2[e]	102	181	15	120	220	17.0
(IV) MMDA-2	163	187	20	130	180	21.0
(V) TMA-3	57	149	35	120	> 1900	< 2.0
(VI) MMDA-3a	106	154	25	40	210	18.0

[a] Effective dosage (as free base in saline, i.p.) at which behavioral changes were first observed.
[b] Effective dosage (as free base, *per os*) defined as the arithmetical mean between the minimum detectable dosage and the dosage above which there is a prolongation rather than an intensification of the psychotomimetic syndrome.
[c] Mescaline Units. The quotient of the effective dosage of mescaline (assumed to be 3750 µg/kg as the base) divided by the effective dosage of the substance in question. It permits a direct comparison of relative potencies, based on mescaline = 1.
[d] Physical data from [4].
[e] Literature values for the nitrostyrene m.p. 101° and for the base·HCl, 187°, see V. BRUCKNER, J. prakt. Chem. *138*, 268 (1933).

more toxic than the 3,4,5-substituted analogs. Compound VI, MMDA 3a, was the most toxic of the group and it alone produced clonic convulsions and vocalization prior to death. The other compounds led to easy deaths, apparently due to respiratory paralysis. All compounds displayed initial behavioral changes at the levels listed. The responses observed were light tremors accompanied by rapid scratching and a huddling tendency. These effects disappeared within 3 h, and there were no noticeable after-effects.


I (TMA)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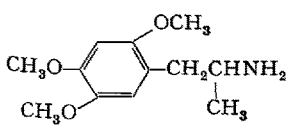
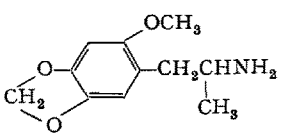
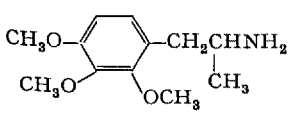
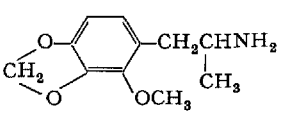

III (TMA-2)


IV (MMDA-2)


V (TMA-3)


VI (MMDA-3a)

The intoxication syndrome in human subjects, resulting from the quantities shown in the Table, is qualitatively similar to that which results from mescaline, except that the color effects, and to a large extent the nausea, are absent. As a generalization, the MMDA series leads to the more empathic and pleasant responses, whereas personal anxiety and restlessness were common with TMA-2. The vicinal analog, TMA-3, demonstrated neither physical nor psychotropic effects, even in dosages in excess of those shown to be adequate for TMA and MMDA. With the other three *ortho*-methoxy derivatives, however, hypnogogic hallucinatory synthesis and total recall are present and are similar to mescaline.

Résumé. Quatre amphétamines analogues aux substances chimiques psychomimétiques connues, la 3,4,5-triméthoxyamphétamine et la 3-méthoxy-4,5-méthylènedioxyamphétamine, ont été synthétisées. Le déplacement d'un méthoxyl à une position *ortho*- de la chaîne aliphatique a montré, dans trois cas une amplification multiple quant à l'efficacité humaine.

A. T. SHULGIN

The Dow Chemical Company, Walnut Creek (California, USA), February 10, 1964.

Adsorption of Hageman Factor (Factor XII) on Collagen

It is generally accepted that collagen fibres play an important role in haemostasis. Several authors[1-3] have described the aggregating effect of suspensions of connective tissues and collagen fibres on blood platelets *in vitro*. The platelets adhering to the traumatized vessel wall form a haemostatic plug. The purpose of our experiments was to study the adsorption of the blood clotting factors on collagen.

Collagen was prepared from bovine tendons according to the method of EINBINDER and SCHUBERT[4]. Two kinds of human citrated plasma were used: (a) platelet-rich plasma (about 400,000 platelets per mm³), and (b) platelet-poor plasma (about 30,000 platelets per mm³) obtained by two-stage centrifugation of 2000 RPM for 10 min and 10,000 RPM for 10 min. Plasma was prepared in siliconized glassware.

The following determinations were made: platelet count (Rees-Ecker method), clotting time of recalcified

[1] J. HUGUES, C.R. Soc. Biol. (Paris) *154*, 866 (1960).
[2] M. B. ZUCKER and J. BORELLI, Proc. Soc. exp. Biol. Med. (New York) *109*, 779 (1962).
[3] T. HOVIG, Thromb. Diath. Haem. *9*, 248 (1963).
[4] J. EINBINDER and M. SCHUBERT, J. biol. Chem. *188*, 335 (1950).