Tabelle II

Vergleichung der Wirksamkeit einiger zyklischer und aliphatischer Amine

Amin	Salz	Ganglioplegische Wirkung %	Hypotensive Wirkung %	Toxizität	
				% a)	mg/kg b)
Mecamylamin	HCl	100	100	100	12,1–13,7
Dimecamin	HBr	100–140	100–140	63–75	17,5–19,0
Penhexamin	HBr	150–200	120–170	43–53	25,3–28,0
PA	HCl	60–80	100–150	18–20	65 –72
PS	HCl	100–125	80–110	15–17	75 –85
Penbutamin	HBr	190–200	150–200	23–26	50 –56

a) Relative LD_{50} im Vergleich zum Mecamylamin; b) LD_{50} intravenös an Mäusen (Amin-Base).

Durch Reduktion mit Lithiumaluminiumhydrid gelangten wir zu sekundären Aminen oder durch alkalische Verseifung zu primären Aminen und von diesen durch Methylierung mit Formaldehyd und Ameisensäure zu tertiären Aminen. Die Tabelle gibt eine Übersicht der von uns hergestellten Amine und ihrer Salze.

Der eingehenderen pharmakologischen und klinischen Untersuchung dieser Amine voran geben wir hier die vorläufigen, mit diesen Aminen erzielten Ergebnisse, in welchen $R = CH_3$ und wo es sich um das primäre (PA), sekundäre (PS) und tertiäre (V = Penbutamin) Amin handelt (im Vergleich zum Mecamylamin, Dimecamin und Penhexamin).

Die ganglioplegische Wirkung wurde bei der narkotisierten Katze (Chloralose mit Phenobarbital) durch Auswertung des Kontraktionsgrades der Nickhaut, die durch präganglionäre Reizung des Halssympathikus hervorgerufen wurde, festgestellt. Als Wirkungsgrad diente jene Dosis, welche die Dämpfung der Kontraktionen um 50 ± 15% bei 80–90% Versuchstieren verursachte. Für die Auswertung der hypotensiven Wirkung bezogen wir uns auf die Blutdrucksenkung um 20 ± 6 mm Hg an Tieren mit einem Ausgangsdruck von 100–150 mm Hg. Jedes Tier erhielt nur eine einzige Applikation. Die relative Wirksamkeit ist entsprechend den Molekulargewichten der Amine angeordnet und in Prozenten im Vergleich zum Mecamylamin ausgedrückt. Die Wirkungsdauer unserer Substanzen ist dieselbe oder auch länger als die des Mecamylamins.

Wie aus der Tabelle hervorgeht, ist die ganglioplegische sowie hypotensive Wirksamkeit des Penbutamins auffallend hoch und von bemerkenswert niedriger Toxizität.

Z. J. VEJDĚLEK und V. TRČKA

Forschungsinstitut für Pharmazie und Biochemie, Prag, 15. Februar 1959.

Summary

A series of primary, secondary, and tertiary 2,2,3-trimethylbutylamines-(3) and their salts substituted in position 3 with a methyl, ethyl, *n*-butyl, phenyl, and benzyl group has been prepared. One member of the series, N,N,2,2,3-pentamethylbutylamine-(3) (Penbutamine) as well as the corresponding amino and methylamino derivatives were compared with other compounds of a similar type as regards their ganglioplegic and hypotensive effect. The tested compound revealed a high degree of activity in both the above mentioned directions.

Hydroxylation and N-demethylation of N,N-dimethyltryptamine

The psychotropic effect of N, N-dimethyltryptamine (DMT) in man has been described recently[1], but relatively little is known about its fate in the body. After its administration to man, only 33% can be accounted for as the deaminated product, 3-indoleacetic acid (free and conjugated)[2]. This report describes a new pathway for the metabolism of DMT *in vitro* and *in vivo*.

Incubating DMT with rabbit liver microsomes[3], soluble supernatant fraction, TPN and semicarbazide[4] resulted in N-demethylation as evidenced by the liberation of formaldehyde. The demethylated metabolite(s) was isolated from the reaction mixture by extraction into n-butanol at an alkaline pH. When the extract was subjected to paper chromatography, a compound was found which had the same *R*f values as N-methyltryptamine in five different solvent systems. This compound also gave a color reaction for secondary amines[5]. No evidence for the presence of tryptamine was obtained, indicating that only one methyl-group was removed.

After the precipitation of proteins with ethanol, the reaction mixture was examined for other indole metabolites. The centrifuged extract was concentrated and subjected to two-dimensional chromatography in n-butanol:acetic acid:water (8:1:1) and isopropanol:ammonia (5%) (8:2) systems. When the chromatogram was sprayed with Ehrlich's reagent (2% p-dimethylaminobenzaldehyde in 1N-HCl) five indolic spots appeared, two of which had the same *R*f values and color reactions as DMT and N-methyltryptamine. The third spot had the same *R*f values and color reactions as DMT-N-oxide[6]. The two remaining spots gave an immediate blue color with Ehrlich reagent which is characteristic for 7-hydroxy substituted indoles[7] and were tentatively identified as 7-hydroxy-DMT and 7-hydroxy-DMT-N-oxide*. Both

[1] A. SAI-HALASZ, G. BRUNECKER, and S. SZARA, Psych. Neurol. *135*, 285 (1958).

[2] S. SZARA, Exper. *12*, 441 (1956).

[3] All animals were pretreated with 100 mg/kg iproniazid phosphate, a mono-amine oxidase inhibitor.

[4] J. AXELROD, J. Pharm. exp. Therap. *114*, 430 (1955).

[5] C. C. SWEELEY and E. C. HORNING, J. Amer. chem. Soc. *79*, 2620 (1957).

[6] M. S. FISH, N. M. JOHNSON, E. D. LAWRENCE, and E. C. HORNING, Biochim. biophys. Acta *18*, 564 (1955).

[7] K. ICHIHARA, A. SAKAMOTO, K. INAMORI, and Y. SAKAMOTO, J. Biochem. (Japan) *44*, 649 (1957).

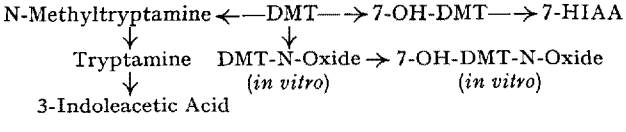
* See Note added in proof.

spots also gave color reactions with reagents claimed to be specific for 7-hydroxy indoles (such as acid diazo p-nitroaniline or sulfanilic acid)[7]. Since authentic 7-hydroxy-DMT and its N-oxide have not been described, we prepared these compounds enzymatically and by the model hydroxylating system[8]. When DMT-N-oxide was incubated with the microsomal enzyme system, only one compound was formed which gave the above-mentioned color reactions for 7-hydroxy indoles and had the same *R*f values as one of the two 7-hydroxy indoles formed from DMT.

These observations suggest that one of the hydroxylated metabolites of DMT is most probably 7-hydroxy-DMT-N-oxide. The remaining spot did not have the same *R*f as 7-hydroxytryptamine (prepared enzymatically from tryptamine), nor did it give a reaction for secondary amines, indicating that it is a tertiary amine, presumably 7-hydroxy-DMT. Additional evidence for the idendity of the latter compound was obtained by comparing it with 7-hydroxy-DMT formed in the model hydroxylating system, using DMT as a substrate. Both had the same *R* f values and color reactions. There was no evidence for hydroxylation on the 5-position by the microsomal enzyme system.

In the *in vivo* studies, rats[9] were given 10 mg DMT intraperitoneally and the urine was collected for 48 h. The urine was adjusted to pH 8·0, extracted with benzene and the benzene extract re-extracted with 1 N-HCl. The acid extract contained compounds having the same *R*f values and color reactions as DMT, N-methyl-tryptamine, 7-hydroxy-DMT (prepared enzymatically) and tryptamine. The residual urine was adjusted to pH 9·5 and extracted with n-butanol. After adding two volumes of n-heptane, the extract was shaken with acid. The acid extract contained compounds having the same *R*f values and color reactions as: 7-hydroxy-DMT (enzymatic), indole acetic acid, and an unidentified compound giving the reactions for 7-hydroxy indoles. When the acidified urine was extracted with n-butanol and the n-butanol phase re-extracted with dilute ammonia after adding n-heptane, two compounds were found having the same *R*f values, color reactions, and fluorescent characteristics as 3-indoleacetic acid and enzymatically produced 7-hydroxy-indole-acetic acid (7-HIAA).

From the results described above, the following scheme for the metabolism of DMT may be provisionally drawn:



Whether or not any of the metabolites of DMT play a role in the production of the psychotic phenomena must remain a question for future study.

Note added in proof. – In the meantime, Dr. JEPSON[9] called to our attention that the blue Ehrlich test and the immediate red color with acid diazo reagents which have been described and held as specific for 7-hydroxyindoles by ICHIHARA *et al.*[7] is not specific for 7-hydroxyindoles since 6-hydroxyindoles also give these tests, although in a slightly different color. We then prepared 6-hydroxy-dimetyltryptamine by total synthesis. This compound proved to be identical in every respect with the hydroxylated derivative of DMT produced by the microsomal enzyme system, by UDENFRIEND's model hydroxylating system, as well as with hydroxy-DMT isolated from urine. Thus, the hydroxyl group in the above studied indole derivatives is most probably in the 6- rather than the 7-position.

S. SZARA and J. AXELROD

Clinical Neuropharmacology Research Center and Laboratory of Clinical Sciences, NIMH, NIH, Washington (D.C.) and Bethesda (Md.), November 12, 1958.

Zusammenfassung

Der intermediäre Stoffwechsel des psychotropen N,N-Dimethyltryptamins wurde untersucht. N-Methyltryptamin, als Produkt der Demethylierung, und 6-Hydroxy-N,N-Dimethyltryptamin, als Produkt der Hydroxylierung, wurden nachgewiesen und papierchromatographisch charakterisiert. An weiteren Stoffwechselprodukten wurden nachgewiesen: N,N-Dimethyltryptamin-N-oxyd und sein 6-Hydroxy-Derivat (*in vitro*), sowie Tryptamin, Indol-3-essigsäure und 6-Hydroxyindol-3-essigsäure (*in vivo*).

Increased Excretion of 5-Hydroxy-indole-acetic Acid after the Administration of 3-Indole-acetic Acid (Heteroauxine)

It has been demonstrated recently that 5-hydroxy-indole-acetic acid (5-HIAA)[1] may be formed from certain exogenous precursors. SZARA[2] has observed an increased excretion of 5-HIAA after the application of dimethyltryptamine, ANDERSON, ZIEGLER, and DOEDEN[3] after consumption of a large amount of bananas. WAALKES *et al.*[4] have shown that besides other substances bananas contain large amounts of serotonine.

3-indole-acetic acid (IAA) is ingested in small amounts with some foods and is formed also as a tryptophan metabolite by the action of the intestinal bacterial flora. It is interesting therefore to follow the fate of IAA in the organism and its influence on the excretion of 5-HIAA. The fate of IAA in the animal was studied by ERSPAMER[5]. This author found that about one third of the administered IAA was excreted unchanged or in a conjugated form. He believes that the other part is probably metabolised after breaking up the indole ring.

In our own metabolic studies we have also investigated the fate of IAA in the human body.

In our experiment, eleven volunteers were given IAA, in the form of a 5% solution of the acid carbonate in tea[6], which was sweetened with saccharine or sucrose. The dosage of the applied IAA is shown on the Table.

[8] S. UDENFRIEND, C. T. CLARK, J. AXELROD, and B. B. BRODIE, J. biol. Chem. *208*, 731 (1954).

[9] J. J. JEPSON, S. UDENFRIEND, and XY. ZALZMANN, Fed. Proc. *81*, 754 (1959). (Personal Communication).

[1] We thank Sandoz, Ltd., Basle and Professor V. ERSPAMER, Institute of Pharmacology, University of Parma (Italy) for the generous gifts of 5-hydroxy-indole-acetic acid.

[2] ST. SZÁRA, Exper. *12*, 444 (1956).

[3] J. A. ANDERSON, M. R. ZIEGLER, and D. DOEDEN, Science *127*, 236 (1958).

[4] T. P. WAALKES, A. SJOERDSMA, C. R. CREVELING, H. WEISSBACH, and S. UDENFRIEND, Science *127*, 648 (1958).

[5] V. ERSPAMER, J. Physiol. *127*, 118 (1955).

[6] I. A. MIRSKY, and D. DIENGOTT, Proc. Soc. exp. Biol. Med. *93*, 109 (1956).