afforded the same compound, to which structure V is assigned on the basis of the molecular formula $C_{12}H_{19}N_3O_2$[9], infra-red spectrum (ν_{max} 1730, 1670, 1640 cm^{-1}, no amide II band) and feeble basicity comparable to that of imidazolones previously described[7]. It follows that the initial product (molecular formula $(C_4H_7NO)_n$, dimorphic ν_{max} (prisms) 1685, 1632, 1585 cm^{-1} or ν_{max} (needles) 1650, 1600 cm^{-1}) from the 'tripeptide oxazolone' must be the cyclol (IV). Inspection of molecular models shows that the concerted electronic shifts shown in (III) are stereochemically feasible. In contrast, the amino group in the 'dipeptide oxazolone' cannot reach the reactive carbonyl group in an intramolecular reaction without distortion of bond angles, and this difference accounts for the greater stability of this compound and its polymerization in preference to cyclization.

Just as structure (I) is formally derived from two amide groups, it may decompose to them. However, the cyclol (IV) is prevented from protropic change into the isomeric cyclic tripeptide by the methyl groups. (The centre of a cyclic tripeptide is too congested to contain anything but three hydrogen atoms[10]). Whether this factor is important in stabilising the structure remains to be seen. Its significance in relation to the stability of the ergot alkaloids has been made clear by EDWARD[11].

Further studies of oxazolones with regard to formation of both cyclols and polymers are in progress.

Zusammenfassung. Das dem α-Methylalanyl-α-methylalanyl-α-methylalanin entsprechende Oxazolon (III) isomerisiert leicht zum kristallisierten Cyclol (IV), dessen Struktur sich aus dem Übergang in das Imidazolon (V) unter Wasserabspaltung ergibt.

D. S. JONES, G. W. KENNER, and R. C. SHEPPARD

Robert Robinson Laboratories, University of Liverpool (England), September 26, 1962.

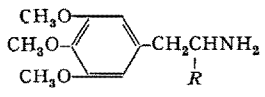
[9] Dr. R. I. REED, Glasgow, kindly determined mol. wt. 237 by mass spectrometry.

[10] G. W. KENNER and J. M. TURNER, Chem. Ind. 602 (1955). – G. W. KENNER, J. chem. Soc. *1956*, 3692.

[11] J. T. EDWARD, Research *8*, S38 (1955).

Psychotomimetic Agents Related to Mescaline

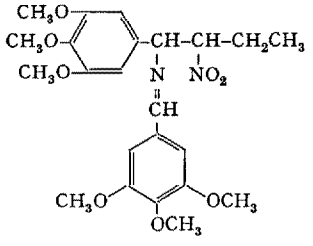
The widely studied pharmacology of mescaline (I; $R = H$)



I

and the recent descriptions of the psychotomimetic effects of *dl*-trimethoxyamphetamine[1,2] (I; $R = CH_3$) have prompted the synthesis of higher homologs (I; $R = C_2H_5$ through C_7H_{15}). All of the amines were prepared by the $LiAlH_4$ reduction[3] of the corresponding nitrostyrenes, which were in turn prepared (with the exception of the nitropropane isomer mentioned below) by the ammonia-catalyzed condensation of the appropriate nitroalkane with 3,4,5-trimethoxybenzaldehyde, in acetic acid.

With nitropropane in acetic acid, the sold product was identified as 3,4,5-trimethoxybenzonitrile[4], and substitution of isopropyl alcohol for the acidic solvent led to the unexpected formation of the Schiff base II,



II

m.p. 151.5–152 from methanol, the structure of which was established by analysis (C = 59.68, H = 6.68, N = 5.84, MW in $CHCl_3$ = 460; $C_{23}H_{30}N_2O_8$ requires C = 59.73, H = 6.54, N = 6.08, MW = 462) and its facile acid hydrolysis to trimethoxybenzaldehyde and, after neutralization, 1-(3,4,5-trimethoxylphenyl)-2-nitrobutylamine. Replacement of the ammonia catalyst with a secondary amine precluded the formation of II, and led to a proper nitrostyrene. The properties and yields of the substances studied appear in the Table.

R	Nitrostyrenes[a] mp °C	yield	Phenethylamines mp °C picrate	mp °C base-HCl	yield
-H	120 -121[b]	64%	214-216	180-181	86%[c]
$-CH_3$	93 - 94[d]	50%	171-173	208-209[e]	62%
$-CH_2CH_3$	72 - 73	29%	177-181	192-193	52%
$-(CH_2)_2CH_3$	82.5- 83.5	32%	182-184	214-218	65%
$-(CH_2)_3CH_3$	73 - 74	34%	168-170	182-184	45%
$-(CH_2)_4CH_3$	54 - 55	24%	162-163	155-158	50%
$-(CH_2)_5CH_3$	51 - 52	21%	149-151	132-134	53%
$-(CH_2)_6CH_3$	43 - 44	19%	148-149	112-116	19%
$-(CH_2)_8CH_3$	46 - 47	16%	—	—	0%

[a] All listed compounds were yellow crystalline solids, recrystallized from methanol.

[b] Literature values are reported from 118 to 121°C. It was found that if the molten material was held at this temperature for a short period, resolidification occurred yielding a new crystal form with a melting point 128–129°C.

[c] Literature value included for comparison, see [3].

[d] Literature value 95°C, see P. HEY, Quart. J. Pharm. Pharmacol. *20*, 129 (1947).

[e] Literature value 219–220°C, see above reference.

[1] D. I. PERETZ, J. R. SMYTHIES, and W. C. GIBSON, J. Mental Sci. *101*, 317 (1955).

[2] A. T. SHULGIN, S. BUNNELL, and T. SARGENT III, Nature *189*, 1011 (1961).

[3] F. A. RAMIREZ and A. BURGER, J. Amer. chem. Soc. *72*, 2781 (1950).

[4] H. M. BLATTER, H. LUKASZEWSKI, and G. DESTEVENS, J. Amer. chem. Soc. *83*, 2203 (1961).

Toxicity and behavioral studies with mice could not distinguish between the first three members of this series. For all, LD_{50}'s were established to be between 200 to 300 mg/kg, i.p., and at 80 mg/kg there was the mild, agitated behavior previously described[1]; complete recovery occurring within 8 h.

In human subjects, the potency of trimethoxyamphetamine (I, $R = CH_3$) has been established as over twice that of mescaline[2]. Evaluation of the immediate homologue, α-ethyl mescaline (I, R = ethyl) at oral levels in excess of 2.5 mg/kg (as the free base), produced neither central activity nor psychic disturbance, thus demonstrating a psychotomimetic potency of less than half that of trimethoxyamphetamine, and suggesting that three carbons represent an optimum chain length.

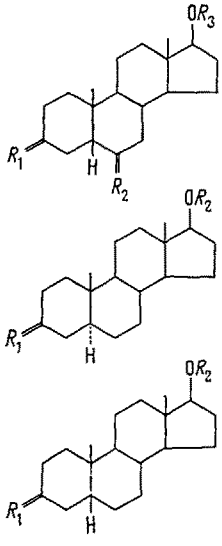
Résumé. Une série homologue à celle des substances chimiques composant la mescaline a été synthétisée. L'évaluation préliminaire a montré qu'elle a un effet psychotomimétique plus faible que celui de la triméthoxyamphétamine.

A. T. SHULGIN

The Dow Chemical Company, Walnut Creek (California, U.S.A.), September 18, 1962.

Synthese von 5α- und 5β-Androstan-17β-ol-3-on-17-acetat aus Hyodesoxycholsäure

Zur Darstellung von 5α-Androstan-17β-ol-3-on-17-acetat (VI) und 5β-Androstan-17β-ol-3-on-17-acetat (VIII) gingen wir von Hyodesoxycholsäure aus, die nach bekannten Methoden[1] in 5β-Androstan-6α,17β-diol-3-on-17-acetat (I) überführt wurde.



(I) R_1: =O; R_2: <H/OH; R_3: –CO–CH_3

(II) R_1: <O–CH_2–CH_2–O; R_2: <H/OH; R_3: –CO–CH_3

(III) R_1: <O–CH_2–CH_2–O; R_2: =O; R_3: –CO–CH_3

(IV) R_1: <O–CH_2–CH_2–O; R_2: –H

(V) R_1: <O–CH_2–CH_2–O; R_2: –CO–CH_3

(VI) R_1: =O; R_2: –CO–CH_3

(VII) R_1: <O–CH_2–CH_2–O; R_2: –H

(VIII) R_1: =O; R_2: –CO–CH_3

Verbindung I setzten wir mit Äthylenglykol und *p*-Toluolsulfonsäure in Benzol[2] um und erhielten 5β-Androstan-6α,17β-diol-3-on-3-äthylenketal-17-acetat (II); Fp. 197–198,5°C; $[\alpha]_D$: + 3°; ν_{max}: 1095, 1730, 3610 cm^{-1}; ber. f. $C_{23}H_{36}O_5$ (392,5) 70,38% C, 9,24% H; gef. 70,70% C, 9,22% H[3]; Ausbeute: 74%.

Oxydation von II mit Chrom-6-oxid in Pyridin[4] ergab 5β-Androstan-17β-ol-3,6-dion-3-äthylenketal-17-acetat (III); Fp.: 165–166°C; $[\alpha]_D$: – 55,5°; ν_{max}: 1100, 1710, 1730 cm^{-1}; ber. f. $C_{23}H_{34}O_5$ (390,5) 70,74% C, 8,78% H; gef. 71,34% C, 8,78% H; Ausbeute: 83%.

Über Verbindung III kamen wir durch reduktive Entfernung der 6-Ketogruppe in wenigen Stufen zu VI und VIII, je nachdem, ob die Reduktion unter Inversion am C-Atom 5 vorgenommen wurde oder nicht.

Zur Darstellung des 5α-Androstan-17β-ol-3-on-17-acetats (VI) wurde III mit Kaliumhydroxid in Diäthylenglykol am C-Atom 5 allomerisiert und anschliessend nach HUANG-MINLON[5,6] reduziert. Wir erhielten 5α-Androstan-17β-ol-3-on-3-äthylenketal (IV); Fp.: 173–176°C; $[\alpha]_D$: + 13°; ν_{max}: 1100, 3610 cm^{-1}; ber. f. $C_{21}H_{34}O_3$ (334,5) 75,41% C, 10,25% H; gef. 75,55% C, 10,74% H; Ausbeute: 71%.

Acetylierung von IV unter üblichen Bedingungen ergab 5α-Androstan-17β-ol-3-on-3-äthylenketal-17-acetat (V); Fp.: 139–140°C; $[\alpha]_D$: + 3° (Pyridin); ν_{max}: 1100, 1730 cm^{-1}; ber. f. $C_{23}H_{36}O_4$ (376,5) 73,37% C, 9,64% H; gef. 74,02% C, 10,02% H; Ausbeute: 92%.

Aus V entstand durch selektive Verseifung der 3-Ketalgruppe mit *p*-Toluolsulfonsäure in Aceton das 5α-Androstan-17β-ol-3-on-17-acetat (VI); Fp.: 158–160,5°C ([7,8] 157° und 158,5–159,5°C); $[\alpha]_D$: + 22° ([9] + 26°); das IR-Spektrum stimmte mit dem einer authentischen Probe überein; ν_{max}: 1715, 1735 cm^{-1}; Ausbeute: 86,5%.

Zur Darstellung des 5β-Androstan-17β-ol-3-on-17-acetats (VIII) wurde die 6-Ketogruppe in III so reduziert, dass keine Inversion am C-Atom 5 erfolgte[6]. Zu diesem Zweck überführten wir III unter neutralen Bedingungen in dessen 6-Hydrazon und setzten dann die Reaktion in alkalischer Lösung fort. Auf diese Weise wurden 82% des 5β-Androstan-17β-ol-3-on-3-äthylenketals (VII) erhalten; Fp.: 155–157°C; $[\alpha]_D$: + 35°; ν_{max}: 1100, 3610 cm^{-1}; ber. f. $C_{21}H_{34}O_3$ (334,5) 75,41% C, 10,25% H; gef. 74,92% C, 9,63% H.

Da die 6-Ketogruppe in der 5β-Reihe sterisch behindert ist, war für die vollständige Umsetzung von III mit 85%igem Hydrazinhydrat dreistündiges Sieden in Diäthylenglykol erforderlich. Wurde die Reaktionszeit

[1] CH. MEYSTRE, H. FREY, A. WETTSTEIN und K. MIESCHER, Helv. chim. Acta *27*, 1815 (1944). – L. H. SARETT, J. Amer. chem. Soc. *69*, 2899 (1947). – K. TAKEDA und J. KAWANAMI, J. Biochem. (Tokyo) *41*, 303 (1954). – DP (DDR) 21610, C. 7994 (1962); DP (DDR) 21658, C. A. 14373 (1962).

[2] Zur Methodik vgl. E. J. COREY und G. E. GREGORIOU, J. Amer. chem. Soc. *81*, 3124 (1959).

[3] Alle Fp. sind unkorrigiert. Drehwerte in Methanol und IR-Spektren in Chloroform, soweit nicht anders vermerkt. C,H-Analysen wurden von Herrn MARTIN (Institut für organische Chemie der Universität Leipzig) ausgeführt.

[4] G. I. POOS, G. E. ARTH, R. E. BEYLER und L. H. SARETT, J. Amer. chem. Soc. *75*, 422 (1953).

[5] HUANG-MINLON, J. Amer. chem. Soc. *68*, 2487 (1946).

[6] HUANG-MINLON, J. Amer. chem. Soc. *70*, 2802 (1948); *71*, 3301 (1949).

[7] A. BUTENANDT, K. TSCHERNING und G. HANISCH, Ber. dtsch. chem. Ges. *68*, 2097 (1935).

[8] A. P. 2143453, C.A. 3078 (1939); A. P. 2387469, C.A. 5536 (1946).

[9] C. DJERASSI, J. org. Chem. *12*, 823, 825 (1947).