aqueous acetone, this acid had m.p. 191–193° (Lit.[9] 189–191°).

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Synthesis of Some β-Phenethylamine Derivatives. I

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β-Phenethylamines are well known for their sympathomimetic activity, which is modified by the presence of substituents both in the side chain as well in the aromatic nucleus.[1] With a view to studying the effects on the physiological activity of different substituent groups like alkyl, alkoxyl, and halogen in various positions in the nucleus a number of β-phenethylamines were synthesized.

These amines were synthesized by the condensation of aromatic aldehydes with nitromethanes in acetic acid solution,[2] to yield the corresponding β-nitrosytrenes. The latter were then reduced with lithium aluminum hydride[3] to the β-phenethylamine derivatives, which were characterized as their picrates and wherever possible as their hydrochlorides.

2,3,5- (XIII) and 2,3,6- (XIV) -Trimethoxy-β-phenethylamines are hitherto unknown analogs of Mescaline. The starting material for the synthesis of XIII was 2,3,5-trimethoxybenzaldehyde.[4] The latter was prepared[5] by the Elb's persulfate oxidation of *o*-vanillin to 2,5-dihydroxy-3-methoxybenzaldehyde and subsequent methylation.

For the synthesis of 2,3,6-trimethoxy-β-phenethylamine, the starting material was 2,3,6-trimethoxybenzaldehyde,[5] whose synthesis was attempted by different routes. The easiest approach to its synthesis appeared to be through 2-hydroxy-6-methoxybenzaldehyde,[6] which on Elb's persulfate oxidation and subsequent methylation, would yield 2,3,6-trimethoxybenzaldehyde. Accordingly, 2,6-dihydroxybenzaldehyde (A) was prepared by the hydrolysis of the known 8-formyl-7-hydroxy-4-methylcoumarin[7] or from 2,6-dihydroxy-3-methoxycarbonylbenzaldehyde[8] by boiling with excess of water. The first method gave very poor yields of (A) and was abandoned. The second afforded a 48% yield of (A). However, persulfate oxidation of 2-hydroxy-6-methoxybenzaldehyde under different conditions proved to be unsuccessful. 2,3,6-Trimethoxybenzaldehyde was finally prepared as described by Merchant *et al.*[5]

During the course of the synthetic work, the decarboxylation of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde, 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde, and their respective anils, was studied under different conditions. It has been observed by Weijlard *et al.*[9] that the anil of opianic acid could be decarboxylated by heating with copper bronze. However, in the above two cases the desired decarboxylated product could not be isolated. Methylation of 3-carboxy-2,5-hydroxy-6-methoxybenzaldehyde resulted in the formation of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde, obtained as an oil and characterized by the preparation of a 2,4-dinitrophenylhydrazone. Hydrolysis of the above oily product gave instead of the expected 3-carboxy-2,5,6-trimethoxybenzaldehyde, a substance of melting point 224–225°, having a different molecular composition. From the analytical data, no definite structure could be assigned to it.

A detailed account regarding the pharmacological properties of the amines will be published elsewhere.

EXPERIMENTAL[10]

β-Nitrostyrenes. A mixture of 5 g. of the aldehyde, 5 ml. of nitromethane, 2 g. of ammonium acetate, and 20 ml. of glacial acetic acid, was refluxed at 130° for 2 hr. The reaction mixture was cooled, and the solid which separated was collected and crystallized from methanol or acetic acid. If no solid separated, the resulting solution was poured into ice water, and the precipitated semisolid mass or oil was extracted with ether. The ether solution was washed with water, dried, and the solvent distilled, when either a solid or an oil was left behind. The solid was purified by crystallization, whereas the oil was directly subjected for reduction.

β-Phenethylamines. The reduction of the β-nitrostyrene with lithium aluminum hydride, to the corresponding β-phenethylamine, was carried out according to the general method followed by Erne and Ramirez.[3]

A solution of 3 g. of the β-nitrostyrene in dry ether was added dropwise to a well stirred suspension of 2 g. of lithium aluminum hydride, in 100 ml. of dry ether. A mixture of ether and benzene was employed for styrenes which were sparingly soluble in ether. The reaction mixture was gently refluxed for 2 hr., and then decomposed with 2*N* sulfuric acid. To the aqueous layer, solid lithium carbonate was

(1) *"Medicinal Chemistry,"* A. Burger, Interscience Publishers, Inc., New York, N. Y., Vol. I, 1951, p. 335; *"Text Book of Organic Medicinal & Pharmaceutical Chemistry,"* C. O. Wilson and O. Gisvold, Lippincott Co., Philadelphia, Pa., 1954, p. 305.

(2) C. B. Gairaud and C. R. Lappin, *J. Org. Chem.*, **18**, 1–3 (1953).

(3) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950); F. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2782 (1950).

(4) W. Baker, N. C. Brown, and J. A. Scott, *J. Chem. Soc.*, 1923 (1939).

(5) J. R. Merchant, R. M. Naik, and A. J. Mountwala, *J. Chem. Soc.*, 4142 (1957).

(6) L. Rao and T. R. Seshadri, *Proc. Ind. Acad. Sci.*, **19A**, 143 (1944).

(7) S. M. Parekh and V. M. Thakor, *J. of Univ. Bombay*, **23**, 37 (1954).

(8) R. C. Shah and M. C. Laiwalla, *J. Chem. Soc.*, 1828 (1938).

(9) J. Weijlard, E. Tashijan, and M. Tishler, *J. Am. Chem. Soc.*, **69**, 2070 (1947).

(10) Melting points are uncorrected and were taken in open capillary tubes.

MELTING POINTS AND ANALYSES OF THE β-NITROSTYRENES AND THE β-PHENETHYLAMINE DERIVATIVES

		β-Nitrostyrene							β-Phenethylamine Picrate					
					Analysis						Analysis			
					Found		Calcd.				Found		Calcd.	
No.	Compound	Ref.[a]	M. P., °C.	Formula	C, %	H, %	C, %	H, %	M.P., °C.	Formula	C, %	H, %	C, %	H, %
I	2,4-Diethoxy-	11	92–93	$C_{12}H_{15}NO_4$	61.0	6.6	60.8	6.3	184–185	$C_{18}H_{22}N_4O_9$	49.0	5.0	49.3	5.0
II	2-Ethoxy-4-methoxy-	12	95–96	$C_{11}H_{13}NO_4$	59.4	6.0	59.2	5.8	161–162	$C_{17}H_{20}N_4O_9$	48.5	4.7	48.1	4.7
III	2-Benzyloxy-2-methoxy-	13	Oil[b]	$C_{16}H_{15}NO_4$	...	...	...	...	143–145	$C_{22}H_{22}N_4O_9$	54.3	5.0	54.3	4.5
IV	2,4-Dimethoxy-6-methyl-	14	117–118	$C_{11}H_{13}NO_4$	59.1	5.6	59.2	5.8	219–221[dec]	$C_{17}H_{20}N_4O_9$	48.0	5.0	48.1	4.7[a]
V	2,4-Diethoxy-6-methyl-	...	115–117	$C_{13}H_{17}NO_4$	62.4	6.7	62.2	6.7	178–180	$C_{19}H_{24}N_4O_9$	50.1	5.4	50.4	5.3
VI	2-Ethoxy-4-methoxy-6-methyl-	15	135–136	$C_{12}H_{15}NO_4$	61.1	6.2	60.8	6.2	188–189	$C_{18}H_{22}N_4O_9$	49.3	5.1	49.3	5.0[b]
VII	2,6-Dimethyl-4-methoxy-	16	115–116	$C_{11}H_{13}NO_3$	63.8	6.2	63.8	6.3	215–216[dec]	$C_{17}H_{20}N_4O_8$	50.3	5.2	50.1	4.9[c]
VIII	2,6-Dimethyl-4-ethoxy-	17	81–82	$C_{12}H_{15}NO_3$	65.4	7.1	65.2	6.8	185–186	$C_{18}H_{22}N_4O_8$	51.2	5.2	51.2	5.2
IX	2,4-Dimethyl-6-methoxy-	18	144–145	$C_{11}H_{13}NO_3$	63.9	6.5	63.8	6.3	188–189	$C_{17}H_{20}N_4O_8$	50.3	5.1	50.1	5.0
X	2,4-Dimethyl-6-ethoxy-	...	113–114	$C_{12}H_{15}NO_3$	65.0	6.5	65.2	6.8	173–174	$C_{18}H_{22}N_4O_8$	51.7	5.2	51.2	5.2
XI	2,6-Dimethoxy-4-methyl-	19	Oil[b]	$C_{11}H_{13}NO_4$	...	...	...	...	178–180[dec]	$C_{17}H_{20}N_4O_9$	48.2	4.6	48.1	4.7
XII	5-Bromo-2,3-dimethoxy-	20	107–108	$C_{10}H_{10}BrNO_4$	41.9	3.3	41.7	3.5	190–192	$C_{16}H_{17}BrN_4O_9$	39.7	3.8	39.3	3.5
XIII	2,3,5-Trimethoxy-	5,6	102–103	$C_{11}H_{13}NO_5$	55.3	5.8	55.2	5.4	158–159	$C_{17}H_{20}N_4O_{10}$	46.7	4.6	46.4	4.5
XIV	2,3,6-Trimethoxy-	6	Oil[b]	$C_{11}H_{13}NO_5$	...	...	...	...	166–167	$C_{17}H_{20}N_4O_{10}$	46.8	4.3	46.4	4.5

[a] The index numbers refer to the methods of preparation.

[b] Subjected directly for reduction without further purification.

[c] Amine Hydrochlorides (a) M.p. 251–252°; Calcd. for $C_{11}H_{15}ClNO_2$: N, 6.3. Found N, 6.1.
(b) M.p. 225–226°; Calcd. for $C_{12}H_{20}ClNO_4$: N, 6.0, Found N, 6.7.
(c) M.p. 225–226°; Calcd. for $C_{11}H_{18}ClNO$: N, 6.9, Found N, 6.8.

(11) F. Tieman and L. Lewy, *Ber.*, **10**, 2215 (1877).
(12) Srinivas Rao, C. Srikantia,, and M. S. Iyengar, *J. Chem. Soc.*, **127**, 558–60 (1925).
(13) H. Richtzenhain, *Ber.*, **77B**, 1–6 (1944).
(14) A. Robertson and R. Robinson, *J. Chem. Soc.*, 220 (1927).
(15) A. Robertson and R. Stephenson, *J. Chem. Soc.*, 1390 (1932).
(16) A. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1862 (1946).
(17) L. Gattermann, *Ann.*, **357**, 362 (1907).
(18) K. Auwers and K. Saurwein, *Ber.*, **55**, 2380 (1922).
(19) R. Adams and J. Mathieu, *J. Am. Chem. Soc.*, **70**, 2120 (1948); R. Adams and R. Carlin, *J. Am. Chem. Soc.*, **65**, 360 (1943).
(20) W. Davies, *J. Chem. Soc.*, **123**, 1586 (1923).

added until its *p*H was about 6. The hot solution was filtered through Kieselguhr and the clear filtrate and washings were added to an alcoholic solution of picric acid. On cooling, the amine picrate separated out, which was recrystallized from methanol. The yield of the picrate in almost all cases ranged from 60 to 70%.

Two grams of the above picrate was boiled with 14 ml. of concentrated hydrochloric acid. After cooling, the precipitated picric acid was filtered. The filtrate was extracted with nitrobenzene and then with ether. The aqueous layer was evaporated to dryness under vacuum. The dark hydrochloride thus obtained was recrystallized from a mixture of methanol and ethyl acetate.

2,6-Dihydroxybenzaldehyde. A mixture of 3 g. of 3-carboxy-2,6-dihydroxybenzaldehyde and 200 ml. of water was refluxed for about 4 hrs. The resulting solution was filtered and the clear filtrate repeatedly extracted with ether. The ether extract was washed with a saturated solution of sodium bicarbonate, and then with water. Evaporation of ether afforded the aldehyde, which was crystallized from water as 1.1 g. of pale yellow needles, m.p. 154°–155°.

Anal. Calcd. for $C_7H_6O_3$: C, 60.9; H, 4.3. Found: C, 60.8; H, 4.2.

Anil of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde. The anil of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde was prepared according to the general method described by Weijlard *et al.*[9] It was crystallized from alcohol in orange colored needles of m.p. 203–205° (dec.).

Anal. Calcd. for $C_{15}H_{13}NO_4$: N, 5.1. Found: N, 5.5.

Anil of 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde. The anil was crystallized from alcohol in red needles, of m.p. 223–225° (dec.).

Anal. Calcd. for: $C_{15}H_{13}NO_5$: N, 4.9. Found: 5.0.

3-Methoxycarbonyl-2,5,6-trimethoxybenzaldehyde. A mixture of 1 g. of 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde, 2 g. of anhydrous potassium carbonate, 2 ml. of dimethyl sulfate, and 55 ml. of dry acetone was gently refluxed for 12 hr. Filtration and removal of acetone left an oil which was washed with dilute sodium hydroxide and extracted with ether. Evaporation of the ether gave 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde as an oil.

Its *2,4-dinitrophenylhydrazone* crystallized from alcohol in tiny needles, m.p. 169°.

Anal. Calcd. for $C_{18}H_{18}N_4O_9$: N, 12.5. Found: 12.0.

Attempted hydrolysis of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde. One gram of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde and 50 ml. of 5% sodium carbonate was heated on a water bath for 1 hr., when the oil slowly went into solution. On cooling, and acidification with hydrochloric acid, a pale yellow compound was obtained, which was crystallized from alcohol in needles, m.p. 225°.

It did not give a coloration with alcoholic ferric chloride solution, but dissolved in sodium bicarbonate; nor did it form a 2,4-dinitrophenylhydrazone or an "anil."

Anal. Found: C, 58.1; 58.4; H, 5.4; 5.8.

No definite structure could be assigned to it from the analytical data.

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Synthesis of 3-Indoleacetamides[1,2]

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The enhancement of activity for parthenocarpic fruit development in the tomato by changes in the ring structure and side chain of 3-indoleacetic acid[4,5] has prompted the preparation of several 3-indoleacetamides.

Various 3-indoleacetyl amino acids have been prepared by using the mixed anhydride procedure[6,7] and the carbodiimide method.[8–10] The classical method of amide formation, Schotten-Baumann reaction, was not used by these investigators since this procedure is contingent upon the preparation of 3-indoleacetyl chloride. This was generally assumed not possible until reported by Shaw and Woolley.[11] The Schotten-Baumann reaction has been used in this laboratory for the preparation of 3-indoleacetamides.

The properties of various 3-indoleacetamides are given in Table 1. All of the compounds exhibited ultraviolet absorption characteristic of the indole nucleus except the *p*-aminobenzoic acid derivative where the strong absorption of the *N*-substituted *p*-aminobenzoic acid moiety masked completely the typical indole ultraviolet absorption (280 to 300 mμ).

EXPERIMENTAL

3-Indoleacetyl chloride.[11] This compound was prepared in 60–70% yields by the reaction of 3-indoleacetic acid with phosphorus pentachloride in anhydrous ether solution at 0°. The product was recrystallized from a mixture of ether and petroleum ether to yield colorless to pink crystals, m.p. 68–70°, trinitrobenzene adduct[12] m.p. 88°.

3-Indoleacetyl derivatives. 3-Indoleacetyl derivatives were synthesized by a method similar to the one used by Wood and Fontaine[13] for the preparation of substituted phenoxyacetyl derivatives. The following description illustrates the general procedure for the synthesis of all of the amino acid derivatives of 3-indoleacetic acid.

Glycine (0.75 g., 0.01 mole) was dissolved in 30 ml. of *N* sodium hydroxide (0.03 mole) and the solution cooled in an ice bath to 0–5°. 3-Indoleacetyl chloride (1.93 g., 0.01 mole) was dissolved in 10 ml. of anhydrous ether, cooled to 0°, and added dropwise with efficient mechanical stirring to the alkaline glycine solution. After 0.5 hr. the ice bath was removed to permit the solution to reach room temperature, and stirring was continued for an additional hour. The alkaline mixture was then thoroughly extracted with ether, the aqueous fraction cooled to 0°, and acidified to *p*H 2 with

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(4) H. M. Sell, S. H. Wittwer, T. L. Rebstock, and C. T. Redemann, *Plant Physiol.*, **28**, 481 (1953).

(5) L. E. Weller, S. H. Wittwer, and H. M. Sell, *J. Am. Chem. Soc.*, **77**, 4937 (1955).

(6) T. Wieland and G. Hörlein, *Ann.*, **591**, 192 (1955).

(7) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

(8) N. E. Good, *Can. J. Chem.*, **34**, 1356 (1956).

(9) H. G. Khorana, *Chem. and Ind. (London)*, 1088 (1955).

(10) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(11) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

(12) T. L. Rebstock, L. E. Weller, and H. M. Sell, *J. Org. Chem.*, **21**, 1515 (1956).

(13) J. W. Wood and T. D. Fontaine, *J. Org. Chem.*, **17**, 891 (1952).