A CONTRIBUTION TO THE CHEMISTRY OF ALKOXYLATED PHENETHYLAMINES - PART 2

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ABSTRACT

Some novel alcoxylated β-phenethylamines were prepared by reduction of corresponding ω-nitrostyrenes with zinc and hydrochloric acid, at pH<3. Isolation as sulphates and use of simple synthetic method gave yields 70-80% of theory. This reduction didn't affect the double bond of allyl group, so allyloxy compounds were prepared. All described sulphates were physiologically active; most active seemed to be non-described before 3,5-dimethoxy-4-allyloxy-β-phenethylamine.

INTRODUCTION

A reduction of ω-nitrostyrenes[1] was chosen for preparation of β-phenethylamines. Rosemund[2] reduced this compounds in two stages: in first stage with zinc and acetic acid (pH>3) to form oxime $RCH_2CH{=}NOH$, in second stage oxime was reduced by sodium amalgam to amine. He isolated only 20-25% of theory, because lot of styrenic polymeres was formed. Späth[3] worked analogous to Rosenmund and also with low yield. Hey[4] tried electroreduction of some ω-nitrostyrene with yield of 47% of theory. A progress in reduction of ω-nitrostyrenes to β-phenethylamines was achieved by use of lithium aluminium hydride, which provided yields 70% of theory[5-7]. Use of complex hydride has some disadvantages, so we reduced ω-nitrostyrenes with zinc in (in contrast to Späth) mineral acid environment, at pH<3, and formed β-phenethylamine we isolate as sulphate from ethanol, because sulphates of β-phenethylamines are only slightly soluble in cold ethanol. We achieved good yields and work procedure was simple.

EXPERIMENTAL

We reduced alkoxylated ω-nitrostyrenes to corresponding β-phenethylamines with zinc and hydrochloric acid, the temperature slowly increasing from 3 to 20°C. The reaction can be described as:

ω-Nitrostyrene + 4 Zn + 9 HCl → β-Phenethylamine·HCl + 4 $ZnCl_2$ + 2 H_2O

Products were isolated as free bases by extraction to benzene. This bases quickly reacted with CO_2 in air and were difficult to obtain in analytically pure state, so sulphates were prepared. Sulphates crystallized good and weren't so soluble as hydrochlorides. Prepared β-phenethylamines were identified as chloroplatinates. As an example of this good-yielding reduction the preparation of 3,5-dimethoxy-4-allyloxy-β-phenethylamine is described.

3,5-dimethoxy-4-allyloxy-β-phenethylamine (**I**)

To ice-cooled and stirred mixture of 42 ml 35% HCl and 42 ml ethanol were alternately in small portions introduced 5.31 g 3,5-dimethoxy-4-allyloxy-ω-nitrostyrene (20 mmol) and 16.5 g zinc powder. Temperature was held at 5°C during this addition, which took 75 min. Mixture was then 1 h stirred at temperature slowly raising from 5 to 10°C and 2 h at 10-12°C. Then 12.5 ml 35% HCl was dropped to mixture during 1 h at 10-15°C. Next 1 h additional 3 g zinc powder were added and stirring was continued 1.5 h at 15-20°C. Remaining zinc was filtered 12 h later and washed with 23 mL water. Clear filtrate was extracted twice with 23 ml benzene to remove non-basic contaminants. Separated water phase was then treated slowly and with cooling with solution 75 g NaOH in 125 ml water; first precipitated $Zn(OH)_2$ finally almost dissolved. Amine was extracted four times 25 ml benzene, united benzene extracts were extracted twice 25 ml water, settled and filtered. Clear slightly yellow filtrate was distilled to remove benzene and then distilled at 10 torr. Amine remained at flask as 4.05 g dense yellow oil (85%), which solidified on cooling to almost colourless crystals with mp 47°C. Free amine was crystallized from hot *n*-hexane (1:10) to form snow-white prisms, mp 50-51°C (dried over KOH at 5 torr).

Anal. calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.08; N 5.91. Found: C, 65.95; H, 8.01; N, 5.75.

3,5-dimethoxy-4-allyloxy-β-phenethylamine sulphate (**II**)

3.56 g 3,5-dimethoxy-4-allyloxy-β-phenethylamine (15 mmol) were dissoved in 16 ml 96% ethanol and 1.48 g 50 % H_2SO_4 (7.5 mmol) were added with stirring and rinsed with 6 ml ethanol. Suspension of crystals was warmed at water bath. After cooling crystals were formed. Product was filtered with suction, washed 15 ml 96% ethanol and dried at 60°C. Colourless, glistening plates weighed 4.20 g (92% of theory). Compound **II** is soluble in hot, slighthly soluble in cold ethanol. Sulphate **II** is also soluble in water; in ether almost insoluble. Crystallization from hot 96% ethanol (1:10) provided big glistening thin plates, which after drying over H_2SO_4 at 5 mmHg had mp 200-204°C and formula $(C_{13}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$.

Anal. calcd. for $(C_{13}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$: H_2O, 5.92; C, 51.30; H, 7.29; N, 4.60; S, 5.27. Found: H_2O, 5.79; C, 51.24; H, 7.65; N, 4.87; S, 5.21.

Table
Neutral Sulfate Salts of the Phenethylamines **III-VI**

No.	Phenethylamine	Sulfate Salt	
		Formula	mp
III	3,5-Dimethoxy-4-*n*-Propoxy-β-Phenethylamine	$(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$	186-188°C
IV	3-Methoxy-4-Ethoxy-β-Phenethylamine	$(C_{11}H_{17}NO_2)_2 \cdot H_2SO_4$	265-270°C
V	3-Methoxy-4-Allyloxy-β-Phenethylamine	$(C_{12}H_{17}NO_2)_2 \cdot H_2SO_4$	240-245°C
VI	3,5-Dimethoxy-4-Ethoxy-β-Phenethylamine	$(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$	250-255°C

Preparation analogous as (**I**), free bases were oils, which didn't solidify at room temp. Sulphates:

It is recommended to keep given stoichiometry of H_2SO_4 during preparation of sulphates; excess H_2SO_4 gives the very soluble hydrogen sulphates, which can be isolated only with difficulty.

PHYSIOLOGICAL ACTIVITY

Physiological effects of compounds **I**-**VI** were examinated only approximately on my body. Sulphates **IV** and **V** in doses 0.1-0.3 g were mild mood-elevators and was also cough calming agents. Compounds **I**, **II**, **III** and **VI** were much more active. Qualitatively there weren't big difference among them and quantitatively their effect decreased: **I** > **II** > **III** > **VI**. As an example effect of sulphate **II** is described. One hour after 20 mg dose per os slight vertigo, light drunkeness and pleasant excitation with locomotion need was observed. Eye perceptions were pricked up, colours seemed to be more warm and objets more plastic. Surroundings was much more interesting than usually. Colourful hallucinations were observed in the dark. Moreover, calming effect to breathing system and some kind of

constriction of digestive system was observed. Sleep at night was restless with bumptious fantasies. Even 12 h after medication described effects were present. More serious studies of physiological activity are in contemplation.

RESULTS AND DISCUSSION

This experimental work provided that reduction of ω-nitrostyrenes with zinc and hydrochloric acid gives yields and quality of β-phenethylamines comparable to use of lithium aluminium hydride. Low yields cited in references had probably this causes: authors reducted with zinc in improper conditions (acetic acid, pH>3) and cooling of the reaction mixture was insufficient, so styrenic derivatives began to polymerize at elevated temperature. They also interrupted the reduction process too soon (we observed minimum 6 h is necessary with good stirring) and didn't always use stoichiometric amount of zinc.

CONCLUSION

Suitable procedure for producing novel alcoxylated β-phenethylamines was introduced and patented[8].
These compounds could be applicated in psychotherapy.

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* *(Karel's voice:)* This is Part 1 of Leminger's *series "The Chemistry of Alkoxylated Phenethylamines"*. It contains a preparation of syringaldehyde by Reimer-Tiemann formylation of 2,6-dimethoxyphenol (33% yield), etherification of that and other phenols with alkyl iodides (67-81%) and condensation of the resulting benzaldehydes with nitromethane in ethanolic KOH (55-67%).