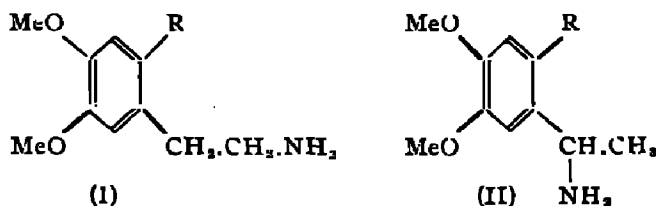


## SEARCH FOR NEW AMOEBACIDES. PART III

By K. L. PATEAK AND B. PATEAK

Some  $\beta$ -(2-alkyl-4:5-dimethoxyphenyl)-ethylamines and  $\alpha$ -(2-alkyl-4:5-dimethoxyphenyl)-ethylamines having  $n$ -C<sub>8</sub>H<sub>17</sub>,  $n$ -C<sub>10</sub>H<sub>21</sub> and  $n$ -C<sub>12</sub>H<sub>25</sub> alkyl substitution have been synthesised.

Syntheses of some  $\beta$ -(2-alkyl-4:5-dimethoxyphenyl)-ethylamines (I) and  $\alpha$ -(2-alkyl-4:5-dimethoxyphenyl)-ethylamines (II) have been described in previous papers (this *Journal*, 1957, 35, 611, 768). Amoebacidal activity of some of these compounds has been described by Kaushiva (*J. Sci. Ind. Res.*, 1957, 16C, 224). In view of the high *in vitro* activity of the compounds (I and II : R =  $n$ -hexyl) it has been considered worthwhile to prepare and examine the activity of compounds of both the series having higher alkyl chains. A few compounds of the type (I) were previously prepared by the Hofmann reaction on the appropriate amides, and it was mentioned in Part I (*loc. cit.*, p. 611) that the yield of the amine decreased with the increase of chain length.



We have failed to prepare the compound (I : R =  $n$ -octyl) by the Hofmann reaction on the appropriate amide. These amines have been prepared by reduction of the  $\beta$ -nitrostyrenes with LiAlH<sub>4</sub>. Yields are poor and vary from 25 to 40% of the theoretical. Appropriate  $\beta$ -nitrostyrenes have been prepared according to the procedure of Lange and Hamburger (*J. Amer. Chem. Soc.*, 1931, 53, 3865).

It has also been observed that the yield of 2-alkyl-4:5-dimethoxy-acetophenone decreases enormously with the increase of chain length.

### \*EXPERIMENTAL

**3:4-Dimethoxyphenyl-*n*-heptyl Ketone.**—A mixture of veratrole (48 g.),  $n$ -caprylic acid chloride (48 g.), dry CS<sub>2</sub> (400 c.c.) and powdered ZnCl<sub>2</sub> (anhyd., 100 g.) was refluxed on a water-bath for 6 hours and then left overnight. CS<sub>2</sub> was removed by distillation and the residue was decomposed by water and then boiled for half an hour with HCl. The mixture was cooled and extracted with benzene. The benzene solution yielded the ketone (42 g.), b.p. 165-68°/4 mm.

The 2:4-dinitrophenylhydrazone was crystallised from alcohol in red needles, m.p. 130-31°. (Found: N, 12.8. C<sub>22</sub>H<sub>22</sub>O<sub>6</sub>N<sub>4</sub> requires N, 12.61%).

\* Melting and boiling points are uncorrected.

3:4-Dimethoxyphenyl-*n*-nonyl ketone was crystallised from alcohol in white needles, b.p. 198-200°/2 mm, m.p. 62°, yield 43%.

The 2:4-dinitrophenylhydrazone was crystallised from alcohol in red needles, m.p. 90-91°. (Found: N, 12.1.  $C_{24}H_{22}O_6N_4$  requires N, 11.87%.)

3:4-Dimethoxyphenyl-*n*-undecyl ketone was crystallised from alcohol in white needles, b.p. 200°/1 mm, m.p. 70-71°, yield 55%.

The 2:4-dinitrophenylhydrazone was crystallised from alcohol in red needles, m.p. 80-81°. (Found: N, 11.3.  $C_{26}H_{24}O_6N_4$  requires N, 11.2%.)

1-*n*-Octyl-3:4-dimethoxybenzene.—3:4-Dimethoxyphenyl-*n*-heptyl ketone (27 g.) in alcohol (30 c.c.) was reduced with amalgamated zinc (90 g.) and HCl. After reduction was over (about 8 hours), the product was diluted with water and the separated oil was extracted with benzene. Benzene was distilled off and the residual oil was distilled in vacuum, b.p. 148-50°/0.4 mm, yield 16 g. (Found: C, 76.6; H, 10.5.  $C_{18}H_{26}O_2$  requires C, 76.81; H, 10.40%.)

1-*n*-Decyl-3:4-dimethoxybenzene.—B.p. 171-72°/2 mm, yield 80%. (Found: C, 77.4; H, 10.6.  $C_{18}H_{26}O_2$  requires C, 77.7; H, 10.79%.)

1-*n*-Dodecyl-3:4-dimethoxybenzene.—B.p. 180°/0.5 mm or 195°/2 mm, yield 59%. (Found: C, 78.01; H, 10.9.  $C_{20}H_{34}O_2$  requires C, 78.4; H, 11.1%.)

2-*n*-Octyl-4:5-dimethoxybenzaldehyde.—Dry HCl gas was passed through a mechanically stirred mixture of 3:4-dimethoxy-*n*-octylbenzene (16 g.), zinc cyanide (12 g.) and dry benzene (110 c.c.) at 0° for 1 hour. Powdered  $AlCl_3$  (anhyd., 8 g.) was then added and the passage of HCl gas was continued. After 3 hours, the temperature was raised to 40-45°, maintained for  $\frac{1}{2}$  hour and finally kept at 50-60° for 2 hours. The mass was then left overnight, decomposed by ice, and refluxed for half an hour. Benzene layer was separated and the aqueous solution was further extracted with benzene. From the combined benzene solution the aldehyde was obtained by distillation; b.p. 170-72°/0.4 mm, yield 6 g. (33.7%).

The 2:4-dinitrophenylhydrazone was crystallised from alcohol in fine red needles, m.p. 185-86°. (Found: N, 12.5.  $C_{23}H_{20}O_6N_4$  requires N, 12.23%.)

2-*n*-Decyl-4:5-dimethoxybenzaldehyde.—B.p. 192-94°/0.4 mm, yield 20%. The aldehyde solidified on cooling. The 2:4 dinitrophenylhydrazone was crystallised from alcohol in red needles, m.p. 167-69°. (Found: N, 11.8.  $C_{25}H_{34}O_6N_4$  requires N, 11.53%.)

2-*n*-Dodecyl-4:5-dimethoxybenzaldehyde.—B.p. 210-12°/1 mm, yield 32%; 2:4-dinitrophenylhydrazone was crystallised from alcohol in red needles, m.p. 151-52°. (Found: N, 11.1.  $C_{27}H_{38}O_6N_4$  requires N, 10.89%.)

2-*n*-Hexyl-4:5-dimethoxy- $\beta$ -nitrostyrene.—2-*n*-Hexyl-4:5-dimethoxybenzaldehyde (7 g.) and nitromethane (1.5 c.c.) were dissolved in alcohol (15 c.c.) and cooled to 5°. To this solution was then slowly added with vigorous stirring an alcoholic KOH solution (3 g. in 25 c.c. alcohol), previously cooled to 5°. The addition was completed in ten minutes and the temperature was not allowed to rise above 15°. After an hour ice-water was added to dissolve the precipitated solid and this solution was then poured with stirring in dilute HCl (10 c.c., conc. HCl in 100 c.c. water). The mass was left for a few hours and filtered. It was crystallised from alcohol in yellow

prismatic needles, m.p. 73-74°, yield 4 g. (Found: C, 65.2; H, 8.1.  $C_{16}H_{23}O_4N$  requires C, 65.5; H, 7.84%).

*2-n-Octyl-4:5-dimethoxy-β-nitrostyrene* was crystallised from alcohol in yellow needles, m.p. 74-75°, yield 20%. (Found: C, 67.5; H, 8.3.  $C_{18}H_{27}O_4N$  requires C, 67.3; H, 8.4%).

*2-n-Decyl-4:5-dimethoxy-β-nitrostyrene* was crystallised from alcohol in yellow needles, m.p. 78-80°, yield 51%. (Found: C, 68.4; H, 8.9.  $C_{20}H_{31}O_4N$  requires C, 68.77; H, 8.88%).

*2-n-Dodecyl-4:5-dimethoxy-β-nitrostyrene* was crystallised from alcohol in yellow needles, m.p. 76-78°, yield 36%. (Found: C, 69.8; H, 9.1.  $C_{22}H_{33}O_4N$  requires C, 70.03; H, 9.28%).

*β-(2-n-Hexyl-4:5-dimethoxyphenyl)-ethylamine Hydrochloride*.—*2-n-Hexyl-4:5-dimethoxy-β-nitrostyrene* (0.01M), dissolved in anhydrous ether, was gradually poured into a suspension of  $LiAlH_4$  (0.04M of commercial variety) in ether. After the addition was over, the mixture was refluxed for 4 hours, cooled and the excess of  $LiAlH_4$  was decomposed with water. The ethereal solution of the amine was filtered, the residual solid was extracted with ether and the combined ethereal solution was washed with water, dried ( $Na_2SO_4$ ) and saturated with dry HCl gas. The precipitated hydrochloride was filtered and crystallised from a mixture of absolute alcohol and ethyl acetate in colorless needles, m.p. 124°, yield 40% of theoretical. Mixed m.p. with our previous sample (*loc. cit.*, p. 617) was undepressed.

*β-(2-n-Octyl-4:5-dimethoxyphenyl)-ethylamine hydrochloride* was crystallised from ethyl acetate in colorless needles, m.p. 120°, yield 33%. (Found: N, 4.4.  $C_{18}H_{29}O_2NCl$  requires N, 4.25%). The *picrate* was crystallised from alcohol in fine needles, m.p. 125-26°.

*β-(2-n-Decyl-4:5-dimethoxyphenyl)-ethylamine hydrochloride* was crystallised from ethyl acetate in colorless needles, m.p. 111°, yield 25% of theoretical. (Found: N, 4.02.  $C_{20}H_{31}O_2NCl$  requires N, 3.9%). The *picrate* was crystallised from alcohol in brown needles, m.p. 123-24°.

*β-(2-n-Dodecyl-4:5-dimethoxyphenyl)-ethylamine hydrochloride* was crystallised from ethyl acetate in colorless needles, m.p. 117-19°, yield 25% of theoretical. (Found: N, 3.7.  $C_{22}H_{33}O_2NCl$  requires N, 3.63%). The *picrate* was crystallised from alcohol in brown needles, m.p. 126°.

*2-n-Octyl-4:5-dimethoxy-acetophenone*.—A mixture of acetyl chloride (3 g.),  $AlCl_3$  (anhyd., 12 g.) and  $CS_2$  (25 c.c.) was cooled in an ice-bath for half an hour. To this mixture was slowly added with shaking *1-n-octyl-3:4-dimethoxybenzene* (9 g.). The mass was left overnight and later on heated on a water-bath till HCl had ceased to evolve.  $CS_2$  was removed by distillation and the mass was decomposed with ice. It was then extracted with benzene, the demethylated product was extracted out with NaOH solution which was subsequently methylated, and the combined product was distilled; b.p. 158-62°/0.4 mm, yield 30% of theoretical. (Found: C, 73.6; H, 9.3.  $C_{18}H_{25}O_3$  requires C, 73.98; H, 9.59%). The semicarbazone could not be prepared in solid state.

*2-n-Decyl-4:5-dimethoxyacetophenone* boiled at 168-70°/0.4 mm, yield 35% of theoretical. (Found: C, 74.8; H, 10.3.  $C_{20}H_{22}O_2$  requires C, 75.01; H, 10.0%).

*2-n-Dodecyl-4:5-dimethoxyacetophenone* was distilled at 198-200°/0.4 mm, yield 25% of theoretical. (Found: C, 75.50; H, 10.20.  $C_{22}H_{26}O_2$  requires C, 75.86; H, 10.35%).

*α-(2-n-Octyl-4:5-dimethoxyphenyl)-ethylamine Hydrochloride*.—Crude *2-n-octyl-4:5-dimethoxyacetophenone oxime* was reduced with sodium in absolute alcohol. The reduced mass was made acidic with HCl (conc.), alcohol was removed by distillation under reduced pressure and the precipitated sodium chloride was dissolved in minimum amount of water. It was filtered and the residual crude hydrochloride was washed with benzene and crystallised from hot water in colorless short needles, m.p. 162-63°. (Found: N, 4.3.  $C_{18}H_{22}O_2NCl$  requires N, 4.25%). The *picrate* was crystallised from alcohol in brown needles, m.p. 180°.

*α-(2-n-Decyl-4:5-dimethoxyphenyl)-ethylamine Hydrochloride*.—Crude *2-n-decyl-4:5-dimethoxyphenylacetophenone oxime* was reduced in the usual manner. The hydrochloride was crystallised from hot water in short needles, m.p. 150-52°. (Found: N, 4.1.  $C_{20}H_{24}O_2NCl$  requires N, 3.9%). The *picrate* was crystallised from dilute alcohol in brown needles, m.p. 146-48°.

*α-(2-n-Dodecyl-4:5-dimethoxyphenyl)-ethylamine hydrochloride* was crystallised from hot water in colorless needles, m.p. 144°. (Found: N, 3.8.  $C_{22}H_{26}O_2NCl$  requires N, 3.63%). The *picrate* was crystallised from dilute alcohol in brown needles, m.p. 160-61°.

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