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Reissert Compound Studies. X. The Synthesis of Armepavine (I)

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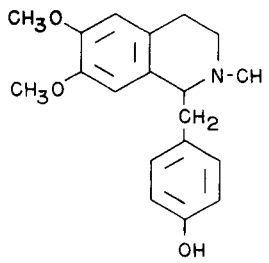
Several total syntheses of the alkaloid armepavine (I) have been reported (3-5). All employed condensation of β-(3,4-dimethoxyphenyl)ethylamine with a substituted phenylacetyl chloride to yield amides of general structure II (R = NO_2, R' = H (3); R = $OCH_2C_6H_5$, R' = H (4); R = R' = $-OCH_2O-$ (5)). Cyclization of the amide by the Bischler-Napieralski reaction, quaternization with methyl iodide, reduction and conversion of the substituents on the benzyl group to hydroxyl gave armepavine in from 5.5 to 30% overall yield.

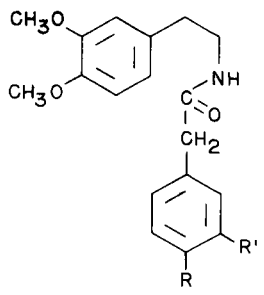
In view of the ability of Reissert compounds to condense with aldehydes (6, 7) and with alkyl halides (8), and the previous utilization of these intermediates for alkaloid synthesis (9-11), it appeared likely that armepavine could be easily synthesized by a similar method employing 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (III) as the key intermediate.

The preparation of III from β-(3,4-dimethoxyphenyl)ethylamine has been previously described (11). Condensation of the anion of this Reissert compound (III) with *p*-benzyloxybenzaldehyde at -40° led to the isolation of *p*-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinyl benzoate (IV; R = $OCOC_6H_5$, R' = $CH_2C_6H_5$) in 82% yield. Hydrolysis with aqueous ethanolic potassium hydroxide afforded *p*-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (IV; R = OH, R' = $CH_2C_6H_5$) in 94% yield. Reduction of this carbinol using hydrogen bromide and zinc dust led to the formation in 95% yield of 1-(*p*-hydroxybenzyl)-6,7-dimethoxyisoquinoline (IV; R = R' = H). When the latter was treated with methyl iodide, a quantitative yield of the methiodide hydrate was formed. Sodium borohydride reduction of the methiodide gave rise to d,l-armepavine (I) in quantitative yield. The melting point of I agreed with that published in the literature (3-5) and its infrared spectra was consistent with the structure assigned. The overall yield of armepavine from β-(3,4-dimethoxyphenyl)ethylamine by this sequence is 44%.

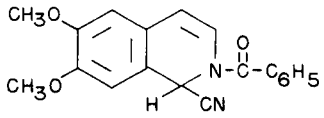
Other routes to the alkaloid also were investigated. The carbinol IV (R = OH, R' = $CH_2C_6H_5$) was oxidized with dichromate to 1-(*p*-benzyloxybenzoyl)-6,7-dimethoxyisoquinoline (V; R = $OCH_2C_6H_5$) in 82% yield but an attempted Wolff-Kishner reduction of this ketone failed. 1-(*p*-Benzyloxybenzyl)-6,7-dimethoxyisoquinoline (IV; R = H, R' = $CH_2C_6H_5$) also was obtained in 22% overall yield by hydrolysis of the condensation product of *p*-benzyloxybenzyl bromide and 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (III). Debenzylation with 15% hydrochloric acid yielded 85% of 1-(*p*-hydroxybenzyl)-6,7-dimethoxyisoquinoline (IV; R = R' = H). Since this was converted to d,l-armepavine (I) as described above, this sequence also comprises a total synthesis of the alkaloid.



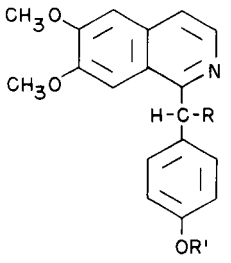
I



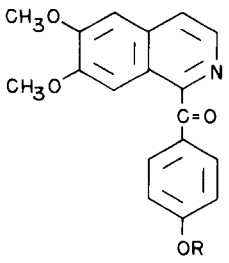
II



III



IV



V

EXPERIMENTAL (12)

p-Benzyloxyphenyl-1-(6, 7-dimethoxyisoquinolyl)carbinyl Benzoate (IV; R = $OCOC_6H_5$, R' = $CH_2C_6H_5$).

Condensation (7) of III (11) with *p*-benzyloxybenzaldehyde in the presence of phenyl lithium at -40° afforded this compound in 82% yield. Recrystallization from ethanol gave fine fluffy needles, m.p. 179-180°.

Anal. Calcd. for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77. Found: C, 76.19; H, 5.34; N, 2.79.

p-Benzyloxyphenyl-1-(6, 7-dimethoxyisoquinolyl)carbinol (IV; R = OH, R' = $CH_2C_6H_5$).

Hydrolysis (6) of the benzoate led to this compound in 94% yield. Recrystallization from ethanol gave a colorless solid, m.p. 135-136°.

Anal. Calcd. for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.81; H, 5.83; N, 3.51.

p-Hydroxyphenyl-1-(6, 7-dimethoxyisoquinolyl)carbinol (IV; R = OH, R' = H).

A solution of 0.001 mole of the carbinol-benzyl ether (IV; R = OH, R' = $CH_2\Phi$) and 10 ml. of 15% hydrochloric acid was refluxed for 30 minutes, diluted with water and washed with chloroform. Ammonium hydroxide was then added and the product isolated in 81% yield. After recrystallization from ethyl acetate-hexane, the colorless solid had a m.p. of 153-155°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 68.93; H, 5.75; N, 4.34.

1-(*p*-Benzyloxybenzoyl)-6, 7-dimethoxyisoquinoline (V; R = $CH_2C_6H_5$).

To a solution of 0.002 mole of IV (R = OH, R' = $CH_2C_6H_5$) in 10 ml. of glacial acetic acid was added 0.66 g. (0.0022 mole) of sodium dichromate in 5 ml. of glacial acetic acid. The mixture was heated on the steam bath for a few minutes, diluted with water and made basic to give a solid in 82% yield. From ethanol-water it had a m.p. of 146-147°.

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.09; H, 5.29; N, 3.47.

1-(*p*-Hydroxybenzoyl)-6, 7-dimethoxyisoquinoline (V; R = H).

Debenzylation of the above ketone with 15% hydrochloric acid afforded a quantitative yield of this compound. From ethanol-water the hydrate had a m.p. of 120-122°.

Anal. Calcd. for $C_{18}H_{15}NO_4 \cdot H_2O$: C, 66.04; H, 5.24; N, 4.28. Found: C, 66.31; H, 5.01; N, 3.91.

Recrystallization of the hydrate from ethyl acetate-hexane gave the anhydrous compound, m.p. 159-160°.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.67; H, 4.86; N, 4.27.

1-(*p*-Hydroxybenzyl)-6, 7-dimethoxyisoquinoline (IV; R = R' = H).

Hydrogen bromide was bubbled through a solution of *p*-benzyloxyphenyl-1-(6, 7-dimethoxyisoquinolyl)carbinol in 20 times its weight of glacial acetic acid for 20 minutes. The mixture was allowed to stand overnight and then treated with an 11 fold excess of zinc dust with stirring over a period of 30 minutes. After heating on the steam bath 30 minutes, the mixture was filtered, diluted with water and made basic to give this compound in 95% yield. From ethanol-ethyl acetate it had a m.p. of 216-218°.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.12; H, 5.75; N, 4.71.

1-(*p*-Hydroxybenzyl)-6, 7-dimethoxyisoquinoline Methiodide Hydrate.

A solution of IV (R = R' = H) in 15 times its weight of methyl iodide and a small amount of methanol was refluxed for 3 hours, poured into ether and filtered to give a 100% yield of product, m.p. 156-160° (from water).

Anal. Calcd. for $C_{18}H_{17}NO_3 \cdot CH_3I \cdot H_2O$: C, 50.14; H, 4.87; N, 3.08; I, 27.88. Found: C, 50.20; H, 4.80; N, 3.12; I, 27.66.

Armepavine (I).

A mixture of 0.13 g. (0.000285 mole) of 1-(*p*-hydroxybenzyl)-6, 7-dimethoxyisoquinoline methiodide hydrate, 0.30 g. of sodium borohydride, 0.5 ml. of water, and 15 ml. of methanol was refluxed for 2 hours with stirring. After removal of most of the methanol, the mixture was poured onto ice. The *p*H was adjusted to about 8 and ether extraction yielded 0.09 g. (100%) of armepaveine, m.p. 159-161° (from ethyl acetate-hexane), reported (3) m.p. 159-161.5°.

p-Benzyloxybenzyl Bromide.

A solution of 20.0 g. (0.0935 mole) of the corresponding alcohol (13) in 300 ml. of anhydrous ether was treated with 9.35 ml. (0.0985 mole) of phosphorus tribromide at 10° with stirring. Stirring was continued in the ice bath for 10 minutes and at room temperature for 75 minutes. After pouring onto ice, the ether was evaporated and filtration yielded 24.4 g. (94%) of solid, m.p. 83-85°. Recrystallization from hexane gave fine needles, m.p. 85-86.5°.

Anal. Calcd. for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found: C, 60.92; H, 4.60.

1-(*p*-Benzyloxybenzyl)-2-benzoyl-6, 7-dimethoxy-1, 2-dihydroisoquinaldonitrile.

Condensation of III (11) (5.5 g., 0.0172 mole) with *p*-benzyloxybenzyl bromide (4.86 g., 0.0176 mole) at -45° in the presence of phenyl lithium (8) yielded a brown gum. This was recrystallized from ethanol, yielding 2.3 g. of cream colored solid, m.p. 174-177°. Evaporation of the mother liquors to about one-half volume caused 1.95 g. (22%) of the desired product to precipitate. Recrystallization from ethanol gave material, m.p. 177-178°.

Anal. Calcd. for $C_{33}H_{28}N_2O_4 \cdot C_2H_5OH$: C, 74.71; H, 6.09; N, 4.98. Found: C, 74.68; H, 5.90; N, 4.81.

The solid of m.p. 174-177° was recrystallized from ethanol-ethyl acetate to give fine colorless needles, m.p. 183-183.5°. The infrared spectrum contained a peak at 3400 cm^{-1} and none in the carbonyl region. This material was not further investigated.

Anal. Found: C, 61.77, 61.69; H, 5.46, 5.54; N, 2.96, 2.82; Br, 16.44.

1-(*p*-Benzyoxybenzyl)-6, 7-dimethoxyisoquinoline (IV; R = H, R' = $CH_2C_6H_5$).

Basic hydrolysis (8) of 1-(*p*-benzyoxybenzyl)-2-benzoyl-6, 7-dimethoxy-1, 2-dihydroisoquinaldonitrile ethanolate afforded this compound in quantitative yield. From hexane it formed fine colorless needles, m.p. 103-105°.

Anal. Calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.64. Found: C, 77.86; H, 6.15; N, 3.27.

1-(*p*-Hydroxybenzyl)-6, 7-dimethoxyisoquinoline (IV; R = R' = H).

Debenzylation of 1-(*p*-benzyloxybenzyl)-6, 7-dimethoxyisoquinoline with 15% hydrochloric acid gave rise to an 85% yield of this compound, identical in all respects to the sample reported above.

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(12) All melting points were taken in capillaries and are corrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

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