

## TOTAL SYNTHESIS OF PSEUDO TYPE OF PROTOPINE ALKALOIDS

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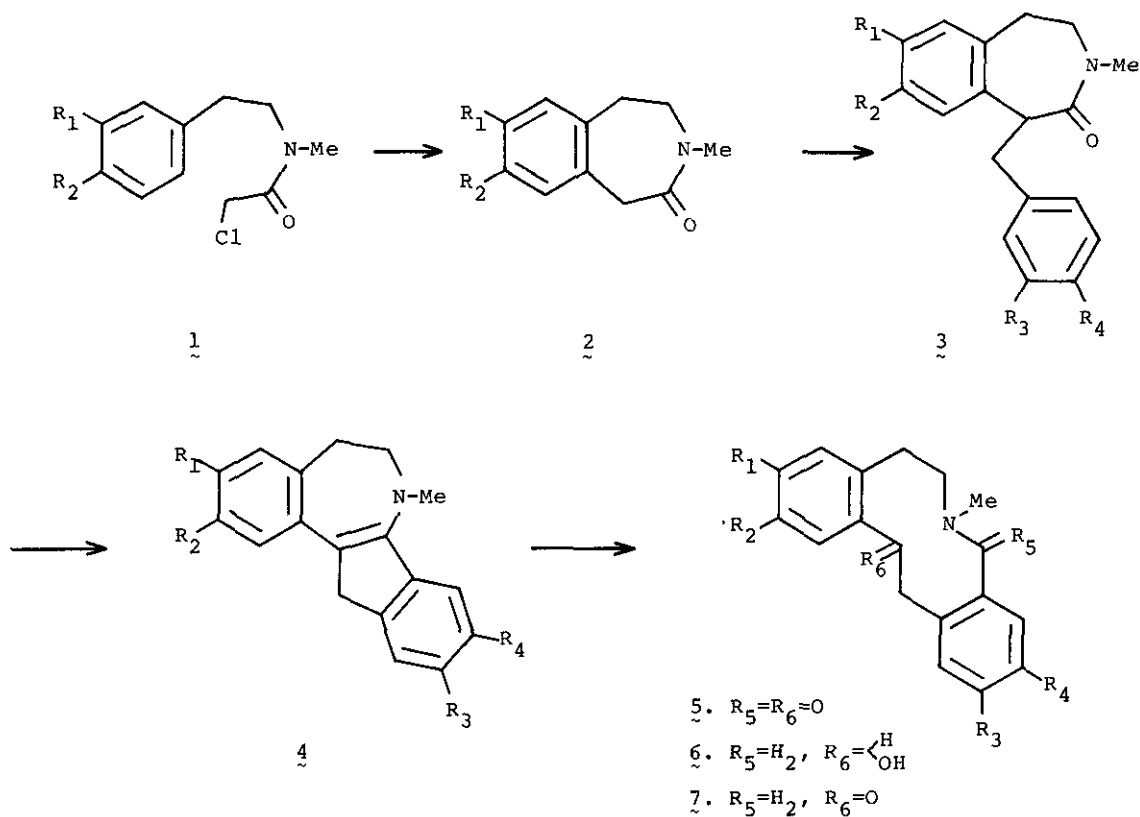
Photolysis of the chloroacetamides (1) gave the benzazepinones (2), whose benzyl derivatives (3) were cyclized to the benz[d]-indeno[1,2-b]azepines (4) by treatment with phosphoryl chloride. Dye-sensitized photo-oxygenation of 4, followed by lithium aluminum hydride reduction and manganese dioxide oxidation of the products 5, led to a total synthesis of pseudoprotopine (7a) and fagarine II (7b) as well as their analogs 7c and 7d.

The synthesis of protopine alkaloids has been performed owing to chemical<sup>1</sup> or photochemical<sup>2</sup> transformation reactions of protoberberine alkaloids. The present communication describes the total synthesis of pseudo type of protopine alkaloids by a common route, consisting of the photo-oxygenative ring enlargement reaction<sup>3</sup> of a tetrahydrobenz[d]indeno[1,2-b]azepine moiety and further elaboration of a resultant dibenzazecinedione product, and leading to pseudoprotopine (7a) and fagarine II (7b) as well as the preconceived alkaloids 7c and 7d.

Base-induced photocyclization<sup>4</sup> of N-chloroacetyl-N-methylphenethylamines 1a and 1b (irradiated with high pressure mercury lamp, two equivalents of sodium hydroxide) provided the 3-benzazepin-2-ones 2a and 2b (>50 %), which were heated with 3,4-methylenedioxy or 3,4-dimethoxybenzyl bromide in a mixture of dry tetrahydrofuran and N,N-dimethyl formamide (10:1 volume %) in the presence of sodium hydride.<sup>5</sup> The resultant 1-benzylazepinone 3a (83 %), mp 182-184 °C,  $[\nu]_{\text{max}}^{\text{Nujol}}$  1645  $\text{cm}^{-1}$ ;  $\delta$  (CDCl<sub>3</sub>) 2.92 (s, 3H, N-CH<sub>3</sub>), 2.8-4.1 (m, 6H), 4.33 (dd, 1H, J = 6, 9 Hz, C<sub>1</sub>-H), 5.93 (s, 4H, 2×OCH<sub>2</sub>O), 6.66, 6.75 (ds, 2H, C<sub>6</sub>- or C<sub>9</sub>-H), 6.79, 6.84 (ds, 3H, C<sub>2',5',6'</sub>-H's) was treated with phosphoryl chloride in toluene (reflux, 5 h) to give 4a (70 %), mp 150-151 °C, which was spectrally identical with 2,3,9,10-bismethylenedioxy-7-methyl-5,6,7,12-tetrahydrobenz[d]indeno[1,2-b]azepine reported

previously by Kametani and his co-workers.<sup>6a</sup> Similar cyclization of 3b, mp 112-115 °C, 3c, mp 169-170 °C, and 3d, mp 157-158 °C, proceeded smoothly to yield the known enamines, 4b (80 %), mp 187-188 °C (lit.<sup>6a</sup> mp 189-191 °C), 4c (85 %), mp 176-179 °C (lit.<sup>6a</sup> mp 175-177 °C) and 4d (79 %), mp 182-183 °C (lit.<sup>6b</sup> mp 187-188 °C), respectively. Thus, the scheme [1→2→3→4] constitutes the convenient alternative route to the benz[d]indeno[1,2-b]azepine ring system.

Photo-oxygenation of 4a was carried out (methylene blue, 650 W-tungsten-iodine lamp, 18-20 °C, 10 min) on the basis of the preliminary experiments.<sup>3</sup> The ir spectrum of the product 5a displayed absorption maxima at 1688 and 1618 cm<sup>-1</sup> due to desoxybenzoin function and amide group, suggesting the presence of the ten-membered amido-ketone ring system, as shown in the figure. Successive reduction of this



1,2: a.  $R_1+R_2=\begin{matrix} O \\ \diagup \\ C \\ \diagdown \\ O \end{matrix}$ ; b.  $R_3=R_4=OMe$

3-7: a.  $R_1+R_2=R_3+R_4=\begin{matrix} O \\ \diagup \\ C \\ \diagdown \\ O \end{matrix}$ ; b.  $R_1+R_2=\begin{matrix} O \\ \diagup \\ C \\ \diagdown \\ O \end{matrix}$ ,  $R_3=R_4=OMe$ ;

c.  $R_1=R_2=OMe, \ R_3+R_4=\begin{matrix} O \\ \diagup \\ C \\ \diagdown \\ O \end{matrix}$ ; d.  $R_1=R_2=R_3=R_4=OMe$

dibenzazecinedione 5a with lithium aluminum hydride in tetrahydrofuran (reflux, 3 h) produced an amino alcohol 6a (79 % from 4a) [ $\nu_{\max}^{\text{Nujol}}$  3545  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 2.12 (s, 3H, N- $\text{CH}_3$ ), 2.2-3.1 (m, 5H,  $\text{C}_5$ -H<sub>2</sub>,  $\text{C}_6$ -H<sub>2</sub> and  $\text{C}_{13}$ -H), 3.23 (d, 1H,  $J = 15$  Hz,  $\text{C}_8$ -H), 3.32 (dd, 1H,  $J = 2, 16$  Hz,  $\text{C}_{13}$ -H), 3.95 (d, 1H,  $J = 15$  Hz,  $\text{C}_8$ -H), 5.38 (dd,  $J = 2, 8$  Hz,  $\text{C}_{14}$ -H), 6.63, 6.67, 6.83, 7.14 (each s, 4H, aromatic H's). Treatment of 6a with activated manganese dioxide<sup>7</sup> in chloroform (room temperature, 1 h) led to the mild oxidation of the hydroxyl function to ketone carbonyl to give pseudoprotopine (7a) (85 %), mp 201-202 °C (lit.<sup>8</sup> mp 200-202 °C, lit.<sup>1d</sup> mp 200-201 °C), whose spectral data (ir, uv and  $^1\text{H}$  nmr) were identical with those of the natural product.<sup>1d,8</sup> In the same manner as described above, 4b, c, d gave the corresponding crystalline amino-alcohols, 6b (74 %), mp 174-175 °C, 6c (72 %), mp 161-170 °C, and 6d (83 %), mp 157-158 °C, through the amido-ketones 5b, c, d of the dibenzazecine type.

Application of the aforementioned oxidation to 6b afforded the alkaloid, fagarine II (7b) (86 %), mp 200-202 °C (lit.<sup>1b,9</sup> mp 200-201 °C), whose ir and uv spectra were identical with those of the authentic specimen.<sup>1b</sup> Further, the  $^1\text{H}$  nmr spectrum of 7b displayed peaks at  $\delta$  ( $\text{CDCl}_3$ ) 1.90 (s, 3H, N- $\text{CH}_3$ ), 2.51 (m, 2H,  $\text{C}_6$ -H), 2.90 (m, 2H,  $\text{C}_5$ -H), 3.54 (s, 2H,  $\text{C}_8$ -H), 3.78 (s, 2H,  $\text{C}_{13}$ -H), 3.89, 3.92 (each s, 4H,  $2 \times \text{OCH}_3$ ), 5.98 (s, 2H,  $\text{OCH}_2\text{O}$ ), 6.67, 6.70 (each s, 2H,  $\text{C}_4$ -H and  $\text{C}_9$ - or  $\text{C}_{12}$ -H), 6.80 (s, 1H,  $\text{C}_{12}$ - or  $\text{C}_9$ -H), 6.99 (s, 1H,  $\text{C}_1$ -H), in good accordance with the data reported for protopine alkaloids.<sup>10</sup>

Similarly, 7c (90 %), mp 160-162 °C (ether), [ $\nu_{\max}^{\text{Nujol}}$  1670  $\text{cm}^{-1}$ ;  $\nu_{\max}^{\text{CHCl}_3}$  1650  $\text{cm}^{-1}$ ;  $\lambda_{\max}^{\text{EtOH}}$  288  $\text{m}\mu$  ( $\epsilon$  9,800);  $\delta$  ( $\text{CDCl}_3$ ) 1.83 (s, 3H, N- $\text{CH}_3$ ), 2.56 (m, 2H,  $\text{C}_6$ -H), 3.00 (m, 2H,  $\text{C}_5$ -H), 3.56 (s, 2H,  $\text{C}_8$ -H), 3.72 (s, 2H,  $\text{C}_{13}$ -H), 3.93 (s, 6H,  $2 \times \text{OCH}_3$ ), 5.99 (s, 2H,  $\text{OCH}_2\text{O}$ ), 6.71, 6.73 (each s, 2H,  $\text{C}_4$ -H and  $\text{C}_9$ - or  $\text{C}_{12}$ -H), 6.80 (s, 1H,  $\text{C}_{12}$ - or  $\text{C}_9$ -H), 7.10 (s, 1H,  $\text{C}_1$ -H)] and 7d (amorphous, 92 %, methiodide mp 173 °C) [free base,  $\nu_{\max}^{\text{Nujol}}$  1660  $\text{cm}^{-1}$ ;  $\nu_{\max}^{\text{CHCl}_3}$  1650  $\text{cm}^{-1}$ ;  $\lambda_{\max}^{\text{EtOH}}$  282  $\text{m}\mu$  ( $\epsilon$  9,500);  $\delta$  ( $\text{CDCl}_3$ ) 1.84 (s, 3H, N- $\text{CH}_3$ ), 2.56 (m, 2H,  $\text{C}_6$ -H), 3.00 (m, 2H,  $\text{C}_5$ -H), 3.58 (s, 2H,  $\text{C}_8$ -H), 3.76 (s, 2H,  $\text{C}_{13}$ -H), 3.89 (s, 3H,  $\text{OCH}_3$ ), 3.93 (s, 9H,  $3 \times \text{OCH}_3$ ), 6.76 (s, 2H,  $\text{C}_4$ -H and  $\text{C}_9$ - or  $\text{C}_{12}$ -H), 6.85 (s, 1H,  $\text{C}_{12}$ - or  $\text{C}_9$ -H), 7.12 (s, 1H,  $\text{C}_1$ -H) were readily obtained in this method.

Thus, the new method offers a total synthesis of four kinds of pseudo type of protopine alkaloids, although any report on the isolation of the latter two 7c and 7d has not yet been presented.

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Received, 1st October, 1979