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NITROGEN BRIDGEHEAD COMPOUNDS PART 16[1]. FACILE TOTAL SYNTHESIS OF 7,8-DIHYDRO--13H-INDOLO[2',3':3,4]PYRIDO[2,1-b]QUINAZOLIN-5-ONE (RUTECARPINE).

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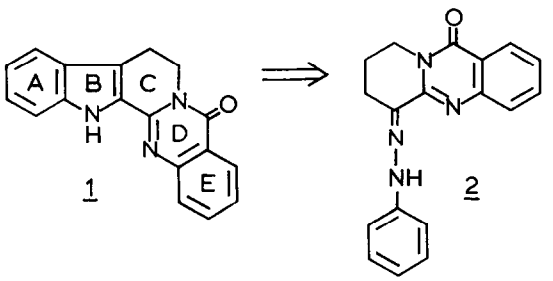
Rutecarpine 1 has been synthetised from hydrazone 2 in high yield by Fischer indole synthesis. Hydrazone 2 has been prepared from 3 with benzenediazonium chloride or 5 with phenylhydrazine. 2 Shows a solvent dependent E-Z isomerism.

The 7,8-dihydro-13H-indolo[2'3':3,4]pyrido[2,1-b]quinazolin-5-one (Rutecarpine) 1 is one of the constituent parts of the Chinese drugs Wu-Chu-Yu[2] and Shih-Hu[3], both obtained from Evodia Rutaecarpa. Rutecarpine 1, itself was reported[4] to increase the arterial pressure. The common principle of Rutecarpine synthesis is to build[5] up the connection of the C and D rings, starting from tryptamine or its derivatives. Another possibility is provided by the synthesis and the rearrangement of the 6-phenylhydrazono-6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one 2, derived from Rutecarpine 1 by retrospective analysis, by the disconnection of the indole ring. The Fischer indole synthesis has been used[6] to synthesise several alkaloids.



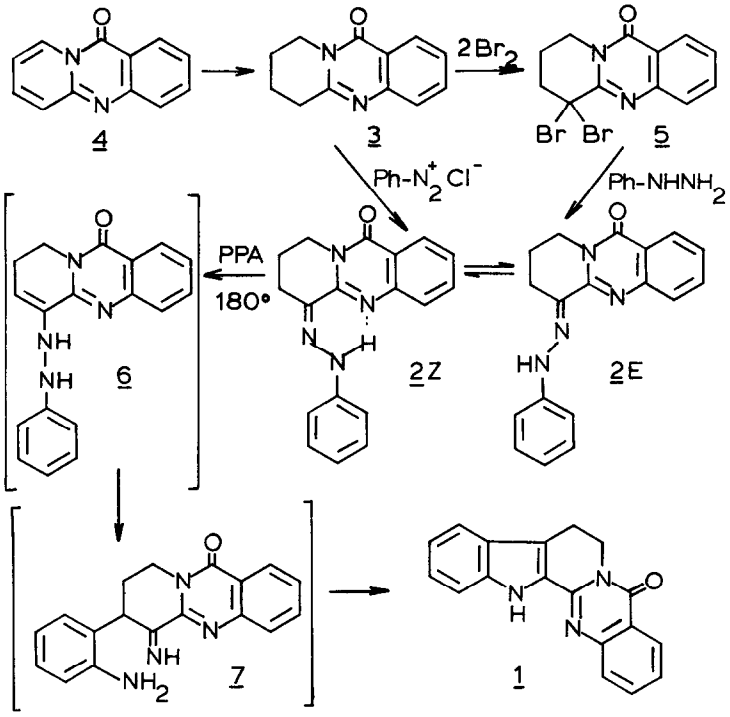
1 2

For the preparation of hydrazone 2 we started from 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolinone 3, for which the reactivity of the 6 position with electrophilic reagents (i.e. bromination, formylation) has been reported[7].

Pyridoquinazoline alkaloide[8] 3 can be prepared in very good yield (90 and 92%, resp.) by reacting[5k,1] 2-piperidone and anthranilic acid, or by the reduction[9] of pyridoquinazoline 4. The latter was prepared[10] from 2-amino-pyridine and 2-chlorobenzoic acid in 75% yield or from 2-bromo-pyridine and anthranilic acid in 85% yield.

From tetrahydro-pyridoquinazoline 3 we prepared hydrazone 2[11] (mp. 182-4 °C, from PrOH; C,H,N) by bromination followed by reaction with phenylhydrazine (50 mmol of 3 was reacted with 100 mmol of bromine in 300 mL of 75% acetic acid, in the presence of sodium acetate (100 mmol) at 50°C for 1h; yield 98%. The resulting dibromo compound[12] (30 mmol) was heated with phenylhydrazine (120 mmol) in

ethanol (120 mL) at boiling point for 4 h, yield 81%], or directly by diazotization with benzenediazonium chloride [10 mmol of 3 in 10mL of 50% acetic acid was reacted 10 mmol of benzenediazonium chloride (prepared from aniline in 5 mL of water) at -5 °C for 3 h; yield 90%]. (see Scheme).



Hydrazone 2 was subjected to Fischer indole synthesis, heating hydrazone 2 (1 g) or its hydrochloride salt (1 g, mp 240 °C decomp. from EtOH) in 10 g of PPA (Fluka) for 0,5 h at 180 °C. After diluting the reaction mixture with water 90 mL the Rutecarpine 1 precipitated in 92 and 98% yield, resp. (mp 258 °C, from EtOAc, whose IR UV and ^{1}H-NMR spectra were superimposable upon those of the authentic sample[5]). The rearrangement of hydrazone 2 takes place from its 8,9-dihydro tautomeric form. (see Scheme).

The generalization of the above synthesis provides a facile synthesis route for the preparation of Rutecarpine derivatives substituted on the A ring, and having favourable biological activity.

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11./ Hydrazone 2 shows a solvent dependent E-Z geometric isomerism. E:Z ratio was found by H^1-NMR in $CDCl_3$ 0:100 [δ2.09 (2,m,8-H_2), 2.85 (2,t,7-H_2), 4.07 (2,t 9-H_2), 6,80-6,80 (8,m,2,3,4-H and Ph), 8.26 (1,d,1-H), 14.60 (1,br,NH)] and DMSO-d_6 45:55 (δNH 9,91 and 14,52ppm). UV EtOH λ_{max}: 388nm (lgε 4.36), 296 (3.94), 250(4,30), 231(4.41); 12./ mp: 146-8 °C; lit(6): 148-9 °C, yield 35%.

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