A New Annelation Reaction of Cyclic Schiff Bases

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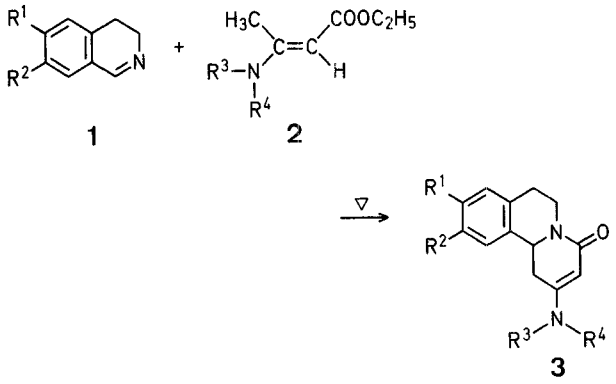
Derivatives of benzo[*a*]quinolizine have been shown to possess valuable pharmacological activity[1], and have also been used as intermediates in the total synthesis of berberines[2,3]. We now report on the synthesis of some previously unknown derivatives of benzo[*a*]quinolizine **3a–g** based on the annelation reaction of cyclic Schiff bases **1** with ethyl 3-amino-2-butenoates **2**.

The 2-amino-4-oxo-1,4,6,7-tetrahydro-11b*H*-benzo[*a*]quinolizines **3** are obtained on heating of an equimolar mixture of 3,4-dihydroisoquinolines **1** and esters **2** at 150 to 210 °C in an inert atmosphere (preferably in a sealed tube) in yields up to 75%.



1 **2** **3**

The structures of all compounds **3** obtained were confirmed by microanalyses, spectral data, and, in some cases, by alternative syntheses from **4**[4] and **5**[5].

2-Amino-4-oxo-1,4,6,7-tetrahydro-11b*H*-benzo[*a*]quinolizines 3; General Procedure:

Equimolar amounts of 3,4-dihydroisoquinoline **1** and the ethyl 3-amino-2-butenoate **2** are placed in a glass tube which is then filled with argon and sealed. The tube is heated for the time and temperature given in the Table, cooled, and opened. The product is isolated either by crystallization from the solvent given or by column chromatography on alumina with ethyl acetate as eluent.

Alternative Synthesis of 3 from 4 and an Amine:

2,4-Dioxo-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine **4** (1 mmol) is dissolved in ethyl acetate (30 ml), heated under reflux, and treated drop-wise with the amine (3 mmol). Boiling is continued until **4** cannot be detected by T.L.C. (alumina plates, ethyl acetate). The solvent is then removed and the residue recrystallized; yield: 64–93%.

Alternative Synthesis of 3 from 5 and an Amine:

A mixture of 6,7-dimethoxy-1-(3-methoxycarbonyl-2-oxopropyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**5**; 0.34 g, 1 mmol) and the amine (4 mmol) in methanol (20 ml) is heated under reflux for 9 h. The solvent is then removed under reduced pressure and the residue chromatographed on a column of alumina, eluting with ethyl acetate to give **3**; yield: 24–78%.

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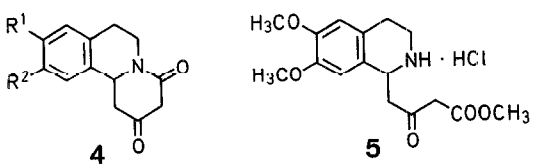
Table. 2-Amino-4-oxo-1,4,6,7-tetrahydro-11b*H*-benzo[*a*]quinolizines **3a–g**

Product No.	R^1	R^2	R^3	R^4	Reaction conditions temperature/time	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (nujol) ν [cm^{-1}]
3a[b]	H	H	C_6H_5	H	210–220 °C/5 h	24	299–301° (C_2H_5OH)	$C_{19}H_{18}N_2O$ (290.4)	3260, 1640, 1590
3b	OCH_3	OCH_3	C_2H_5	C_2H_5	150–160 °C/6 h	48	120–122° (ether)	$C_{19}H_{26}N_2O_3$ (330.4)	1610, 1580
3c	OCH_3	OCH_3	*t*-C_4H_9	H	170–180 °C/7 h	26	246–248° (C_2H_5OAc)	$C_{19}H_{26}N_2O_3$ (330.4)	3270, 1620, 1570
3d	OCH_3	H	CH_3	CH_3	150–160 °C/5 h	73	84–86° (ether)	$C_{16}H_{20}N_2O_2$ (272.3)	1610, 1560
3e	OCH_3	OCH_3	$(CH_2)_2$–O–$(CH_2)_2$		160–170 °C/9 h	58	218–220° (C_2H_5OAc)	$C_{19}H_{24}N_2O_4$ (344.4)	1640, 1590
3f	OCH_3	OCH_3	$(CH_2)_5$		210–220 °C/6 h	37	132–134° (THF/hexane)	$C_{20}H_{26}N_2O_3$ (342.4)	1610, 1580
3g	H	H	$(CH_2)_5$		200–210 °C/6 h	48	118–120° (C_2H_5OAc)	$C_{18}H_{22}N_2O$ (282.4)	1630, 1580

[a] The microanalyses were in good agreement with the calculated values, C ± 0.19, H ± 0.19, N ± 0.18.

[b] The ^{1}H-N.M.R. spectrum (300 MHz) is in accord with the structure.



4 **5**

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