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A NEW SYNTHESIS OF BENZO[a]QUINOLIZINES RELATED TO IPECAC ALKALOIDS

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Acylation of 1-methyl-3,4-dihydroisoquinolines with substituted acryloyl chlorides followed by photocyclization provided a useful synthetic route for benzo[a]quinolizines (6-9).

A number of methods of synthesizing benzo[a]quinolizines have been developed, because emetine, one of the representative alkaloids of this class of heterocyclic ring systems, is known for its potent clinical activity.[1]

As an extension of the photocyclization of enamides[2], we now report that the 2-acryloyl-1-methylenetetrahydroisoquinolines (3a-c) underwent ready photocyclization to yield the benzo[a]-quinolizines (5a-c)[3] , thus adding a new route to the previously established preparations.

Treatment of a benzene solution of the 1-methyl-3,4-dihydroisoquinoline (1) with substituted acryloyl chlorides (2a-c)[4] in the presence of triethylamine afforded the corresponding 1-methylene-2-acryloylisoquinolines (3a-c) quantitatively, which showed i.r. absorptions at ν max 1610 (3a) and 1655 (3b and c) cm^{-1} due to an enamide grouping. Due to instability of the enamides (3a-c), which were readily oxidised to the oxo-amides (4a-c), the benzene filtrate of the acylation mixture, without further purification, was irradiated with a low pressure mercury lamp at room temperature. T.l.c. of the reaction mixture showed complete conversion after 5-10 hr's irradiation.

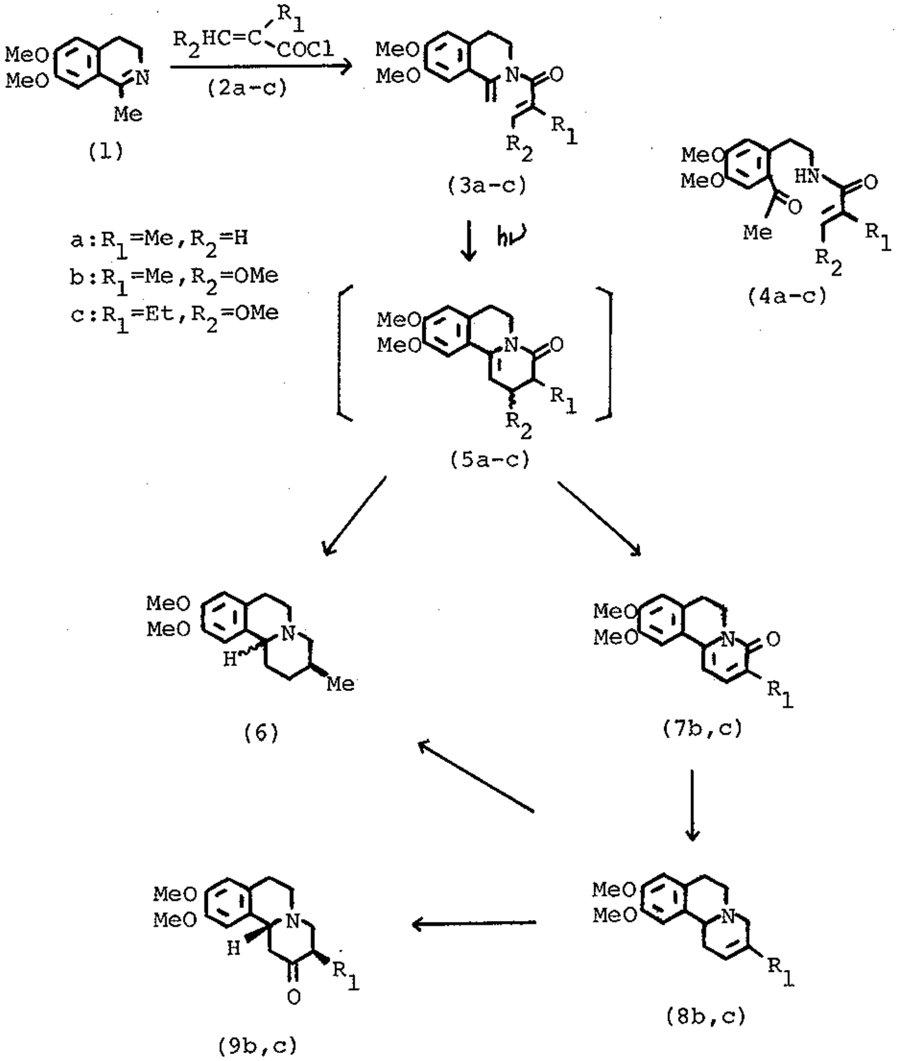
The structure of the unstable photoproduct (5a) was confirmed by the conversion into the hydrobenzo[a]quinolizine (6) [oil, δ 0.92 (3H, d, J=6Hz, 3-Me)] by reduction with lithium aluminium hydride and sodium borohydride in 31 % yield from the starting compound (1). An equatorial configuration of the methyl group in 6 was suggested from the above n.m.r. spectrum.

However, when a crude mixture of the photoproducts (5b and c) was treated with 10% hydrochloric acid, the unsaturated lactams (7b and c) were obtained in 57 and 44 % yields from 1 respectively as the result of elimination of methanol [(7b); m.p. 177-178°, ν max 1640 cm^{-1}, δ 7.23 (1H, d, J=7Hz, 1-H), 6.48 (1H, d, J=7Hz, 2-H), and 2.18 (3H, s, 3-Me), and (7c); m.p. 125-127°, ν max 1640 cm^{-1}, δ 7.15 (1H, d, J=8Hz, 1-H), 6.34 (1H, d, J=8Hz, 2-H), 2.62 (2H, q, J=8Hz, 3-$C\underline{H}_2CH_3$) and 1.22 (2H, t, J=8Hz, 3-$CH_2C\underline{H}_3$)].

Reduction of the unsaturated lactams (7b and c) with lithium aluminium hydride followed by sodium borohydride afforded the corresponding amines (8b and c) in 94 and 98 % yields respectively, Their structures were deduced from their n.m.r. spectra [(8b), δ 5.50 (1H, m, 2-H), and 1.68 (3H, br s, 3-Me); (8c), δ 5.57 (1H, m, 2-H)], and the conversion of 8b into the saturated amine (6) by catalytic hydrogenation in the presence of platinum oxide.

Conversion of the unsaturated amines (8b and c) into the target ketones (9b and c) was achieved by reduction with sodium borohydride and excessive boron trifluoride etherate in a diglyme solution followed by treatment with 20% hydrogen peroxide and the Pfitzner-Moffatt oxidation[5]. Thus, the ketones, (9b), [m.p.136-137° (lit.[6a] 129-130°), ν max 1710 (CO) cm^{-1}, δ 6.60, 6.53 (each 1H, s, 8- and 11-H), 1.06 (3H, d, J=6Hz, 3-Me)] in 21 % yield from 8b, and (9c)[7], [m.p. 107-108° (lit.[6b] 109-110°), ν max 1710 (CO) cm^{-1}, δ 6.63, 6.58 (each 1H, s, 8- and 11-H), 0.93 (3H, t, J=6Hz, 3-$CH_2\underline{CH_3}$)] in 18 % yield from 8c, were obtained. The identities of these ketones with those reported suggest these ketones (9b and c) having stable conformations as reported.

Since the ketone (9c) has been known as an important intermediate for the synthesis of Ipecac alkaloids, the above process provides a new and convenient route to a group of benzo[a]quinolizine alkaloids.


MeO
MeO
N
Me
(1)
R2HC=C(R1)COCl
(2a-c)
(3a-c)
hν
(4a-c)
HN
a:R1=Me,R2=H
b:R1=Me,R2=OMe
c:R1=Et,R2=OMe
(5a-c)
(6)
H
Me
(7b,c)
R1
(8b,c)
(9b,c)
O

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* Unless otherwise mentioned, i.r. spectra were measured in chloroform.

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7 The presence of epimeric isomers with respect to the configuration of ethyl group at C-3 was suggested from t.l.c., i.r. and n.m.r. of the crude mixture of the oxidation products, though only a stable isomer could be isolated.

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