

Niigata College of Pharmacy, Kamishin'ei-Cho, 5829,

Niigata, 950-21, Japan

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Substituted julolidines were prepared by a single step of reactions from substituted anilines.

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In the course of the studies of quaternary amino-Claisen rearrangement (1) we were in need of julolidines (2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizines) having a substituent on the aromatic ring. There is a standard method to prepare julolidine from 1,2,3,4-tetrahydroquinoline (2). This method is suitable for the preparation of 9-alkyljulolidines. The drawback of this method is the cleavage of the ether linkage during refluxing in 1,3-bromochloropropane (bp 142-145°). A more serious problem was encountered in the preparation of 8-methyljulolidine. The reaction product was a mixture of two compounds (2/3) in favour of the undesired by-product which was difficult to eliminate (3). The acid-catalyzed reaction of *N,N'*-diaryl-1,3-diaminopropanes was used for the preparation of the substituted julolidines (4) but the contamination of the primary and secondary amines and the poor yields do not encourage its wide application. There is a brief report that the reaction of *m*-anisidine with 1,3-bromochloropropane at refluxing temperature afforded 8-hydroxyjulolidine, the ether-cleaved product, in 30% yield (5). This pathway is attractive but no scope of its generality is described. We were interested in this method to construct the julolidine skeleton by a single-step reaction sequence and investigated the reaction conditions which would prevent cleavage of the ether linkage.

The anilines in 1,3-bromochloropropane solution were refluxed in the presence of sodium carbonate in order to remove the acid generated that is responsible for ether-cleavage. The moisture thus formed was removed by filtering the condensate through molecular sieves to avoid hydrolysis of the intermediate halides. The reaction was

monitored by glc and was terminated at the maximum formation of the desired product. The crude julolidines were purified as the hydrobromides. The results are summarized in the Table.

The advantage of this method is that it requires only readily available anilines as starting materials instead of the costly 1,2,3,4-tetrahydroquinolines. The yields are regarded as good, considering the ready availability of the anilines and the single-step reaction sequence.

EXPERIMENTAL

Melting points were measured on a Yanako MP-3 hot stage apparatus. The mp and bp are uncorrected. The infrared (ir) spectra were measured with a Hitachi 215 grating infrared spectrometer and nmr were taken with JEOL JNM-PMX 60 using tetramethylsilane as an internal standard.

General Procedure.

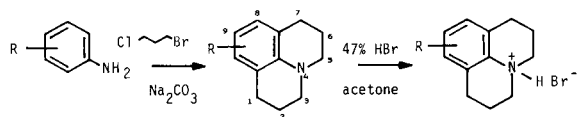
A glass column which was equipped with sintered glass and by-passing column for vapour was placed between the reaction vessel and the condenser and packed with molecular sieves (4A, 10 g). Aniline (0.1 mole), sodium carbonate (0.4 mole) and 1,3-bromochloropropane (1.5 moles) were added to the reaction vessel and the reaction mixture was heated with vigorous stirring under an atmosphere of nitrogen by a gradual increase of the bath temperature (70°/1 hour, 100°/2 hours, 160°/12 hours). The reaction mixture was treated with concentrated hydrochloric acid (100 ml) then steam-distilled to recover 1,3-bromochloropropane. The residual solution, which contained some tarry substances, was basified with sodium hydroxide and extracted with ether (3 × 70 ml). After brief washing with water the ethereal extracts were shaken with 2*N* hydrochloric acid (2 × 80 ml). The acidic extracts were basified with sodium hydroxide and extracted with ether (3 × 70 ml). Organic extracts were washed with brine (3 × 50 ml), dried over anhydrous sodium sulfate and removed ether to give the crude julolidine. Treatment of the crude product with 47% hydrobromic acid (1.2 equivalents) in acetone (30 ml) afforded hydrobromide of julolidine which was more than 98% pure on glc after freeing. The purification of the crude julolidines by Kugelrohr distillation (170°/15 mm Hg) make the precipitation of the hydrobromides easier. During distillation some crystals appeared in the distillate. Crystals were formed by the reaction of distillate with acid halides which might be generated by the cyclization reaction of half-cyclized reaction products present in the crude reaction product.

Julolidine (2).

This compound had mp 39-40°, bp 93°/0.25 mm Hg [bp 105-110°/1 mm Hg (2)]; ir (film): 1595, 1495, 1308, 1203, 730 cm⁻¹; nmr (deuteriochloroform): δ 2.00 (quintet, J = 6 Hz, H-2 + H-6, 4H), 2.80 (t, J = 6 Hz, H-1 + H-7, 4H), 3.13 (t, J = 5.5 Hz, H-3 + H-5, 4H), 6.4-6.9 (m, aromatic, 2H).

Julolidine Hydrobromide.

This compound had mp 246-249° (in a sealed tube) (methanol-acetone);



R =	R =	crude yield [%] (a)	yield [%]
H	H	95 (64)	58
p-CH ₃	9-CH ₃	92	58
p-OCH ₃	9-OCH ₃	81	42
m-CH ₃	8-CH ₃	93	46
m-OCH ₃	8-OCH ₃	96 (56)	50

(a) Yields in parentheses are those after Kugelrohr distillation of the crude products.

ir (potassium bromide): 2430, 1470, 1422, 1168, 1005, 895, 810 cm^{-1} ; nmr (perdeuteriomethanol): δ 2.30 (quintet, $J = 6$ Hz, H-2 + H-6, 4H), 3.06 (t, $J = 6$ Hz, H-1 + H-7, 4H), 3.63 (t, $J = 5.5$ Hz, H-3 + H-5, 4H), 7.23 (m, aromatic, 3H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{BrN}$: C, 56.70; H, 6.35; N, 5.51; Br, 31.44. Found: C, 56.67; H, 6.30; N, 5.41; Br, 31.36.

9-Methyljulolidine (2).

This compound had bp 158-160°/10 mm Hg (2); ir (film): 2850, 1620, 1505, 1470, 1310, 855 cm^{-1} ; nmr (deuteriochloroform): δ 1.97 (quintet, $J = 5.5$ Hz, H-2 + H-6, 4H), 2.17 (s, CH_3 , 3H), 2.77 (t, $J = 6$ Hz, H-1 + H-7, 4H), 3.10 (t, $J = 5.5$ Hz, H-3 + H-5, 4H), 6.60 (s, aromatic, 2H).

9-Methyljulolidine Hydrobromide.

This compound had mp 276-279° dec (in a sealed tube) (methanol-acetone); ir (potassium bromide): 2400, 1425, 910, 878 cm^{-1} ; nmr (deuteriochloroform): δ 2.30 (s, CH_3 , 3H), 2.50 (broad m, H-2 + H-6, 4H), 2.97 (broad m, H-1 + H-7, 4H), 3.47 (broad m, H-3 + H-5, 4H), 6.90 (s, aromatic, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{BrN}$: C, 58.22; H, 6.76; Br, 29.79; N, 5.22. Found: C, 58.42; H, 6.74; Br, 30.06; N, 5.34.

9-Methoxyjulolidine (6a).

The compound had bp 125-127°/1 mm Hg; ir (film): 1611, 1493, 1280, 1205, 1148, 1090, 1048, 855 cm^{-1} ; nmr (deuteriochloroform): δ 1.97 (m, H-2 + H-6, 4H), 2.77 (t, $J = 7$ Hz, H-1 + H-7, 4H), 3.06 (distorted t, $J = 5$ Hz, H-3 + H-5, 4H), 3.73 (s, OCH_3 , 3H), 6.47 (s, aromatic, 2H).

9-Methoxyjulolidine Hydrobromide.

This compound had mp 202-203° (in a sealed tube) (dichloromethane-acetone); ir (potassium bromide): 3530 (water), 2400, 1600, 1485, 1298, 1180, 1050, 875, 860 cm^{-1} ; nmr (deuteriochloroform): δ 2.47 (m, H-2 + H-6, 4H), 2.97 (m, H-1 + H-7, 4H), 3.43 (m, H-3 + H-5, 4H), 3.83 (s, OCH_3 , 3H), 6.63 (s, aromatic, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{BrNO}$: C, 54.94; H, 6.38; Br, 28.12; N, 4.93. Found: C, 54.81; H, 6.45; Br, 28.24; N, 4.85.

8-Methyljulolidine (4a).

The compound had bp 172-180°/17 mm Hg (4a); ir (film): 1602, 1495, 1480, 1310, 888 cm^{-1} ; nmr (deuteriochloroform): δ 2.03 (m, H-2 + H-6, 4H), 2.13 (s, CH_3 , 3H), 2.63 (t, $J = 5.5$ Hz, H-1 + H-7, 4H), 2.73 (t, $J = 6$ Hz, H-3 + H-5, 4H), 6.45 (d, $J = 8$ Hz, aromatic, 1H), 6.75 (d, $J = 8$ Hz, aromatic, 1H).

8-Methyljulolidine Hydrobromide.

This compound had mp 170-172° dec (in a sealed tube) (acetone); ir (potassium bromide): 3520, 3450 (water), 2550, 1615, 1413, 1008, 838, 818 cm^{-1} ; nmr (perdeuteriomethanol): δ 2.23 (s, CH_3 , 3H), 2.23-2.53 (m, H-2 + H-6, 4H), 2.87 (t, $J = 6.5$ Hz, H-1, 2H), 3.00 (t, $J = 6.5$ Hz, H-7,

2H), 3.57 (t, $J = 5.5$ Hz, H-3 + H-5, 4H), 7.07 (d, $J = 8$ Hz, aromatic, 1H), 7.20 (d, $J = 8$ Hz, aromatic, 1H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{BrN}$: C, 58.22; H, 6.76; Br, 29.79; N, 5.22. Found: C, 58.14; H, 6.88; Br, 29.89; N, 5.09.

8-Methoxyjulolidine (4b).

The compound had bp 140-160°/3 mm Hg (4b); ir (film): 1615, 1502, 1318, 1140, 1070, 780 cm^{-1} ; nmr (deuteriochloroform): δ 1.93 (m, H-2 + H-6, 4H), 2.70 (t, $J = 6$ Hz, H-1, 2H), 2.73 (t, $J = 6$ Hz, H-7, 2H), 3.10 (t, $J = 5.5$ Hz, H-3 + H-5, 4H), 3.77 (s, OCH_3 , 3H), 6.59 (d, $J = 8$ Hz, aromatic, H), 6.74 (d, $J = 8$ Hz, aromatic, 1H).

8-Methoxyjulolidine Hydrobromide.

This compound had mp 198-201° (methanol-acetone); ir (potassium bromide): 2400, 1618, 1500, 1250, 1102, 1030, 830, 812 cm^{-1} ; nmr (perdeuteriomethanol): δ 2.30 (m, H-2 + H-6, 4H), 2.87 (t, $J = 7$ Hz, H-1, 2H), 3.00 (t, $J = 7$ Hz, H-7, 2H), 3.57 (t, $J = 5.5$ Hz, H-3 + H-5, 4H), 3.87 (s, OCH_3 , 3H), 6.7-7.3 (m, aromatic, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{BrNO}$: C, 54.94; H, 6.38; Br, 28.12; N, 4.93. Found: C, 54.71; H, 6.62; Br, 28.31; N, 4.88.

REFERENCES AND NOTES

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(3) The mixture, which was derived from the reaction of 7-methyl-1,2,3,4-tetrahydroquinoline (10.3 g) and 1,3-bromochloropropane (73 g, 99% pure) at refluxing temperature for 15.5 hours, consisted of 8-methyljulolidine (41.5%) and a by-product (57.9%) according to glc analysis. Both compounds have close Rf values on tlc (silica gel, chloroform). The preparative glc (20% SE-30, 5 mm \times 2 m); 240°; nitrogen 42 ml/minute) yielded 8-methyljulolidine and the by-product ($M^+ m/e$ 229) in pure state. The by-product was identified with 8-methyl-9-propyljulolidine which was independently prepared by the amino-Claisen rearrangement of *N*-allyl-8-methyljulolidinium bromide and the subsequent hydrogenation of the rearrangement product (unpublished results) [cf. (1b)].

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