Tetrahedron Vol 40, No 18, pp 3431 to 3436, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd

SYNTHESIS OF 2-ISOPROPYLFURO(2,3-b)QUINOLINES-A NEW SYNTHESIS OF (±)-LUNACRINE, (±)-LUNASINE AND (±)-DEMETHOXYLUNACRINE

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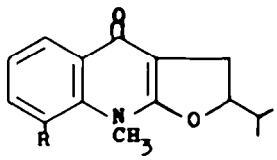
(*Received in UK 10 May 1984*)

Abstract : A new and convenient synthesis of 2-isopropylfuro-(2,3-b)quinolines (4) from 3-(3-methylbut-1-enyl)-2-quinolones (2) is described. A neat synthesis of the alkaloids (±)-lunacrine (1a), (±)-lunasine (12a) and (±)-demethoxylunacrine (1b) is also reported.

Lunacrine has been recognised as a constituent of several Lunasia species[1-4] (Rutaceae) and shown to be the isopropylfuroquinoline 1a on the basis of chemical[3,5] and spectral[5,6] evidence. Hitherto only one report has appeared



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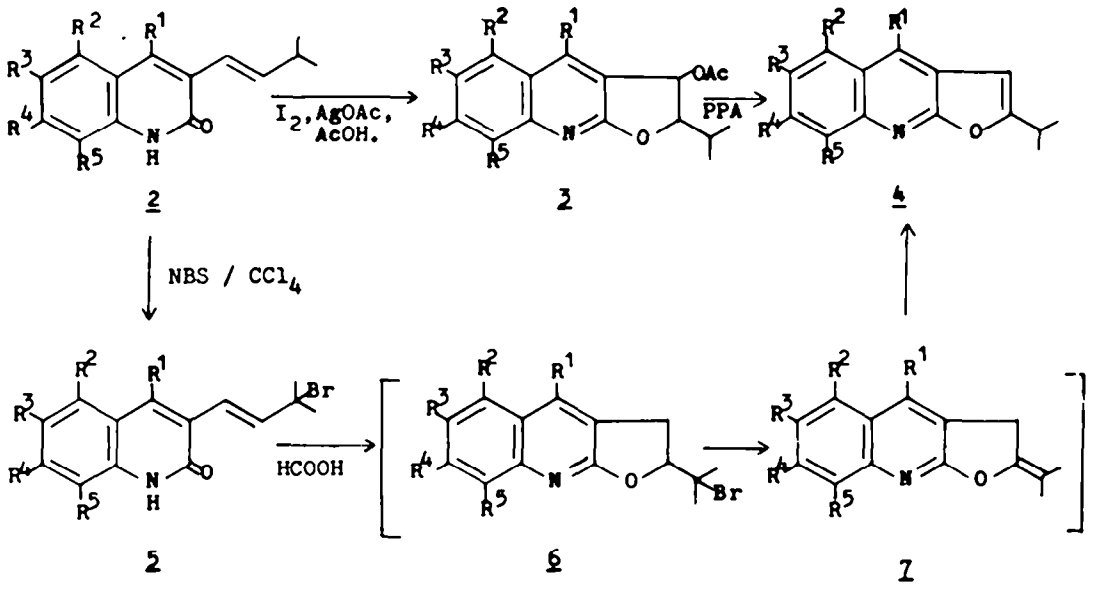
a : R = OCH_3

b : R = H

on its synthesis and that was due to Grundon et al.,[7] who obtained it as result of a four-stage process from N-methyl-o-anisidine and diethyl (3-methylbut-2-enyl)-malonate, but in an overall yield of only 3.4%.

Huffman et al.,[8-10] considered an alternative possibility of arriving at the synthesis of 1a, via 3-(3-methylbut-1-enyl)-4-hydroxy-8-methoxy-2-quinolone (2j), but the proposed intermediate viz., 2j eluded their attempts at synthesis. In a recent communication[11] we have reported a method which provided the feasibility of obtaining several 3-(3-methylbut-1-enyl)-2-quinolones including 2j. It was based on the condensation of appropriately substituted 2-quinolone-3-acetic acids with isobutyraldehyde.

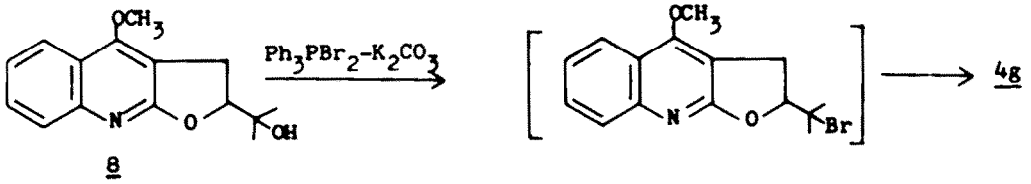
In this paper, we would like to report a facile synthesis of 2-isopropyl-furo(2,3-b)quinolines (4) based on the above precursors and on a novel synthesis of lunacrine (1a), lunasine (12a) and demethoxylunacrine (1b). Two methodologies were found to be successful for the transformation of the butenylquinolone (eg. 2a) to the isopropylfuro(2,3-b)quinoline (4a). One involved a Prevost reaction of 2a with iodine in the presence of silver acetate in glacial acetic acid followed by dehydro-



	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	H	H	CH_3	H	H
c	H	CH_3	H	H	CH_3
d	H	H	H	-CH=CH-CH=CH-	
e	CH_3	H	H	H	H
f	C_6H_5	H	Cl	H	H
g	OCH_3	H	H	H	H
h	p-$OCH_3C_6H_4$	H	H	H	H
i	OCH_3	H	H	H	OCH_3
j	OH	H	H	H	OCH_3

acetoxylation of the resulting 3-acetoxy-2-isopropyl-2,3-dihydrofuro(2,3-b)quinoline (3a) to give the furoquinoline (4a). The synthetic transformation of 2a→3a→4a was similar to the one employed earlier[12] for the transformation of 3-vinyl-2-quinolone to furo(2,3-b)quinoline.

In the other procedure, 2a was treated with NBS in CCl_4 and the resulting bromoallyl compound 5a was then heated with formic acid to afford the furoquinoline 4a identical in all respects (TLC, mp, IR, NMR) with that derived through the other method. Extension of these techniques to 2b - 2i gave rise to the corresponding furoquinolines 4b - 4i respectively. The bromointermediate 5 need not be isolated in a pure state, though it has been done in the cases of 2a and 2g. The reaction of 5 with formic acid to give 4 can be interpreted in terms of ring-closure of 5 to 6 and dehydrobromination of 6 to 7, which on isomerisation furnishes 4. Our assumption was based on a similar one proposed[13] in the transformation of platydesmine (8) to 4-methoxy-2-isopropylfuro(2,3-b)quinoline (4g) by treatment with Ph_3PBr_2 and K_2CO_3 and on the actual isolation[14] of 9 in the treatment of ptelatinum (10)



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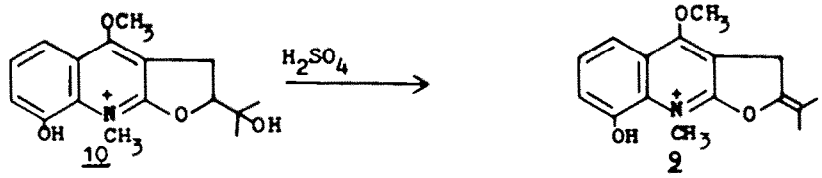
with sulphuric acid.



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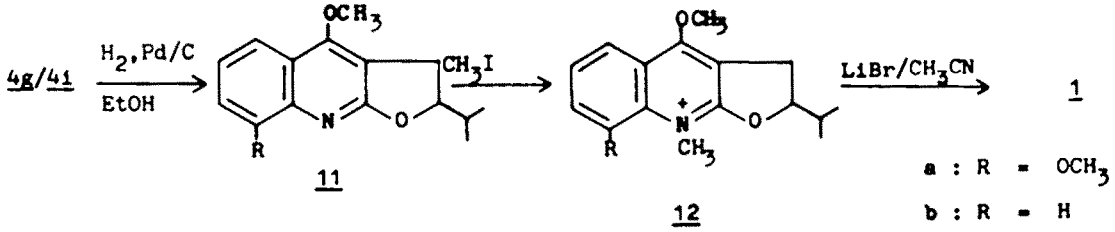
When hydrogenated over Pd-C (5%) in ethanol 4g as well as 4i readily underwent saturation of the furan double bond to give the dihydrofuroquinolines 11b[10] and 11a respectively. Reaction of 11b with methyl iodide afforded the unst-



able demethoxylunasine salt (12b) which on heating with lithium bromide in acetonitrile was smoothly converted into demethoxylunacrine (1b) in excellent yield. Lunacrine (1a) was derived in a similar manner from 11a via 12a. The mp and spectral characteristics of 1a and 12a exactly corresponded to that of the authentic sample of lunacrine[7] and lunasine iodide[3,5] respectively.

EXPERIMENTAL

Melting points were determined on a Boetius microheating table and are uncorrected. The H-NMR spectra were recorded on a Hitachi R-600 spectrometer. The IR spectra were recorded on a Perkin-Elmer model 597 spectrophotometer.

General Procedure :

Synthesis of 3-acetoxy-2-isopropyl-2,3-dihydrofuro(2,3-b)quinolines (3) : To a solution of 2 (0.001m) in glacial acetic acid (15ml) silver acetate (0.002m) was added and the suspension was well stirred at room temperature. To this, powdered iodine (0.001m) was added in portions, over a period of 1hr. After the addition, the reaction mixture was stirred for an additional hr. The silver iodide precipitate was filtered and washed with chloroform. The filtrate and the washings were combined and diluted with water and extracted with chloroform. The chloroform extract was successively washed with dilute solutions of sodium bicarbonate, sodium thiosulphate and finally with water. It was dried over anhydrous sodium sulphate and evaporated. The residue obtained, was placed over a column of alumina and eluted with benzene. Evaporation of the solvent furnished 3.

The physical and spectral data of 3 are given in Table - I.

Synthesis of 2-isopropylfuro(2,3-b)quinolines (4) : 3 (0.001m) was heated with

Table - I : 3-acetoxy-2-isopropyl-2,3-dihydrofuro(2,3-b)quinolines

Compound	mp °C (C_6H_6)	Yield (%)	IR $\nu_{(max)}$ cm^{-1}	^1H - NMR (δ ppm) CDCl3 $-CH(CH_3)_2$ 2d, 3H each	$-CH(CH_3)_2$ m, 1H	C_2 - H m, 1H	C_3 - H d, 2H	$-OCOCH_3$ s, 3H	Aromatic H m	Other H	Mass (M^+)
3a	125-126	85	*2995,1720,1600	0.9, 1.1	1.55	4.25	6.15	1.95	6.9-7.7	8.1(s,1H,C_4-H)	271
3b	144-145	88	●2995,1720,1600	0.9, 1.15	1.62	4.2	6.25	2.02	7.3-8.0	2.5(s,3H,CH_3), 8.15(s,1H,C_4-H)	285
3c	129-130	87	*3000,1710,1605	1.0, 1.1	1.95	4.15	6.3	2.05	7.1-8.0	2.65(s,6H,2xCH_3) 8.1(s,1H,C_4-H)	-
3d	181-182	85	●2995,1720,1600	1.0, 1.2	1.9	4.3	6.5	2.05	7.3-7.5 8.1(d,1H) 9.0(m,1H)	8.0(s,1H,C4-H)	-
3e	108-110	85	●3000,1725,1570	1.0, 1.2	2.0	4.05	6.15	2.05	7.0-8.05	2.55(s,3H,CH_3)	285
3f	152-153	85	●3005,1720,1595	0.95,1.15	1.85	4.35	5.95	2.05	6.9-7.5	...	-
3g	150-151	85	*2960,1740,1580	1.0, 1.22	1.65	4.15	6.21	2.05	7.0-7.5 7.7(dd,1H, C_5-H)	4.29(s,3H,OCH_3)	301

* Phase : CCl_4
● Phase : KBr

Table - III : 2-Isopropyl-2,3-dihydrofuro(2,3-b)quinolines

Compound	mp °C	Yield (%)	$-CH(CH_3)_2$	$-CH(CH_3)_2$	^1H - NMR (δ ppm) $CDCl_3$ C_2 - H	C_3 - H	Aromatic H	Other H
11a	131-132	60	1.05(d,6H,J=6 Hz)	2.15(m, 1H)	4.35(m, 1H)	3.4(dd, 2H)	7.1-7.83(m, 3H)	4.0,4.2(2s,2 x OCH_3)
11b	125-126 (lit[10] 125-126)	65	0.95(d,6H,J=6 Hz)	2.0(m, 1H)	4.35(m, 1H)	3.35(dd, 2H)	7.0-7.76(m,4H)	4.0(s,3H, OCH_3)
1a	146-147 (lit[7] 146-148)	99	0.95,1.05(2d, 3H each, J=6 Hz)	2.05(m,1H)	4.75(m, 1H)	3.3(m,2H)	7.05-7.75(m,2H) 8.0(dd,1H,C_5-H)	3.8(s,3H, NCH_3) 3.9(s,3H, OCH_3)
1b	152-154	98	0.95,1.05(2d, 3H each, J=6 Hz)	2.2(m, 1H)	4.5(m, 1H)	3.5(dd,2H)	7.0-7.65 (m,3H) 7.9(dd,1H,C_5-H)	3.65(s,3H,NCH_3)

Table - II : 2-Isopropylfuro(2,3-b)quinolines

Compound	mp °C (C_6H_6)	Yield (%) 3 → 4	Yield (%) 2 → 4	IR $\nu_{(max)}cm^{-1}$	^1H - NMR (δ ppm) CDCl3 $-CH(C\underline{H}_3)_2$ 2d, 3H each J = 6 Hz	$-C\underline{H}(CH_3)_2$ m	C_3 - H s	Aromatic H m	Other H	Mass (M^+)
4a	93-94	85	65	*2990,1605	0.95, 1.25	3.10	6.50	7.00 - 8.00	8.10(s,1H,C_4-H)	211
4b	108-110	90	55	●2990,1600	1.00, 1.15	3.25	6.70	6.95 - 7.95	2.65(s,3H,$C\underline{H}_3$) 8.05(s,1H,C_4-H)	225
4c	110-112	85	70	*2995,1600	1.00, 1.25	3.30	6.75	7.00 - 8.05	2.45,2.65(2s, 3H each,2 x $C\underline{H}_3$)	239
4d	140-142	85	60	*3000,1605	0.95 (d, 6H)	3.15	6.65	6.90 - 7.90(m,4H) 8.20(d, 1H) 9.10(m, 1H)	8.1(s,1H,C_4-H)	-
4e	78-79	85	65	●2995,1600	0.95, 1.15	3.15	6.65	7.00 - 8.05	2.65(s,3H,$C\underline{H}_3$)	-
4f	136-137	85	68	●3000,1600	0.95, 1.10	3.05	6.60	7.00 - 7.80	..	-
4g	105-106	90	70	*2995,1600	1.35 (d,6H)	3.15	6.55	7.30 - 8.10(m,3H) 8.20(dd,1H,C_5-H)	4.40(s,3H,$OC\underline{H}_3$)	241
4h	121-122	-	65	●2990,1600	0.95 (d,6H)	3.00	6.55	7.00 - 7.95	4.00(s,3H,$OC\underline{H}_3$)	317
4i	123-124	-	68	●2995,1600	1.25 (d,6H)	2.90	6.70	7.00 - 7.60(m,2H) 8.00(dd,1H,C_5-H)	4.45,4.15(2s, 3H each, 2x $OC\underline{H}_3$)	-

* Phase : CCl_4

● Phase : KBr

poly-phosphoric acid (2g) on a steam bath for 4hr and then poured into ice water. Filtered and the filtrate was basified with dilute ammonia solution and then extracted with chloroform. Evaporation of the dried extract furnished a residue, which when subjected to chromatography (alumina, benzene) afforded 4.

In Table - II are shown the physical and spectral data of 4.

The NBS - HCOOH method : A mixture of 2 (0.001m), NBS (0.001m) and a few crystals of benzoyl peroxide was taken in dry CCl_4 (30ml) and the solution was refluxed for 4hr. It was filtered, washed with water and then dried. Evaporation of the solvent under diminished pressure gave the allylbromide (5).

(5a : mp. 151-160° dec.; Yield : 75%; IR(KBr): 3000, 1650 cm^{-1}; H-NMR ($CDCl_3$) : 0.8, 1.15 (2s,3H each,$-C(CH_3)_2$), 6.45 (d,1H, $=CH-C(CH_3)_2$), 7.2-7.6 (m,5H, ArH and Ar-CH=CH-), 7.8 (s,1H,C_4-H) and 13.0 (br.s,1H,NH)ppm.

Reaction of 5 with formic acid : 5 (0.001m) was taken in formic acid (90%, 10ml) and heated on a steam bath for 3hr. It was then cooled, diluted with water and filtered. The clear filtrate was basified with aqueous ammonia and extracted with chloroform. The dried extract on evaporation furnished a residue which, when subjected to chromatography (alumina, benzene) afforded 4.

Hydrogenation of 4g : To a solution of 4g (0.001m) in ethanol (50ml) was added Pd-C (5%, 75mg) and shaken with H_2 at 50 psi in a Parr hydrogenator, for 3.5hr. The catalyst was removed by filtration and the filtrate was concentrated to a small bulk under reduced pressure. The residue obtained was placed over a column of alumina and eluted with benzene, when 4-methoxy-2-isopropyl-2,3-dihydrofuro(2,3-b)quinoline (11b) was obtained after evaporation of the solvent.

4,8-dimethoxy-2-isopropyl-2,3-dihydrofuro(2,3-b)quinoline (11a) was likewise obtained from 4i.

The physical and spectral data of 11a and 11b are indicated in Table- III

Synthesis of (±)-demethoxylunacrine (1b) : A solution of 11b (100mg) and methyl iodide (15ml) was heated on a steam bath for 15min and then allowed to stand overnight. The excess reagent was removed to furnish the demethoxylunasine salt (12b) as a viscous mass. 12b was heated with lithium bromide (3.5g) in acetonitrile(30ml) for 4hr and then poured into ice-water. It was extracted with chloroform and the extract dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished 1b.

Synthesis of (±)-lunasine (12a) and (±)-lunacrine (1a) : 11a was treated with methyl iodide as described above and 12a was obtained as fine crystals. Yield: 85% mp. 130-132° dec. (lit[3]. mp.130°). Treatment with lithium bromide, as in the case of 12b, 12a furnished 1a.

The physical and spectral data of 1a and 1b are given in Table - III.

ACKNOWLEDGEMENTS

This work was supported by a grant from Department of Science and Technology, Govt. of India. We thank Dr. S. Rajappa, CIBA - GEIGY, Bombay for the analysis and the mass spectra and Mr. M. Palanisamy for the IR and H-NMR spectra. MR and PS thank the DST for the research fellowships.

REFERENCES

1. W.G. Boorsma, Bull. Inst. Bot. Buitenzorg., 1904, 21, 8.
2. F.A. Steldt and K.K. Chen, J. Am. Pharm. Ass., 1943, 32, 107.
3. S. Goodwin and E.C. Horning, J. Am. Chem. Soc., 1959, 81, 1908.
4. E.R. Johnstone, J.R. Price and A.R. Todd, Aust. J. Chem., 1958, 11, 562.
5. J.R. Price, Aust. J. Chem., 1959, 12, 458.
6. S. Goodwin, J.N. Shoolery and L.F. Johnson, J. Am. Chem. Soc., 1959, 81, 3965.
7. E.A. Clarke and M.F. Grundon, J. Chem. Soc., 1964, 438.
8. J.W. Huffman, J. Org. Chem., 1961, 26, 1470.
9. J.W. Huffman and L.E. Browder, J. Org. Chem., 1964, 29, 2598.
10. J.W. Huffman and J.H. Cecil, J. Org. Chem., 1969, 34, 2183.
11. M. Ramesh, V. Arisvaran, S.P. Rajendran and P. Shanmugam, Tetrahedron Lett., 1982, 23, 967.
12. P. Shanmugam, R.Palaniappan, N. Soundararajan, T.K. Thiruvengadam and K. Kanakarajan, Mh. Chem., 1977, 108, 725.
13. J.L. Caston, M.F. Grundon and K.J. James, J.Chem. Soc., Perkin Trans I,1980,1136.
14. L.A. Mitscher, M.S. Bathala, G.E. Clark and J.L. Beal, Lloydia, 1975,38, 109.