SYNTHESIS OF (±)-JATROPHAM, AN ANTITUMOR ALKALOID FROM *JATROPHA MACRORHIZA*

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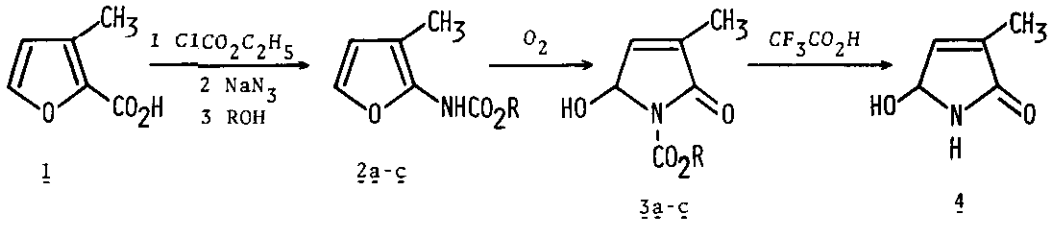
Abstract—The synthesis of jatropham, assigned as 5-hydroxy-3-methyl-3-pyrrolin-2-one 4, and of its 4-methyl isomer 14 is achieved utilizing an autoxidation of 2-furylcarbamates 2 and 11 as the key step.

Jatropham is an alkaloid isolated from *Jatropha macrorhiza* (Euphorbiaceae), and has inhibitory activity toward the P-388 lymphocytic leukemia test system[1]. An earlier study of the structure of jatropham by Cole et al.[1] led to proposal of structure 14, 5-hydroxy-4-methyl-3-pyrrolin-2-one for the base. However, our recent spectral studies of some synthetic analogues of this alkaloid indicated that the structure should be revised to 5-hydroxy-3-methyl-3-pyrrolin-2-one 4[2]. We here report the confirmation of the structure of jatropham by the first synthesis of 4 [(±)-jatropham] and its isomer 14 through a brief and novel route involving an autoxidation[3] of 2-furylcarbamates 2 and 11.

The synthetic route to 4 is shown in Scheme 1. 3-Methyl-2-furylcarbamates 2a-c were prepared from 3-methyl-2-furoic acid 1[4] by a usual method. On standing in

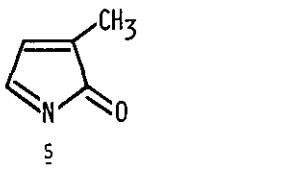


1 2a-c 3a-c 4

a; $R=CH_2C_6H_5$ b; $R=CH_2C_6H_4OCH_3$-*p* c; $R=C(CH_3)_3$

Scheme 1

benzene solution at room temperature, 2a-c undergo an autoxidation to hydroxypyrrolinones 3a-c in 45-55% yield after 7 days. The removal of N-benzyloxycarbonyl group of 3a was performed by treatment with CF_3COOH at 10-20° for 24 h. However, the yield of 4 was only 5%, and the formation of other products 6-8 derived from the imino intermediate 5 through the concerted elimination of hydroxy group, was observed[5]. On the other hand, treatment of 3b with CF_3COOH at 0° for 30 min. afforded 4 in 20% yield. In the case of 3c, the similar reaction (CF_3COOH, 0°, 30 min.) cleanly proceeded to give 4 in 70% yield. The par-



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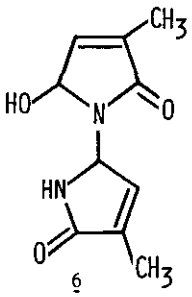

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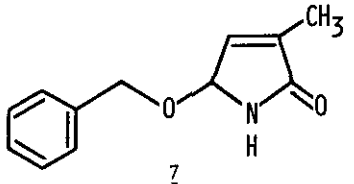

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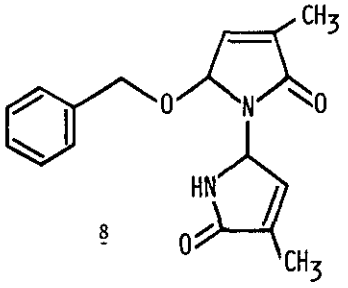

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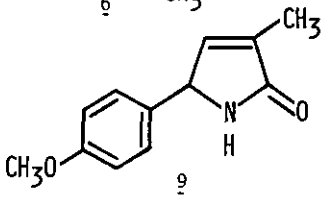

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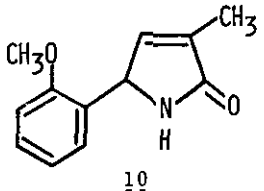

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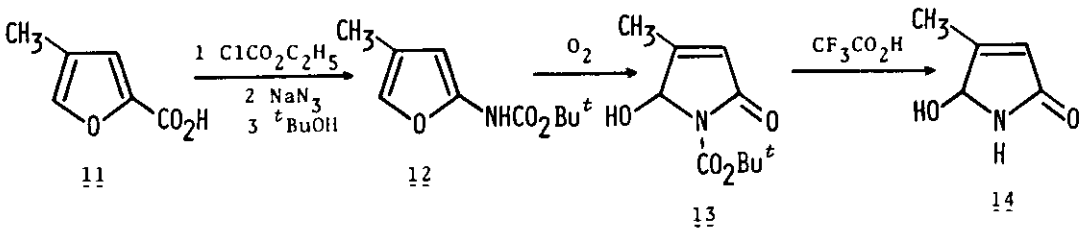
ticipation of imino intermediate 5 was supported from the reaction of 3c in the presence of anisole, which gave 5-*p*-methoxyphenyl-3-methyl-3-pyrrolin-2-one 9 and 5-*o*-methoxyphenyl-3-methyl-3-pyrrolin-2-one 10[6]. Thus, the *tert* - butoxycarbonyl group is suitable as the N-substituent for the synthesis of 4, which was obtained in 33% yield from 3-methyl-2-furoic acid 1[7].

Similarly, 5-hydroxy-4-methyl-3-pyrrolin-2-one 14, proposed structure for jatropham by Cole et al.[1], was also synthesized in 26% yield from 4-methyl-2-furoic acid 11[8] as indicated in Scheme 2.

The physical and spectral data for 4 and 14 are shown in Table I. The distinct differences between 4 and 14 in PMR and CMR spectra are observed expectedly, and the data for 4 show good similarities with those reported for jatropham[1,9].

In earlier structural studies of jatropham by Cole et al., they reported that 4-methyl-2-pyrrolidone was afforded as one of the hydrogenation products of this alkaloid. However, the identification of this compound was not satisfactory,



11 12 13 14

Scheme 2

and erroneous structural assignment probably occurred.

On the basis of the synthetic evidence described above, the structure of jatropham is unambiguously assigned to the revised formula 4, 5-hydroxy-3-methyl-3-pyrrolin-2-one.

Table I. Physical and Spectral Data for Jatropham 4 and Its Isomer 14

	4	14	Jatropham (Lit.) $[\alpha]_D$ -62°
m.p. (°C)	115-118	154-157	131-132
Appearance	colorless needles	colorless needles	colorless needles
IR (CH_3CN) cm^{-1}	3600, 3520, 3420, 1715, 1645	3620, 3530, 3440, 1705, 1630	3550, 3450, 3400, 1725, 1640
UV (EtOH) nm	230	230	230
(log ε)	(3.00)	(3.07)	(3.06)
MS *m/e*	113, 98, 85, 69	113, 98, 85, 69	113
PMR (acetone-d_6) δ			
NH	7.54 (br)	7.24 (br)	7.6 (s)
olefinic-H	6.59 (s)	5.60 (s)	6.5 (s)
C-5	5.48 (br d, J=8Hz)	5.33 (br s)	5.4 (d)
OH	4.92 (d, J=8Hz)	5.06 (br)	4.9 (d)
CH_3	1.78 (s)	2.01 (s)	1.7 (s)
CMR (acetone-d_6) δ		(CD_3OD)	
C-2	173.58 (s)	175.39 (s)	
C-3	136.25 (s)	122.33 (d)	
C-4	142.16 (d)	163.34 (s)	
C-5	79.33 (s)	83.43 (s)	
CH_3	10.41 (q)	13.46 (q)	

References and Notes

1. R. M. Wiedhopf, E. R. Trumbull and J. R. Cole, J. Pharm. Sci., 1973, 62, 1206.
2. K. Yakushijin, M. Kozuka, Y. Ito, R. Suzuki and H. Furukawa, Heterocycles, 1980, 14, 1073.
3. The autoxidation of 2-furylcarbamates is already described: see ref. 2.
4. D. M. Burness, Org. Syntheses, 1963, Coll. Vol. 4, 628.
5. Compound 6: PMR (acetone-d_6): δ 7.30 (br, 1H), 6.66 (br s, 1H), 6.55 (br s, 1H), 5.99 (br s, 1H), 5.28 (br d, J=8Hz, 1H), 4.96 (d, J=8Hz, 1H), 1.78 (s, 6H). IR (CH_3CN): 3590, 3510, 1700, 1620 cm^{-1}. MS *m/e*: 208 (M^+), 180, 167, 113, 111, 98 (base), 96, 85, 69.

   Compound 7: PMR ($CDCl_3$): δ 7.22 (s, 5H), 6.47 (br s, 1H), 6.04 (br, 1H), 5.42 (br s, 1H), 4.45 (br s, 2H), 1.90 (br s, 3H). IR ($CHCl_3$): 3440, 1710, 1650 cm^{-1}.

   Compound 8: PMR ($CDCl_3$): δ 7.32 (s, 5H), 6.48 (br s, 2H), 6.27 (br, 1H), 6.07 (br, 1H), 5.73 (br s, 1H), 5.08 (s, 2H), 1.87 (s, 6H). IR ($CHCl_3$): 3430, 1715, 1650 cm^{-1}. MS *m/e*: 298 (M^+), 246, 207, 192, 166, 139, 98 (base).
6. Compound 9: PMR ($CDCl_3$): δ 7.08 (d, J=8Hz, 2H), 6.81 (d, J=8Hz, 2H), 6.61 (br s, 1H, 6.60 (br, 1H), 5.01 (br s, 1H), 3.78 (s, 3H), 1.92 (s, 3H). IR (KBr): 3140, 3030, 1665, 1595 cm^{-1}. MS *m/e*: 203 (M^+), 188, 174, 160, 134, 83 (base).

   Compound 10: PMR ($CDCl_3$): δ 7.30-6.78 (m, 5H), 6.46 (br, 1H), 5.47 (br s, 1H), 3.86 (s, 3H), 1.91 (s, 3H). IR (KBr): 3360, 1665, 1580 cm^{-1}. MS *m/e*: 203 (M^+), 188, 174, 160, 144, 83 (base).
7. At the preparation of this communication, Dr. T. Nagasaka (Tokyo College of Pharmacy) informed his alternative synthesis of 4 in his private communication.
8. T. Reichstein and H. Zschokke, Helv. Chim. Acta, 1931, 14, 1270.
9. The direct comparison with natural jatropham was not carried out, because the authentic sample could not be available from Dr. Cole.

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