RING TRANSFORMATION OF 2-FURYLCARBAMATES TO 5-HYDROXY-3-PYRROLIN-2-ONES. REVISED STRUCTURE OF JATROPHAM

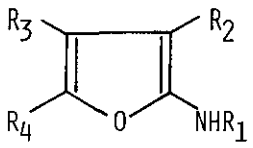
Kenichi Yakushijin, Masamichi Kozuka, Yoko Ito, Rika Suzuki and Hiroshi Furukawa*

Faculty of Pharmacy, Meijo University, Yagoto, Tempaku, Nagoya 468, Japan

Abstract——2-Furylcarbamates 1-7 react with oxygen under stirring or irradiation in benzene at room temperature to give the corresponding N-substituted 5-hydroxy-3-pyrrolin-2-ones 8-14. In the syntheses and NMR experiments of these pyrrolinone derivatives, the structure of jatropham 27, one of pyrrolinone derivatives proposed by Cole et al., is revised to the formula 11 (R_1=H).

The physiological importance of oxidized hemopyrrole and kryptopyrrole[1], and antitumor activity of jatropham[2], one of 5-hydroxy-3-pyrrolin-2-one derivatives, have been reported. We recently found the novel ring transformation of 3,4-diphenyl-2-furylcarbamates to hydroxypyrrolinones by the autoxidation[3]. In our further studies of this reaction, we here report on the formation of the corresponding 5-hydroxypyrrolinones 8-14 from non-substituted 2-furylcarbamates 1-3 and methyl substituted 2-furylcarbamates 4-7.

2-Furylcarbamates 1-7 were prepared in good yields by the reaction of the various 2-furoyl azides with alcohols[4]. As a typical procedure for unsensitized photooxygenation using 400W high pressure mercury lamp (Method A), the formation of 8 is illustrative. A solution of benzyl N-(2-furyl)carbamate 1 (0.5g) in benzene (200ml) was irradiated with oxygen at room temperature for 5 min. After removal of the solvent, the residue was chromatographed on silica gel eluted with $CHCl_3$-ether (7:3). Further purification with preparative silica gel thin layer chromatography afforded N-carbobenzyloxy-5-hydroxy-3-pyrrolin-2-one 8 (13%) [IR ($CHCl_3$) 3530, 1780, 1742, 1698 cm^{-1}; UV (EtOH) 218 nm (ε 3.60), 231 sh (3.45); MS m/e 233 (M^+), 215, 127, 109, 107, 91; NMR ($CDCl_3$) δ 4.46 (d, J=5 Hz, OH, vanishing with D_2O), 5.29 (s, CH_2), 5.98 (br d, J=5 Hz, C_5-H, collapsing with D_2O to dd, J=1, 2



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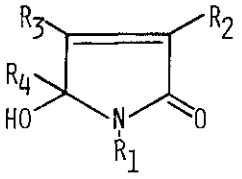
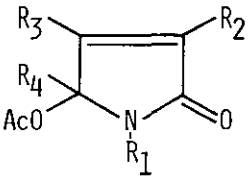


8-14



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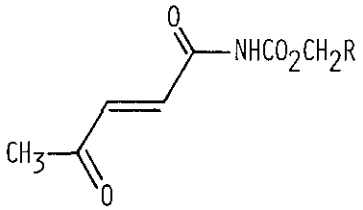
1, 8, 15; $R_1=CO_2CH_2C_6H_5$, $R_2=R_3=R_4=H$
2, 9, 16; $R_1=CO_2CH_2CH_3$, $R_2=R_3=R_4=H$
3, 10, 17; $R_1=CO_2CH(CH_3)_2$, $R_2=R_3=R_4=H$
4, 11, 18; $R_1=CO_2CH_2C_6H_5$, $R_2=CH_3$, $R_3=R_4=H$
5, 12, 19; $R_1=CO_2CH_2C_6H_5$, $R_3=CH_3$, $R_2=R_4=H$
6, 13, 20; $R_1=CO_2CH_2C_6H_5$, $R_4=CH_3$, $R_2=R_3=H$
7, 14, 21; $R_1=CO_2CH_2CH_3$, $R_4=CH_3$, $R_2=R_3=H$



22; $R=C_6H_5$
23; $R=CH_3$

Hz), 6.09 (dd, J=1, 6 Hz, C_3-H), 7.00 (dd, J=2, 6 Hz, C_4-H), 7.35 (m, Ph)]. On the other hand, a trace of 8 was also prepared from stirring of 1 in benzene at room temperature for 7 day (Method B). In the both methods, the starting material 1 was not remained, and amorphous solids were obtained as major products. Similar reactions of 2-furylcarbamates 2-7 by method A and B gave the corresponding N-substituted 5-hydroxy-3-pyrrolin-2-ones 9-14 as shown in Table I. These structures of pyrrolinones 8-14 were characterised by their elemental analyses and their spectral data. In the case of 5-methyl-2-furylcarbamates 6 and 7, *trans*-γ-ketoamides 22 (mp 82-84°, 10%) and 23 (mp 96-98°, 11%) were obtained along with 13 and 14. Acetylation of 13 and 14 with acetic anhydride in pyridine led to the formation of 22 (15%) and 23 (13%) along with the normal reaction products, acetates 20 (65%) and 21 (72%), although the similar treatment of 8-12 afforded acetates 15-19 in quantitatively.

The formation of hydroxypyrrolinones 8-14 from 2-furylcarbamates 1-7 were assumed to occur through the ring-chain tautomerism of *cis*-γ-ketoamides[5] produced from furan endoperoxides[6].

Table I. Formation of 5-Hydroxypyrrolinones

	mp (°C)	appearance	Method A react. time (min)	Method A yield (%)	Method B react. time (day)	Method B yield (%)
8	-	colorless oil	5	14	7	trace
9	-	colorless oil	5	8	-	-
10	-	colorless oil	5	11	-	-
11	92-93	colorless needles	10	43	7	52
12	103-104	colorless needles	10	10	7	35
13	77-78	colorless needles	10	34	7	45
14	-	colorless oil	10	30	7	40

In the course of the studies of ring transformation of methyl 2-furylcarbamates to methyl hydroxypyrrolinones described above, we found that NMR spectral properties of jatropham[2] which was isolated from *Jatropha macrorhiza* (Euphorbiaceae), and the structure was assigned as 5-hydroxy-4-methyl-3-pyrrolin-2-one 27 by Cole et al[2]., were not explicable on the basis of the structure 27. NMR spectral data of jatropham and our synthesized 5-hydroxypyrrolinones 8, 11 and 12 were shown in Table II[7]. In the comparisons of the chemical shift values of methyl-H and olefinic-H, both chemical shift values of jatropham were more similar with those of compound 11 having methyl group at C_3 position of the ring than those of compound 12 having methyl group at C_4. On the compounds 24-26 prepared by

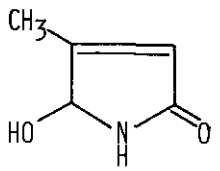


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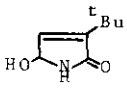
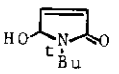
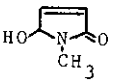
Table II. NMR Spectral Data in Acetone-d_6 ( ): in $CDCl_3$

	CH_3	olefinic-H		C_5-H
jatropham	1.7	6.5		5.4
8	-	(6.09)	(7.00)	(5.98)
11	1.82	6.81		5.99
	(1.86)	(6.60)		(5.83)
12	2.07	5.88		5.78
	(2.08)	(5.82)		(5.75)

Table III.
NMR Spectral Data in $CDCl_3$

		olefinic-H		C_5-H
	24	6.56		5.53
	25	5.98	6.88	5.60
	26	6.05	6.93	5.29

Lightner et al[8]., the similar relationships were also observed as shown in Table III. On the basis of these evidences, jatropham should be assigned the revised structure 11 (R_1=H)[9].

References

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2. R. M. Wiedhopf, E. R. Trumbull and J. R. Cole, J. Pharm. Sci., 1973, 62, 1206.
3. K. Yakushijin, M. Kozuka and H. Furukawa, Chem. Pharm. Bull. (Tokyo), in press; K. Ito and K. Yakushijin, Heterocycles, 1978, 9, 1603.
4. 3-Methyl-2-furoic acid: D. M. Burness, Org. Syntheses, 1963, Coll. Vol. 4, 649. 4-Methyl-2-furoic acid: T. Reichsten and H. Zschokke, Helv. Chim. Acta, 1931, 19, 1270. 5-Methyl-2-furoic acid: A. L. Mndzhoian, Proc. Acad. Sci. Armenian SSR., 1953, 17, 167.
5. We are confirming that the hydroxypyrrolinones having the various phenyl substituents at 5 position of compound 8 exist in ring-chain tautomeric equilibrium with the *cis*-γ-ketoamides by NMR spectra.
6. W. Adam and A. Rodriguez, J. Amer. Chem. Soc., 1980, 102, 404; A. A. Gorman, I. R. Gould and I. Hamblett, Tetrahedron Lett., 1980, 1087.
7. We requested the authentic sample and/or NMR chart of jatropham to Dr. Cole, but we could not received. The values of NMR spectral data of jatropham is followed by reference 2.
8. D. A. Lightner and C. S. Pak, J. Org. Chem., 1975, 40, 2724; D. A. Lightner, G. S. Bisacchi and R. D. Norris, J. Amer. Chem. Soc., 1976, 98, 802.
9. Several attempts of removal of carbobenzyloxy group in 11 or 12 (Pd/C-H_2, liq. NH_3-Na) were unsuccessful.

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