New Novel Synthesis and Antibacterial Activity of 1-(Substituted phenyl)-2-phenyl-4-(3'-halo, 4'-hydroxy 5'-methoxy benzylidene)-imidazole-5-ones

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Received January 18, 2001

Keywords : Lodovanillin, Bromovanillin, Hippuric acid, Oxazolones, Imidazolones.

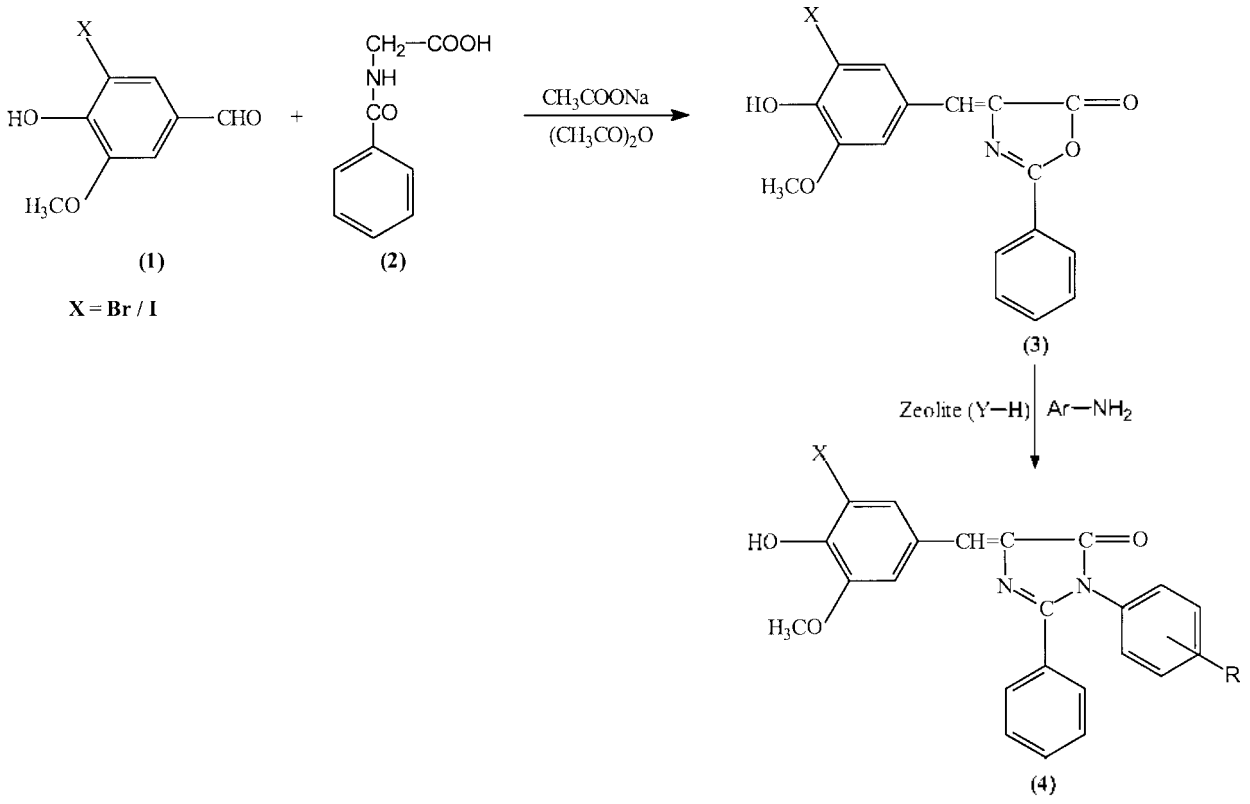
Imidazolones have been found to be associated with several pharmacological activities.[1-4] Imidazolidinones have been reported to possess potent CNS depressant activity. Some imidazoles and substituted imidazolones have been reported to possess monoamine oxidase (MAO) inhibitory and anti-convulsant activities.[5-7] Benzylidene derivatives are also reported to possess anticonvulsant and MAO inhibitory activity. This observation prompted us to synthesize new 1-(substituted phenyl)-2-phenyl-4-(3'-iodo/bromo, 4'-hydroxy, 5'-methoxy benzylidene)-imidazole-5-one by a new method and evaluate their antimicrobial activity.

Early the imidazolones (**4**) have been prepared by heating a mixture of 5-oxazolone derivatives (**3**) with aromatic and substituted aromatic amines in presence of pyridine for 10-15 hours. The yield of the imidazolones (**4**) was very poor and the reaction was a long time reaction.

In the context of studies we have introduced some new imidazolone (**4**), synthesized by the condensation of aromatic and substituted aromatic amines with 5-oxazolone derivative (**3**) in presence of (Y-H) Zeolite (Scheme 1). The reaction takes place in 3-5 hours with excellent yield. The 5-oxazolone derivatives (ozalactone) are prepared by the condensation of hippuric acid with 5-bromo/iodo-4-hydroxy-3-methoxy benzaldehyde in presence of sodium acetate and acetic anhydride.

The compounds were crystallized from alcohol. The products have been identified on the basis of elemental analysis and spectral data (Table 1).

Antibacterial activity. The synthesized compounds were screened for their antimicrobial activity using *Escherischia Coli* (EC), *Azotobacteria* (AZ) *Bacillus subtillis* (BS) *Salmonella typhi* (ST) and *Salmonella dysentrae* (SD) bacteria.



Scheme 1

Table 1. Physical data and antibacterial activity of compound **4a–4t**

Sr.No.	R	Molecular formula	M.P. (°C)	Yield (%)	Zone of inhibition in mm				
					EC	AZ	BS	ST	SD
4a	H	$C_{23}H_{17}N_2O_3I$	170	79	5	6	4	7	8
4b	4 -Br	$C_{23}H_{16}N_2O_3IBr$	141	75	17	18	16	15	16
4c	4-I	$C_{23}H_{16}N_2O_3I_2$	80	74	14	16	18	13	14
4d	4-Cl	$C_{23}H_{16}N_2O_3ICl$	85	68	5	4	6	3	2
4e	4-OCH_3	$C_{24}H_{19}N_2O_4I$	135	75	12	10	14	18	16
4f	4-CH_3	$C_{24}H_{19}N_2O_3I$	130	69	4	6	7	9	10
4g	4-OH	$C_{23}H_{17}N_2O_4I$	105	62	2	5	8	11	5
4h	2,4,6-Br	$C_{23}H_{14}N_2O_3IBr_3$	160	69	5	6	7	4	3
4I	4-NO_2	$C_{23}H_{16}N_3O_5I$	129	65	9	8	6	5	4
4j	Pyridine	$C_{22}H_{16}N_3O_3I$	205	71	8	4	2	6	6
4k	H	$C_{23}H_{17}N_2O_3Br$	98	75	7	8	5	6	4
4l	4-Br	$C_{23}H_{16}N_2O_3Br_2$	110	78	14	10	12	17	15
4m	4-I	$C_{23}H_{16}N_2O_3IBr$	83	72	15	11	14	16	14
4n	4-Cl	$C_{23}H_{16}N_2O_3ClBr$	125	75	5	10	12	5	7
4o	4-OCH_3	$C_{24}H_{19}N_2O_4Br$	85	69	12	14	10	16	11
4p	4-CH_3	$C_{24}H_{19}N_2O_3Br$	180	70	5	7	8	6	7
4q	4-OH	$C_{23}H_{17}N_2O_4Br$	105	65	8	9	4	10	9
4r	2,4,6-Br	$C_{23}H_{14}N_2O_3Br_4$	128	69	8	5	7	9	4
4s	4-NO_2	$C_{23}H_{16}N_3O_5Br$	102	61	6	4	5	7	2
4t	Pyridine	$C_{22}H_{16}N_3O_3Br$	170	73	5	8	4	5	7
				Tetracycline	20	20	20	20	20

The activities of these compounds were tested using disc diffusion method as 150 ppm concentration using 5 mm filter papers disc. The area of zone of inhibition was measured using tetracycline drug as standard compound.

The compounds **4b**, **4c**, **4e**, **4l**, **4m**, and **4o**, showed highest antibacterial activity against all bacteria. Compound **4n** shows highest activity against the *Bacillus subtillis* organism. Compound **4g** shows highest activity against the *Salmonella typhi* organism. Another interesting point is that *Salmonella dysentrae* recorded lowest inhibition against all tested compounds as compare to other bacteria. Remaining other compound showed moderate to poor activity (Table 1).

Experimental Section

Melting points were determined in open capillary tubes and were uncorrected. TLC checks purity of the compounds using silica gel G. IR Spectra are recorded in nujol on Perkin-Elmer-237 spectrophotometer. ^{1}H NMR were recorded in $CDCl_3$ on a Perkin-Elmer R-32 spectrometer using TMS as internal standard (Chemical shift are given in δ ppm).

Preparation of Oxazolone (3). A mixture of 3-iodo-4-hydroxy-5-methoxy benzaldehyde (0.01 mole), hippuric acid (0.01 mole), acetic anhydride (0.03 mole) and sodium acetate (0.01 mole) was heated on electric hot plate with constant shaking in a conical flask. As soon as the mixture was liquified completely, the flask heated on water bath for two hours. Ethanol (5 mL) was added slowly to the contents of flask, the mixture was allowed to stand over night. The separated crystalline solid was filtered, washed with ice-cold alcohol and hot water successively to obtain **3**.

IR: 1625-1605 cm^{-1} (C=N), 1610-1580 cm^{-1} (C=C), 1660-1650 cm^{-1} (C=O), 3720 cm^{-1} (OH).

^{1}H NMR: δ3.9 (s, 3H. OCH_3), 6.8 (s, 1H. Ph-CH), 6.8-7.2 (m, 7H, Ar-H), 9.9 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{17}H_{12}NO_4I$ (421): C, 48.48; H, 2.87; N, 3.33; I, 30.13. Found: C, 48.45; H. 2.84; N, 3.32; I, 30.11.

Preparation of Imidazolone (4). Oxazolone **3** (0.01 mole) was heated with an equimolar quantity of aromatic amine in pyridine (0.01 mole) with Zeolite (Y-H) catalyst in an oil bath at 150 °C for 5 hours. The excess of pyridine was distilled off. The mixture was cooled and pour into crushed ice and HCl. The product was filtered and recrystlised from ethanol to give **4**.

Similarly other compounds were also prepared (Table 1).

4a. IR: 1625-1605 cm^{-1} (C=N), 1615-1580 cm^{-1} (C=C), 1655-1635 cm^{-1} (C=O). 3680 cm^{-1} (OH). ^{1}H NMR: δ3.9 (s, 3H. OCH_3). 6.9 (s. 1H, Ph-CH). 7.1-8.2 (m. 12H, Ar-H), 9.7 (s, 1H. Ar-OH).

Anal. Calcd. For $C_{23}H_{17}N_2O_3I$ (496): C, 55.66; H. 3.45; N. 5.64; I. 25.57. Found: C. 55.56; H, 3.44; N. 5.62; I, 25.51.

4b. IR: 1635-1615 cm^{-1} (C=N), 1610-1595 cm^{-1} (C=C), 1650-1630 cm^{-1} (C=O). 3710 cm^{-1} (OH). ^{1}H NMR: δ4.1 (s. 3H. OCH_3). 6.6 (s. 1H, Ph-CH). 6.8-7.6 (m, 11H. Ar-H). 9.9 (s, 1H. Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_2O_3IBr$ (575): C. 48.03; H. 2.80; N, 4.87; I. 22.06. Br, 13.89. Found: C. 48.08; H, 2.75; N, 4.81; I, 22.05, Br, 13.86.

4c. IR: 1635-1610 cm^{-1} (C=N). 1620-1595 cm^{-1} (C=C),

1665-1640 cm^{-1} (C=O). 3690 cm^{-1} (OH). ^1H NMR: δ 4.0 (s, 3H, OCH_3). 6.9 (s, 1H, Ph-CH). 7.2-8.2 (m, 11H, Ar-H). 9.7 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_2O_3I_2$ (622): C, 44.40; H, 2.59; N, 4.50; I, 40.79. Found: C, 44.35; H, 2.55; N, 4.47; I, 40.73.

4d. IR: 1640-1620 cm^{-1} (C=N), 1610-1580 cm^{-1} (C=C), 1665-1645 cm^{-1} (C=O), 3705 cm^{-1} (OH). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 6.8 (s, 1H, Ph-CH), 6.9-7.6 (m, 11H, Ar-H), 9.8 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_2O_3ICl$ (530): C, 52.05; H, 3.04; N, 5.28; I, 23.91, Cl, 6.68 Found: C, 52.10; H, 3.10; N, 5.22; I, 23.81, Cl, 6.65.

4e. IR: 1637-1619 cm^{-1} (C=N), 1615-1595 cm^{-1} (C=C), 1660-1645 cm^{-1} (C=O), 3710 cm^{-1} (OH). ^1H NMR: δ 3.7 (s, 3H, OCH_3), 6.9 (s, 1H, Ph-CH), 4.1 (s, 3H, $-OCH_3$), 7.2-8.2 (m, 11H, Ar-H), 9.5 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{24}H_{19}N_2O_4I$ (526): C, 54.77; H, 3.64; N, 5.32; I, 24.11. Found: C, 54.71; H, 3.61; N, 5.22; I, 24.15.

4f. IR: 1630-1610 cm^{-1} (C=N), 1610-1590 cm^{-1} (C=C), 1660-1640 cm^{-1} (C=O), 3700 cm^{-1} (OH). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 6.8 (s, 1H, Ph-CH), 2.3 (s, 3H, $-CH_3$), 7-8.2 (m, 11H, Ar-H), 9.9 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{24}H_{19}N_2O_3I$ (510): C, 56.49; H, 3.75; N, 5.49; I, 24.87. Found: C, 56.46; H, 3.64; N, 5.42; I, 24.81.

4g. IR: 1620-1625 cm^{-1} (C=N), 1615-1580 cm^{-1} (C=C), 1670-1650 cm^{-1} (C=O), 3705 cm^{-1} (OH). ^1H NMR: δ 4.0 (s, 3H, OCH_3), 6.9 (s, 1H, Ph-CH), 8.3 (s, 1H, OH), 7.1-8.2 (m, 11H, Ar-H), 9.5 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{17}N_2O_4I$ (512): C, 53.92; H, 3.34; N, 5.47; I, 24.77. Found: C, 53.86; H, 3.24; N, 5.42; I, 24.75.

4h. IR: 1630-1610 cm^{-1} (C=N), 1610-1580 cm^{-1} (C=C), 1680-1660 cm^{-1} (C=O), 3685 cm^{-1} (OH). ^1H NMR: δ 4.0 (s, 3H, OCH_3), 6.9 (s, 1H, Ph-CH), 6.8-7.8 (m, 9H, Ar-H), 9.7 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{14}N_2O_3IBr_3$ (733): C, 37.69; H, 1.93; N, 3.82; I, 17.31, Br, 32.70. Found: C, 37.65; H, 1.87; N, 3.81; I, 17.41, Br, 32.65.

4i. IR: 1630-1618 cm^{-1} (C=N), 1612-1594 cm^{-1} (C=C), 1670-1650 cm^{-1} (C=O), 3705 cm^{-1} (OH). ^1H NMR: δ 4.1 (s, 3H, OCH_3), 7.0 (s, 1H, Ph-CH), 6.9-7.6 (m, 11H, Ar-H), 10.1 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_3O_5I$ (541): C, 51.04; H, 2.98; N, 7.76; I, 23.44. Found: C, 50.95; H, 2.94; N, 7.70; I, 23.51.

4j. IR: 1630-1610 cm^{-1} (C=N), 1610-1590 cm^{-1} (C=C), 1660-1640 cm^{-1} (C=O), 3700 cm^{-1} (OH). ^1H NMR: δ 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, Ph-CH), 7.3-8.2 (m, 11H, Ar-H), 9.5 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{22}H_{16}N_3O_3I$ (497): C, 53.14; H, 3.24; N, 8.45; I, 25.52. Found: C, 53.10; H, 3.14; N, 8.52; I, 25.55.

4k. IR: 1640-1620 cm^{-1} (C=N), 1615-1590 cm^{-1} (C=C), 1655-1640 cm^{-1} (C=O), 3700 cm^{-1} (OH). ^1H NMR: δ 4.2 (s, 3H, OCH_3), 7.0 (s, 1H, Ph-CH), 7.2-8.2 (m, 11H, Ar-H), 9.9 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{17}N_2O_3Br$ (449): C, 61.48; H, 3.81; N, 6.23; Br, 17.78. Found: C, 61.46; H, 3.84; N, 6.28; Br, 17.71.

4l. IR: 1635-1605 cm^{-1} (C=N), 1650-1580 cm^{-1} (C=C), 1665-1645 cm^{-1} (C=O), 3715 cm^{-1} (OH). ^1H NMR: δ 3.8 (s, 3H, OCH_3), 6.8 (s, 1H, Ph-CH), 6.9-7.6 (m, 11H, Ar-H), 8.7 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_2O_3Br_2$ (528): C, 52.30; H, 3.05; N, 5.30; Br, 30.26. Found: C, 52.35; H, 3.04; N, 5.32; Br, 30.25.

4m. IR: 1630-1600 cm^{-1} (C=N), 1615-1595 cm^{-1} (C=C), 1665-1640 cm^{-1} (C=O), 3700 cm^{-1} (OH). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 6.9 (s, 1H, Ph-CH), 7-7.8 (m, 11H, Ar-H), 9.8 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_2O_3IBr$ (575): C, 48.03; H, 2.80; N, 4.87; I, 22.06, Br, 13.89 Found: C, 48.08; H, 2.84; N, 4.82; I, 22.05; Br, 13.85.

4n. IR: 1630-1610 cm^{-1} (C=N), 1630-1570 cm^{-1} (C=C), 1665-1650 cm^{-1} (C=O), 3700 cm^{-1} (OH). ^1H NMR: δ 4.1 (s, 3H, OCH_3), 6.9 (s, 1H, Ph-CH), 7.2-8.2 (m, 11H, Ar-H), 9.9 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_2O_3BrCl$ (483): C, 57.11; H, 3.33; N, 5.79; Br, 16.52, Cl, 7.33. Found: C, 57.16; H, 3.34; N, 5.72; Br, 16.55, Cl, 7.30.

4o. IR: 1640-1615 cm^{-1} (C=N), 1610-1570 cm^{-1} (C=C), 1660-1640 cm^{-1} (C=O), 3680 cm^{-1} (OH). ^1H NMR: δ 4.1 (s, 3H, OCH_3), 6.6 (s, 1H, Ph-CH), 3.9 (s, 3H, $-OCH_3$), 7-7.8 (m, 11H, Ar-H), 9.8 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{24}H_{19}N_2O_4Br$ (479): C, 60.14; H, 4.00; N, 5.84; Br, 16.67. Found: C, 60.16; H, 4.04; N, 5.82; Br, 16.61.

4p. IR: 1635-1620 cm^{-1} (C=N), 1640-1580 cm^{-1} (C=C), 1660-1640 cm^{-1} (C=O), 3710 cm^{-1} (OH). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 6.7 (s, 1H, Ph-CH), 2.3 (s, 3H, $-CH_3$), 7.2-8.2 (m, 11H, Ar-H), 9.8 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{24}H_{19}N_2O_3Br$ (463): C, 62.22; H, 4.13; N, 6.05; Br, 17.25. Found: C, 62.26; H, 4.14; N, 6.09; Br, 17.20.

4q. IR: 1630-1615 cm^{-1} (C=N), 1610-1590 cm^{-1} (C=C), 1660-1640 cm^{-1} (C=O), 3685 cm^{-1} (OH). ^1H NMR: δ 4.0 (s, 3H, OCH_3), 6.7 (s, 1H, Ph-CH), 8.8 (s, 1H, OH), 7.2-8.0 (m, 11H, Ar-H), 10.1 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{17}N_2O_4Br$ (465): C, 59.37; H, 3.68; N, 6.02; Br, 17.17. Found: C, 59.36; H, 3.64; N, 6.08; Br, 17.23.

4r. IR: 1630-1610 cm^{-1} (C=N), 1610-1570 cm^{-1} (C=C), 1670-1640 cm^{-1} (C=O), 3700 cm^{-1} (OH). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 6.8 (s, 1H, Ph-CH), 7.3-8.2 (m, 9H, Ar-H), 10.5 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{14}N_2O_3Br_4$ (686): C, 40.27; H, 2.06; N, 4.08; Br, 46.59. Found: C, 40.30; H, 2.04; N, 4.10; Br, 46.51.

4s. IR: 1630-1610 cm^{-1} (C=N), 1640-1570 cm^{-1} (C=C), 1660-1630 cm^{-1} (C=O), 3725 cm^{-1} (OH). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 6.9 (s, 1H, Ph-CH), 7-7.7 (m, 11H, Ar-H), 9.9 (s, 1H, Ar-OH).

Anal. Calcd. For $C_{23}H_{16}N_3O_5Br$ (494): C, 55.89; H, 3.26; N, 8.50; Br, 16.16. Found: C, 55.76; H, 3.24; N, 8.52; Br, 16.12.

4t. IR: 1630-1610 cm^{-1} (C=N), 1610-1540 cm^{-1} (C=C), 1660-1640 cm^{-1} (C=O), 3705 cm^{-1} (OH). ^1H NMR: δ 3.9 (s,

3H. OCH_3), 6.8 (s. 1H, Ph-CH), 7-7.8 (m, 11H, Ar-H), 9.9 (s. 1H. Ar-OH).

Anal. Calcd. For $C_{22}H_{16}N_3O_3Br$ (450): C. 58.68; H, 3.58; N, 9.33; Br. 17.74. Found: C, 58.72; H. 3.54; N, 9.30; Br. 17.69.

Acknowledgment. The authors are thankful to Dr. W.N. Jadhav. Dnyanopasak College. Parbhani and Dr. B. M. Bhawal, Dr. P. P. Wadgaonkar. National Chemical Laboratory. Pune for their valuable guidance.

References

1. Wright, W. B.; Brabander, H. J. *J. Org. Chem.* **1961**, *26*, 4051.
2. Niedbalia, V.; Buettcher, I. *Chem. Abstr.* **1981**, *94*, 15732.
3. Pande, K.; Kalsi Kalpana, R.; Bhalla, T. N.; Barthwal *Pharmzine* **1987**, *42*, 269.
4. Wright, W. B.; Brabander, H. S.; Hardy, R. A.; Osterberg, A. C. *J. Med. Chem.* **1966**, *9*, 852.
5. Lingi, A.; Alfonso, M.; Pierluigi, R.; Afro, G.; Enzo, Z.; Nicola, D. T.; Walter, M. *J. Med. Chem.* **1969**, *12*, 12.
6. Brik, F.; Godefrot: Reatge, J. *J. Med. Chem.* **1972**, *15*, 336.
7. Verma, M.; Charturvedi, A. K.; Chaudhry, A.; Parmar, S. S. *J. Parm. Sci.* **1974**, *463*, 1740.
8. Collins, C. H. *Microbiological Methods*; Bulter Worths: London, 1974; p 364.