FORMATION OF ANOMALOUS PRODUCTS IN THE LEUCKART REACTION OF THE 2-BROMO-4,5-DIMETHOXYBENZYL 2-HYDROXY-3,4-DIMETHOXYPHENYL KETONE

Esther Domínguez*, Esther Lete, M. Jesús Villa and Carmen Iriondo
Departamento de Química, Facultad de Ciencias,
Universidad del País Vasco, Bilbao, Spain

Abstract—The Leuckart reaction of the 2-bromo-4,5-dimethoxybenzyl 2-hydroxy-3,4-dimethoxyphenyl ketone (2) afforded, not the expected amine, but three anomalous products: the stilbene (3), the isoflavone (4) and the pyrimidine (5). Their structures have been established on the basis of their spectral data.

The Leuckart reaction[1] is a well-known procedure for the direct conversion of aldehydes and ketones to primary amines upon heating with formic acid or certain of its derivatives. Although this reaction has been applied successfully to many aromatic and aliphatic-aromatic ketones, it is not free from side reactions[2]. For example, unexpected by-products were encountered when aromatic ketones possessing an active methylene group or nitroaryl ketones were used. Thus, it was shown[3] that 2-propionylthiophene gave a thienyl substituted pyrimidine in significant yield(11%), an anomalous Leuckart product, in addition to the expected 1-(2-thienyl)-1-aminopropane. On the other hand, Srinivasan and Rampal[4] reported that when the Leuckart reaction was applied to β-nitrobenzoylthiophenes, the nitro group participated in the reaction leading to quinazoline derivatives as the major products. Moreover, in case of phenolic ketones the reaction gave unsatisfactory results, probably due to polimerization reactions[2]. It therefore appeared worthwhile to study the effect of an hydroxyl substituent in the ortho position of an aryl ketone possessing an active methylene group. Thus, it was decided to investigate the behaviour of the 2-bromo-4,5-dimethoxybenzyl 2-hydroxy-3,4-dimethoxyphenyl ketone (2) under Leuckart reaction conditions.

Since it is known[5,6] that a phenolic methyl ether group ortho to a carbonyl group can be selectively removed by treatment with $AlCl_3$, 1,2,3-trimethoxybenzene was reacted with the 2-bromo-4,5-dimethoxyphenylacetyl chloride (1) in the presence of $AlCl_3$ to give the 2-bromo-4,5-dimethoxybenzyl 2-hydroxy-3,4-dimethoxyphenyl ketone (2). In fact, the absence of "free" hydroxyl bands in the ir spectrum and the appearance of a phenolic proton as a singlet at low-field (δ12) in the pmr spectrum, indicated the presence of a phenolic group in the ortho position to the carbonyl group.

Therefore, the above facts together with the aromatic protons resonances, confirmed both the expected cleavage of the methoxy group and the site of acylation.

Leuckart reaction ($HCOOH/HCOONH_4$) of the ketone (2) and subsequent flash chromatography afforded, instead of the corresponding amine derivative, three anomalous Leuckart products:

i) 1-(2-bromo-4,5-dimethoxyphenyl)-2-(2-hydroxy-3,4-dimethoxyphenyl)ethylene (3) (Yield 28%).

ii) 3-(2-bromo-4,5-dimethoxyphenyl)-7,8-dimethoxyisoflavone (4) (Yield 15%).

iii) 5-(2-bromo-4,5-dimethoxyphenyl)-4-(2-hydroxy-3,4-dimethoxyphenyl)pyrimidine (5) (Yield 11%).

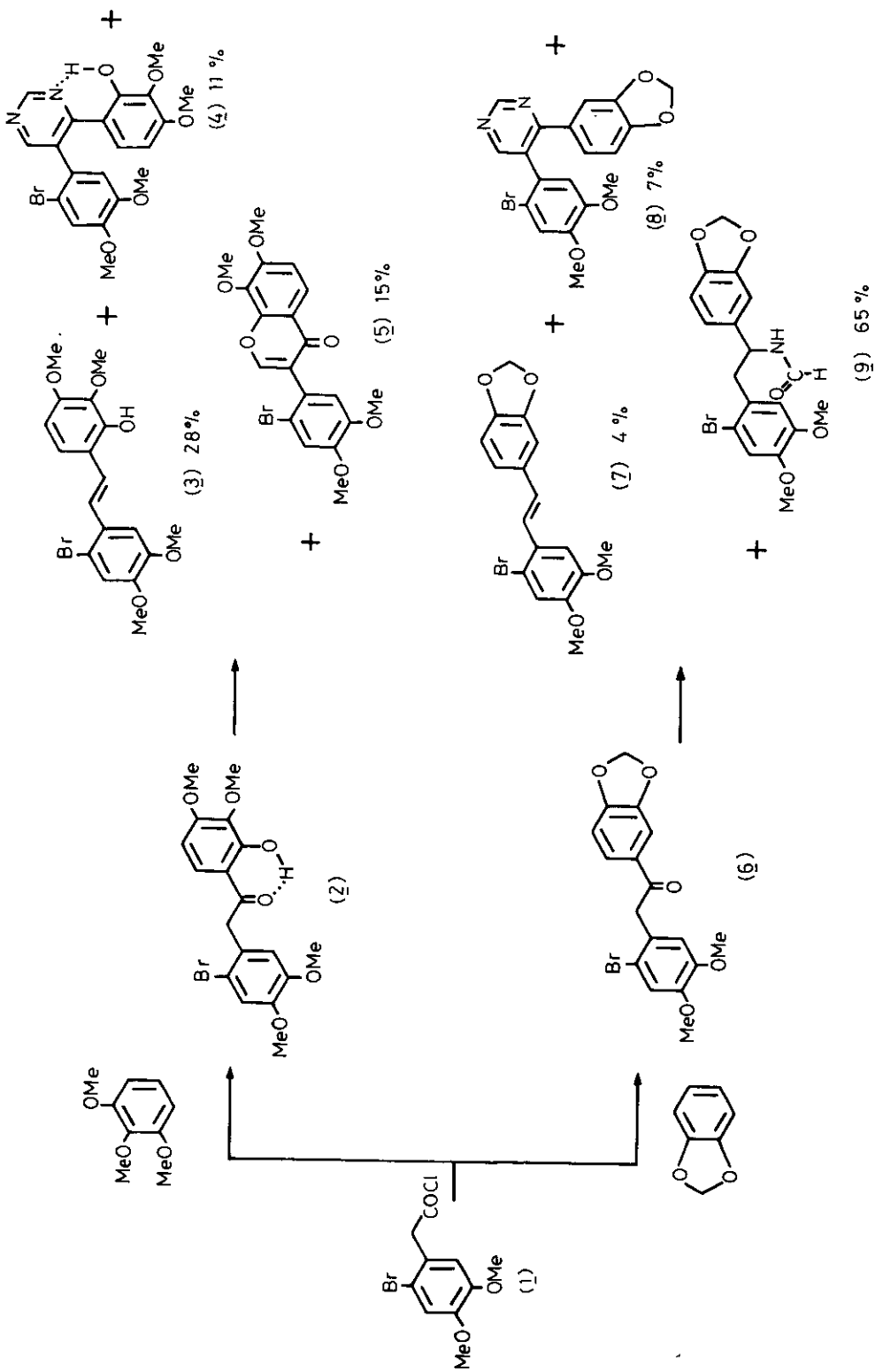
Although a variety of reaction conditions have been investigated in order to obtain the amine derivative, the ketone (2) always led to the same reaction products (Table 1).

Table 1. Leuckart reaction of the 2-bromo-4,5-dimethoxybenzyl 2-hydroxy-3,4-dimethoxyphenyl ketone (2).

Amounts used Ketone/$HCOONH_4$/HCOOH/$HCONH_2$ (mmol) (mmol) (ml) (ml)	Conditions Temp.(°C)/ time (h)	Yield[a] (%) of Stilbene (3)	Isoflavone (4)	Pyrimidine (5)
3.0 / 30 / – / –	185-190/3.0	31	14	14
7.4 / 74 / 0.74 / –	185-190/4.5	28	15	11
8.1 / 81 / 0.81 / 0.81	185-190/5.5	27	15	20
3.0 / – / 0.05 / 0.50	185-190/4.5	27	22	24
3.0 / – / – / 1.75	185-190/4.0	10	16	24

a) Yield of pure, isolated product.

The stilbene structure (3) was proved unambiguously by the X-Ray crystallographic study[7]. Its formation may be explained by assuming that an elimination reaction took place under the Leuckart reaction conditions employed.
The molecular formulae of the isoflavone (4), $C_{19}H_{17}BrO_6$, and the pyrimidine (5), $C_{20}H_{19}BrN_2O_5$, were obtained from their mass spectra and elemental analysis, and their structures deduced from their spectral data (ir, uv, pmr and cmr).
Thus, the pmr spectrum of the isoflavone (4) exhibited, in addition to the resonances of four methoxy groups, the characteristic singlet (δ 8.0) due to the vinylic proton of isoflavones[8], and the signals of two ortho- and two para-coupled aromatic protons, assigned to the H-atoms of the chromone and bromobenzene rings,


(1)
(2)
(3) 28%
(4) 11 %
(5) 15%
(6)
(7) 4 %
(8) 7%
(9) 65 %

respectively. In the cmr spectrum of (4), the most characteristic signals were those of the carbonyl carbon C-4 (δ 175.0) and the methine carbon C-2 (δ154.3) of the chromone ring[9]. These evidences, together with the uv, ir and ms data are only compatible with the structure (4) for this compound.

Moreover, as alkali degradation of this compound produced the starting ketone (2) and formic acid, the assigned structure was confirmed beyond doubt as the isoflavone (4). The formation of this compound may proceed through a similar mechanism to the one involved in the typical synthesis of isoflavones starting from a benzyl phenyl ketone and ethyl orthoformate[10].

The pmr spectrum of the pyrimidine (5) exhibited two low-field singlets at 9.1 and 8.6, characteristic of pyrimidine resonances and the chemical shifts were virtually identical with those found for similar compounds[3]. Furthermore, the signals of the four aromatic protons, the phenolic proton and the four methoxy groups were observed. The cmr spectrum clearly showed the typical signals of the two methine carbons of the pyrimidine ring (δ 161.9, C-2, and δ 155.1, C-6). In addition, the uv, ir and ms data fitted well with the proposed structure (5).

Hill and Loev[3] have previously reported the formation of a pyrimidine derivative under Leuckart reaction conditions and suggested that pyrimidines might also be formed as by-products in other Leuckart reactions, though they had not been isolated. Moreover, these authors proposed a mechanistic pathway to explain the formation of pyrimidines in this kind of reaction.

Consequently, the isolation of this new pyrimidine derivative (5) supports the above mentioned hypothesis. Additionally, we undertook the Leuckart reaction of the 2-bromo-4,5-dimethoxybenzyl 3,4-methylenedioxyphenyl ketone (6), prepared according to the procedure described by Dyke et al.[11], obtaining the following compounds:

i) 1-(2-bromo-4,5-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethylene (7) (Yield 4%).

ii) 5-(2-bromo-4,5-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)pyrimidine (8) (Yield 7%).

iii) N-1-(2-bromo-4,5-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethylformamide (9) (Yield 65%).

These results lead us to propose that when applying the Leuckart reaction to benzyl aryl ketones, pyrimidine and stilbene derivatives are always obtained, whereas the isoflavone formation needs the participation of a phenolic group in the ortho position to the carbonyl group.

EXPERIMENTAL

Melting points were determined on either Electrothermal 1A 6304 or Buchi apparatus and are uncorrected. For thin-layer chromatography Merck Kieselgel GF 254 plates (0.2 mm thick) were used. Visualization was accomplished by uv light or by spraying with Draguendorff's reagent. Microanalysis and mass spectra were performed by the "Instituto de Química Bio-Orgánica de Cataluña". Uv and ir spectra were recorded on a Beckman 5260 and a Perkin-Elmer 1430 spectrophotometers respectively. Pmr spectra were run on a Perkin-Elmer R-12 (60 MHz) apparatus and cmr spectra on a Varian XL-200 spectrometer.

2-bromo-4,5-dimethoxybenzyl 2-hydroxy-3,4-dimethoxyphenyl ketone (2)

Thionyl chloride (4.1 ml) was added to a solution of 2-bromo-4,5-dimethoxyphenylacetic acid (8.3 g, 0.03 mole) in dry toluene (165 ml) at 30°C and the whole was allowed to stand for 3/4 h, then heated under reflux for 3 h. The solvent and the excess of thionyl chloride were evaporated under reduced pressure, thus obtaining the 2-bromo-4,5-dimethoxyphenylacetyl chloride (1) as an oil. Then, to a solution of this chloride and 1,2,3-trimethoxybenzene (5.5 g, 0.03 mole) in dry dichloromethane (50 ml), anhydrous $AlCl_3$ (5.6 g, 0.04 mole) was added. The mixture was heated under reflux for 3 h. The cooled solution was poured into a stirred mixture of water (10 ml), 12 M HCl (22 ml) and ice (31 g). The organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$ anh.) and the solvent evaporated to yield a brown oil. Crystallization from ethanol/dichloromethane gave the ketone (2) as a white solid. Yield: 7.6 g (62%), mp 182-183°C. Anal. Calcd. for $C_{18}H_{19}BrO_6$: C, 52.55%; H, 4.62%; Br, 19.46%. Found : C, 52.98%; H, 4.53%; Br, 19.85%.
Ir(KBr) ν_{max} cm^{-1} : 1630 (-CO-). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 243 (4.18), 287 (4.40).
Pmr ($CDCl_3$), δ: 12.2 (1H, s, OH, exchangeable with D_2O), 7.75 (1H, d, J=9Hz, H-6'), 7.1 (1H, s, H-3), 6.8 (1H, s, H-6), 6.55 (1H, d, J=9Hz, H-5'), 4.35 (s, 2H,-CH_2CO-), 3.95(3H, s, OMe), 3.9 (3H, s, OMe), 3.85 (3H, s, OMe), 3.80(3H, s, OMe).

2-bromo-4,5-dimethoxybenzyl 3,4-methylenedioxyphenyl ketone (6).

To a stirred mixture of methylenedioxybenzene (8.4 g, 0.07 mole) and $SnCl_4$ (20.5 g, 0.08 mole) in dry dichloromethane (60 ml) at -10°C under nitrogen, a solution of 2-bromo-4,5-dimethoxyphenylacetyl chloride (1) in dry dichloromethane (60 ml) was added. The mixture was allowed to attain room temperature and stirred for 2 h, then poured into 6M HCl (120 ml) and stirred for further 16 h. Work-up as described above afforded the ketone (6) as a white solid. Yield: 19.5 g (68%), mp 144-145°C (from ethanol/dichloromethane). Anal. Calcd. for $C_{17}H_{15}BrO_5$: C, 53.83%; H, 3.96%; Br, 21.11%. Found: C, 53.91%; H, 4.00%; Br, 21.02%.

Ir(KBr) ν_{max} cm^{-1} : 1670 (-CO-). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε) : 242 (4.06), 278 (4.08), 296 (3.99, sh), 308 (3.96, sh).

Pmr($CDCl_3$), δ: 7.65 (1H, dd, J=9 and 2 Hz, H-6'), 7.50 (1H, d, J=2 Hz, H-2'), 6.9-7.1 (2H, m, H-6 and H-5'), 6.80 (1H, s, H-3), 6.05 (2H, s, $-OCH_2O-$), 4.3 (2H, s, $-CH_2CO-$), 3.90 (3H, s, OMe), 3.80 (s, 3H, OMe).

Cmr($CDCl_3$), δ: $-\underline{C}H_2CO-$, 44.9 (t); CH_3O-, 55.8 (q), 55.9 (q); $-OCH_2O-$, 101.7 (t); C-Br, 114.7 (s); aromatic $-\underline{C}H-$, 107.8 (d), 107.9 (d), 113.7 (d), 115.3 (d), 124.6 (d); aromatic $\underline{C}-CH_2-$, 126.7 (s); aromatic $\underline{C}-CO-$, 131.2 (s); aromatic C-O-, 148.0 (s), 148.3 (s), 148.5 (s), 151.8 (s); -CO-, 194.6 (s).

Reaction of the 2-bromo-4,5-dimethoxybenzyl 2-hydroxy-3,4-dimethoxyphenyl ketone(2) under Leuckart conditions (Typical procedure).

A mixture of the ketone (2) (3 g, 7.3 mmole), ammonium formate (4.7 g, 73 mmole) and 99% formic acid (0.74 ml) was heated at 185-190°C, until complete consumption of the ketone (monitored by tlc on silica gel using dichloromethane/ethyl acetate, 9:1) was achieved. Then, the reaction mixture was cooled to room temperature, water added and the resulting solid filtered off. As the crude product showed (tlc) the presence of three main products, it was chromatographed under pressure on silica gel by eluting with dichloromethane/ethyl acetate (9:1) to afford:

1-(2-bromo-4,5-dimethoxyphenyl)-2-(2-hydroxy-3,4-dimethoxyphenyl)ethylene (3):

R_f= 0.61, 806 mg (Yield 28%), colorless crystals of mp 176-177°C (from chloroform/ethanol). Anal. Calcd. for $C_{18}H_{19}BrO_5$: C, 45.58%; H, 4.81%; Br, 20.23%. Found: C, 45.34%; H, 4.65%; Br, 20.53%.
Ir(KBr) ν_{max} cm^{-1} : 3400 (free OH). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 246 (4.21), 298 (4.20), 336 (4.23).

Pmr($CDCl_3$), δ: 9.3 (1H, s, OH, exchangeable with D_2O), 7.3 (3H, m, H-6" and -CH=CH-), 7.05 (1H, s, H-3'), 6.5 (1H, d, J=9 Hz, H-5"), 6.35 (1H, s, H-6'), 3.95 (6H, s, 2 x OMe), 3.90 (6H, s, 2 x OMe).

3-(2-bromo-4,5-dimethoxyphenyl)-7,8-dimethoxyisoflavone (4):

R_f= 0.38, 441 mg (Yield 15%), white solid of mp 213-215°C (from ethyl acetate/dichloromethane). Anal. Calcd. for $C_{19}H_{17}BrO_6$: C, 54.16%; H, 4.04%; Br, 18.98%. Found: C, 54.47%; H, 3.88%; Br, 19.33%.
Ms , m/e (%) : 420/422 (M^+, 5), 341 (100).
Ir(KBr) ν_{max} cm^{-1}: 1650, 1620 (-CO- and/or $-\underline{C}=CH-O-$). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 256 (4.42), 294 (4.17).

Pmr(DMSO-d_6), δ: 8.1 (1H, s, H-2), 7.6 (1H, d, J=8.6 Hz, H-5), 7.15-7.0 (2H, m, H-6 and H-3'), 6.75 (1H, s, H-6'), 3.8 (3H, s, OMe), 3.75 (3H, s, OMe), 3.65 (3H, s, OMe), 3.60 (3H, s, OMe).

Cmr($CDCl_3$), δ: CH_3O-, 55.9 (q), 56.0 (q), 56.2 (q), 61.3 (q); aromatic $-\underline{C}H-$, 110.1 (d), 114.8 (d), 115.7 (d), 121.4 (d); C-Br, 119.0 (s); C-3 and C-4a, 124.6 (s), 124.7 (s); C-1', 138.1 (s); aromatic C-O, 148.2 (s), 149.6 (s); C-2, 154.3 (d);

C-8a, 156.3 (s); -CO-, 175.0 (s).

5-(2-bromo-4,5-dimethoxyphenyl)-4-(2-hydroxy-3,4-dimethoxyphenyl)pyrimidine (5)

R_f= 0.25, 348 mg (Yield 11%), yellow crystals of mp 162-163°C (from ethanol).
Anal. Calcd. for $C_{20}H_{19}BrN_2O_5$: C, 53.68%; H, 4.25%; N, 6.26%; Br, 17.90%. Found: C, 53.65%; H, 4.45%; N, 6.34%; Br, 18.22%.
Ms, m/e (%): 446/448 (M^+, 21), 367 (100).

Ir(KBr) ν_{max} cm^{-1} : 1620 (C=N). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 246 (4.25), 307 (4.18), 330 (4.15, sh).

Pmr($CDCl_3$), δ: 13.0 (1H, s, OH, exchangeable with D_2O), 9.1 (1H, s, H-2 pyrimidine), 8.6 (1H, s, H-6 pyrimidine), 7.15 (1H, s, H-6'), 6.75 (2H, m, H-3' and H-6"), 6.15 (1H, d, J=9 Hz, H-5"), 3.95 (3H, s, OMe), 3.90 (3H, s, OMe), 3.80 (3H, s, OMe), 3.75 (3H, s, OMe).

Cmr($CDCl_3$), δ: CH_3O-, 55.8 (q), 56.3 (q), 60.5 (q); aromatic -CH-, 102.9 (d), 113.5 (d), 116.1 (d), 125.6 (d); C-Br, 113.0 (s); C-1", 129.7 (s); C-5, 131.1 (s); C-1', 137.3 (s); aromatic C-O, 149.3 (s), 150.1 (s), 154.8 (s), 155.7 (s); C-6, 155.0 (d); C-2, 160.3 (d); C-4, 161.9 (s).

Reaction of the 2-bromo-4,5-dimethoxybenzyl 3,4-methylenedioxyphenyl ketone (6) under Leuckart conditions.

A mixture of the ketone (6) (17.7 g, 0.05 mole), ammonium formate (29.4 g, 0.5 mole) and 99% formic acid (4.6 ml) was heated at 185-190 °C for 4 h. After the usual work-up, crystallization of the crude product afforded the N-1-(2-bromo-4,5-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethylformamide (9) as a white solid of mp 199-200°C (from methanol/chloroform). Yield: 12.3 g (65%). Anal. Calcd. for $C_{18}H_{18}BrNO_5$ C, 53.00%; H, 4.45%; N, 3.43%; Br, 19.58%. Found: C, 52.73%; H, 4.42%; N, 3.36%; Br, 19.77%.
Ir(KBr) ν_{max} cm^{-1} : 3300 (NH), 1660 (C=O). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 244 (4.11), 288 (4.05).

Pmr(DMSO-d_6), δ: 8.6 (1H,broad d, NH), 8.0 (1H, s, -CHO), 6.7-7.2 (5H, m, aromatic protons), 6.0 (2H, s,-OCH_2O-), 4.9-5.3 (1H, m, -$CH_2\underline{CH}$-), 3.7 (3H, s, OMe), 3.65 (3H, s, OMe), 2.95 (2H, d, J=7.7 Hz, -$\underline{CH_2}CH$-).

In addition, the filtrates were evaporated to dryness and the residue chromatographed on silica gel under pressure with chloroform/ethyl acetate (9:1) as eluent to furnish the following by-products:

1-(2-bromo-4,5-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethylene (7):

R_f= 0.87, 675 mg (Yield 4%), white crystals of mp 168-170°C (from methanol).
Anal. Calcd. for $C_{17}H_{15}BrO_4$: C, 56.19%; H, 4.13%; Br, 20.01%. Found: C, 55.86%; H, 4.01%; Br, 20.34%.
Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 244 (4.12), 299 (4.11), 342 (4.22).

Pmr($CDCl_3$), δ: 7.5-6.7 (7H, m, aromatic and ethylenic protons), 6.0 (2H, s,-OCH_2O-), 3.95 (3H, s, OMe), 3.90 (3H, s, OMe).

5-(2-bromo-4,5-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)pyrimidine (8)

R_f= 0.25, 1.20 g (Yield 7%), beige crystals of mp 130-132°C (from ethyl ether/ethanol). Anal. Calcd. for $C_{19}H_{15}BrN_2O_4$: C, 54.95%; H, 3.61%; N, 6.74%; Br, 19.25%. Found: C, 54.42%; H, 3.53%; N, 6.82%; Br, 19.58%.

Ir(KBr) ν_{max} cm^{-1} : 1620 (C=N). Uv $\lambda_{max}^{CHCl_3}$ nm (log ε): 246 (4.27), 279 (4.31), 290 (4.29).

Pmr($CDCl_3$), δ: 9.3 (1H, s, H-2 pyrimidine), 8.7 (1H, s, H-6 pyrimidine), 7.3-6.8 (5H, m, aromatic protons), 6.0 (2H, s, -OCH_2O-), 3.95 (3H, s, OMe), 3.75 (3H, s, OMe).

REFERENCES

1. R. Leuckart, Chem. Ber., 1885, 18, 2341.
2. M. L. Moore, Org. React., 1949, 5, 301.
3. D. T. Hill and B. Loev, J. Org. Chem., 1973, 38, 2102.
4. M. Srinivasan and J. B. Rampal, Tetrahedron Lett., 1974, 33, 2883.
5. M. Kulka, J. Am. Chem. Soc., 1954, 76, 5469.
6. E. Hardegger, E. Widmer, K. Steiner and A. Pfiffner, Helv. Chim. Acta, 1964, 47, 2027.
7. J. M. Arrieta, E. Domínguez, E. Lete, M. J. Villa and G. Germain, Acta Cryst., in press.
8. N. Minhaj, H. Khan, S. K. Kapoor and A. Zaman, Tetrahedron, 1976, 32, 749.
9. H. Wagner, V. Mohan Chari, J. Sonnenbichler, Tetrahedron Lett., 1976, 21,1799; B. Ternai and K. R. Markham, Tetrahedron, 1976, 32, 565.
10. W. B. Whalley, 'Heterocyclic Compounds', ed. by R. C. Elderfield, John Wiley & Sons, Inc., New York, 1961, 7, 56-195.
11. S. F. Dyke, D. W. Brown, M. Sainsbury and G. Hardy, Tetrahedron, 1971, 27, 3495.

Received, 3rd February, 1984