Methoxy-substituted Benzyl Isothiocyanates and

N-Benzylthioureas

ERIK BACH and ANDERS KJÆR*

Department of Organic Chemistry, Royal Veterinary and Agricultural College,
Copenhagen, Denmark

In connection with current studies of naturally occurring gluco-
sinolates, the complete series of dimethoxybenzyl isothiocyanates, and
the corresponding thioureas, are synthesised, with the appropriately
substituted dimethoxybenzylamines serving as starting materials.

Piperonyl and 3,4,5-trimethoxybenzyl isothiocyanate, and the
corresponding thioureas, are likewise prepared.

The chromatographic behaviour of the various isothiocyanates
and thioureas is reported and discussed.

Benzylglucosinolates, substituted in 3- or 4-position of the aromatic ring
with a hydroxy group, or in each or both positions with a methoxy-group,
are well-established natural products;[1] recently, 3,4,5-trimethoxybenzyl-
glucosinolate was added to the series.[2] Upon enzymic hydrolysis, the methoxy-
substituted benzylglucosinolates typically afford the corresponding methoxy-
benzyl isothiocyanates, easily converted into crystalline N-substituted thi-
oureas on reaction with ammonia. As an aid in current and future glucosinolate
studies, including chromatographic analyses, it became of interest to prepare,
additionally to the known 2-,[3] 3-,[4] 4-,[5] and 3,4-methoxylated [6] benzyl iso-
thiocyanates, and the corresponding thioureas, the five isomeric dimethoxy-
benzyl isothiocyanates (I), the 3,4-methylenedioxy-(piperonyl) (II), and 3,4,5-
trimethoxy-(III) substitutes, as well as the corresponding N-thioureas. We
describe the syntheses in the present communication.

The di- or tri-O-substituted benzylamines, serving as starting materials,
were either commercial products, or synthesised by lithium aluminium hy-
dride reduction of the appropriately substituted aldoximes or nitriles (cf.
Experimental). Conversion of the amines into isothiocyanates upon reaction
with thiocarbonyl chloride, in the presence of triethylamine, was unexcep-
tional. The physical constants and analytical compositions of the synthetic
isothiocyanates are presented in Table 1.

---

* Address correspondence to this author at the Department of Organic Chemistry, Technical
University of Denmark, DK-2800 Lyngby, Denmark.
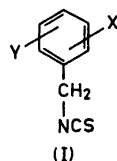
I a: X = 2-MeO; Y = 3-MeO
I b: X = 2-MeO; Y = 4-MeO
I c: X = 2-MeO; Y = 5-MeO
I d: X = 2-MeO; Y = 6-MeO
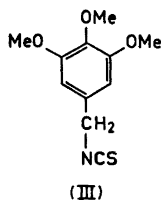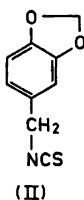I e: X = 3-MeO; Y = 4-MeO
I f: X = 3-MeO; Y = 5-MeO

Table 1. Methoxy- and methylenedioxy-substituted benzyl isothiocyanates, (I), (II), and (III).

Formula	Substituents	B.p.° (mm)	n_{D25}	m.p.°	Analyses %		
					C	H	N
Ia	2,3-MeO-[a]	102 (0.1)	1.5818		57.60	5.32	6.78[g]
Ib	2,4-MeO-[b]	Bath 70 (0.05)[d]	1.5942		Not analysed[f]		
Ic	2,5-MeO-[a]	108 (0.01)	1.5873	< 20[e]	57.62	5.24	6.72
Id	2,6-MeO-[a]	Subl.		80 − 1	57.57	5.32	6.61
Ie	3,4-MeO-[c]	135 − 7 (0.3)[c]	1.5960[c]	22 − 4[c]	57.36	5.32	6.60[c]
If	3,5-MeO-[a]	98 (0.05)		45 − 6	54.47	5.37	6.51
II	3,4-OCH₂O-[a]	103 (0.1)	1.6142		56.03	3.70	7.30[h]
III	3,4,5-MeO-[b]	131 (0.1)	1.5824		55.11	5.55	5.90[i]

[a] Prepared by procedure (A), *cf.* Experimental. [b] Prepared by procedure (B), *cf.* Experimental. [c] Previously described.[6] [d] Decomposes readily, short-path distilled in small portions. [e] Crystalline in the ice-box (*ca.* 5°). [f] Too unstable for analysis. [g] Calc. for dimethoxybenzyl isothiocyanates, $C_{10}H_{11}O_2NS$: C 57.38; H 5.30; N 6.69. [h] Calc. for $C_9H_7O_2NS$: C 55.95; H 3.65; N 7.25. [i] Calc. for $C_{11}H_{13}O_3NS$: C 55.20; H 5.47; N 5.85.

Conversion of the individual isothiocyanates into the corresponding N-substituted thioureas on reaction with ammonia in methanol presented no problems. Physical constants and analytical data for the individual thioureas are presented in Table 2.

In a previous communication,[6] an unexpected behaviour of 3,4-dimethoxy-benzylthiourea on paper chromatography in certain solvent systems was noted. Access to the complete series of mono- and di-methoxybenzyl isothiocyanates, and the corresponding thioureas, has now occasioned a comparative study of their chromatographic characteristics, the results of which we describe. TLC chromatography of the isothiocyanates on silica gel, with benzene as a solvent, silver nitrate as a spray reagent, and phenyl isothiocyanate as an internal standard (R_{Ph} 1.00), showed a moderate spread in R_{Ph}-values for

Table 2. Methoxy- and methylenedioxy-substituted *N*-benzylthioureas.

Substituents	M.p.°	C	Analyses % H	N
2,3-MeO	150	52.99	6.18	12.17[c]
2,4-MeO-	166	53.05	6.28	12.45
2,5-MeO-	124	53.32	6.32	12.16
2,6-MeO-	205	53.32	6.30	12.17
3,4-MeO-[b]	193			
3,5-MeO-	112	53.12	6.38	12.23
3,4-OCH₂O-	153	51.40	4.83	13.18[d]
3,4,5-MeO-	194[a]	51.65	6.29	10.77[e]

[a] Recrystallised from methanol; all other thioureas recrystallised from anhydrous ethanol. [b] Previously reported.[6] [c] Calc. for dimethoxybenzylthioureas, $C_{10}H_{14}O_2S$: C 53.07; H 6.23; N 12.38. [d] Calc. for $C_9H_{10}O_2N_2S$: C 51.40; H 4.79; N 13.32. [e] Calc. for $C_{11}H_{16}O_3N_2S$: C 51.54; H 6.29; N 10.93.

mono- and di-methoxylated benzyl isothiocyanates, with the notable exceptions of the 3,4- and 3,4,5-methoxylated species, both possessing considerably lower R_{Ph}-values (*cf.* Table 3). This effect is not observable when the corresponding thioureas are subjected to TLC in chloroform: ethanol (Table 3). Perhaps the most striking case of the special behaviour of 3,4- and 3,4,5-methoxy-thiourea is found, however, on paper chromatograms run in solvent systems containing aromatic hydrocarbons; here, the two naturally derived thioureas [2,6] migrate conspicuously slower than any other thiourea studied

Table 3. TLC and paper chromatographic data for methoxy- and methylenedioxy-substituted benzyl isothiocyanates and thioureas.

Substituents	TLC $R_{Ph}{}^{a}$	$R_{Ph}{}^{b}$	Paper chromatography A[c]	B[d]	C[e]	D[f]
2-MeO-[g]	1.66	0.98	1.26	1.39	1.22	1.16
3-MeO-[h]	1.60	0.88	1.19	1.15	0.81	0.97
4-MeO-[i]	1.58	0.90	1.17	1.13	0.78	0.96
2,3-MeO-	1.30	1.00	1.18	1.29	1.10	1.16
2,4-MeO-	1.55	0.99	1.25	1.33	1.13	1.19
2,5-MeO-	1.48	0.96	1.23	1.24	1.04	1.15
2,6-MeO-	1.63	1.26	1.33	1.61	1.56	1.28
3,4-MeO-[j]	0.74	0.90	0.79	0.58	0.23	0.95
3,5-MeO-	1.34	0.90	1.17	1.15	0.85	1.02
3,4-OCH₂O-	1.49	0.86	1.11	1.01	0.66	0.85
3,4,5-MeO-	0.47	0.83	0.75	0.69	0.21	0.92

[a] Isothiocyanates (silicagel; benzene, C_6H_5NCS, R_{Ph} 1.00).
[b] Thioureas (silicagel; chloroform:ethanol (9:1); $C_6H_5NHCSNH_2$. R_{Ph} 1.00).
[c] Thioureas (toluene:butanol:water (10:1:2)).
[d] Thioureas (benzene:ethanol:water (5:1:2)).
[e] Thioureas (toluene:acetic acid:water (5:2:4)).
[f] Thioureas (chloroform:water (*cf.* Ref. 15)).
[g] Ref. 3; [h] Ref. 4; [i] Ref. 5.; [j] Ref. 6.

(Table 3). We have no convincing explanation for the observed deviations, plausibly caused by several factors, but expect the reported data to be of assistance in connection with future exploratory studies of aromatic glucosinolates in Nature.

EXPERIMENTAL

Melting points are uncorrected, those below 80° are determined in a water-bath, whereas higher m.p.'s are determined in an electrically heated oil bath.

Methoxy-substituted benzylamines

2,3-Dimethoxybenzylamine. 2,3-Dimethoxybenzaldoxime (0.045 mol), dissolved in ether (100 ml), was added, in the course of 1 h, to a stirred solution of LiAlH$_4$ (0.7 mol). The mixture was refluxed for 3 h, and excess hydride reagent was destroyed on adding wet ether and water (20 ml). The combined filtrate and ether washings was dried over solid KOH; the ether was removed by evaporation, and the resulting amine (65 % yield) was distilled, b.p. 69°/0.05 mm, n_D^{25} 1.5409. The hydrochloride was prepared in ethereal solution, m.p. 157 – 159°. (Lit.[7] b.p. 137°/11 mm; HCl: m.p. 159°.)

2,4-Dimethoxybenzylamine. Prepared from 2,4-dimethoxybenzaldoxime by the same procedure in 48 % yield, b.p. 92°/0.5 mm, n_D^{25} 1.5521. (Found: C 64.84; H 7.95; N 8.39. Calc. for C$_9$H$_{13}$NO$_2$: C 64.66; H 7.83; N 8.38.) The hydrochloride was prepared in ethereal solution, m.p. 180 – 183° (dec.). (Found: C 52.62; H 7.01; N 6.87. Calc. for C$_9$H$_{14}$NO$_2$Cl: C 53.07; H 6.93; N 6.88.) After the completion of the present work, Weygand *et al.*[8] reported the same amine with b.p. 100°/0.1 mm, 142 – 143°/15 mm (hydrochloride m.p. 186°).

2,5-Dimethoxybenzylamine. 2,5-Dimethoxybenzaldehyde was converted into *2,5-dimethoxybenzaldoxime,* not previously described, which was recrystallised twice from aqueous ethanol before analysis, m.p. 104 – 105°. (Found: C 59.56; H 6.09; N 7.84. Calc. for C$_9$H$_{11}$NO$_3$: C 59.65; H 6.12; N 7.73.) The oxime was reduced to *2,5-dimethoxybenzylamine* as described above (56 % yield), b.p. 72°/0.05 mm, n_D^{25} 1.5487. (Found: 64.74; H 7.86; N 8.27.) The *hydrochloride* was prepared in ether, m.p. 178 – 179°. (Found: C 53.12; H 6.83; N 6.80.) The amine has been mentioned in a recent paper,[9] apparently without reported physical constants.

2,6-Dimethoxybenzylamine. 2,6-Dimethoxybenzonitrile (0.06 mol) (Aldrich) was placed in the thimble of a Soxhlet extractor and gradually washed down into a stirred ether solution (400 ml) of LiAlH$_4$ (0.09 mol). After reflux for a total of 3 h, water was cautiously added. The ethereal phase, combined with the ether washing, was concentrated to dryness. The solid amine (95 % yield) was purified by vacuum sublimation (0.05 mm, bath 100°) to give colourless needles, m.p. 83 – 84°. (Found: C 64.87; H 7.46; N 8.19.) The *hydrochloride* (from ether) had m.p. 225 – 226°. (Found: C 52.96; H 6.97; N 6.57.) After the present work was completed, the same amine was reported by Weygand *et al.*[8] with m.p. 85 – 86°.

3,5-Dimethoxybenzylamine. This amine was prepared by LiAlH$_4$-reduction of 3,5-dimethoxybenzaldoxime by the procedure described above. Distillation (b.p. 67°/0.01 mm) afforded the pure amine as a solid, m.p. 37 – 38° (57 % yield). On reaction with 2,4-dinitrofluorobenzene,[10] it was converted into its 2,4-DNP-derivative, m.p. 112 – 113°. (Found: C 54.08; H 4.57; N 12.61. Calc. for C$_{15}$H$_{15}$N$_3$O$_6$: C 54.05; H 4.54; N 12.61.) The UV-spectrum (in EtOH) was found to be in good agreement with the spectrum reported for a synthetic specimen of the amine, b.p. 94 – 96°/0.1 mm, giving a 2,4-DNP-derivative with a reported m.p. 134 – 135°.[10]

3,4,5-Trimethoxybenzylamine. The amine was produced by LiAlH$_4$-reduction of 3,4,5-trimethoxybenzonitrile (Aldrich) as described above for the 2,6-isomer (*cf.* also Ref. 11). The crude reaction product was dissolved in 2 N HCl and freed from unreacted nitrile by CHCl$_3$-extraction. The aqueous phase was made alkaline, the amine was transferred to ether by continuous extraction, and distilled, b.p. 106/0.1 mm, n_D^{25} 1.5450. A small portion of the amine was converted into 3,4,5-trimethoxybenzyltrimethylammonium

iodide, m.p. 217—220° (Lit.[12] m.p. 218°). The amine has been repeatedly reported in the literature.[11-14]

Piperonyl- and veratryl-amine. Commercial samples (Fluka) of these two amines were employed in the further syntheses.

Methoxy-substituted isothiocyanates

Synthetic procedure (A). A chloroform solution of the substituted benzylamine and triethylamine, in a molar ratio of 1:2, was added, with stirring and cooling to −5°, to a chloroform solution of thiocarbonyl chloride (10 % excess) in the course of 1 h. The chloroform phase was washed with acid, base, and water, and dried over Na_2SO_4.

Synthetic procedure (B). A chloroform solution of the amine was added, in the course of 1 h, to a heterogeneous system of thiocarbonyl chloride (50 % excess) in chloroform, and $NaHCO_3$ in water, vigorously stirred at −5°. The chloroform phase was worked up as described under procedure (A).

In several cases (Ia, Ic, Id, II), the crude isothiocyanate fraction was passed through a column of silica gel (Woelm, activity 1), and eluted with benzene, prior to further purification by distillation or sublimation (*cf.* Table 1).

Substituted *N*-benzylthioureas

The various, substituted benzyl isothiocyanates (200—300 mg) were left standing overnight with 2—3 ml of methanol, saturated at 0° with anhydrous ammonia. The crystalline residues were crystallized from anhydrous ethanol or methanol before analysis (*cf.* Table 2). Infrared spectra were recorded for all thioureas.

Chromatography

TLC chromatography was performed on Kieselgel G nach Stahl (Merck). In the case of isothiocyanates, benzene was used as the mobile phase, phenyl isothiocyanate (R_{Ph} 1.00) as an internal standard, and ammoniacal $AgNO_3$ as the spraying reagent. When thioureas were chromatographed, the solvent was chloroform:ethanol (9:1), and the internal standard *N*-phenylthiourea (R_{Ph} 1.00); the plates were sprayed with a mixture of equal volumes of a 1 % $K_3Fe(CN)_6$ and a 5 % $FeCl_3$ solution, mixed immediately before use.

Paper chromatography was performed by the descending technique on Whatman paper No. 1, in the four solvent systems specified in Table 3. The thioureas were revealed as blue spots on spraying with Grote's reagent (*cf.* Ref. 15).

The authors are grateful to Dr. M. Ettlinger for having suggested the application of solvent systems (A), (B), and (C) for paper chromatography.

Microanalyses were performed by Mr. G. Cornali and his staff.

REFERENCES

1. For a review, see: Ettlinger, M. G. and Kjær, A. In Mabry, T. J., Alston, R. E. and Runeckles, V. C. *Recent Advances in Phytochemistry*, Appleton-Century-Crofts, New York 1968, p. 58, and literature cited therein.
2. a. Kjær, A., Schuster, A. and Park, R. J. *Phytochem.* **10** (1971) 455; b. Kjær, A. and Wagnières, M. *Phytochem.* **10** (1971) 2195.
3. Kjær, A. and Boe Jensen, R. *Acta Chem. Scand.* **10** (1956) 141.
4. Ettlinger, M. G. and Lundeen, A. J. *J. Am. Chem. Soc.* **78** (1956) 1952.
5. Kjær, A., Gmelin, R. and Boe Jensen, R. *Acta Chem. Scand.* **10** (1956) 26.
6. Ettlinger, M. G., Kjær, A., Thompson, C. P. and Wagnières, M. *Acta Chem. Scand.* **20** (1966) 1778.

7. Douetteau, R. *Bull. Soc. Chim. France* [4] **9** (1911) 932.
8. Weygand, F., Steglich, W., Bjarnason, J., Akhtar, R. and Chytil, N. *Chem. Ber.* **101** (1968) 3623.
9. Kudrin, A. N. and Koroza, G. S. *Farmakol. i Toksikol.* **28** (1965) 697; *Chem. Abstr.* **64** (1966) 10266e.
10. Kuehne, M. E. and Lambert, B. F. *J. Am. Chem. Soc.* **81** (1959) 4278.
11. Schiemenz, G. P. and Engelhard, H. *Chem. Ber.* **94** (1961) 353.
12. Heffter, A. and Capellmann, R. *Ber.* **38** (1905) 3634.
13. Bennington, F., Morin, R. D. and Clark, Jr., L. C. *J. Org. Chem.* **21** (1956) 1545.
14. Amos, D. *Austr. J. Chem.* **18** (1965) 2049.
15. Kjær, A. and Rubinstein, K. *Acta Chem. Scand.* **7** (1953) 528.