# 2-ISOTHIOCYANATOBENZYLPYRIDINIUM BROMIDE — AN INTERMEDIATE FOR THE SYNTHESIS OF 2-ARYLAMINO--4*H*-BENZO[*d*][1,3]THIAZINES

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2-Bromomethylphenyl isothiocyanate reacts with pyridine to yield 2-isothiocyanatobenzylpyridinium bromide, which afforded N-aryl-N′-(2-benzylpyridinium)thiourea bromides. Deprotonization of the latter with aqueous NaOH gave N-aryl-N′-(2-benzylpyridinium) thioureates; these freed pyridine upon heating to give 2-arylamino-4*H*-benzo[*d*][1,3]thiazines. Structure of these compounds was evidenced by IR, $^1$H, $^{13}$C NMR and mass spectral data and backed by elemental analysis.

Our preceding paper[1] concerned the synthesis and reactions of 2-bromoethylphenyl isothiocyanate with the aim to ascertain the selectivity of its both reaction centers. As found, the primary aliphatic and aromatic amines reacted exclusively with the NCS group to furnish 4*H*-benzo[*d*][1,3]thiazine derivatives, whereas some other nucleophiles as *e.g.* $I^-$, $SCN^-$, 4-$CH_3C_6H_4SO_2^-$ afforded the substitution products of bromine.

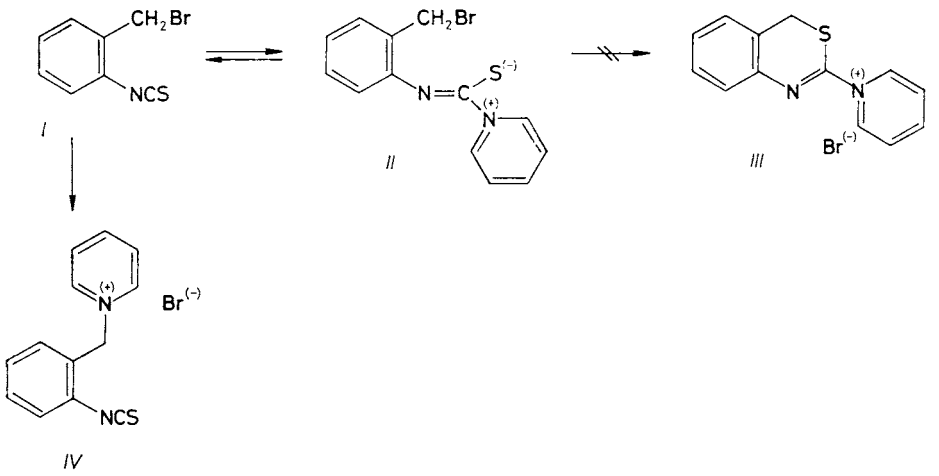
The goal of this contribution was to study the reaction of 2-bromomethylphenyl isothiocyanate with pyridine in order to find suitable starting material for the synthesis of hetrocyclic compounds. The above-mentioned isothiocyanate can react in two ways (Scheme 1). The addition product *II*, formed by addition of pyridine to the NCS group, can be stabilized by its cyclization to the corresponding benzothiazine derivative *III*, whereas the attack of the benzyl carbon can generate the pyridinium salt *IV*. We found that treatment of isothiocyanate *I* with pyridine in ether proceeded exclusively under formation of 2-isothiocyanatobenzylpyridinium bromide *IV* in 87% yield (Scheme 1). Its structure was proved by spectral methods.

2-Isothiocyanatobenzylpyridinium bromide *IV* gave with aromatic amines in methanol the corresponding thioureas *V* in a quantitative yield (Scheme 2). Thioureas *V* are quite hygroscopic; they separate from the reaction medium by addition of a less polar solvent as *e.g.* ether as oily products (Table I). They partly crystallize when stored over phosphorus pentoxide for a longer time. Addition of methanolic NaOH to the methanolic solution of thioureas *V* resulted in crystallization of N--aryl-N′-2-benzylpyridinium thioureates *VI* (Scheme 2, Table II). Since there is no

TABLE I

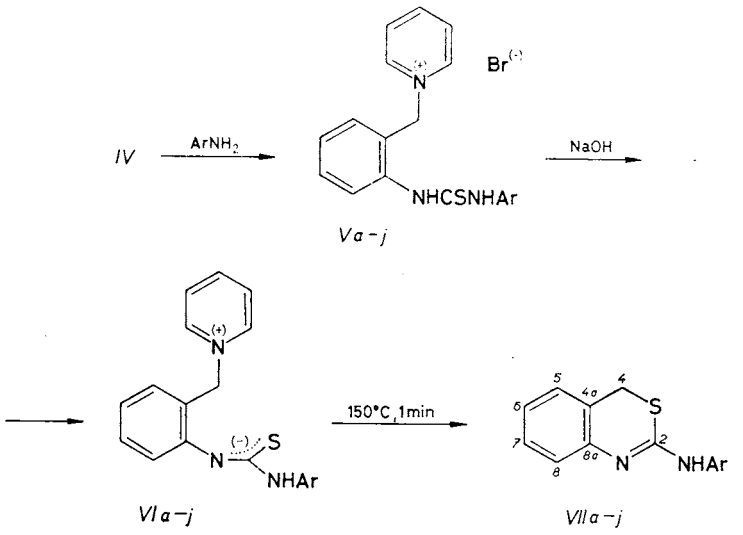
N-Aryl-N′-(2-benzylpyridinium)thiourea bromides *Va*—*Vj*

| Product | Ar | Formula ($M_r$) | Yield, % | M.p., °C | IR ($cm^{-1}$, $CHCl_3$) | Calculated/found | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | ν(NH) | % C | % H | % N |
| *Va* | $C_6H_5$ | $C_{19}H_{18}BrN_3S$ (400·3) | 100 | 145—148 | 3 430, 3 380 | 57·00<br>57·07 | 4·53<br>4·51 | 10·49<br>10·39 |
| *Vb* | 2-$CH_3C_6H_4$ | $C_{20}H_{20}BrN_3S$ (414·4) | 91 | oil | 3 425, 3 381 | | | |
| *Vc* | 4-$CH_3C_6H_4$ | $C_{20}H_{20}BrN_3S$ (414·4) | 98 | 167—169 | 3 438, 3 380 | 57·97<br>57·90 | 4·86<br>4·83 | 10·14<br>10·08 |
| *Vd* | 2-$CH_3OC_6H_4$ | $C_{20}H_{20}BrN_3OS$ (430·4) | 94 | oil | 3 439, 3 378 | | | |
| *Ve* | 3-$CH_3OC_6H_4$ | $C_{20}H_{20}BrN_3OS$ (430·4) | 100 | 138—141 | 3 430, 3 385 | 55·81<br>55·76 | 4·68<br>4·71 | 9·76<br>9·67 |
| *Vf* | 4-$CH_3OC_6H_4$ | $C_{20}H_{20}BrN_3OS$ (430·4) | 100 | 172—173 | 3 436, 3 300 | 55·81<br>55·78 | 4·68<br>4·53 | 9·76<br>9·81 |
| *Vg* | 3-$ClC_6H_4$ | $C_{19}H_{17}BrClN_3S$ (434·8) | 100 | 181—182 | 3 478, 3 381 | 52·48<br>52·39 | 3·94<br>3·95 | 9·66<br>9·64 |
| *Vh* | 4-$BrC_6H_4$ | $C_{19}H_{17}Br_2N_3S$ (479·2) | 93 | 162—164 | 3 482, 3 380 | 47·62<br>47·58 | 3·57<br>3·51 | 8·76<br>8·75 |
| *Vi* | 1-naphthyl | $C_{23}H_{20}NrN_3S$ (450·4) | 94 | 196—199 | 3 480, 3 376 | 61·33<br>61·21 | 4·47<br>4·38 | 9·32<br>9·25 |
| *Vj* | 2-naphthyl | $C_{23}H_{20}BrN_3S$ (450·4) | 95 | 178—181 | 3 482, 3 374 | 61·33<br>61·39 | 4·47<br>4·52 | 9·32<br>9·28 |



SCHEME 1

need to purify the thioureas, a mere addition of aqueous hydroxide is sufficient to obtain thioureates *VI* in almost quantitative yield. Thioureates *VI* are darkyellow crystals melting within 138–141°C under decomposition. They are very little soluble even in polar organic solvents. The IR spectra of these substances measured as



SCHEME 2

TABLE II

N-Aryl-N'-(2-benzylpyridinium)thioureates *VIa*—*VIj*

| Product[a] | Ar | Formula ($M_r$) | Yield, % | M.p.[c], °C | IR ($cm^{-1}$, KBr) | Calculated/found | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | ν(NH) | % C | % H | % N |
| *VIa* | $C_6H_5$[b] | $C_{19}H_{17}N_3S$ (319·4) | 98 | 141 | 3 198 | 71·44<br>71·33 | 5·36<br>5·31 | 13·15<br>13·21 |
| *VIb* | 2-$CH_3C_6H_4$ | $C_{20}H_{19}N_3S$ (333·5) | 96 | 140 | 3 190 | 72·03<br>72·13 | 5·74<br>5·81 | 12·60<br>12·56 |
| *VIc* | 4-$CH_3C_6H_4$ | $C_{20}H_{19}N_3S$ (333·5) | 94 | 140 | 3 205 | 72·03<br>72·08 | 5·74<br>5·70 | 12·60<br>12·68 |
| *VId* | 2-$CH_3OC_6H_4$ | $C_{20}H_{19}N_3OS$ (349·5) | 100 | 142 | 3 200 | 68·74<br>68·71 | 5·47<br>5·38 | 12·02<br>12·09 |
| *VIe* | 3-$CH_3OC_6H_4$[d] | $C_{20}H_{19}N_3OS$ (349·5) | 95 | 142 | 3 203 | 68·74<br>68·67 | 5·47<br>5·42 | 12·02<br>12·10 |
| *VIf* | 4-$CH_3OC_6H_4$ | $C_{20}H_{19}N_3OS$ (349·5) | 87 | 141 | 3 209 | 68·74<br>68·70 | 5·47<br>5·47 | 12·02<br>12·00 |
| *VIg* | 3-$ClC_6H_4$ | $C_{19}H_{16}BrN_3S$ (353·9) | 88 | 142 | 3 201 | 64·48<br>64·46 | 4·55<br>4·58 | 11·87<br>11·93 |
| *VIh* | 4-$BrC_6H_4$ | $C_{19}H_{16}BrN_3S$ (398·3) | 89 | 140 | 3 195 | 57·29<br>58·31 | 4·04<br>4·10 | 10·54<br>10·49 |
| *VIi* | 1-naphthyl | $C_{23}H_{19}N_3S$ (369·5) | 96 | 141 | 3 198 | 74·76<br>74·53 | 5·18<br>5·26 | 11·37<br>11·43 |
| *VIj* | 2-naphthyl | $C_{23}H_{19}N_3S$ (369·5) | 98 | 142 | 3 200 | 74·76<br>74·75 | 5·18<br>5·10 | 11·37<br>11·41 |

[a] The $^1H$ NMR spectra ($C^2H_3COO^2H$) of compounds *VIa*—*VIj* showed proton signals of $CH_2$ groups at $\delta$ = 5·79—5·81 ppm, those of pyridine ring $\delta(H^\alpha)$ = 9·39—9·41 ppm (d), $\delta(H^\beta) \approx$ 8·5 ppm (m), $\delta$ ($H^\gamma$) = 8·87—5·95 ppm (m); [b] mass spectrum, *m/z* (relat. intens., %): 240 $M^+$ − 79 (100), 206 (21), 180 (18), 136 (87), 104 (54); [c] decomposition; [b] mass specrum, *m/z* (relat. intens., %): 270 $M^+$ − 79 (100), 165 (31), 137 (89), 104 (41).

solids showed distinctive bands at 3 209–3 190 $cm^{-1}$, ascribable to vibrations of associated NH groups. The $^1H$ NMR spectra characteristic of the presence of $CH_2$ group signals at $\delta \sim 5{\cdot}80$ ppm are little influenced by the nature of the substituent. Little influenced are also the chemical shifts of pyridine protons $\delta(H^{\alpha}) \approx 9{\cdot}4$ ppm, $\delta(H^{\beta}) \approx 8{\cdot}5$ ppm, $\delta(H^{\gamma}) \approx 8{\cdot}9$ ppm. Formation of 1,2-dihydro derivatives resulting from an intramolecular addition of the thiolate anion to α position of pyridine was not observed. Mass spectra of these substances displayed the fragment ions $M^+ - 79$, corresponding to the loss of pyridine molecule at the transition from the solid phase to a dilute gaseous state in the ion source of the spectrometer; the absence of peaks of molecular radical ions indicates the instability of these particles.

TABLE III

2-Arylamino-4*H*-benzo[*d*][1,3]thiazines *VIIa*–*VIIj*

| Compound R | Formula ($M_r$) | M.p., °C Solvent[a] | Yield, % | Calculated/found | | |
|---|---|---|---|---|---|---|
| | | | | % C | % H | % N |
| *VIIa* | $C_{14}H_{12}N_2S$ | 199–200[b] | 90 | 69·97 | 5·03 | 11·65 |
| $C_6H_5$ | (240·3) | $CHCl_3$–LP | | 69·85 | 5·00 | 11·60 |
| *VIIb* | $C_{15}H_{14}N_2S$ | 169–170[d] | 95 | 70·83 | 5·54 | 11·01 |
| 2-$CH_3C_6H_4$ | (254·4) | $CHCl_3$–hexane | | 70·75 | 5·47 | 11·00 |
| *VIIc* | $C_{14}H_{14}N_2S$ | 188–189[c] | 96 | 70·83 | 5·54 | 11·01 |
| 4-$CH_3C_6H_4$ | (254·4) | $CHCl_3$–hexane | | 70·71 | 5·50 | 11·00 |
| *VIId* | $C_{15}H_{14}N_2OS$ | 116–117[d] | 71 | 66·64 | 5·22 | 10·36 |
| 2-$CH_3OC_6H_4$ | (270·4) | $CHCl_3$–LP | | 66·70 | 5·20 | 10·33 |
| *VIIe* | $C_{15}H_{14}N_2OS$ | 168–170[d] | 92 | 66·64 | 5·22 | 10·36 |
| 3-$CH_3OC_6H_4$ | (270·4) | $CHCl_3$–hexane | | 66·58 | 5·19 | 10·31 |
| *VIIf* | $C_{15}H_{14}N_2OS$ | 179–180 | 94 | 66·64 | 5·22 | 10·36 |
| 4-$CH_3OC_6H_4$ | (270·4) | $CHCl_3$–hexane | | 66·61 | 5·20 | 10·31 |
| *VIIg* | $C_{14}H_{11}ClN_2S$ | 178–179 | 88 | 61·20 | 4·04 | 10·19 |
| 3-$ClC_6H_4$ | (274·8) | $CHCl_3$ | | 61·23 | 4·09 | 10·.1 |
| *VIIh* | $C_{14}H_{11}BrN_2S$ | 232–233 | 93 | 52·68 | 3·46 | 8·77 |
| 4-$BrC_6H_4$ | (319·2) | $CHCl_3$ | | 52·71 | 3·50 | 8·75 |
| *VIIi* | $C_{18}H_{14}N_2S$ | 207–208 | 86 | 74·45 | 4·86 | 9·64 |
| 1-naphthyl | (290·4) | $CHCl_3$–LP | | 74·51 | 4·90 | 9·61 |
| *VIIj* | $C_{18}H_{14}N_2S$ | 217–219 | 90 | 74·45 | 4·86 | 9·64 |
| 2-naphthyl | (290·4) | $CHCl_3$–LP | | 74·41 | 4·78 | 9·71 |

[a] LP – light petroleum; [b] m.p. 197°C (ref.[2]); [c] m.p. 187°C (ref.[3]); [d] m.p. and other constants are identical with those in ref.[1].

A short heating of thioureates *VI* (1 min, 150°C, dimethylformamide) led to the cleavage of pyridine and origination of 4*H*-benzo[*d*][1,3]thiazines *VII*; some of them have also been prepared by reacting 2-bromoethylphenyl isothiocyanate with amines. The reaction is quantitative and therefore, it could be well employed for the preparation of 2-arylamino derivatives (Scheme 2, Table III).

This synthetic method for obtaining thiazine derivatives indicates that the role of tertiary bases in their preparation is multifunctional and can involve some steps: quaternization, formation of thioureas, deprotonization to betains and their thermal decomposition. This method is not suitable for the synthesis of the corresponding aliphatic derivatives[1].

## EXPERIMENTAL

The IR spectra of chloroform solutions or KBr pellets were measured with an IR 75 (Zeiss, Jena) spectrophotometer in the 800—4 000 $cm^{-1}$ range. The $^1H$ and $^{13}C$ NMR spectra were recorded with Tesla BS 497 (80 MHz) and Tesla BS 567 (25·04 MHz) apparatuses, respectively. Signals of the $^{13}C$ NMR spectra were ascribed by the method of selective decoupling of protons. The mass spectra were run with an MS 902 S (AEI Manchester) spectrometer at 70 eV ion source energy.

TABLE IV
Spectral data of benzothiazines *VIIa—VIIj*

| Compound | IR ($cm^{-1}$)[a] | | $^1H$ NMR (ppm, $\delta$)[b] | | | Further protons |
|---|---|---|---|---|---|---|
| | $\nu$(NH) | $\nu$(C=N) | $CH_2$ | $H_{Ar}$ | NH | |
| *VIIa*[c] | 3 443 | 1 622 | 3·91 | 6·96—7·65 | — | |
| *VIIb* | 3 423, 3 385 | 1 605 | 3·82 | 6·83—7·20 | — | 2·2 (s, $CH_3$) |
| *VIIc* | 3 425, 3 385 | 1 602 | 3·88 | 7·03—7·50 | 9·72 | 2·28 (s, $CH_3$) |
| *VIId* | 3 420, 3 385 | 1 602 | 4·15 | 7·08—7·40 | 9·42 | 3·97 (s, $CH_3$) |
| *VIIe* | 3 430 | 1 630 | 4·20 | 7·15—7·45 | 9·75 | 3·92 (s, $CH_3$) |
| *VIIf* | 3 433 | 1 629 | 3·90 | 6·75—7·57 | — | 3·78 (s, $CH_3$) |
| *VIIg* | 3 430 | 1 632 | 3·90 | 6·87—7·80 | 9·08 | |
| *VIIh* | 3 435 | 1 620 | 3·94 | 7·08—7·70 | — | |
| *VIIi* | 3 440 | 1 618 | 4·15 | 7·10—8·13 | 10·6 | |
| *VIIj* | 3 440 | 1 622 | 4·22 | 7·20—8·05 | 10·02 | |

[a] Compounds *VIIa*, *VIIe—VIIj* in KBr; *VIIb—VIId* in $CHCl_3$; [b] compounds *VIIa*, *VIIf—VIIh* in $C^2HCl_3$—$(C^2H_3)_2SO$ (5 : 1); *VIIa*, *VIIc—VIIe*, *VIIi*, *VIIj* in $C^2HCl_3$; [c] $^{13}C$ NMR ($C^2HCl_3$), $\delta$, ppm: 128·3, 126·6, 123·0, 122·2 ($C_{(5-8)}$), 144·1 ($C_{(8a)}$), 120·1 ($C_{(4a)}$), 28·6 ($C_{(4)}$), 150·2 ($C_{(2)}$), 199·8, 128·3, 127·7 ($C_o$, $C_m$, $C_p$), 141·9 ($C_i$).

2-Isothiocyanatobenzylpyridinium Bromide (*IV*)

Pyridine (10 mmol) was added to 2-bromomethylphenyl isothiocyanate (10 ml) dissolved in ether (50 ml) and the mixture was left to stand for 48 h. The separated quaternary salt was suction-filtered, washed with ether and crystallized from chloroform–ether. Yield 87%, m.p. 174°C. For $C_{13}H_{11}BrN_2S$ (307·2) calculated: 50·82% C, 3·61% H, 9·11% N; found: 50·79% C, 3·62% H, 9·08% N. IR spectrum ($CHCl_3$), $cm^{-1}$: 2 098 $\nu$(NCS). $^1H$ NMR ($C^2HCl_3$), $\delta$, ppm: 6·33 (2 H, s, $CH_2$), 7·63–7·81 (4 H, m, $H_{arom}$), 8·46 (2 H, m, $H^{\beta}Py$), 8·39 (1 H, d, $H^{\gamma}Py$), 9·38 (2 H, d, $H^{\alpha}Py$). $^{13}C$ NMR ($C^2HCl_3$), $\delta$, ppm: 136·6 (N=C=S), 59·6 ($CH_2$).

Bromides of N-Alkyl-N′-2-benzylpyridiunium Thioureas (*Va–Vj*)

The respective amine (10 mmol) in methanol (10 ml) was added to compound *IV* (10 mmol) in methanol (20 ml). After 5 h ether (50 ml) was added, the separated compound was filtered off and crystallized from chloroform–hexane. Compounds, which separated as oils (*Vb, d, e, f, g*) were washed with ether, and deposited over $P_2O_5$. These hygroscopic compounds crystallize within some days (Table I).

N-Aryl-N′-2-Benzylpyridinium Thioureates (*VIa–VIj*)

Potassium hydroxide (10 ml) in water (50 ml) was added to the thiourea *Va–Vj* (10 mmol) in methanol (50 ml) and the mixture was allowed to stand for 4 h. The separated crystals were filtered off, washed with methanol and ether and dried in air. Compounds *VIa–VIj* are virtually insoluble in organic solvents; an crystallization attempt from dimethylformamide or dimethyl sulfoxide resulted in decomposition (Table II).

2-Arylamino-4*H*-benzo[*d*][1,3]thiazines (*VIIa–VIIj*)

The suspension of the respective N-aryl-N′-2-benzylpyridinium thioureate (10 mmol) in dimethylformamide was boiled for 1 min and then poured into ice-cold water. The separated solid was filtered off and crystallized from an appropriate solvent (Tables III and IV).

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REFERENCES

1. Gonda J., Kristian P.: This Journal, in press.
2. Paal C., Vanvolxem L.: Chem. Ber. *27*, 2413 (1894).
3. Gabriel S., Posner T.: Chem. Ber. *28*, 1095 (1895).

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