Preparations of Perhydroimidazo[1,5-*a*]pyridine-3-thiones and Thiazole-5-spirocyclopropan-4(5*H*)-ones from Thioureas and α,γ-Dibromobutyryl Chloride under Phase-transfer Conditions

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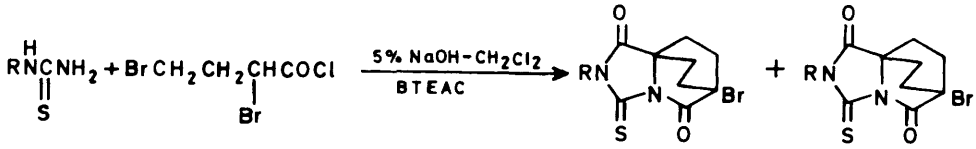
The reaction of *N*-monosubstituted thioureas (**1**) with α,γ-dibromobutyryl chloride (**2**) was carried out in 5% NaOH–CH_2Cl_2 to afford 2-alkyl(aryl)-6-bromo-2,3,7,8-tetrahydro-3-thioxo-6,8a-ethanoimidazo[1,5-*a*]pyridine-1,5(6*H*,8a*H*)-diones (**3**) and 2-alkyl(aryl)-aminothiazole-5-spirocyclopropan-4(5*H*)-ones (**5**).

Although the formation of four-, five-, and six-membered heterocyclic compounds by the reaction of thioureas with α- and β-halogenocarboxylic acid derivatives has been well documented,[1-5] there has been no report of the synthesis of heterocycles from thioureas and α,γ-dihalogenocarboxylic acid derivatives. We now report the novel synthesis of 2-alkyl(aryl)-6-bromo-2,3,7,8-tetrahydro-3-thioxo-6,8a-ethanoimidazo[1,5-*a*]pyridine-1,5(6*H*,8a*H*)-dione (**3**) and 2-alkyl(aryl)amino-oxothiazole-5-spirocyclopropane-4(5*H*)-ones (**5**) by treating *N*-monosubstituted thioureas (**1**) with α,γ-dibromobutyryl chloride (**2**) under phase-transfer conditions.



(**1**) a; Me
b; Bu
c; c-C_6H_{11}
d; $PhCH_2$
e; Ph

(**2**)

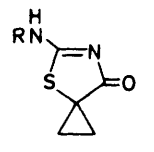
(**3**) a; Me
b; Bu
c; c-C_6H_{11}
d; $PhCH_2$
e; Ph

(**4**) a; Bu
b; Ph

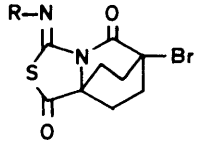
Scheme 1.

The reaction was successfully carried out by treating the chloride (**2**) with the thiourea (**1**) in 5% NaOH–CH_2Cl_2 in the presence of benzyltriethylammonium chloride at room temperature. The resulting products (**3**) and (**5**) were purified by silica-gel column chromatography ($CHCl_3$–benzene, 8:2). The results are shown in Table 1 and 2.

The structure of compound (**3**) was assigned as follows. On the basis of mass spectral data and elemental analyses, it is evident that the product was obtained by the reaction of compounds (**1**) with (**2**) in the ratio of 1:2. The i.r. spectra showed absorptions assignable to two carbonyl groups at 1 728—1 740 and 1 640—1 660 cm^{-1}. Several other isomeric structures for the product are also possible, although all except (**3**) and (**6**) are extremely strained; in view of this the carbonyl absorptions of (**3**) and (**6**) would be expected to be at lower frequency than those for the other isomers. The thioureido absorption was observed[6] at 1 500—1 520 cm^{-1}, a result which is supportive of structure (**3**) over that of (**6**). The ^{13}C n.m.r. spectra exhibited carbonyl signals at 185.5 and 182.1 p.p.m., and a thione signal at 191.9 p.p.m.[7] The ^1H n.m.r. and mass spectral data also supported the structural assignment of the product as (**3**).



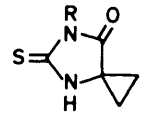
(**5**) a; Bu
b; c-C_6H_{11}
c; $PhCH_2$
d; Ph
e; 1-Naph



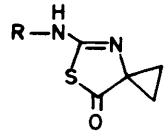
(**6**)

For compounds with R = Bu and c-C_6H_{11}, the debromo compounds (**4**) derived from compounds (**5**) were isolated. Structural assignments were made on the basis of a comparison of their spectral data compared with those of compounds (**3**). However, the path for the debromination is unclear.

In assigning a structure for product (**5**), the isomeric structures (**7**) and (**8**) were also considered. The i.r. spectra of product (**5**) showed carbonyl and C=N absorptions at 1 670—1 700 and 1 640 cm^{-1}, respectively, but thioureido absorption



(**7**)



(**8**)

was absent. This denies the possibility of the structure being (**7**), but can not discriminate between structures (**5**) and (**8**). Therefore, the hydrolysis of the product was carried out in 15% NaOH–EtOH under reflux to afford the disulphide (**9**) and amine. This result supports the assigned structure (**5**).

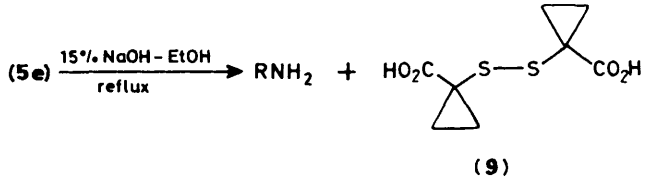
Table 1. 2-Alkyl(aryl)-6-bromo-2,3,7,8-tetrahydro-3-thioxo-6,8a-ethanoimidazo[1,5-*a*]pyridine-1,5(6*H*,8a*H*)-diones (**3**)

(3)	M.p. (°C)	Yield (%)	$\nu_{max.}$(KBr) (cm^{-1})	δ_H in $CDCl_3$	*m/z* (M^+)	Formula	Found (%) (Required) C	H	N
a	127—128	32	1 729 (C=O) 1 640 (C=O) 1 510 [NC(S)N]	1.40—1.97 (m, CH_2 × 4, 8 H) 3.30 (s, CH_3N, 3 H)	302 304	$C_{10}H_{11}BrN_2O_2S$	39.90 (39.62)	3.68 (3.66)	9.08 (9.24)
b	86—87	26	1 740 (C=O) 1 660 (C=O) 1 520 [NC(S)N]	0.93—1.87 (m, C_3H_7 and CH_2 × 4, 15 H), 3.85 (t, CH_2N, 2 H)	344 346	$C_{13}H_{17}BrN_2O_2S$	45.06 (45.22)	4.90 (4.96)	8.18 (8.11)
c	177—178	24	1 735 (C=O) 1 640 (C=O) 1 500 [NC(S)N]	1.03—1.94 (m, CH_2 × 4 and c-C_6H_{11}, 19 H)	370 372	$C_{15}H_{19}BrN_2O_2S$	48.49 (48.52)	5.13 (5.16)	7.52 (7.54)
d	122—123	36	1 728 (C=O) 1 655 (C=O) 1 500 [NC(S)N]	1.50 and 1.73 (m, CH_2 × 4, 8 H) 4.98 (s, CH_2N, 2 H), 7.32 (s, Ph, 5 H)	378 380	$C_{16}H_{15}BrN_2O_2S$	50.95 (50.67)	3.96 (3.99)	7.37 (7.39)
e	157—158	31	1 728 (C=O) 1 655 (C=O) 1 510 [NC(S)N]	1.47 and 1.80 (m, CH_2 × 4, 8 H), 7.10—7.50 (m, Ph, 5 H)	364 366	$C_{15}H_{13}BrN_2O_2S$	49.50 (49.33)	3.66 (3.59)	7.64 (7.67)

[a] ^{13}C N.m.r. ($CDCl_3$–TMS): δ = 19.2(CH_2), 22.9(CH_2), 24.6(C), 36.5(CH_2), 50.2(CH_2), 52.4(C), 54.1(CH_2), 134.5, 135, 2 136.0, 142.9 (Ph), 182.1 (C=O), 185.5 (C=O), and 191.9 (C=S).

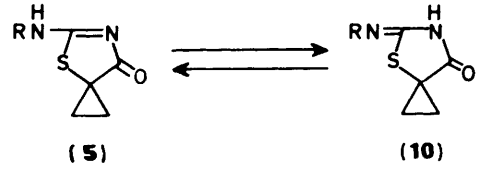
Table 2. 2-Alkyl(aryl)aminothiazole-5-spirocyclopropan-4(5*H*)-ones (**5**)

(5)	M.p. (°C)	Yield (%)	$\nu_{max.}$(KBr) (cm^{-1})	δ_H in $CDCl_3$	*m/z* (M^+)	Formula	Found (%) (Required) C	H	N
a	140—141	15	3 210 (NH) 1 695 (C=O)	0.95—1.91 (m, CH_2 × 4 and CH_3, 11 H), 3.92 (t, CH_2N, 2 H)	198	$C_9H_{14}N_2OS$	54.71 (54.42)	7.19 (7.12)	14.36 (14.13)
b	192—193	29	3 160 (NH) 1 690 (C=O)	1.13—1.87 (m, CH_2 × 7, 14 H) 3.20 (m, CH, 1 H), 10.77 (br, NH, 1 H)	224	$C_{11}H_{16}N_2OS$	59.04 (58.90)	7.23 (7.19)	12.26 (12.49)
c	99—100	18	3 260 (NH) 1 700 (C=O)	1.23 (m, CH_2, 2 H), 1.67 (m, CH_2, 2 H) 4.93 (s, CH_2N, 2 H), 7.33 (m, Ph, 5 H), 7.83 (br, NH, 1 H)	232	$C_{12}H_{12}N_2OS$	62.26 (62.04)	5.06 (5.21)	12.22 (12.06)
d	179—180	22	3 200 (NH) 1 695 (C=O)	1.29 (m, CH_2, 2 H), 1.60 (m, CH_2, 2 H), 7.20—7.43 (m, Ph, 5 H), 7.90 (br, NH, 1 H)	218	$C_{11}H_{10}N_2OS$	60.56 (60.53)	4.80 (4.62)	12.62 (12.83)
e	147—148	40	3 300 (NH) 1 680 (C=O)	1.42 (m, CH_2, 2 H), 1.80 (m, CH_2, 2 H), 7.45—7.43 (m, Naph, 7 H), 7.90 (br, NH, 1 H)	268	$C_{15}H_{12}N_2OS$	66.95 (67.14)	4.31 (4.51)	10.31 (10.44)



(**9**)

Scheme 2.

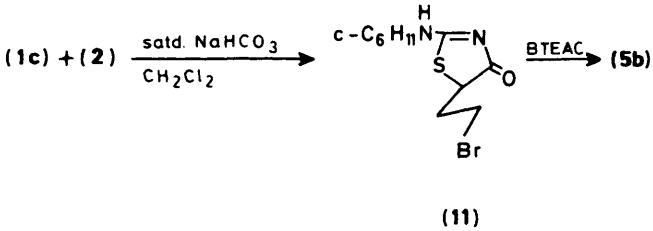


(**5**) (**10**)

Scheme 3.

For the compound (**5**), the tautomer (**10**) was also considered. We have recently reported that the i.r. spectra of 2-iminothiazolidin-4-ones similar to (**10**) showed carbonyl absorptions at 1 720—1 735 cm^{-1}.[8] The carbonyl absorption observed in the product supports structure (**5**), the conjugated imino group shifting the carbonyl absorption to lower frequency.

When the reaction of the thiourea (**1**) with the chloride (**2**) was performed in saturated $NaHCO_3$–CH_2Cl_2, 5-bromoethylthiazol-4(5*H*)-one (**11**) was afforded in 64—79% yields.



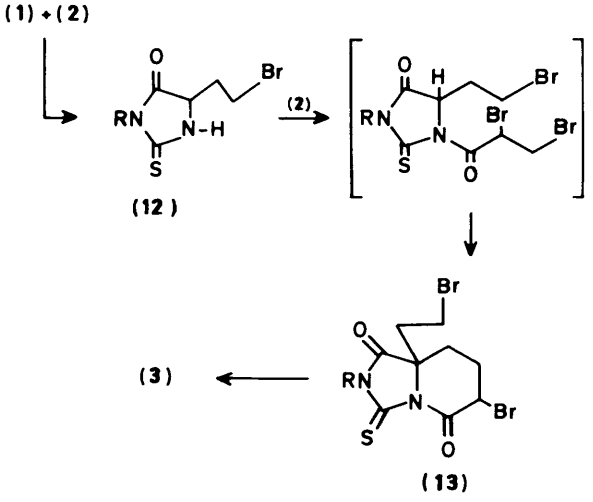
(**11**)

Scheme 4.

Compound (**11**) was easily cyclized to the spiro compound (**5**) under phase-transfer conditions in fairly good yield.

The pathway of the reaction forming (**3**) from (**1**) and (**2**) is presumed to be as follows. Initially formed 4-bromoethyl-2-thiohydantoin (**12**) reacts with additional compound (**2**) to

afford the intermediate (**13**); this then undergoes intramolecular cyclization with elimination of hydrogen bromide to give (**3**). In fact, the intermediate (**13**) was isolated for the compound with R=$PhCH_2$.



Scheme 5.

Experimental

M.p.s were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. I.r. spectra were recorded with a JASCO IRA-1 grating i.r. spectrometer. ^1H N.m.r. spectra were determined with a JEOL-60H spectrometer and ^{13}C n.m.r. spectra were measured with a JEOL-FX-100 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were measured with a JEOL-01 SG mass spectrometer.

α,γ-Dibromobutyryl Chloride (**2**).—α,γ-Dibromobutyric acid was prepared from γ-butyrolactone and bromine according to Phillip's method,[9] and then treated with $SOCl_2$ under reflux.

2-Alkyl(aryl)-6-bromo-2,3,7,8-tetrahydro-3-thioxo-6,8a-ethanoimidazo[1,5-a]*pyridine-1,5(6H,8aH)-dione* (**3**), *the Corresponding Debromo Compound* (**4**), *and 2-Alkyl(aryl)amino-thiazole-5-spirocyclopropan-4(5H)-one* (**5**).—To a stirred mixture of thiourea (**1**) (5 mmol), CH_2Cl_2 (20 ml), and aqueous 5% NaOH (5 ml) was gradually added dibromobutyryl chloride (**2**) (2.64 g, 10 mmol) with ice–water cooling. Additional 5% NaOH (20 ml) and benzyltriethylammonium chloride (20 mg) were then added with stirring, and the latter was continued for 12 h at room temperature. The CH_2Cl_2 layer was separated, washed with water (15 ml × 2), dried (Na_2SO_4), and evaporated. The residue was purified by a silica-gel column chromatography ($CHCl_3$–benzene, 8:2) [See Table 1 for compound (**3**) and Table 2 for compound (**5**)]: (**4a**) (0.15 g, 11%), m.p. 170—171 °C (Found: C, 58.85; H, 6.85; N, 10.55. $C_{13}H_{18}N_2O_2S$ requires C, 58.62; H, 6.81; N, 10.52%); $\nu_{max.}$(KBr) 1 703 (C=O), 1 684 (C=O), and 1 490 cm^{-1} [NC(S)N]; $\delta_H(CDCl_3)$ 0.95—2.00 (16 H, m, C_3H_7, CH_2 × 4, and CH), and 4.33 (2 H, t, CH_2N); *m/z* 266 (M^+); (**4b**) (0.12 g, 8%), m.p. 228—229 °C (Found: C, 62.8; H, 4.8; N, 9.65. $C_{15}H_{14}N_2O_2S$ requires C, 62.96; H, 4.93; N, 9.78%); $\nu_{max.}$(KBr) 1 729 (C=O), 1 650 (C=O), and 1 490 cm^{-1} [NC(S)N]; $\delta_H(CDCl_3)$ 1.13—1.95 (2 H, m, CH_2), 2.47 (2 H, t, CH_2), 3.28 (1 H, t, CH), and 7.23—7.55 (5 H, m, Ph); *m/z* 286 (M^+).

Hydrolysis of 2-(1-Naphthylamino)thiazole-5-spirocyclopropan-4(5H)-one (**5e**).—A solution of compound (**5e**) (0.27 g, 12 mmol) in 15% NaOH (5 ml) and EtOH (5 ml) was refluxed for 4 h after which it was evaporated under reduced pressure; the alkaline solution was then extracted with CH_2Cl_2 (8 ml × 2). The extract was washed with water (8 ml × 2), dried (Na_2SO_4), and evaporated to afford 1-naphthylamine. The alkaline solution was acidified with 6M-HCl. The acidic solution was extracted with Et_2O (10 ml × 2), and the extract was dried (Na_2SO_4) and evaporated to yield a residue which was recrystallized from EtOH to give bis(1-carboxycyclopropyl) disulphide (0.043 g, 36%), m.p. 194-195 °C (Found: C, 40.85; H, 4.2. $C_8H_{10}O_4S$ requires C, 41.01; H, 4.30%); $\nu_{max.}$(KBr) 1 700 cm^{-1} (C=O); *m/z* 234 (M^+).

2-Cyclohexylamino-5-bromoethylthiazol-4(5H)-one (**11**).—To a stirred solution of the thiourea (**1c**) (5 mmol) in saturated $NaHCO_3$ (8 ml)–CH_2Cl_2 (15 ml) was gradually added compound (**2**) (1.32 g, 5 mmol) (8 ml) with ice–water cooling. The reaction mixture was stirred for 8 h at room temperature after which the CH_2Cl_2 layer was separated, washed with water (10 ml × 2), dried (Na_2SO_4). Evaporation yielded a residue which was recrystallized from EtOH to give compound (**11**) (1.2 g, 79%), m.p. 171—172 °C (Found: C, 43.65; H, 5.55; N, 9.3. $C_{11}H_{17}BrN_2O$ requires C, 43.28; H, 5.62; N, 9.18%); $\nu_{max.}$(KBr) 3 160 (NH) and 1 700 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.20—2.18 (13 H, m,c-C_6H_{11} and CH_2), 3.57 (2 H, t, CH_2Br), 4.27 (1 H, m, CH), and 10.63 (1 H, br, NH); *m/z* 304, 306 (M^+).

Conversion of 5-Bromoethyl-2-cyclohexylaminothiazol-4(5H)-one (**11**) *into 2-Cyclohexylaminothiazole-5-spirocyclopropan-4(5H)-one* (**5b**).—A solution of compound (**11**) (2 mmol) in 5% NaOH (5 ml)—CH_2Cl_2 (10 ml) was stirred for 8 h in the presence of benzyltriethylammonium chloride (10 mg). The solution was worked up by the same method as described above.

Isolation of 2-Benzyl-6-bromo-8a-bromoethyl-2,3,7,8-tetrahydro-2-thioxoimidazo[1,5-a]*pyridine-1,5(6H,8aH)-dione* (**13**; R = $PhCH_2$).—Treatment of compound (**1d**) with compound (**2**) in 5% NaOH–CH_2Cl_2 in the presence of benzyltriethylammonium chloride in the same method as described above afforded compound (**13**; R = $PhCH_2$) after silica-gel column chromatography and recrystallization from EtOH, m.p. 212—214 °C (Found: C, 41.45; H, 3.5; N, 5.95. $C_{16}H_{16}Br_2N_2O_2$ requires C, 41.76; H, 3.50; N, 6.09%); $\nu_{max.}$(KBr) 1 730 (C=O), 1 650 (C=O), and 1 500 cm^{-1} [NC(S)N]; *m/z* 459, 461 (M^+).

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Received 15*th October* 1985; *Paper* 5/1778