O-Ethyl Thiocarbamates. A Convenient Route to 2-Aryliminoimidazolidines

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The reaction of *N*-aryl thionocarbamates and ethylenediamine lead to the corresponding 2-aryliminoimidazolidines, whose structure in pharmacology is well known. But, the behaviour of the *N*-alkyl thionocarbamates is quite different under operative conditions and these compounds afford with ethylenediamine, to 2-(2'-aminoethylamino)-Δ^2-imidazoline, according to a mechanism which is discussed.

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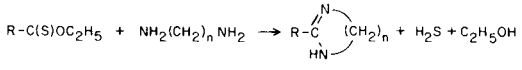
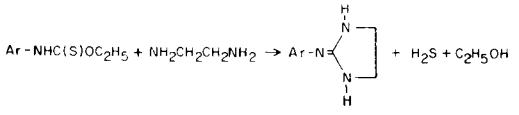
We have already reported (1) that the reaction of *O*-alkyl thioesters with ethylenediamine led to the corresponding 2-substituted-Δ^2-imidazolines according to Scheme I.

Scheme I



We wished to extend this reaction to the *O*-ethyl thiocarbamates in order to prepare 2-aryliminoimidazolidines (2) (Scheme II).

Scheme II



Besides the medicinal interest of these compounds, we hoped to proceed further with the investigation of the reactivity of the functional group $-C(S)OC_2H_5$.

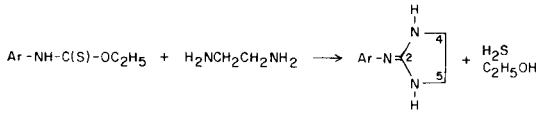
The quite different behaviour of the *N*-aryl and *N*-alkyl thionocarbamates with ethylenediamine is the striking feature of this reaction. Whereas the former gave the expected 2-aryliminoimidazolidines according to Scheme II, we observed with the second, a surprising reaction leading to 2-(2'-aminoethylamino)-Δ^2-imidazoline **(6)**. Indeed, at the end of the reaction, we obtained by distillation, ethanol and alkylamine. Also, this reaction gave imidazolidine-2-thione (17%) and traces of the expected 2-alkylamino-Δ^2-imidazoline.

These data can be explained by an examination of the mechanism of these reactions. Whatever the aromatic or

Table I

2-Aryliminoimidazolidines

Reaction of *O*-Ethyl *N*-Arylthiocarbamate (1 mole) with Diamine (3 moles) by Refluxing Without Solvent



Compound No.	Ar (a)	Refluxing Time (hours)	Yield %	M.p. °C	^{1}H Nmr δ	^{13}C Nmr δ
3a (b)		3	71	132-134	3.45 (s, 4H, H4 and H5), 5.43 (s, 2H, NH), 6.93-7.40 (m, 5H aryl)	42.62 (C4, C5), 121.67 (C4'), 122.92 (C2', C6'), 129.15 (C3', C5'), 149.71 (C1'), 158.51 (C2)
3b (c)		4	75	131-133	3.51 (s, 4H, H4 and H5), 5.40 (s, 2H, NH), 6.68-7.50 (m, 4H, aryl)	42.50 (C4, C5), 122.50 (C4'), 124.68 (C6'), 127.38 (C5'), 128.04 (C2'), 129.77 (C3'), 147.18 (C1'), 158.56 (C2)
3c (c)		5	100	153-155	3.42 (s, 4H, H4 and H5), 5.61 (s, 2H, NH), 6.95-8.31 (m, 7H aryl)	42.32 (C4, C5), 117.67 (C2'), 121.75, 124.15 (C4', C8'), 124.89 (C7'), 125.79 (C6'), 126.29 (C3'), 127.78 (C5'), 129.57 (C8'a), 134.67 (C4'a), 146.88 (C1'), 158.89 (C2)

(a) Analytical data: **3a**, recrystallized from water (*Anal.* Calcd. for $C_9H_{11}N_3$: C, 67.08; H, 6.83; N, 26.09. Found: C, 67.15; H, 6.81; N, 26.00.); **3b**, recrystallized from ethanol-water (50%) (*Anal.* Calcd. for $C_9H_{10}ClN_3$: C, 55.24; H, 5.11; N, 21.48. Found: C, 55.34; H, 5.09; N, 21.38.); **3c**, recrystallized from ethanol-water (50%) (*Anal.* Calcd. for $C_{13}H_{13}N_3$: C, 73.93; H, 6.16; N, 19.90. Found: C, 73.90; H, 6.20; N, 19.79). (b) Obtained by heating the 1-phenyl-3-(aminoethyl)thiourea (yield, 20%) (3). (c) Obtained by condensation of arylthioureas methyl iodides with ethylendiamine (4).

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Table II

Reaction Mechanisms

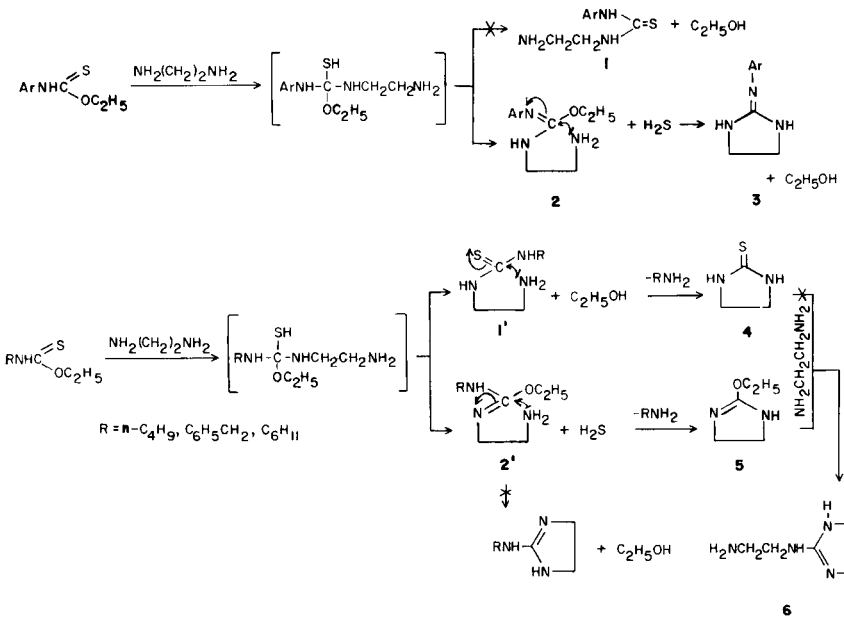
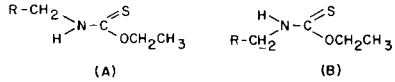


Table III

Thiocarbamates ^{1}H NMR Data



Thioncarbamate	R	CH_2	NH	CH_2	CH_3	*cis/trans* %	IR
			^{1}H NMR δ				
n-$C_4H_9NHC(S)OC_2H_5$	n-C_3H_7 0.83 to 1.16 (m)	B, 3.11 q (a) A, 3.56 q (a)	B, 6.91 *m* A, 6.33 *m*	4.50 q 4.58 q		58/42	3250, 1520, 1190
$C_6H_5CH_2NHC(S)OC_2H_5$	C_6H_5 7.35 s	B, 4.68 q A, 4.78 q	B, 6.05 *m* A, 7.08 *m*	4.46 q 4.48 q	1.33 t	40/50	3250, 1520, 1180
$C_6H_5NHC(S)OC_2H_5$	7.33	—	8.06 *m*	4.63 q	1.40 t	—	3210, 1600, 1200

(a) $^3J_{NH\text{-}CH_2}$ = 5 Hz, as described in the literature (9).

Table IV

N-Aryl Thiocarbamates

Aryl	Yield %	M.p. °	B.p. ° (mm)	Molecular Formula	Analytical Data
C_6H_5	98	66		$C_9H_{11}NOS$	Calcd: C, 59.67; H, 6.08; N, 7.73. Found: C, 59.52; H, 6.10; N, 7.66.
o-Cl-C_6H_4 (10)	58	104		$C_9H_{10}ClNOS$	Calcd: C, 50.12; H, 4.64; N, 6.50. Found: C, 50.24; H, 4.58; N, 6.47.
1-naphthyl (11)	70		114-116 (0.15 mm)	$C_{13}H_{13}NOS$	Calcd: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.62; H, 5.58; N, 6.16.

aliphatic thionocarbamate, the first step of the reaction is an unstable sp^3 intermediate which eventually leads to the formation of an *N*-substituted thiourea **1** and **1'**, or of an isourea **2** and **2'**, according to whether a molecule of alcohol or hydrogen sulfide is evolved. With aromatic thionocarbamates, the isourea **2**, which is mainly formed, cyclises immediately into 2-aryliminoimidazolidine. With aliphatics, the intermediate is converted simultaneously into **1'** and **2'**, giving respectively, the imidazolidine-2-thione **4** and the 2-ethoxy-Δ^2-imidazoline **5**.

The imidazolidine-2-thione does not react with ethylenediamine, as we have shown elsewhere; therefore, 2-(2'-aminoethylamino)-Δ^2-imidazoline arises necessarily from the reaction of ethylenediamine with **5**, as we have proved by the reaction of the diamine with **5** (prepared by treating 2-methylmercapto-Δ^2-imidazoline with sodium ethoxide (5)).

Removal of alkoxy or alkylamino groups, leading to 2-arylaminoimidazolidine **3** with *N*-arylthionocarbamates, is the surprising feature which seems to be governed by the position of the double bond -C(I)=N- in the isoureas **2** or **2'**. In aromatics **2**, it must conjugate with the aromatic group. At the time of the electronic doublet's return, the only possibility is the removal of the ethoxyl group (**2** → **3**). Spectroscopic data (2) show that **3** exists in the "phenylimino form" and not in the "anilino form" (6). With arylaliphatic or aliphatic isoureas, two positions of the double bond may be written, but **2'** is here favoured because the +I effect of the group R and the cyclisation is accompanied by the expulsion of the alkylamino group.

The 2-(2'-aminoethylamino)-Δ^2-imidazoline **6** has previously been obtained by Aspinall and Bianco, (7) who treated 2-methylmercapto-Δ^2-imidazoline with ethylenediamine in alcohol; this method remains the better. However, the synthesis of 2-aryliminoimidazolidines from *N*-aryl thionocarbamates is a new and interesting method.

EXPERIMENTAL

Melting points were measured in a slowly heated mercury bath. Ir spectra were obtained with a Perkin-Elmer 177 instrument. ^1H and ^{13}C nmr spectra were recorded, respectively, with a Varian T60 and CFT20 spectrometers (solutions in deuteriochloroform or dimethyl sulfoxyde with internal tetramethylsilane as standard). The chemical shifts are expressed in ppm: s, t, q, *m* designate singlet, triplet, quartet, multiplet and broad resonance, respectively.

O-Ethyl *N*-Alkylthiocarbamates.

These were prepared by treating alkylamines with diethyl dithiocarbonate, which was obtained by reaction of potassium *O*-ethyl dithiocarbonate with ethyl iodide according to the literature (8).

O-Ethyl *N*-Butylthiocarbamate.

An ethanolic solution of *n*-butylamine (3.65 g., 0.05 mole) and of diethyl dithiocarbonate (5.40 g., 0.036 mole) was heated under reflux for 8 hours until no more ethyl mercaptan was evolved. The cooled mixture was concentrated to dryness under vacuum and the residue was distilled at 127-128° and 14 mm (yield, 75%); spectral data: see Table III.

Anal. Calcd. for $C_7H_{15}NOS$: C, 52.17; H, 9.32; N, 8.69. Found: C, 25.33; H, 9.50; N, 8.85.

O-Ethyl *N*-Benzylthiocarbamate.

This experiment was identical to the previous one; the residue was distilled at 126-127° and 0.5 mm (yield, 81%); spectral data: see Table III.

Anal. Calcd. for $C_{10}H_{13}NOS$: C, 61.53; H, 6.66; N, 7.18. Found: C, 61.73; H, 6.61; N, 7.35.

O-Ethyl *N*-Arylthiocarbamates.

These were prepared by heating the corresponding isothiocyanate (1 mole) with an excess of ethanol (5 mole) under reflux, until the ir band at 2200 cm^{-1} had disappeared. The data are given in Table IV.

2-Aryliminoimidazolidines.

The syntheses can be exemplified by the preparation of:

2-(1'-Naphthyl)iminoimidazolidine.

O-Ethyl *N*-(1-naphthyl)thiocarbamate (3 g., 0.013 mole) was heated under reflux with anhydrous distilled ethylenediamine (2.35 g., 0.039 mole). The mixture was dark green. The excess of diamine was removed under vacuum and the crystalline residue was washed with water, dried and recrystallized from ethanol-water (50%). For spectral and analytical data, see Table I.

2-(2'-Aminoethylamino)-Δ^2-imidazoline.

a) From *O*-Ethyl *N*-Butylthiocarbamate.

O-Ethyl *N*-butylthiocarbamate (16 g., 0.1 mole) was heated under reflux for 6 hours with ethylenediamine (18 g., 0.3 mole). A green coloration developed while hydrogen sulfide was evolved. At the end of the reaction, the mixture was distilled at atmospheric pressure. The fraction boiling at 81° was collected and consisted of ethanol and butylamine. The excess of diamine was eliminated under 0.1 mm for 1 hour. The oily residue gave a very basic reaction and after trituration with ether, was dried. The residue was distilled at 147° and 0.05 mm to give a very viscous and hygroscopic oil (18%); ir (film): 3300, 1675, 1625 and 1540 cm^{-1}. nmr (DMSO-d_6): δ 2.63 (t, 2H, H_2N-CH_2CH_2), 3.03 (t, 2H, CH_2CH_2NH), 3.33 [s, 4H, equivalent protons of the imidazolinic methylene (amidinic structure)], 3.46 (s, 4H, protons of the NH groups). This product was analyzed as its dihydrochloride.

Anal. Calcd. for $C_5H_{12}N_4 \cdot 2HCl$: C, 34.70; H, 6.93; N, 16.18. Found: C, 34.97; H, 7.02; N, 16.35.

At the end of the distillation, we collected a product from the Vigreux column identified as imidazolidine-2-thione (17.5%) m.p. 195°; ir (potassium bromide): 3250, 2580 (SH), 1520 cm^{-1}.

Anal. Calcd. for $C_3H_6N_2S$: C, 35.29; H, 5.88; N, 27.45. Found: C, 35.43; H, 5.80; N, 27.25.

b) From 2-Methylmercapto-Δ^2-imidazoline (6).

2-Methylmercapto-Δ^2-imidazoline hydroiodide (12.25 g. 0.05 mole) was dissolved in anhydrous methanol (20 ml.) and ethylene diamine (3.5 ml.) was added. Methanethiol began to evolve immediately. After heating for 1.5 hours, the solvent was evaporated under vacuum. After trituration in ether, the hygroscopic monohydroiodide crystallised (yield, 78%).

The base was removed from the salt by a stoichiometric quantity of sodium methoxide. After removal of the alcohol, the residue was distilled at 148° and 0.07 mm. Ir and nmr spectra were identical to those described in a).

c) From *O*-Ethyl *N*-Benzyl and *O*-Ethyl *N*-Cyclohexylthiocarbamates.

Experiments and data were identical to those obtained with *O*-ethyl *N*-butylthiocarbamate.

Reaction of 2-Ethoxy-Δ^2-imidazoline with Ethylenediamine.

Compound **5** was prepared by the method of Poos, *et al.* (5), m.p. 50°; yield, 20%; ir (potassium bromide): 3250, 1630 and 1030 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, 3H), 3.60 (s, 4H, protons of the imid-

azoline methylenes), 4.23 (q, 3H, OCH_2 and NH together).

To ethylenediamine (0.60 g., 0.01 mole), was added progressively **5** (1.14 g., 0.01 mole). The mixture, after heating under reflux for 2.5 hours, was cooled and extracted with ether. The insoluble oil was decanted and dried under vacuum. The ir and nmr spectra identified 2-(2'-aminoethylamino)-Δ^2-imidazoline.

REFERENCES AND NOTES

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(2) The spectroscopic data (ir, ^1H and ^{13}C nmr) given in Experimental, show that these compounds exist in the imidazolidine form and not in the Δ^2-imidazoline form; these data agree with previous work (6). Indeed, the cyclic methylene are for **3** magnetically equivalent and the ^{13}C chemical shifts appear nearly at 42.5 ppm. On the other hand, the 2-aryl-Δ^2-imidazolines or 2-alkyl-Δ^2-imidazolines have also equivalent cyclic methylenes; this involves a prototropy of the hydrogen of NH group, as in the amidines. This delocalized doubled bond explains the equivalence and the deshielding of the cyclic carbons at 49.4 ppm. The difference between the ^{13}C chemical shifts of the methylenes for these compounds conform with the exocyclic position of the doubled bond N=C in the 2-aryliminoimidazolidines.

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