

The Direct Introduction of Carboxyl-derived Functions into Pyrroles and Indoles

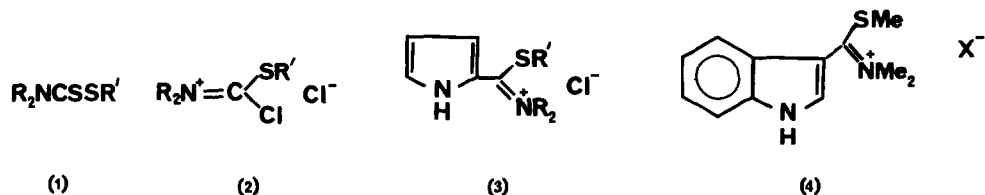
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Whereas introduction of carboxyl or carboxylate groups into pyrroles and indoles may be achieved by several methods<sup>1</sup>, the subsequent conversion of the resulting acids into derivatives other than simple amides or esters often poses problems because of their inherent instability and the difficulty of preparing the corresponding acid chlorides. This communication reports a new and essentially one-step synthesis of pyrrole and indole carboxylic acid derivatives including esters, amides, thioamides, amidinium salts, and thioformamidinium salts.

Readily available N,N-dialkyl dithiocarbamates (1)<sup>2</sup> react with phosgene in inert solvents giving chlorothioformamidinium salts (2)<sup>3</sup>. These hygroscopic salts react with pyrroles and indole in benzene solution at room temperature or above giving fair to excellent yields of the corresponding pyrrolyl (or indolyl) thioformamidinium salts (e.g. 3), isolated usually as the perchlorate or picrate.



The preparation of 3-indolylthioformamidinium perchlorate (4,  $X = ClO_4$ ) is typical. S,N,N-Trimethylchlorothioformamidinium chloride<sup>3</sup> (34.6 g, 0.2 mol.) was added to a solution of indole (11.7 g, 0.1 mol.) in benzene (200 ml) and the mixture stirred, protected from moisture, for 24 hr at room temperature. The benzene was decanted from the resulting gummy solid, water (100 ml) was added and stirring continued for 15 min. The aqueous solution was filtered through Kieselguhr, extracted with ether and 20% aqueous sodium perchlorate added until no further product

precipitated. The perchlorate salt (4, X = ClO<sub>4</sub>) was obtained as a pale yellow gum which rapidly crystallised; it was collected, washed with water and dried in vacuo over phosphorus pentoxide. The crude product was recrystallised from acetone-ethyl acetate and formed colorless plates, m.p. 150-153° dec. (yield, 50-60%) (Found: C, 45.16; H, 4.71; N, 9.03. C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>ClO<sub>4</sub>S requires C, 45.21; H, 4.74; N, 8.79%). The nmr spectrum (dmsO-d<sub>6</sub>) showed signals centred at δ2.41 (singlet, 3 protons, SMe), 3.67 (doublet, 6 protons, NMe<sub>2</sub>), 7.48 (multiplet, 4 protons, aromatic CH), 8.07 (doublet, sharpening to singlet on deuteration, α-CH of pyrrole ring), and 16.7 (broad signal, exchanging on deuteration, pyrrolic NH).

The salt (4, X = ClO<sub>4</sub>) is a useful reactive intermediate, and undergoes a number of reactions leading to esters, thioesters, dithioesters, amides, thioamides and amidinium salts derived from indole-3-carboxylic acid. The isolation of the perchlorate salt is not always necessary, however, and most of the above products can be obtained in comparable yields directly from the aqueous solution of (4, X = Cl).

Analogous reaction sequences to those described above have been carried out on simple pyrroles and in this way a number of novel pyrrolyl thioamides and amidinium salts have been obtained. Further studies on the properties of pyrrolyl and indolyl thioformamidinium salts are in progress, and the reaction of chlorothioformamidinium salts (2) with other reactive heterocyclic, aromatic and aliphatic systems is currently being explored.

#### References

1. (a) H. Fischer and H. Orth, *Die Chemie Des Pyrrols*, Vol. 1, p. 234, Akademische Verlags. Leipzig, 1934 (b) E. Baltazzi and L.I. Krimen, Chem. Rev. **63**, 511, (1963).
2. *Methoden der organ. Chemie* (Houben-Weyl), 4. Aufl., Bd. IX, p. 837, Georg Thieme Verlag, Stuttgart, 1955.
3. H. Eilingsfeld and Leander Mobius, Chem. Ber. **98**, 1293, (1965).
4. The structures of all new compounds described were confirmed by elemental analyses, ir, nmr and mass spectra.