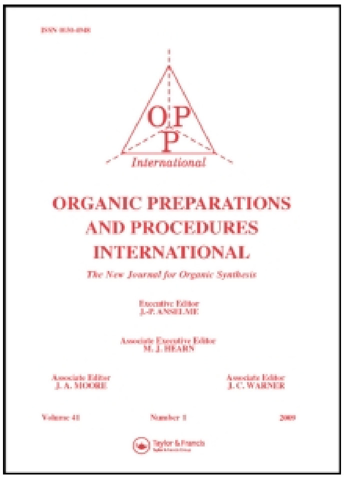

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SYNTHESIS OF TRICYCLIC AND TETRACYCLIC THIAZOLOIMIDAZOLE ACETIC ACIDS

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OPPI BRIEFS

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SYNTHESIS OF TRICYCLIC AND TETRACYCLIC THIAZOLOIMIDAZOLE ACETIC ACIDS

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(9/19/77)

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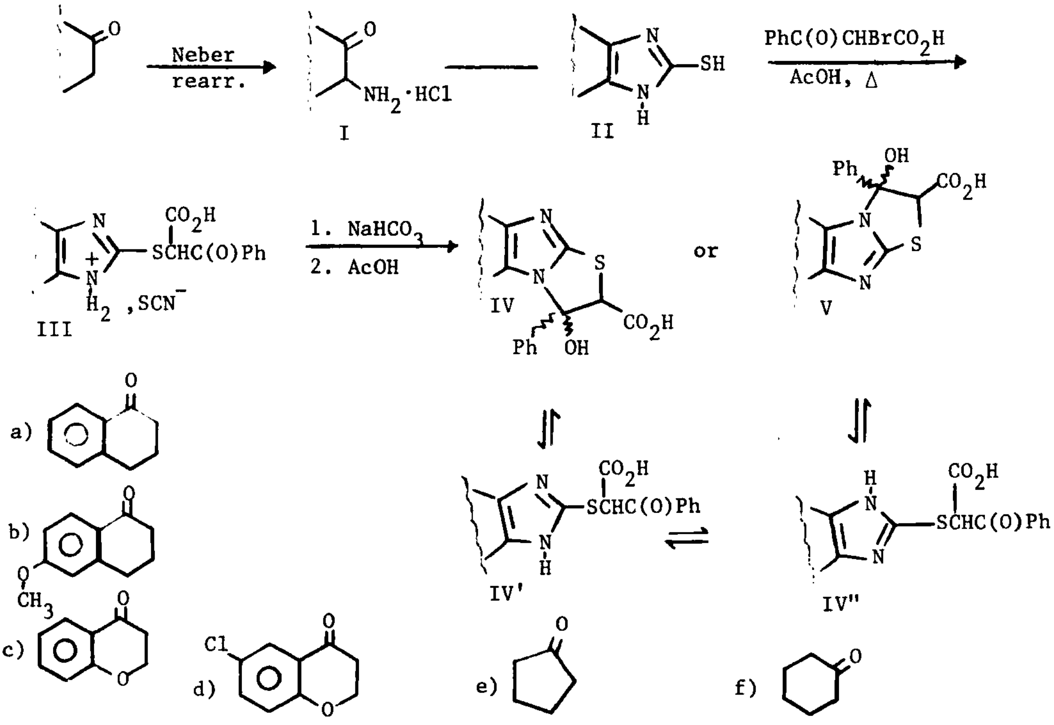
Very active interest in levamisole[1-3] prompts the report of the synthesis of certain tricyclic and tetracyclic derivatives which have the levamisole system incorporated into a pericyclic skeleton. Imidazolethiols



IIc, IIe, and IIf were obtained according to published procedures.[4-7] While the imidazolethiols from Ic and Id easily separated out from the reaction mixture when the latter was boiled with an aqueous solution of potassium thiocyanate, separation did not occur when the aminotetralones were boiled with aqueous potassium thiocyanate. Instead, there was obtained the corresponding thiocyanate salt. A suspension of the above thiocyanate salt, when heated in xylene to reflux with azeotropic removal of water, was converted to the required imidazolethiol. Condensation of the imidazolethiols with β-bromo-β-benzoylpropionic acids gave thiazoloimidazole acetic acids IV or V. The spectrum of IV (or V) in DMSO displayed two C=O absorptions (1705-1710 and 1665-1670 cm^{-1}) suggesting that forms IV' and IV" exist in solution.[3] There is only one C=O band (1705-1710 cm^{-1}) in the IR spectra run as a KBr pellet.[8]

EXPERIMENTAL

4,5-(3,4-Dihydronaphth[1,2-d]imidazole-2-thiol)(IIa).- A mixture of 2-aminotetralone hydrochloride (Ia, 1.07 g, 0.005 mole) and potassium thiocycanate (0.5 g, 0.005 mole) in 10 ml of water was heated to reflux under N_2 for 2.5 hrs. During this period a small amount of dark polymeric material separated. The reaction mixture was filtered hot and removal of water from the filtrate under reduced pressure left a yellow mass. The yellow organic material was taken up in anhydrous ethanol (30 ml). After filtration through carbon (Nuchar C-190-N) and concentration, dilution with dry ether (15 ml) gave greenish-yellow shiny, crystals of the thiocyanate salt. This salt was suspended in dry xylene (50 ml) and heated to reflux for 1 hr. with azeotropic removal of water. Rearrangement occurred to give imidazolothiol IIa. The cooled reaction mixture was filtered, and the solid was washed with cold ethanol and recrystallized from pyridine-water, 1:2, to yield 0.6

g (56%) of IIa, mp. 330°.

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.35; H, 4.95; N, 13.86; S, 15.84%.
Found: C, 64.96; H, 4.81; N, 13.98; S, 15.49%.

Nmr (DMSO-d_6) δ 12.17 and 12.5 (2s, 2H, NH and SH; each exchanged with D_2O); 6.8-8 (m, 4 H, ArH); 2.5-3.2 ppm (m, 4 H, ring CH_2).

4,5-(3,4-Dihydro-6-methoxynaphth[1,2-d]imidazole-2-thiol)(IIb).- Compound IIb was prepared from 2-amino-6-methoxytetralone hydrochloride (Ib, 1.1 g; 0.005 mole) and potassium thiocyanate (0.48 g; 0.005 mole) in 10 ml of water as above; yield of IIb was 0.7 g (65%), mp. 325°.

Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.07; H, 5.17; N, 12.07; S, 13.79%.
Found: C, 62.31; H, 5.28; N, 11.88; S, 13.74%.

Nmr (DMSO-d_6) δ 12.6 and 13 (2s, 1 H, each NH and SH exchanged with D_2O); 7.4 [d, J = 8 Hz, 1 H, H(9)]; 6.7-7.0 [m, 2 H, H(7) and H(8)]; 3.75 (s, 3 H, OCH_3); 2.5-3.2 ppm (m, 4 H, ring CH_2).

4,5-Chroman-imidazole-2-thiol(IIc).- A mixture of 3-aminochroman-4-one hydrochloride (Ic, 2 g; 0.01 mole) and potassium thiocyanate (1.1 g; 0.011 mole) in 20 ml of water was boiled under N_2. The remainder of the procedure was similar to that published.[4]

Nmr (DMSO-d_6) δ 12.22 and 12.75 (2 s, 1 H each, NH and SH; exchanged with D_2O); 6.7-7.5 (m, 4 H, ArH); 5.3 ppm (s, 2 H, OCH_2) was found for IId.

4,5-(8-Chlorochroman)[2,3-d]imidazole-2-thiol(IId).- A mixture of 6-chloro-3-aminochroman-4-one hydrochloride[4] (Id, 2.4 g; 0.01 mole) and potassium thiocyanate (1.2 g, 0.01 mole) in 20 ml of water was boiled under N_2. Within 20 min., a yellow, powdery material began to separate. Heating was continued for 2.5 hrs. The reaction mixture was cooled and the solid formed was filtered and washed several times (H_2O). Crystallization from ethanol:water (1:1) gave 1.2 g (50%) of IId as pale yellow crystals, mp. 287°.

Anal. Calcd. for $C_{10}H_7ClN_2OS$: C, 50.53; H, 2.52; Cl, 14.94; N, 11.78; and S, 13.47%.

Found: C, 50.92; H, 2.90; Cl, 15.13; N, 11.49 and S, 13.20%.

Nmr (DMSO-d_6) δ 12.3 and 12.7 (2 s, 1 H each, NH and SH; exchanged with D_2O); 7.45 [d, $J_{H(9)-H(7)}$ = 2.5 Hz, 1 H, H(9)]; 7.0-7.2 [two doublets with ortho and meta couplings, $J_{H(7),H(6)}$ and $J_{H(7),H(9)}$ = 2.5 Hz and 8.5 Hz, 1 H, H(7)]; 6.85 [doublet with ortho coupling, $J_{H(6),H(9)}$ = 8.5 Hz, 1 H, H(6)]; 5.3 ppm (s, 2 H, ring CH_2).

Condensation of the Imidazolethiols with Bromobenzoylpropionic Acid. Preparation of III and IV (or V).- The condensation procedure for the different imidazolethiols is similar to that reported[3] with a modification in the amount of acetic acid used and time employed for maximizing yields. A typical representative procedure for the case of 4,5-(3,4-dihydro-6-methoxynaphthyl)[1,2-*d*] imidazolethiol is described. Tables I and II summarize the revelant data for the title compounds.

4,5-(3,4-Dihydro-6-methoxynaphthyl)[1,2-*d*]imidazolethiol (IIb, 0.232 g; 0.001 mole) and β-bromo-β-benzoylpropionic acid (0.257 g; 0.001 mole) in aceitc acid (5 ml) were heated on a steam bath with occasional shaking for 3 hrs. After 10-15 min. of heating, most of the starting materials had dissolved and 20 min. later a yellow, crystalline material separated. After 3 hrs., the cooled reaction mixture was filtered and the solid IIIb was washed with a minimum amount of cold acetic acid (*ca* 1-2 ml) and air dried. This solid was then dissolved in saturated sodium bicarbonate solution. After separation of the small amount of undissolved material by filtration, acidification of the filtrate with acetic acid gave the thiazoloimidazole acetic acid IVb (or Vb) which was crystallized from methanol:water (1:2).

Table 1. Physical Data of Thiazoloimidazole Acetic Acids (IV or V)[a]

Cmpd	Solvent[b] (ml.)	Yield (%)	mp (°C)	Combustion Analysis:Calculated(Found) C	H	N	S
IVa	3.5	43	135-136	66.67 (66.63)	4.76 (4.84)	7.41 (7.26)	8.47 (8.10)
IVb	5.0	25	181-184(d)	64.74 (65.15)	4.90 (5.25)	6.96 (6.70)	7.84 (7.51)
IVc	4.0	58	161-162	63.16 (62.97)	4.21 (4.30)	7.37 (6.99)	8.42 (8.30)
IVd	5.0	23	191-193(d)	57.90 (57.75)	3.62 (4.06)	6.76 (6.75)	7.73[c] (7.50)
IVe	0.5[d]	39	149-151(d)	60.76 (60.58)	5.06 (5.23)	8.86 (8.54)	10.13 (9.92)
IVf	1.0	47	178-179	61.81 (62.01)	5.46 (5.60)	8.49 (8.47)	9.69 (9.62)

a) All compounds were crystallized from methanol-water; times of reflux were 3 hrs. unless otherwise specified. b) Volume of solvent per mM of fluid used. c) Calcd Cl: 8.56; Found: Cl, 8.40. d) Time of reflux: 2 hrs.

Table 2. NMR Data of Thiazoloimidazole Acetic Acids[a]

Cmpd	$N\underline{H}$ & $CO_2\underline{H}$	$Ar\underline{H}$	$C\underline{H}CH_2CO_2H$	Ring $C\underline{H}_2$ & $C\underline{H}_2CO_2H$
IVa	12.5 (bs, 2 H)	7-8.2(m, 9 H)	5.25(dd, 2 H, J=5 Hz)	2.7-3.3(m, 6 Hz)
IVb	12.5 (bs, 2 H)	6.7-8.2(m, 8 H)	5.1-5.35 (dd, 1 H, J=5 Hz)	2.7-3.4(m, 6 H)[b]
IVc	12.5 (bs, 2 H)	6.8-7.2(m, 9 H)	5.1-5.4 (dd, 2 H)[c]	2.8-3.4(m, 2 H)[d]
IVd	12.6 (bs, 2 H)	6.8-8.0(m, 8 H)	5.1-5.4 (dd, 2 H)[c]	2.9-3.4(m, 2 H)[d]
IVe[e]			4.9-5.2 (dd, 1 H, J=5 Hz)	2.8-3.3(m, 2 H)[f]
IVf	13.6 (bs, 2 H)	7.6-8.4(m 5 H)	4.9-5.2 (dd, 1 H, J=6 Hz)	2.8-3.3(m, 2 H)[g]

a) Obtained in DMSO-d_6 and reported in δ values. b) $C\underline{H}_3O$; 3 H, s, 3.75. c) A broadened singlet appeared in this same area for the ring $C\underline{H}_2$. d) The signal is only for the $C\underline{H}_2CO_2H$. e) A multiplet at 7.0-8.5 contained protons for $N\underline{H}$, $CO_2\underline{H}$, and Ar-$\underline{H}$. f) A broadened signal appeared at δ 2.27 for the 6 ring $C\underline{H}_2$. g) Broad singlets appeared at δ 1.7 and 2.4 for 8 ring $C\underline{H}_2$.

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8. Thus, IVc or Vc could come from IV'c or IV"c, respectively. A Courtauld model of Vc could not be constructed without extreme distortion of the bonds implied that form Vc was highly strained with considerable steric repulsion between the trigonal nitrogen and groups on the two asymmetric carbon atoms in the thiazole ring. We favor IVc, the Courtauld model of which appeared relatively strain free with the C_6H_5 and CH_2CO_2H groups in an anti arrangement. Quite probably an X-ray analysis will be needed to resolve the stereochemical assignment.