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THIENO[3,4-b]PYRIDINE AND THIENO[3,4-c]PYRIDINE


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4 Claims

ABSTRACT OF THE DISCLOSURE

Thieno[3,4-b]pyridine and thieno[3,4-c]pyridine have been prepared.

There are six theoretically possible thienopyridines, viz. thieno[2,3-b]pyridine (I), thieno[2,3-c]pyridine (II), thieno[3,2-b]pyridine (III), thieno[3,2-c]pyridine (IV), thieno[3,4-b]pyridine (V) and thieno[3,4-c]pyridine (VI).


There is pharmacological interest in the thienopyridines in that they are isomeric with quinoline and isoquinoline systems. Additionally, the thienopyridines are useful for the preparation of dyes and dyestuffs, biocides, e.g. antimalarials, herbicides, pesticides and as an additive to lubricating oils. For example, the above-identified thienopyridines may be incorporated in petroleum lubricating oils in amounts in the range 0.01—1.0% by weight to improve the lubricating and extreme pressure properties of the lubricating oils.

It is an object of this invention to provide thienopyridines and derivatives thereof not heretofore available.

It is another object of this invention to provide a process for the manufacture of certain thienopyridines, particularly thieno[3,4-b]pyridine and thieno[3,4-c]pyridine and derivatives thereof, such as halogen, e.g. Cl and Br, —NO₂, phenyl, acetoxy, hydrogen, carboxalkoxy and cyanosubstituted derivatives thereof.

How these and other objects of this invention are achieved will become apparent in the light of the accompanying disclosure. In at least one embodiment of the practice of this invention at least one of the foregoing objects will be achieved.

Thienopyridines, not available heretofore, have been prepared. Specifically, thieno[3,4-b]pyridine has been prepared and thieno[3,4-c]pyridine has been prepared.

In accordance with this invention 2,3-dimethylpyridine and 3,4-dimethylpyridine have been converted into thieno[3,4-b]pyridine (V) and thieno[3,4-c]pyridine (VI), respectively. By employing the practices of this invention derivatives of (V) and (VI) with selected substituents, such as a chloro group, in the pyridine ring are prepared by starting with a suitably substituted dimethylpyridine.

The preparation of thieno[3,4-b]pyridine (V) from 2,3-dimethylpyridine in accordance with one embodiment of this invention is schematically illustrated hereinafter in Scheme A.

The preparation of thieno[3,4-c]pyridine from 3,4-dimethylpyridine in accordance with another embodiment of this invention is schematically illustrated hereinafter in Scheme B.

The preparation of thieno[3,4-b]pyridine in accordance with one embodiment of the practice of this invention as schematically illustrated in accordance with Scheme A hereinafore is as follows: A vigorously stirred solution of 10 ml. (9.4 g., 0.088 mol) of 2,3-dimethylpyridine and 24 g. (0.18 mol) of N-chlorosuccinimide in 900 ml. of CCl₄ was refluxed under nitrogen gas in a round-bottom flask while it was irradiated by means of a juxtaposed 200-watt Hanovia lamp for 24 hours. The mixture was cooled, filtered to remove succinimide and unreacted N-chlorosuccinimide, treated with fresh N-chlorosuccinimide (24 g.), and reacted further for an additional 24 hours.

The cooled reaction mixture was filtered and treated with excess anhydrous HCl. The gummy precipitate was
crystallized from isopropanol to give 14.3 g (77%) of VII: M.P. 148.5–149.5°. A sample for analysis was recrystallized from isopropanol and sublimed three times (once just prior to analysis) at 80° (0.1 mm.) to give a white solid: M.P. 147.5–148.5° (dec.).

**Analysis.**—Calcd. for C₃H₅Cl₂N₂O (percent): C, 42.86; H, 2.21; N, 15.38; S, 8.80. Found (percent): C, 43.18; H, 2.27; N, 15.05; S, 8.53.

The preparation of thieno[3,4-c]-pyridine in accordance with one embodiment of the practice of this invention as schematically illustrated in accordance with Scheme B hereinabove is as follows: In the same manner as used to photochlorinate 2,3-dimethylpyridine, as described hereinbefore, a stirred, refluxing solution of 3,4-dimethylpyridine (4 g, 0.037 mol) and N-chlorosuccinimide (14 g, 0.1 mol) in 1.5 l. of CCl₄ was irradiated for 7.5 hours in a nitrogen atmosphere. Filtration of the cooled reaction mixture and treatment of the filtrate with anhydrous HCl gave a gum which crystallized on standing at 3°. It was recrystallized from acetone and sublimed slowly at 100–120° (0.3 mm.) to give 5.2 g. (67%) of white solid, M.P. 157–159° (dec.).

**Analysis.**—Calcd. for C₃H₅Cl₂N₂O (percent): C, 39.56; H, 3.79; Cl, 50.05; N, 6.59. Found (percent): C, 39.55; H, 3.77; Cl, 50.27; N, 6.57.

1,3-dihydrothieno[3,4-c]-pyridine, XII, was prepared from XI in a manner closely similar, as described previously before, to that used for its isomer VIII. However, to avoid decomposition of the product, the reaction mixture was treated directly (without preceding evaporation) with an equal volume of benzene. This mixture was then washed with water, dried, and evaporated to give XII as a slightly yellow liquid (81%) which was not purified further. The picrate, formed in absolute EtOH was obtained as colorless yellow crystals from hexane-CH₂Cl₂: M.P. >180° (dec.).

**Analysis.**—Calcd. for C₃H₅N₂Cl₂O (percent): C, 42.63; H, 2.75; N, 15.30. Found (percent): C, 42.53; H, 2.69; N, 15.29.

1,3-dihydrothieno[3,4-c]-pyridine 2-oxide, XIII, was prepared by oxidation of XII with iodobenzene dichloride in the manner used to convert VIII to IX. Chromatography by means of Florisil plus benzene (to remove iodobenzene formed) and then 0.5–1.5 MeOH in EtOAc gave XIII (67%) as a red-brown liquid; infrared band (in CHCl₃) at 1055–1040 cm⁻¹ (S=O).

In the manner used for the preparation of V, a deposit of fresh sulfoxide XII on alumina at 100–120° but at 0.3 mm. to give VI as a slightly yellow liquid (37%); I.R. max. (CHCl₃) 3221 cm⁻¹ (lone aromatic hydrogen): UV. max. (abs. EtOH) 224 nm (ε 10,000), 270 nm (10,200), 280 (2890), 291 (2050), 342 (2960); UV. max. (96% EtOH+HCl) 236 nm (ε 24200), 281 (4900), 290 (3470), 380 (2740); nmr (CDCl₃, 60 MHz) δ 6.38 (slightly split d, 2 H, J = 7.4 Hz, H-1), 7.64 (3 d, 1 H, J = 3 Hz, H-3 or H-1), 8.02 (d, 1 H, H-1 or H-3), 8.04 (d overlapping 8.02 signal, 1 H, H-6), 9.12 (broadened s, 1 H, H-4).

The picrate, formed in absolute EtOH, was obtained as yellow needles from benzene-hexane: M.P. 234–235° (dec.).

**Analysis.**—Calcd. for C₃H₅N₂SO₃H (percent): C, 42.86; H, 2.21; N, 15.38; S, 8.80. Found (percent): C, 42.76; H, 2.10; N, 15.22 S, 8.63.

As will be apparent to those skilled in the art in the light of the foregoing disclosure many modifications, alterations and substitutions are possible in the practice of this invention without departing from the spirit or scope thereof.

We claim:

1. A method for the preparation of thieno[3,4-b]-pyridine which comprises reacting 2,3-dimethylpyridine and N-chlorosuccinimide in an inert solvent while refluxing the resulting reaction mixture under an inert gas and irradiating the refluxing reaction mixture with ultraviolet radiation, cooling and filtering the resulting reaction mixture to remove succinimide and unreacted N-chlorosuccinimide, reacting the resulting cooled and filtered reaction mixture with excess anhydrous HCl and recovering there-
from the resulting bis-chloromethyl derivative as the hydrochloride salt having the formula,

reacting the resulting recovered bis-chloromethyl hydrochloride derivative with ethanolic sodium sulfide to produce the corresponding sulfide derivative having the formula,

oxidizing the resulting sulfide derivative by reaction with iodobenzene dichloride in the presence of aqueous acetonitrile and triethylamine to produce the resulting sulfoxide having the formula,

recovering the resulting sulfoxide and heating a solution of said sulfoxide in the presence of activated alumina under reduced pressure and at an elevated temperature to produce a distillate fraction the aforesaid thieno[3,4-b]pyridine having the formula,

2. A method for the preparation of thieno[3,4-c]pyridine which comprises reacting 3,4-dimethylpyridine and N-chlorosuccinimide in an inert solvent while refluxing the resulting mixture under an inert gas and irradiating the refluxing reaction mixture with ultraviolet radiation, cooling and filtering the reaction mixture to remove succinimide and unreacted N-chlorosuccinimide, reacting the resulting cooled and filtered reaction mixture with excess anhydrous HCl and recovering therefrom the resulting bis-chloromethyl derivative as the hydrochloride salt having the formula,

3. The compound thieno[3,4-b]pyridine.
4. The compound thieno[3,4-c]pyridine.

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