A Novel Di-hetero Azulene: 4*H*-Thieno[3,4-*d*]-azepine

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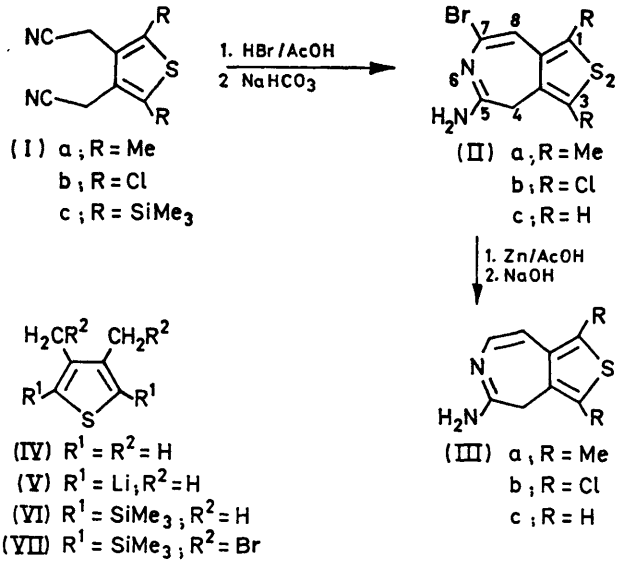
Summary Derivatives of the novel heterocycle 4*H*-thieno-[3,4-*d*]azepine have been prepared by cyclisation of 3,4-bis(cyanomethyl)thiophens; their spectral data are discussed.

MOST condensed bicyclic heterocycles of formula (II) in which the heteroatoms are O, S, or N are unknown. We report on the synthesis of derivatives of the novel system 4*H*-thieno[3,4-*d*]azepine (IIa—c, IIIa—c), which have been obtained by an acid cyclisation of 3,4-bis(cyanomethyl)thiophens (Ia—c). Compound (Ia)‡ was prepared[1] by a standard method, and compound (Ib) was made from 2,5-dichloro-3,4-bis(chloromethyl)thiophen[2] and KCN in Me_2SO–H_2O below 30° (3 h), brownish crystals m.p.



(I) a; R = Me
b; R = Cl
c; R = $SiMe_3$

(II) a; R = Me
b; R = Cl
c; R = H

1. Zn/AcOH
2. NaOH

(IV) $R^1 = R^2 = H$
(V) $R^1 = Li$; $R^2 = H$
(VI) $R^1 = SiMe_3$; $R^2 = H$
(VII) $R^1 = SiMe_3$; $R^2 = Br$

(III) a; R = Me
b; R = Cl
c; R = H

144—146° (benzene–ether), 61%. Compound (Ic) was synthesised from 3,4-dimethylthiophen[3] (IV). Dilithiation of (IV) with a 2·6-fold excess of butyl-lithium in hexane–Et_2O at reflux (20 h) gave (V), which upon reaction with $ClSiMe_3$ (addition at 0°, ½ h reflux) gave (VI), 78%, b.p. 138—142°/14 mm Hg, m.p. *ca.* 21°. Reaction of (VI) with *N*-bromosuccinimide and dibenzoyl peroxide in CCl_4 (45 min. reflux) yielded (VII) (oil). Without purification, (VII) was transformed with NaCN in 50% aqueous EtOH (1 h, reflux) into (Ic), m.p. 141—143°, 56% yield from (VI).

When (Ia) was stirred with HBr–HOAc, 30 w/w %, at room temperature (3 h) according to a literature procedure,[4] the HBr salt of (IIa) precipitated, 91%, m.p. 245—260° (methanol); i.r. (KBr): bands at 3048 (very broad) and 1675 (v.s.), 1637 (sh), and 1605 cm^{-1} (sh); u.v.: λ_{max} (MeOH) 218 nm log ϵ 4·23), 244 (sh., 3·93), and 288 (3·81). The free base (IIa) was obtained by stirring the salt at room temperature (2 h) with 12% aqueous $NaHCO_3$, 91%, m.p. 190—195° dec. (dimethoxyethane); i.r. (KBr): sharp bands at 3460 and 3289 (free NH), 3086 (associated NH; disappears in solution), and a strong doublet at 1642 and 1587 cm^{-1}. The differences observed in the i.r. spectrum of (IIa) and its HBr salt in the 3300 and 1600 cm^{-1} region are comparable with those of 2-aminopyridine and its HCl salt,[5] in agreement with a cyclic amidine structure. The u.v. spectrum shows λ_{max} (MeOH) 217 nm (log ϵ 4·36) and 310 (3·98); n.m.r. [60 MHz, $(CD_3)_2CO$]: τ 7·72 and 7·65 (s, 3H, s, 3H, 1- and 3-CH_3), 6·60 (s, 2H, 4-CH_2), 3·2 (s, broad, 2H, 5-NH_2), and 3·74 (s, 1H, 8-H). The fact that one single peak is observed for the two amine protons at τ 3·2 indicates that the amidine (IIa) is best represented by its amino-tautomer as shown in the formula.

Similarly the HBr salts and their corresponding free bases (IIb) and (IIc) were obtained: (IIb, HBr), dec. 250° (methanol), 88%; (IIb), m.p. 202—205° dec., 92%. During the acid cyclisation of (Ic) the Me_3Si groups were cleaved in the acid medium[6] and the 1,3-unsubstituted (IIc) was obtained as its HBr salt: m.p. 230—245° dec. (methanol–benzene), 79%; (IIc), m.p. 182—185°, 97%.

Debromination of (IIa) with Zn powder in acetic acid at room temperature (20 h, stirring) gave the HBr salt of (IIIa): m.p. 275—285° dec. (ethanol–acetone), 80%. The latter gave with a calculated amount of 4N-aq.NaOH in methanol (IIIa): 97%, m.p. 150—155° dec.; n.m.r. [60 MHz, $(CD_3)_2SO$]: τ 7·71 and 7·79 (s, 3H, s, 3H, 1- and 3-CH_3), 6·88 (s, 2H, 4-CH_2) 3·5 (s, broad, 2H, 5-NH_2), 3·56 (d, 1H, 7-H),

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‡ All compounds gave satisfactory elemental analyses.

and 4·29 (d, 1H, 8-H), $J_{8,7}$ 8·5 Hz. The corresponding debrominated products (IIIb) and (IIIc) and their HBr salts were also prepared: (IIIb, HBr), dec. 255—260° (dimethylformamide), 80%; (IIIb), m.p. 130—133° (acetone), 47%; (IIIc, HBr), m.p. 205—215°, 73%; (IIIc), dec. 187—190°, 67%. The spectral data of (IIb,c) and (IIIa—c) show the same characteristics as those of (IIa), whereas their HBr salts resemble in this respect the HBr salt of (IIa). Consequently, we conclude that all amidines discussed here are predominantly in the amino-form.

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[1] M. S. Kondakova and Ya. L. Goldfarb, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1958, 590, *Chem. Abs.*, 1958, **52**, 20114i.
[2] M. Winn and F. G. Bordwell, *J. Org. Chem.*, 1967, **32**, 1610.
[3] A. F. Shepard, A. L. Henne, and T. Midgley, jun., *J. Amer. Chem. Soc.*, 1934, **56**, 1355.
[4] (a) J. H. Osborn, *Diss. Abs.*, 1959, **19**, 2475, *Chem. Abs.*, 1959, **53**, 14934; (b) J. Gardent, *Compt. rend.*, 1964, **259**, 4724; (c) F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.*, 1965, **2**, 26; (d) See also F. Johnson and R. Madronero, *Adv. Heterocyclic Chem.*, 1966, **6**, 141.
[5] E. Spinner, *J. Chem. Soc.*, 1962, 3119 and refs therein.
[6] C. Eaborn, "Organosilicon Compounds", Butterworth, London, 1960, p. 148.