

N-Quaternary Compounds

Part XXIV.¹ Isoquinoline Analogues

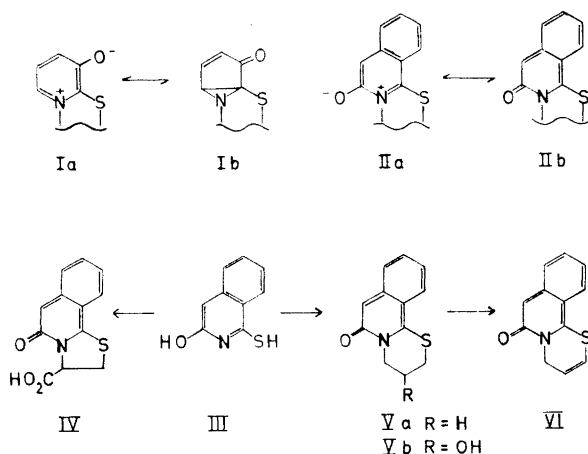
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3-Hydroxy-1-mercaptoisoquinoline has been condensed with difunctional 1,2-ethane and 1,3-propane derivatives. The products are isoquinolinones as shown by their physical-chemical properties.

3-Hydroxypyridine derivatives, in which a dihydrothiazolo,² thiazolo,³ [1,3]thiazino or dihydro[1,3]thiazino⁴ moiety is part of a ring with the pyridyl nitrogen at a bridgehead position, have physical-chemical properties as a betaine (Ia) rather than as a non-charged valence isomer (Ib). The same is true for the product obtained on *N*-alkylation of 3-hydroxypyridine, but not from 2-hydroxypyridine which gives a lactam. A betaine structure for the latter would increase the energy due to charge separation while the 3-hydroxypyridine derivatives would have to form a cyclopentenone structure to become covalent, and in this case a betaine structure is preferred in the ground state. On heating in the mass spectrometer, however, the betaines are readily volatilized without structural rearrangements.^{5,6} Therefore these molecules must thermally assume a valence isomeric structure or be excited in a such way that a canonical resonance form similar to Ib must be a major contributor to the actual structure. Our studies have now been extended to α -lactams with a phenyl group condensed onto the pyridyl ring in such a way that a covalent lactam structure would involve breakage of the common double bond, which at least in naphthalenes is thought to be partially localized. Assuming double bond localisation in the isoquinolines, the excess energy required for breaking this bond might be enough to affect the electronic state of the molecule in such a way that the true structure would incorporate enough of a resonance form with charge separation to be manifested in its physical properties.

The syntheses followed established routes.^{3,4,7} Condensation between 3-hydroxy-1-mercaptoisoquinoline⁸ and 1,3-dibromopropane furnished the dihydro[1,3]thiazine (Va). Addition to α -bromoacrylic acid followed by cyclisation of the intermediate adduct to IV proceeded as in the 3-hydroxypyrid-2-thione series.⁷ For the synthesis of the thiazine (VI), the thiol (III) was first condensed with 1,3-dibromo-2-hydroxypropane and the 3-hydroxy



derivative (Vb) dehydrated by means of cold sulphuric acid. The water elimination proceeded without any skeletal rearrangement. We have previously reported³ that in water elimination of the quaternary pyridinium compound, 3-hydroxy-6-methyl-dihydro[1,3]thiazino[3,2-a]pyridinium-9-oxide, water elimination results in skeletal rearrangement to the corresponding 2-methylthiazole derivative. In the NMR spectrum in TFA the thiazine formed has its methylene protons absorbing around 5.3 τ . The $\text{CH}_2\text{-N}$ protons in the simple dihydrothiazine (Va) are centered at about 5.2 τ and the S-CH_2 protons at 6.4 τ . The reaction product therefore must be assigned the 4H-thiazine structure (VI). In the NMR spectrum there is no evidence for the presence of the 2H-isomer. Therefore, as in the case of 6-methyl[1,3]thiazino[3,2-a]pyridinium-9-oxide,⁴ the 4H-isomer is thermodynamically the more stable as this is the only isomer obtained under the vigorous reaction conditions used.

All the compounds prepared were found almost insoluble in water but readily soluble in organic solvents such as ethyl acetate and benzene. The betaine contribution to the actual structure is therefore very small and the molecules must be formulated in the covalent lactam form. This conclusion is supported by strong carbonyl absorption in the region 1620–1640 cm^{-1} (KBr). This should be compared with the pyridinium oxides which have no marked absorption above 1560–1580 cm^{-1} in the carbonyl region.

EXPERIMENTAL

3-Carboxydihydrothiazolo[3,2-a]isoquinolin-5-one (IV). A solution of 3-hydroxy-1-mercaptoisoquinoline (8.9 g, 0.05 mol) and α -bromoacrylic acid (10.8 g, 0.055 mol) in ethyl acetate (300 ml) was stirred in the cold overnight, the precipitated hydrobromide of the title compound collected (14.0 g), dissolved in aq. NaOH and reprecipitated by acid neutralisation, m.p. 150–151°. (Found: C 57.85; H 3.68; N 5.61. Calc. for $\text{C}_{12}\text{H}_9\text{NO}_3\text{S}$: C 58.29; H 3.67; N 5.67.)

Dihydro[1,3]thiazino[3,2-a]isoquinolin-6-one hydrobromide (Va). 3-Hydroxy-1-mercaptoisoquinoline (1.8 g, 0.01 mol) was dissolved in methanolic (75 ml) sodium methoxide

(0.01 mol) and a solution of 1,3-dibromopropane (3.0 g, 0.015 mol) in methanol (10 ml) was added slowly. The reaction mixture was then heated at 50° for 5 h, the solvent evaporated at reduced pressure, the residue suspended in ethyl acetate (50 ml), the suspension extracted with water (2 × 20 ml), and the ethyl acetate solution dried and strongly concentrated. The solid precipitate formed was recrystallized from isopropanol; yield 1.7 g (74 %), m.p. 210–220°. (Found: C 48.81; H 4.07; N 5.02; S 11.16. Calc. for C₁₂H₁₁NOS.HBr: C 48.33; H 4.06; N 5.02; S 10.75.)

3-Hydroxydihydro[1,3]thiazino[3,2-a]isoquinolin-6-one (Vb). This compound was prepared as above from 1,3-dibromopropanol-2 in 73 % yield, m.p. 213°. (Found: C 61.47; H 4.51; N 5.83. Calc. for C₁₂H₁₁NO₂S: C 61.78; H 4.75; N 6.00.)

4H-[1,3]-Thiazino[3,2-a]isoquinolin-6-one (VI). 3-Hydroxydihydro[1,3]thiazino[3,2-a]isoquinolin-6-one (2.3 g, 0.01 mol) was dissolved in cold, concentrated sulphuric acid (10 ml), the solution left in the cold overnight, poured into water (10 ml), the pH was brought to 3.5 with 6 N NaOH, and the solution, extracted with aqueous phenol (phenol: H₂O, 9 : 1) (3 × 50 ml). The phenol extracts were washed with water (2 × 25 ml), ether (600 ml) was added to the phenolic solution and the aqueous layer which separated was collected, the ethereal solution was extracted with water (2 × 25 ml), the aqueous solution and washings were combined and washed with ether (2 × 50 ml), and the aqueous solution was evaporated to dryness. The residual, yellow solid was recrystallized from ethanol; yield 1.3 g (61 %), m.p. 195–197°. (Found: C 66.84; H 3.98; N 6.35. Calc. for C₁₂H₉NOS: C 66.95; H 4.21; N 6.51.)

REFERENCES

1. Grønneberg, T. and Undheim, K. *Acta Chem. Scand.* **26** (1972) . *In press*.
2. Undheim, K., Nordal, V. and Tjønneland, V. *Acta Chem. Scand.* **23** (1969) 1704.
3. Undheim, K. and Reistad, K. R. *Acta Chem. Scand.* **24** (1970) 2956.
4. Undheim, K. and Reistad, K. R. *Acta Chem. Scand.* **24** (1970) 2949.
5. Grønneberg, T. and Undheim, K. *Acta Chem. Scand.* **25** (1971) 2807.
6. Reistad, K. R. and Undheim, K. *Acta Chem. Scand.* **25** (1971) 2954.
7. Undheim, K. and Borka, L. *Acta Chem. Scand.* **23** (1969) 1715.
8. Smith, P. A. S. and Kan, R. O. *Org. Syn.* **44** (1964) 91.

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