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SYNTHESIS OF QUINOLINO HETEROCYCLES*

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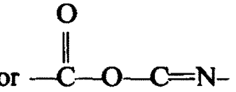
Abstract—Starting from 4-hydroxycarbostyril, a synthesis of 2,3,9,10-tetrahydro-3,10-diketo-quinolino [3.4-b] 1,4-thioxin and 2,3-dihydro-3-keto-9-chloro-4-methyl quinolino [3.2-b] thiazin derivatives has been achieved. The spectral data of the intermediates as well as the final transformation products are discussed.

AMONG the known tricyclic fused quinolino heterocyclic compounds are 2-methyl thiazolo[4.5-c]quinolines,[1] thiazolo[4.5-b]quinolines and thiazolo[5.4-b]quinolines.[2,3] The synthesis of 2,3-dihydro-3-keto quinolino[3.4-b]1,4-thioxin and 2,3-dihydro-3-keto-4H-quinolino[3.2-b]thiazine derivatives are described in this paper.

4-Hydroxy carbostyril (I) was converted to 3,3-dichloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (II) by the method described by Ziegler *et al.*[4] and modified by Baeyer and Bloem.[5] The use of H_2O_2–HCl in dioxan–water mixture brought about the oxidation in excellent yield. The IR spectrum of the dichloro compound II showed the acetophenone carbonyl band at 1740 cm^{-1} and a much stronger amide band at 1705 cm^{-1}. The higher frequency of these bands can be attributed to the *gem*-dichloro effect.

Treatment of II with zinc and acetic acid[4] resulted in the formation of 3-chloro-4-hydroxycarbostyril (III). It was found that the chlorine atom when displaced by the strongly nucleophilic sulfhydryl anion obtained from the sodium salt of ethyl thioglycollate gave an excellent yield of 3-(S-carbethoxymethyl)mercapto-4-hydroxycarbostyril (IV), which shows in the IR spectrum the carbonyl peak of the ester at 1710 cm^{-1} and of the amide as a broad band in the 1660–1638 cm^{-1} region.

After hydrolysis of the above ester, treatment of the acid V, with thionyl chloride gave 2,3,9,10-tetrahydro-3,10-diketo quinolino[3.4-b] 1,4-thioxin (VI). The IR spectrum of this enol lactone shows the carbonyl band at 1785 cm^{-1} which is higher than that expected for γ–δ unsaturated δ-lactones (1760 cm^{-1}) or for  $-\overset{\overset{\large O}{\|}}{C}-O-C{=}N-$ structure (1770 cm^{-1}).[6] The enolic character of the carbonyl in the 4-position of the quinoline–dione molecule is proved by reaction of the lactone with excess of methylamine and formation of primary compound VII with an eneamine structure.

The lactone VI on treatment with excess of methylamine in alcohol gave the quinoline derivative VII; warming with dilute hydrochloric acid gave the quinolinedione derivative VIIIa. The amide could be cyclized using phosphorous oxychloride to the tricyclic compound 2,3-dihydro-3-keto-9-chloro-4-methyl 4(H)-quinolino-

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[3.2-b]thiazine (X). It was found that the optimum conditions for the formation of the tricyclic compound had to be followed rigorously for a successful repetition of the experiment. The formation of X probably is *via* the intermediate dichloro compound IX which is in accord with the greater reactivity of the 2-Cl over 4-Cl in quinoline nucleus.[7] It therefore follows that the cyclization proceeds in the linear fashion to give quinolino[3.2-b]thiazine derivative.

Treatment of VI in an analogous way with alcoholic ammonia and cyclization of the amide VIIIb under conditions described gave the unstable dichloro compound XI which was readily hydrolysed to 2,3-dihydro-3-keto-9-chloro-4(H)-quinolino-[3.2-b]thiazine (XII). The spectral data of XII are in agreement with X.

The effect of alkyl and halogen substituents on the UV spectrum of the quinoline nucleus has been studied by Knight *et al.*[8] It is pertinent to note that in the transformation VIIIa → X, the modified E-band of quinoline shifts from λ_{max} 252 mμ (log ε 4·06) to λ_{max} 268 mμ (log ε 4·66), the peak at 268 mμ being the most prominent peak of the spectrum; the B-band of quinoline shifts from λ_{max} 309 mμ (log ε 4·01) to λ_{max} 352 mμ (log ε 3·98). In the above transformation the length of 1:4 axis of the quinoline molecule is increased owing to the presence of the halogen atom and the length of the axis at right angles to the 1:4 axis of the molecule is also increased owing to the formation of quinolino[3.2-b]thiazine nucleus. It follows therefore that the spectral data of the tricyclic compounds are consistent with the generalizations[9] concerning the spectra of quinoline derivatives.

EXPERIMENTAL

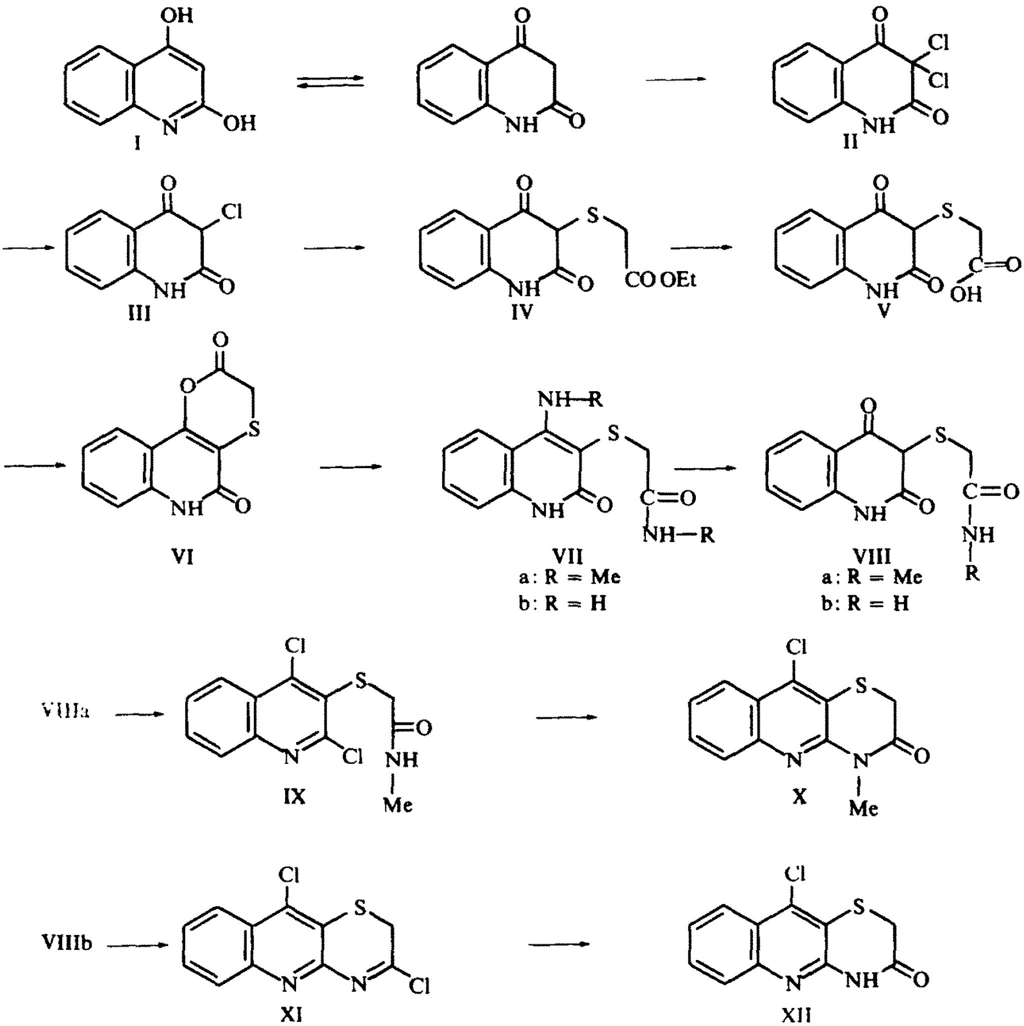
All m.ps were taken in soft glass capillary tubes and are uncorrected. The IR spectra of the samples were examined as Nujol mulls on a Perkin–Elmer Model 237B spectrophotometer. NMR spectra were recorded on a Varian Associates A-60 spectrophotometer (TMS as internal standard). UV measurements were recorded on Beckmann DB model spectrophotometer.

3,3-*Dichloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline*(II). The above compound was prepared starting from the disodium salt of 2,4-dihydroxyquinoline according to the procedure followed by Ziegler *et al.*[3] IR spectrum: 1705 cm^{-1} (C=O bands). UV spectrum (EtOH): 364 mμ log ε 3·63; $\lambda_{infl.}$ 280 mμ log ε 3·63; $\lambda_{infl.}$ 280 mμ log ε 3·66; 240 mμ log ε 4·33. NMR spectrum (CD_3COCD_3): δ = 7·2–8·18 (4 aromatic protons) and δ = 10·82 (NH).

3-*Chloro-4-hydroxycarbostyril* (III). Compound II was reduced with Zn dust and AcOH according to directions given by Ziegler *et al.*,[3] yield 80% m.p. 276°, lit[3] m.p. 273°. IR spectrum: 1660–1675 cm^{-1} (broad) (C=O bands). UV spectrum: 319 mμ log ε 3·98; 288 mμ log ε 3·99; 276 mμ log ε 3·99 and 226 mμ log ε 4·68. NMR spectrum (CF_3—COOH): δ = 7·5–8·33 (4 aromatic protons).

3-(S-*carbethoxymethyl*)*mercapto-4-hydroxycarbostyril* (IV). Ethyl thioglycollate (1·5 g) in EtOH (50 ml was treated with 0·36 g Na metal and to the Na salt so obtained 3 g of III was added and the mixture refluxed for 6 hr. The solvent was evaporated under reduced press and after addition of water residue was filtered off, dried and crystallized from EtOH giving colourless needles, m.p. 178°, yield 3·01 g. IR spectrum: 1710 cm^{-1} ($-\overset{\overset{O}{\|}}{C}-OEt$); 1660–1638 cm^{-1} (broad) (C=O bands). UV spectrum (EtOH): 320 mμ log ε 3·93; 280 mu log ε 3·94; 226 mμ log ε 4·86. NMR spectrum (CF_3—COOH): δ = 1·38 (triplet, C—Me); δ = 4·46 (quartet, $C-O-CH_2-\overset{\overset{O}{\|}}{C}-$); δ = 3·78 (multiplet, $S-CH_2-\overset{\overset{O}{\|}}{C}-O-$); δ = 7·5–8·83 (4 aromatic protons). (Found: C, 55·78; H, 4·64; S, 11·23. $C_{13}H_{13}NO_4S$ requires: C, 55·91; H, 4·70; S, 11·47%.)

3-(S-*carboxymethyl*)*mercapto-4-hydroxycarbostyril* (V). The above ester (10 g) was refluxed with acetone (150 ml), conc HCl (8 ml) and water (50 ml) for 6 hr. The ppt obtained after cooling was filtered off and



crystallized from MeOH to give 8·5 g of colourless crystals, m.p. 245°. The IR spectrum showed the presence of a broad C=O band in 1700–1640 cm^{-1} region. (Found: C, 52·43; H, 3·82; S, 12·91. $C_{11}H_9NO_4S$ requires: C, 52·59; H, 3·61; S, 12·74%.)

2,3,9,10-*Tetrahydro*-3,10-*diketo-quinolino*[3.4-b]1,4-*thioxin* (VI). The acid V (5 g) was suspended in dioxan (50 ml) and $SOCl_2$ (20 g) was added to the stirred soln drop by drop so that the reaction did not become too violent. After this addition, the soln was refluxed for 2 hr (oil bath at 80°). The excess of reagents was evaporated off and the residue washed with water, filtered, dried and recrystallized from acetone–MeOH as colourless crystals, m.p. 300°, yield 3·4 g. IR spectrum: 1785 cm^{-1} and 1640 cm^{-1} (C=O bands). UV spectrum (EtOH): 328 mμ log ε 4·04; 290 mμ log ε 4·01; 228 mu log ε 4·44. NMR spectrum (CF_3—COOH): $\delta = 3{\cdot}85$ (singlet, S—CH_2); $\delta = 7{\cdot}5$–$8{\cdot}25$ (4 aromatic protons). (Found: C, 56·30; H, 3·14; S, 12·37. $C_{11}H_7NSO_3$ requires: C, 56·66; H, 3·03; S, 12·64%.)

3-(S-N-*methylcarboxamidomethyl*)*mercapto-4-hydroxycarbostyril* (VIIIa). The lactone VI (3 g) was stirred with a 33% soln of $MeNH_2$ in MeOH (25 ml) for 3 hr at room temp. The soln was warmed at 50° for 30 min to granulate the amorphous ppt. On recrystallization from MeOH colourless crystals of VIIa were obtained m.p. 178°, yield 2·91 g. NMR spectrum (CF_3—COOH): $\delta = 3{\cdot}0$ (multiplet,  $—\overset{\overset{\large O}{\|}}{C}—NH—CH_3$)

and (C═C—NH—CH_3); δ = 3·86 (singlet, S—CH_2) δ = 7·6–8·5 (4 aromatic protons). (Found: C, 53·23; H, 5·63; N, 14·65. $C_{13}H_{15}N_3SO_2 \cdot H_2O$ requires: C, 52·87; H, 5·80; N, 14·23%.)

The amide VIIa (2·8 g) was warmed at 50° with 0·5N HCl (50 ml) for 20 min and then cooled. The residue was crystallized from EtOH to give colourless crystals of VIIIa m.p. 238°, yield 2·1 g. IR spectrum: 1640–1660 cm^{-1} (C═O); 3280 cm^{-1} (NH); UV (MeOH): 309 mμ log ε 4·01; λ_{infl} 252 mμ log ε 4·06; 221 mμ log ε 4·76. NMR spectrum (CF_3—COOH): δ = 3·1 (singlet $\overset{\overset{O}{\|}}{C}$—NH—Me); δ = 3·9 (multiplet, S—CH_2) δ = 7·6–8·4 (4 aromatic protons). (Found: C, 53·98; H, 4·81; N, 11·10; S, 12·52. $C_{12}H_{12}N_2SO_3$ requires: C, 54·54; H, 4·58; N, 10·60; S, 12·11%.)

3-(*S-carboxamidomethyl*)*mercapto-4-hydroxycarbostyril* (VIIIb). The lactone VI (3 g) was treated with a 30% soln of ammonia in MeOH (50 ml). After treatment with dil HCl, 2·6 g of colourless crystalline material was obtained and recrystallized from MeOH yielding 2·52 g of VIIIb, m.p. 253°. IR spectrum: 1650–1670 cm^{-1} (C═O); 3270 (NH). UV spectrum (MeOH): 310 mμ log ε 4·07; λ_{infl} 252 mμ log ε 4·10. NMR spectrum on the material could not be obtained owing to the very poor solubility in any suitable solvent. (Found: C, 52·68; H, 3·96; N, 10·92; S, 13·13. $C_{11}H_{10}N_2SO_3$ requires: C, 52·80; H, 4·03; N, 11·19; S, 12·79%.)

2,3-Dihydro-3-keto-9-chloro-4-methyl-4(H)*-quinolino*[3.2-b]*thiazin* (X). The amide VIIIa (2·0 g) was suspended in tetrachloroethane (20 ml) and $POCl_3$ (5 ml) was added dropwise. The soln was gently refluxed for 2 hr. Removal of the excess of reagents gave a colourless residue which was treated with cold dil $NaHCO_3$aq. The crystalline material so obtained was filtered off and recrystallized from EtOH to give 1·5 g of X which melted at 170°. IR spectrum: 1670 cm^{-1} (C═O). UV spectrum (MeOH): 352 mμ log ε 3·98; 268 mμ log ε 4·66; 230 mμ log ε 4·14. NMR spectrum (CF_3—COOH): δ = 3·99 (singlet of 5 protons due to coalescing of C—NH—CH_3 and S—CH_2 protons); δ = 7·8–8·3 (4 aromatic protons). (Found: C, 54·49; H, 3·89; N, 11·14; Cl, 13·95. $C_{12}H_9N_2SOCl$ requires: C, 54·45; H, 3·43; N, 11·34; Cl, 13·4%.)

Cyclization of 3-(*S-carboxamidomethyl*)*mercapto-4-hydroxycarbostyril*. The amide VIIIb (1·5 g) was treated with tetrachloroethane (15 ml) and $POCl_3$ (4 ml) and the mixture refluxed gently for 2 hr. Treatment of the residue obtained after removal of excess of reagents in vacuum with cold dil $NaHCO_3$aq gave 1·2 g of a crystalline compound m.p. 74°, presumably the dichloro XI. Treatment of this with sat. $NaHCO_3$aq at room temp and then with EtOH gave 0·95 g of a colourless crystalline material, m.p. 210° which could be assigned structure XII. IR spectrum: 1655 cm^{-1} (C═O); 3300 cm^{-1} (NH). UV spectrum (MeOH): 349, 274 and 224 mμ. Because of the poor solubility of the compound the UV spectra could not be run on a quantitative basis. NMR spectrum (CF_3—COOH): δ = 3·96 (singlet, S—CH_2) δ = 7·8–8·4 (4 aromatic protons). (Found: C, 50·22; H, 3·51; Cl, 13·67. $C_{11}H_7N_2SOCl\frac{1}{2}H_2O$ requires: C, 50·81; H, 3·10; Cl, 14·15%.)

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REFERENCES

[1] G. B. Bachman, D. E. Welton, G. L. Jenkins and J. E. Christian, *J. Am. Chem. Soc.* **69**, 369 (1947).
[2] I. Tănăsesous and I. Dines, *Chem. Ber.* **90**, 495 (1957).
[3] I. Tănăsesous, I. Dines and Gh. Rusu, *Ibid.* **90**, 1295 (1957).
[4] E. Ziegler, R. Salvader and Th. Kappe, *Monatsh Chem.* **93**, 1376 (1962).
[5] E. Baeyer and H. Bloem, *Ber. Dtsch. Chem. Ges.* **15**, 2150 (1881).
[6] S. El Zanfally, M. Khalifa and Y. M. Abon-zeid, *Tetrahedron* **22**, 2308 (1966).
[7] R. J. Rowlett, Jr. and Robert E. Lutz, *J. Am. Chem. Soc.* **68**, 1288 (1946); F. J. Buchmann and C. S. Hamilton, *Ibid.* **64**, 1357 (1942).
[8] S. B. Knight, R. H. Wallick and J. Bowen, *Ibid.* **76**, 3780 (1954); S. B. Knight, R. H. Wallick and C. Balch, *Ibid.* **77**, 2577 (1955).
[9] A. E. Gillam and E. S. Stern, *An introduction to electronic absorption spectroscopy in Organic Chemistry* p. 159. Arnold, London (1957).