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PYRIMIDINES

V. Syntheses of Pyrimodoquinoline Derivatives Based on Tetrahydroquinolone*

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It is shown that it is possible to use heterocyclic ketones to synthesize condensed pyrimidine derivatives in the case of 1-(p-toluenesulfo)-1, 2, 3, 4-tetrahydroquinol-4-one, which on reaction with benzylidene-bisurea gives 2-hydroxy-4-phenyl-6-(p-toluenesulfo)-3, 4, 5, 6-tetrahydropyrimido [5, 4-c] quinoline, and the latter, after dehydrogenation via the 2-hydroxy, 2-chloro derivatives, was converted to 4-phenyl-pyrimido [5, 4-c] quinoline, a new heterocyclic system.

Among condensed heterocyclic compounds containing the pyridine ring, are many which are valuably physiologically active [1], so that undoubted interest attaches to the search for new synthetic routes to compounds of that kind. As was previously shown [2, 3], the reaction of ketones with benzalbisurea (or of an aldehyde with urea), can be utilized to prepare pyrimidine derivatives. We have shown that use in the analogous reaction of a heterocyclic ketone (with a CO group in the ring) as the ketone component, makes it possible to prepare condensed systems with a pyrimidine ring. In the present work, 1, 2, 3, 4-tetrahydroquinol-4-one (I), was used as the ketone. Preliminary experiments showed that condensation of ketone I with benzalbisurea takes place in a more complex manner. Actually this complication is bound up with the fact that I contains a reactive secondary amino group, so subsequently 1-(p-toluenesulfo)-1, 2, 3, 4-tetrahydroquinol-4-one (II) was used. It was thought that the marked electron-accepting character of the tosyl group would enhance ketone reactivity. Actually, condensation of II, benzaldehyde, and urea together in the presence of HCl gave an approximately 80% yield of 2-hydroxy-4-phenyl-6-(p-toluenesulfo)-3, 4, 5, 6-tetrahydropyrimido [5, 4-c] quinoline (III), whose structure was established from its chemical properties, and confirmed by IR spectroscopy data. The IR spectrum of III has absorption bands, indicating the presence of the following groups: $>CH_2$ (1470 cm^{-1}), >CO in ureides (1690 cm^{-1}), =NH in secondary amides (1165, 1350 cm^{-1}), and there were also a number of bands characteristic of aromatic compounds [4].

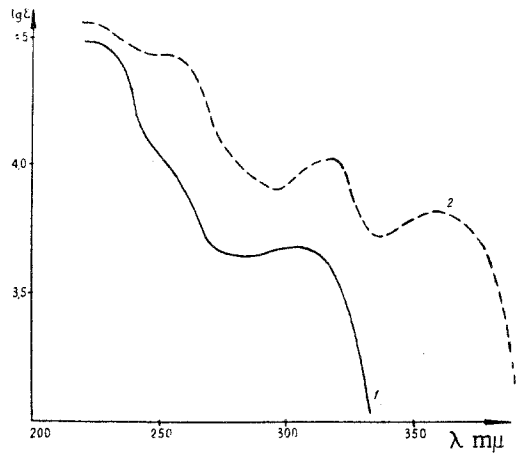


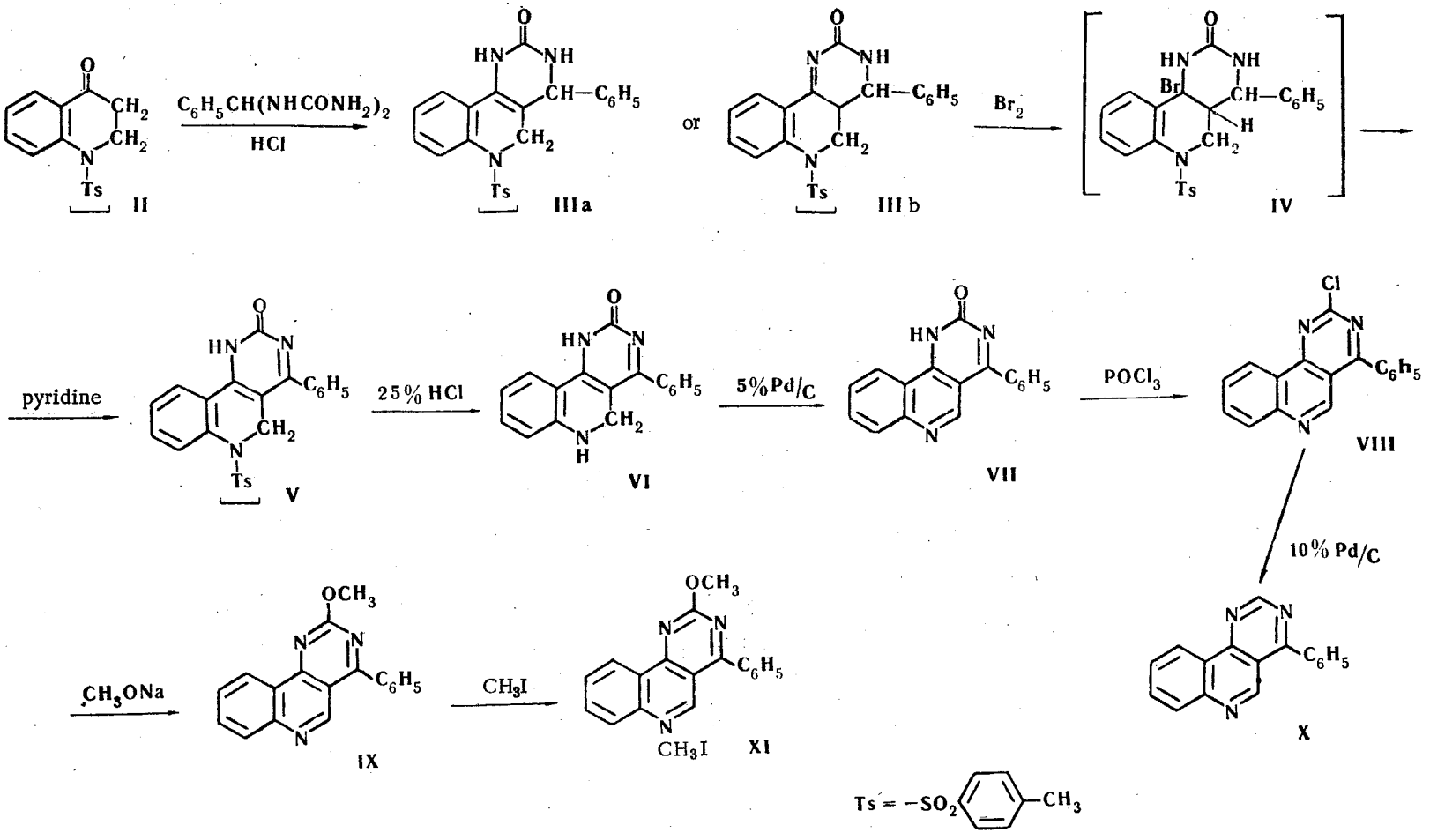
Fig. 1. UV spectra. 1) 2-Hydroxy-4-phenyl-6-(p-toluenesulfo) 3, 4, 5, 6-tetrahydropyrimido-[5, 4-c] quinoline; 2) 2-hydroxy-4-phenyl-6-(p-toluenesulfo)-5, 6-dihydropyrimido [5, 4-c]-quinoline.

Since the reaction studied leads to formation of hydrogenated heterocyclic systems, it is of interest to investigate ways of aromatizing them. Bromination-dehydrobromination [3, 5, 6] is a method which is often used to dehydrogenate pyrimidine derivatives containing a double bond. Application of the method to dehydrogenation of compound III showed that bromination and dehydrobromination proceeded very satisfactorily, (total yield over 70%), but that usually [3] drastic conditions were required for both steps. The resistance to bromination may be connected with a need for prior tautomeric change of IIIb into IIIa (if III contains a considerable amount of isomer with the arrangement of bonds >C=N−) [5]. Still it is more probable that the presence of the toluenesulfamide group is inimical to electrophilic addition to bromine to >C=C<.

In the IR spectrum of the 2-hydroxy-4-phenyl-6-(p-toluenesulfo)-5, 6-dihydropyrimido [5, 4-c] quinoline (V) prepared, the CO absorption band lies on the 1660 cm^{-1} region, i.e., compared with the CO absorption for the tetrahydro derivative III, there was displacement towards the low frequency side. This was expected on account of the carbonyl group's participating in the conjugated chain. In the UV spectrum increase in the degree of conjugation is characterized by a bathochromic shift, and change in the character of absorption in the longwave region (Fig. 1).

Dehydrogenation of the quinoline ring is connected with a need to remove the tosyl group, usually removed by acid hydrolysis [7]. When compound V is boiled with 25% hydrochloric acid, hydrolysis occurs rather easily, to give

* For Part IV see [13].


C6H5CH(NHCONH2)2
HCl
II
IIIa
or
IIIb
Br2
IV
pyridine
V
25% HCl
VI
5%Pd/C
VII
POCl3
VIII
10% Pd/C
X
CH3ONa
IX
CH3I
XI
Ts = −SO2 CH3

2-hydroxy-4-phenyl-5,6-dihydropyrimido-[5,4-c] quinoline (VI). The IR spectrum of base VI lacks sulfamide group absorption bands, and there is a band at 1325 cm^{-1}, corresponding to valence vibrations of a C–N bond of secondary amines. Dehydrogenation of VI was effected by various methods, using chloranil [8], 2% $PdCl_2$ [9], 5% Pd/C in ethylene glycol [10]. A positive result was secured only when dehydrogenating with 5% Pd/C and raising the temperature slowly to 275–280° C. With 2-hydroxy-4-phenylpyrimido [5,4-c]-quinoline formed, aromatization of the system leads to a complicated UV spectrum displaced towards the long wavelength region (Fig. 2).

Replacement of the hydroxyl group by chlorine was effected when VII was treated with phosphorus oxychloride. The chlorine atom in 2-chloro-4-phenylpyrimido [5,4-c] quinoline (VIII) must have quite a high mobility, since in addition to the activating effect of the pyrimidine ring, an additional effect will also be exhibited by the quinoline ring. Enhanced chlorine activity shows itself, for example, in ease of reaction with sodium methoxide, the reaction being quantitative at room temperature, and giving 2-methoxy-4-phenylpyrimido [5,4-c] quinoline (IX). The action of methyl iodide gives 2-methoxy-4-phenylpyrimido-[5,4-c] quinoline methiodide (XI).

The chlorine in chloro derivatives of pyrimidine is best replaced by hydrogen by hydrogenating with 10% Pd/C in the presence of magnesium oxide [11]. When the chloro derivative VIII is hydrogenated under those conditions, 1 mole of hydrogen is absorbed, but a mixture of products is formed. Separation of this mixture by thin-layer chromatography on alumina gave two main products, the starting compound VIII (18%), and 4-phenylpyrimido [5,4-c] quinoline (X) (49%), but along with these are found small amounts of colored products of undetermined nature. Compound X is a colorless crystalline compound which is readily soluble in the usual organic solvents and solvents for acids.

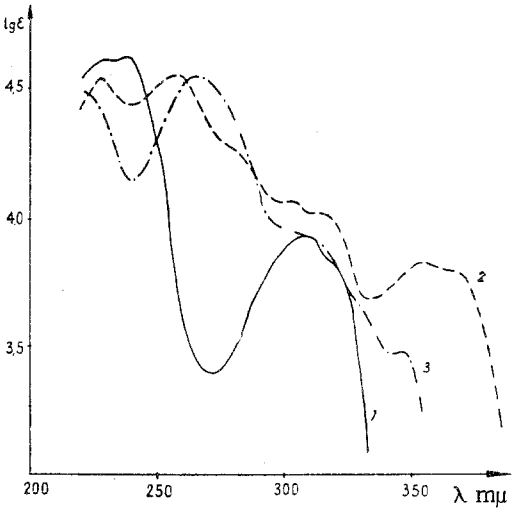


Fig. 2. UV spectra. 1) 2-Hydroxy-4-phenyl-5,6-dihydropyrimido [5,4-c] quinoline; 2) 2-hydroxy-4-phenylpyrimido [5,4-c] quinoline; 3) 4-phenylpyrimido [5,4-c] quinoline.

Experimental

UV spectra were determined with an SF-4 spectrophotometer, the solvent was EtOH, and the concentration of the solution 10^{-4} M. The IR spectra were recorded with a UR-10 spectrophotometer. The specimens were prepared by tabletting with KBr (0.5%).

1-(p-Toluenesulfo)-1,2,3,4-tetrahydroquinol-4-one (II). Obtained [12] in 60–65% yield, mp 141–142° C. The literature [12] gives mp 141–142° C.

2-Hydroxy-4-phenyl-6-(p-toluenesulfo)-3,4,5,6-tetrahydropyrimido-[5,4-c] quinoline (III). a) A suspension of 16.2 g (0.054 mole) preceding compound II, 12.3 g (0.059 mole) benzylidenebisurea in 70 ml dry n-BuOH containing 1.1 g (0.030 mole) dry HCl, were refluxed for 40 min, cooled, the precipitate of minute white needles filtered off, carefully washed with EtOH, and then with ether. Yield III 16.0 g, mp 249–254° C. On standing the filtrate deposited 1.0 g II. After evaporation under reduced pressure, the filtrate gave an additional 2.4 g III. Total yield of III 78–79%, mp 256–257° C (ex EtOH). Very sparingly soluble in the usual organic solvents. Found: C 67.3, 67.4; H 5.02, 5.17; N 9.88, 9.92; S 7.73, 7.92%. Calculated for $C_{24}H_{21}N_3O_3S$: C 67.0; H 4.88; N 9.75; S 7.42%. UV spectrum: λ_{max} (lg ε): 300–308 (3.68); 220–225 (4.48).

b) A suspension of 1.5 g II (0.005 mole), 0.4 g (0.007 mole) urea, 0.5 g (0.005 mole) benzaldehyde in 8 ml dry n-BuOH containing 0.1 g (0.003 mole) HCl, were refluxed for 30 min, and the products worked up as described above, to give a 70–72% yield of III.

2-Hydroxy-4-phenyl-6-(p-toluenesulfo)-5,6-dihydropyrimido [5,4-c] quinoline (V). a) A suspension of 5.5 g III (0.013 mole) in 30 ml glacial AcOH was stirred vigorously, held at 40–50° C, and a solution of 2.2 g (0.027 mole) bromine in 5 ml glacial AcOH slowly added dropwise. After 7 hr the yellow precipitate of bromo derivative was filtered off, washed with glacial AcOH, then with MeOH. The bromo derivative was suspended in 10 ml MeOH and 20 ml pyridine, and refluxed for 2 hr, the mixture cooled, the white precipitate filtered off, washed with MeOH, and then with ether. Yield of V 72–73%, mp 296–297° C (needles ex EtOH). Found: C 67.4, 67.7; H 4.83, 4.67; N 10.1, 10.2; S 7.67, 7.55%. Calculated for $C_{24}H_{19}N_3O_3S$: C 67.1; H 4.47; N 9.78; S 7.46%. UV spectrum: λ_{max} (lg ε) 248–254 (4.42); 316–318 (4.00); 356-318 (3.79). V was very sparingly soluble in the usual organic solvents.

b) 0.8 g bromo derivative was suspended in 2 ml MeOH, 3.5 ml Et_3N added with stirring, after 30 min the white precipitate was filtered off, washed with MeOH, then with ether. Yield of V, 72—73%.

2-Hydroxy-4-phenyl-5,6-dihydropyrimido [5, 4-c] quinoline (VI). A suspension of 1.7 g (0.004 mole) V in 31 ml 25% HCl, was refluxed for 7 hr, the mixture cooled, the blue precipitate filtered off, dissolved in water, neutralized with 10% Na_2CO_3 solution, and the cream precipitate then filtered off, and dried in a vacuum-desiccator over P_2O_5. Yield of VI 0.8 g, mp 264–266° C (colorless needles ex EtOH). The quinoline VI was sparingly soluble in the usual organic solvents. Found: C 74.3, 74.2; H 4.65, 5.07; N 15.3, 15.3%. Calculated for $C_{17}H_{13}N_3O$: C 74.2; H 4.76; N 15.3%. UV spectrum: λ_{max} (lg ε): 234 (4.61); 310 (3.93).

2-Hydroxy-4-phenylpyrimido [5, 4-c] quinoline (VII). A carefully ground mixture of 2.0 g (0.007 mole) VI and 1.0 g 5% Pd/C was heated for 2 hr at 250° C, then for 3 hr at 275–280° C. The reaction products were boiled with 100 ml glacial AcOH, the catalyst filtered off, the filtrate evaporated to dryness under reduced pressure, the residue washed with EtOH, then with ether. Yield of VII 70–72%, mp 359–362° C (decomp, lemon-colored plates from glacial AcOH). VII was soluble in glacial AcOH and dimethylformamide. Found: N 15.0, 15.1%. Calculated for $C_{17}H_{11}N_3O$: N 15.4%. UV spectrum: λ_{max} (lg ε): 228 (4.54); 260 (4.55); 304 (4.05); 3.16 (4.00); 356 (3.82); 368 (3.79).

2-Chloro-4-phenylpyrimido [5, 4-c] quinoline (VIII). A suspension of 0.9 g (0.003 mole) VII in 10 ml (0.065 mole) $POCl_3$ was refluxed for 5 hr, excess $POCl_3$ distilled off under reduced pressure, the residual oil dissolved in benzene, then neutralized, with cooling, with 10% $NaHCO_3$ solution. The benzene layer was separated off, dried over $MgSO_4$, the benzene distilled off under reduced pressure, to give a dry residue, yield of VII 78–80%, mp 170–171° C (needles ex Me_2CO). The quinoline VIII was quite soluble in the usual organic solvents. Found: Cl 11.9, 12.1; N 14.2, 14.3%. Calculated for $C_{17}H_{10}ClN_3$: Cl 12.1; N 14.4%. UV spectrum: λ_{max} (lg ε): 224 (4.61); 270 (4.56); 334 (3.69); 352 (3.64).

2-Methoxy-4-phenylpyrimido [5, 4-c] quinoline (IX). A solution of 0.10 g (0.004 mole) Na in 5 ml dry MeOH was added to a solution of 0.34 g (0.001 mole) VIII in 20 ml dry MeOH, and the mixture carefully stirred for 3 hr at room temperature. The whole was left overnight, then the precipitate filtered off, and washed with water; yield of IX 0.24 g. The filtrate was evaporated under reduced pressure, and the residue extracted with benzene. A further 0.1 g IX was obtained from the benzene solution. Total yield of IX 95%, mp 117–119° C (needles ex petrol ether). Compound IX was readily soluble in the usual organic solvents. Found: C 75.7, 75.1; H 4.57, 4.73; N 14.5, 14.4% . Calculated for $C_{18}H_{13}N_3O$: C 75.3; H 4.56; N 14.6%. UV spectrum: λ_{max} (lg ε): 258 (4.56); 336 (3.68); 350 (3.69).

0.5 g (0.003 mole) MeI was added to a solution of 0.3 g (0.001 mole) IX in 5 ml dry benzene, at room temperature. After 24 hr the crystalline precipitate was filtered off, and washed with EtOH; it was 2-methoxy-4-phenyl [5, 4-c] pyrimidoquinoline XI, yield 0.41 g, mp 200° C (decomp), moderately soluble in water. Found: N 9.93, 9.88%. Calculated for $C_{19}H_{16}IN_3O$: N 9.79%.

4-Phenylpyrimido [5, 4-c] quinoline (X). 0.44 g (0.001 mole) VIII, 0.30 g 10% Pd/C, 0.04 g (0.001 mole) MgO in 40 ml MeOH was hydrogenated at room temperature, under atmospheric pressure, for 5 hr (35 ml hydrogen absorbed). The catalyst was filtered off and washed with ethanol. The total filtrate was evaporated under reduced pressure, and the compounds in the mixed products were separated by thin-layer chromatography on neutral aluminum oxide, activity grade III, the solvent system being benzene-$CHCl_3$ (2:1 by volume). UV light revealed 4 zones: 1st (blue, R_f 0.50–0.65) VIII; 2nd (orange, R_f 0.40–0.50); 3rd (blue, R_f 0.30–0.40), X; 4th (yellow, R_f 0.15–0.30). Repeated separation of the materials in zones 2 and 4, showed that they consisted of compounds VIII and X, along with colored products. Elution with ethanol gave VIII 18%, X 49%, mp of X 146–149° C (needles ex octane). Found: C 79.9, 79.8; H 4.40, 4.40; N 16.5, 16.5%. Calculated for $C_{17}H_{11}N_3$: C 79.4; H 4.30; N 16.3%. UV spectrum: λ_{max} (lg ε): 264 (4.56); 346 (3.43).

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