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Reactivity of 3—Bromoacetyl—1,2,3,4—tetrahydro—2,4—dioxo—1—phenylquinoline Towards Cyclization and Redox Amidation Reactions

by

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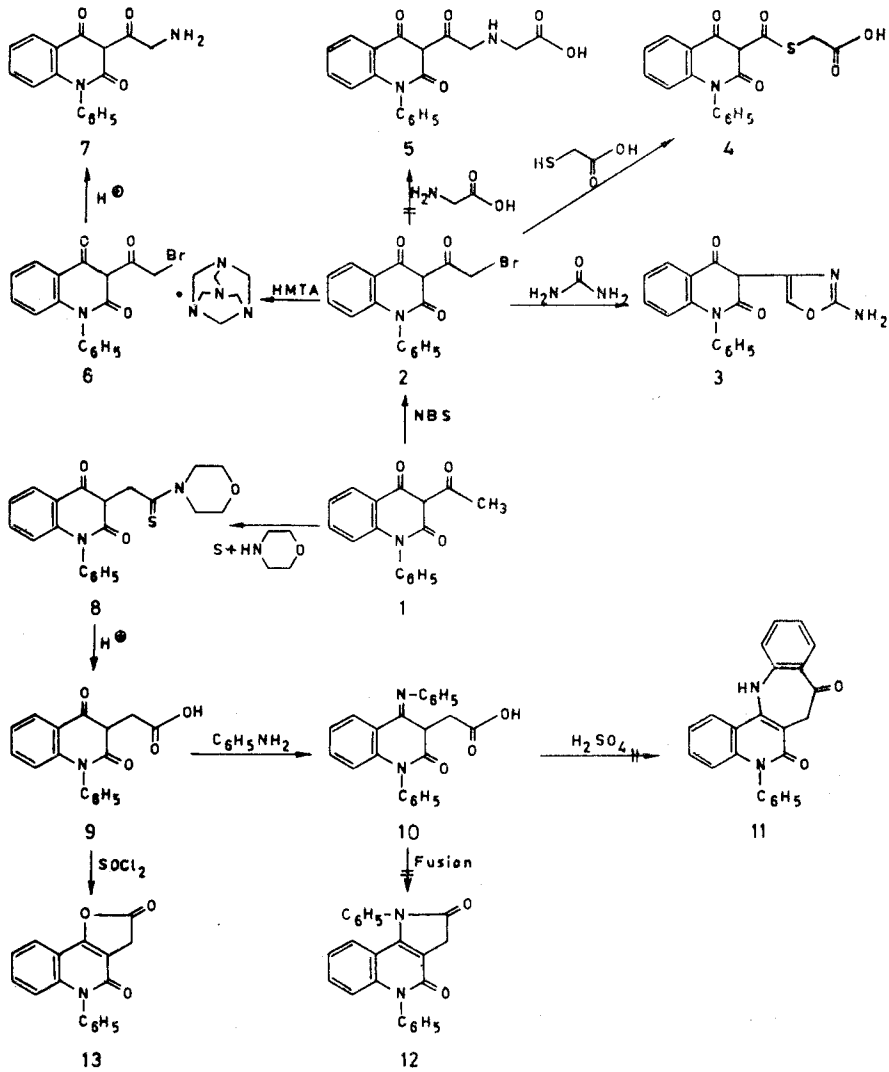
SUMMARY

The bromoacetyl derivative 2 was subjected to cyclization and redox amidation reactions to give 3 and 4, respectively. Also, condensation of 2 with glycine and thioglycollic acid was studied. The acetic acid derivative 9 was obtained from the acetyl derivative 1 following Willgerodt-Kindler conditions. Trials for cyclization of the acid 9 and its anil 10 were also investigated.

The promising pharmacological properties of the oxazole moiety in the field of chemothrerapy[1–3] led us to study and synthesize a new oxazole derivative which incorporates a quinoline moiety. Furthermore, the importance of ∝— haloketones as they serve as a versatile intermediate for the synthesis of heterocyclic compounds emphasized the synthesis of 3— (∝— bromoacetyl) —1,2,3,4— tetrahydro —2,4— dioxo —1— phenylquinoline (2) through the bromination of the corresponding 3— acetyl derivative 1[4] with N—bromosuccinimide (NBS). Thus treatment of compound 2 with urea afforded 3— (2—amino —4— oxazolyl) —1— phenyl —2,4— (1H, 3H) quinolinedione (3). Moreover, treatment of compound 2 with thioglycollic acid gave ((((1,2,3,4— tetrahydro— 2,4— dioxo, —1— phenylquinolyl) carbonyl)— methyl) thio) acetic acid (4). Whereas a similar treatment of 2 with glycine in order to obtain compound 5 failed. However, the glycine fragment was successfully introduced in the three position of the quinoline nucleus via the hydrolysis of the intermediate hexamethylenetetramine salt 6 to give 3—glycyl-1,2,3,4— tetrahydro —2,4— dioxo —1— phenylquinoline (7). Compound 6 was obtained by the action of hexamethylenetetramine (HMTA) upon compound 2.

Following the Willgerodt-Kindler reaction[5,6], the acetylquinoline derivative 1 was converted to 1,2,3,4—tetrahydro —2,4— dioxo —1— phenylquinoline —3— acetic acid (9) via the thiomorpholide derivative 8.

In view of the synthetic approaches based on γ— keto acids as intermediates, the acid 9 was treated with aniline to give the corresponding phenylimino derivative 10. The cyclization reaction of 9 and 10 was investigated as a route for the synthesis of some heterocycles fused to the



quinoline nucleus. Therefore, trials to prepare compounds 11 and 12 through cyclization of 10 either by concentrated sulphuric acid or by fusion were unfruitful. On the other hand, lactonization of 9 to give compound 13 was affected by the use of thionly chloride.

All the synthesized compounds gave satisfactory elemental analysis. Further support of their structures was derived from IR or NMR spectral data.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded using KBr wafer technique on a SP 2000 Pye Unicam spectrophotometer. ^{1}H NMR spectrum was measured on Varian EM-360 (60 MHz) spectrometer. The nomenclature of the compounps described in this paper is in line with the IUPAC rules of organic nomenclature.

3—Bromoacetyl—1,2,3,4— tetrahydro —2,4— dioxoquinoline (2)

A mixture of the acetyl derivative 1 (2.6 g; 0.01 mole), N-bromosuccinimide (1.93 g; 0.01 mole) and catalytic amount of benzoyl peroxide in carbon tetrachloride (40 ml) was refluxed for 6 hr, after which the precipitated succinimide was removed by filteration and the filtrate was cooled. The yellow crystals that formed after short time were removed by filtration then crystallized from benzene to give 2 as a yellow crystals, m.p. 172°C (76 % yield).

3— (2— Amino —4— oxazolyl) —1— phenyl —2,4— (1 H, 3H) quinolinedione (3).

A mixture of 2 (3.6 g; 0.01 mole) in ethanol (50 ml) and urea (0.6 g; 0.01 mole) in water (3 ml) was heated for 2 hr while stirring on a steam bath, after which it was cooled and treated with sodium hydroxide (2.5 g). The mixture was then poured onto water (100 ml), the mass that precipitated was filtered off and crystallized from ethanol to give 3 as a buff crystals, m.p. 222°C (73 % yield). IR (KBr): 3650 (OH, enolic), 3350 (NH_2), 1690—1660 (C = O, amide) and 1620 cm^{-1} (C = N).

((((1,2,3,4— Tetrahydro —2,4— dioxo —1— phenyl —3— quinolyl) carbonyl) —methyl) thio) acetic acid (4).

To a mixture of 2 (28.1 g; 0.1 mole), thioglycollic acid (13.8 g; 0.15 mole) and ethanol (400 ml) was added over a period of 4 hr a solution of sodium hydroxide 12 % (100 ml) while stirring on a steam bath. The reaction mixture was filtered off and the filtrate was neutralized with dilute hydrochloric acid. The orange precipitate that formed was filterted off then washed with water, dried and crystallized from ethanol-mixture (1:1) to give 4 as an orange crystals, m.p. 220°C (85 % yield).

Hexamethylenetetramine salt of compound 2.

To a mixture of powdered hexamethylenetetramine (9.4 g; 0.067 mole), chlorobenzene (57 ml) was added in one portion while stirring a solution of 2 (17 g; 0.061 mole) in chlorobenzene (57 ml). The reaction mixture was heated at 50—52°C for 8 hr, cooled and filtered. The filter cake was stirred with ethanol (40 ml). filtered and washed with ethanol (10 ml). The solid which obtained was crystallized from ethanol to give 6 as a greyish green crystals, m.p. 215°C (65 % yield). Compound 6 was taken without further purification to the next step.

3— Glycyl —1— phenyl —2,4 (1H, 3H) —quinolinedione (7).

To a solution of ethanol (17.5 ml; 95 %) and concentrated hydrochloric acid (8.5 ml) at 25°C was added the hexamethylene-tetramine salt 6 (obtained from 0.02 mole of 2). The resulting suspension was stirred at room temperature for 16 hr, cooled to 5°C and filtered. The crystalline product, which consists of the amine hydrochloride and ammonium chloride, was stirred with water (10 ml) at room temperature then cooled and filtered. The product was dried and crystallized from benzene to give 7 as a grey crystals, m.p. 225°C (45 % yield). IR (KBr): 3650 (OH, enolic), 3350 (NH_2), 1690—1660 (C = O, β—diketone and amide). ^1H NMR (DMSO—d_6): δ 2.5 (s, 2H, —NH_2) and δ 3.0 ppm (S, 2H, CH_2).

1,2,3,4— Tetrahydro —2,4— dioxo —1— phenylquinoline —3— acetic acid (9)

A mixture of 1 (12.8 g; 0.05 mole), sulphur (3.5 g; 0.11 mole) and morpholine (9.7 g; 0.112 mole) was heated gently until hydrogen sulp-

hide gas evolved then refluxed for 14 hr. The reaction mixture was poured onto warm water (40 ml), left to crystallize, the solid which separated was filtered off then washed with cold ethanol to give the morpholide derivative 8, m.p. 305°C. Hydrolysis of the thiomorpholide 8 (13 g; 0.034 mole) was affected by a mixture of glacial acetic acid (27 ml), concentrated sulphuric acid (4 ml) and water (6 ml) through refluxing for 5 hr followed by pouring onto cold water (200 ml) then left to stand overnight. The solid which obtained was digested with a solution of 5 % sodium hydroxide then filtered. The filtrate was acidified with dilute hydrochloric acid. The precipitate that formed was filtered off then washed with water and crystallized from ethanol to give 9 as a brown crystals, m.p. above 315°C (73 % yield).

Reaction of compound 9 with aniline.

A mixture of 9 (3.1 g; 0.01 mole) and aniline (0.93 g; 0.01 mole) in acetic acid (40 ml) was heated on a steam bath for 15—20 minutes. The reaction mixture was left to stand overnight, diluted with water to give a dirty green precipitate which crystallized from acetone-ether mixture (1:1) to give 10 as a dirty green powder, m.p. above 315°C (quantitative yield).

Lactonization of compound 9.

A mixture of 9 (0.4 g; 0.0014 mole) and thionyl chloride (2.5 g; 0.025 mole) was heated on a steam bath for 30 minutes and the excess of thionyl chloride was evaporated under vacuo. The solid which obtained was crystallized from ethanol-benzene mixture (1:1) to give 13 as a brown crystals, m.p. above 315°C (76 % yield).

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