Pyrimido[5,4-*b*]quinolines. II. Reactions at the Heterocyclic Ring-Carbon and Nitrogen Atoms (1)

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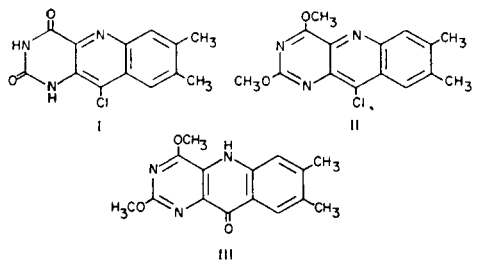
Received March 22, 1977

10-Chloro-7,8-dimethylpyrimido[5,4-*b*]quinolin-2,4(1*H*,3*H*)dione (I) was unreactive toward ammonia but it reacted with 2 molecules of *n*-butylamine, presumably *via* Dimroth-type ring-opening and closure, to give the N_3-butyl,N_{10}-butylamino derivative (IV). In similar reactions of 10-chloro-2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinoline (II) only the 4-methoxyl was displaced by either ammonia or *n*-butylamine. Alkyllithium reagents also displaced the 4-methoxyl as well as added to the 3,4 double bond of II to yield the corresponding *gem*-dialkyl substituted (C_4) derivatives; the C_{10} chlorine remained unreactive. 2,4-Dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinoline-10-one (III) could be alkylated only in the form of the thallium salt. Treatment of the benzyl derivative of III with methylmagnesium bromide led only to the displacement of the 4-methoxyl by a methyl group.

J. Heterocyclic Chem., **14**, 611 (1977).

In a previous paper (2a), we described the syntheses of 2,4,10-substituted-7,8-dimethylpyrimido[5,4-*b*]quinolines, a series of compounds containing the substituted ring system of the hypothetical 9-deaza analog of riboflavin (2b). Subsequent efforts, aimed at the introduction of alkyl or alkylamino side chains into the C_{10} position of compounds I, II and III, have led to some unexpected results which revealed the interesting reactivities of this heterocyclic system; these are described in the present paper.

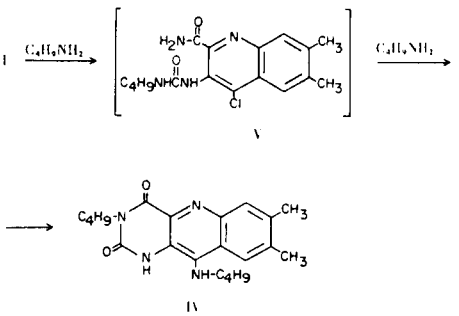


I II III

It was anticipated that the chlorine at C_{10} (γ position of central pyridine ring) of compounds I and II would be similarly reactive and amenable to nucleophilic displacement as are the analogous C_5-chlorine atom of known 5-chloroacridines (3), 5-chloroanthyridines (4), and 5-chloropyrimido[4,5-*b*]quinolines (5) (the latter being ring isomers of the corresponding 10-chloropyrimido[5,4-*b*]-quinolines). However, compounds I and II showed different behavior.

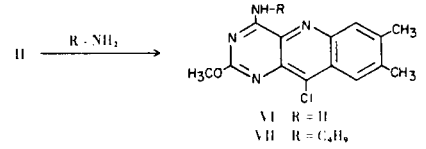
Attempts to react I with methanolic ammonia, or liquid ammonia, in a steel bomb at elevated temperature were unsuccessful, as they led only to the recovery of unchanged starting material. However, when I was heated in a bomb with *n*-butylamine, a product was isolated which, instead of the expected 10-*n*-butylamino-7,8-dimethylpyrimido[5,4-*b*]quinoline-2,4(1*H*,3*H*)dione, was found to be the 3-*n*-butyl derivative IV. A probable reaction mechanism to explain the formation of this product would involve a Dimroth-type opening of the pyrimidine ring at C_2 by the strong base, *n*-butylamine, followed by displacement of the (now more reactive) chlorine of the intermediate 4-chloroquinoline V by a second molecule of *n*-butylamine and concomitant recyclization of the pyrimidine ring with the loss of ammonia (see Scheme I).

Scheme I



I V IV

In the case of compound II, treatment with either methanolic ammonia or *n*-butylamine resulted in facile nucleophilic displacement of the 4-methoxyl group. The chlorine at the 10 position remained unreactive even upon further heating with an excess amount of the reagent.



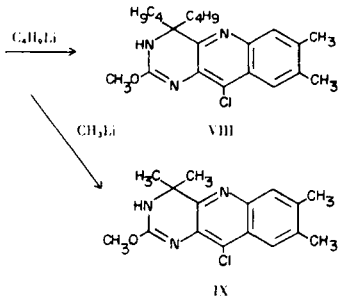
VI R = H
VII R = C_4H_9

It was thought that the chlorine atom in compound II may react with organolithium compounds by undergoing a halogen-metal interconversion, or direct displacement

by an alkyl carbanion. However, when compound II was treated with *n*-butyllithium, the unexpected 10-chloro-4,4-dibutyl-3,4-dihydro-7,8-dimethyl-2-methoxypyrimido-[5,4-*b*]quinoline (VIII) was obtained, as indicated by the ir, nmr and mass spectral data. Subsequently, compound II was treated with excess methyllithium to give a quantitative yield of the analogous 10-chloro-3,4-dihydro-2-methoxy-4,4,7,8-tetramethylpyrimido[5,4-*b*]quinoline (IX) which had the expected mass spectrum (showing, in addition to the molecular ion, an intense peak corresponding to the loss of one methyl group), elemental analysis, and nmr spectrum (showing a 6 proton singlet at δ 1.64 ppm for the geminal methyl groups). Further confirmation of this structure including the position of the geminal methyl groups on the pyrimidine ring, was obtained by X-ray crystallography (6).

In view of the observed lability of the 4-methyl group of II (see above), it seems probable that the first step of the reactions leading to the unusual products VIII and IX, respectively, was displacement of the 4-methoxyl group by an alkyl carbanion, and this was followed by the addition of a second molecule of the alkyllithium reagent to the azomethine linkage (N_3-C_4). The chlorine at the 10 position again failed to participate in the reaction (see Scheme 2).

Scheme 2

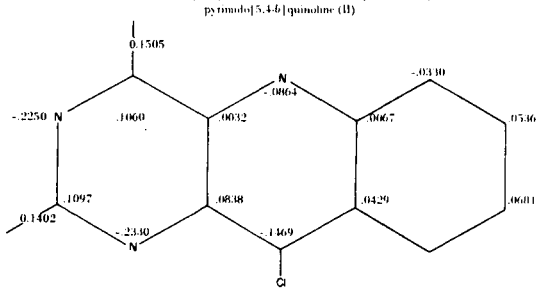


A possible explanation for the lack of reactivity of the chlorine atom at C_{10}, as compared to the facile displacement of the methoxyl group at C_4, may be construed on the basis of the charge density map derived from molecular orbital calculations according to the modified PPP-SCF method of Coburn, *et al.* (7). This shows an unusually high negative charge density at C_{10} which could conceivably cause repulsion of a nucleophilic attack at this position (see Fig. 1). In addition, the superdelocalizability indices for nucleophilic attack at position 2, 4, and 10 are 0.44, 0.63, and 0.03, respectively.

Compound III was considered as the third potential starting material for the synthesis of 10-alkyl substituted derivatives, although both positive (8) and negative (9) results were reported in the literature of the reactions of the analogous carbonyl group in various 5-acridanones with Grignard reagents. Attempts to react III directly

Figure 1

Charge Density Map of 10-Chloro-2,4-dimethoxy-7,8-dimethyl-pyrimido[5,4-*b*]quinoline (II)



with methyllithium or methylmagnesium iodide failed because of the poor solubility of III in ethereal solvents and/or possible tautomerization of the 4-pyridone moiety. Several attempts were made to alkylate, or acylate III in the N_5 position. However, the strongly alkaline reaction conditions used in the case of the acridanones (9b) could not be applied due to the lability of the 4-methoxyl group. Thus, either the starting material was recovered unchanged or the previously described (2a) 2-methoxy-4-hydroxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-10-one was isolated from the reaction mixtures.

Finally, application of the thallium method of Taylor (10) was investigated. The thallium salt of III was readily formed and precipitated from absolute ethanol; it was suspended in dimethylformamide and reacted with benzyl bromide. The purified product, obtained in 62% yield, gave the correct analysis for the benzyl derivative of III. Since, in the alkylation of heterocyclic amides *via* the thallium salts, conducting the reaction at low temperature generally favors *N*-alkylation over *O*-alkylation (11), it was presumed that the benzylation would occur at N_5; however, the spectral data obtained did not permit unambigous assignment of the position of the benzyl group. Treatment of the benzyl derivative with an excess of methylmagnesium bromide led to displacement of the 4-methoxyl group by a methyl group, but no reaction occurred at C_{10}. Thus, our efforts to introduce an alkyl side chain at the C_{10} position of the preformed tricyclic system remained unsuccessful.

EXPERIMENTAL

All melting points were taken by the capillary method on a Mel-Temp apparatus and those below 230° are corrected. Ultraviolet spectra were determined on Perkin-Elmer Model 202 and Beckman DB-G spectrophotometers. Microanalyses performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nuclear magnetic resonance spectra were determined on a Varian A-60 spectrophotometer, using tetramethylsilane (TMS) as an internal standard except with trifluoroacetic acid solvent in which case TMS in chloroform was used as an external standard. Proton signals are reported in ppm downfield from TMS and are corrected. The mass spectra were recorded on a Perkin-Elmer Hitachi RMU 6D spectrometer (70 eV) using glass inlet insertion.

Attempted Amination of 10-Chloro-7,8-dimethylpyrimido[5,4-*b*]-quinolin-2,4(1*H*,3*H*)dione (I).

Compound I (100 mg.) was placed in a bomb with 25 ml. of 20% methanolic ammonia. The bomb was heated at 90° in an oil bath for 3 days. After evaporation, crystallization of the residue from tetrahydrofuran gave only starting material (80 mg.).

When liquid ammonia was used (5 ml.) instead of methanolic ammonia, no reaction was observed and starting material was recovered.

3-Butyl-10-butylamino-7,8-dimethylpyrimido[5,4-*b*]quinoline-2,4-(1*H*,3*H*)dione (IV).

10-Chloro-7,8-dimethylpyrimido[5,4-*b*]quinoline-2,4(1*H*,3*H*)-dione (I) (100 mg.) was heated in a bomb with 5 ml. of *n*-butylamine at 150-160° for 3 days. The yellow solution was evaporated to dryness and the residue crystallized from methanol to yield 60 mg. (53%) of pale yellow plates, m.p. 216-217°; uv λ max (methanol): nm, 254, 305, 318, 353, 367; ir ν (potassium bromide): 3350 (broad) (NH), 1735 (imide-C_4) and 1665 cm^{-1} (ureido-C_2); nmr (deuteriochloroform): δ 7.89 (2, s, Ar-H), 4.35 (2, t, N_3-butyl, CH_2) 3.50 (2, t, BuNH,CH_2) 2.50 (6, s, CH_3), 1.68 (8, m, CH_2CH_2), 1.00 (6, t, CH_3).

Anal. Calcd. for $C_{21}H_{28}N_4O_2$: C, 68.35; H, 7.66; N, 15.20. Found: C, 68.49; H, 7.32; N, 15.08.

4-Amino-10-chloro-7,8-dimethyl-2-methoxypyrimido[5,4-*b*]quinoline (VI).

10-Chloro-2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinoline (II) (67 mg.) was placed in a bomb with 15 ml. of 20% methanolic ammonia and heated in an oil bath at 90° for 4 hours. Filtration of the mixture and washing with methanol gave yellow crystals. Recrystallization from 1,2-dimethoxyethane gave the analytical sample (50 mg.), m.p. 286-288° dec. An additional 4 days at 100° produced no further reaction; uv λ max (methanol): nm, 257, 325, 340, 370, 389, 410; ir ν (potassium bromide): 3510 cm^{-1} (NH_2); nmr (TFA): δ 7.93 (1, s, Ar-H), 7.85 (1, s, Ar-H), 4.04 (3, s, OCH_3), 2.32 (6, s, CH_3).

Anal. Calcd. for $C_{14}H_{13}N_4ClO$: C, 58.24; H, 4.54; N, 19.40; Cl, 12.28. Found: C, 58.12; H, 4.69; N, 19.23; Cl, 12.05.

4-Butylamino-10-chloro-7,8-dimethyl-2-methoxypyrimido[5,4-*b*]-quinoline (VII).

10-Chloro-2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinoline (II) (100 mg.) was dissolved in 1 ml. of *n*-butylamine by warming on a steam bath. The canary yellow solution was evaporated to dryness and the residue crystallized from petroleum ether to yield 85 mg. (75%) of yellow crystals, m.p. 129-130°; uv λ max (methanol): nm, 257, 293, 327, 342, 375 sh, 391, 405; ir ν (potassium bromide): 3300 (NH), 1610 cm^{-1} (aromatic); nmr (deuteriochloroform): δ 8.02 (1, s, Ar-H), 7.83 (1, s, Ar-H), 7.58 (1, br, NH), 4.19 (3, s, OCH_3), 3.75 (2, t, CH_2), 2.49 (6, s, CH_3), 1.60 (4, m, CH_2), 1.00 (3, t, CH_3).

Anal. Calcd. for $C_{18}H_{21}N_4ClO$: C, 62.69; H, 6.14; N, 16.25; Cl, 10.28. Found: C, 62.60; H, 6.06; N, 15.90; Cl, 9.98.

10-Chloro-4,4-dibutyl-3,4-dihydro-7,8-dimethyl-2-methoxypyrimido[5,4-*b*]quinoline (VIII).

10-Chloro-2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinoline (II) (200 mg.) was dissolved with heating in 50 ml. of freshly distilled (sodium hydride, oil bath) tetrahydrofuran, cooled to 0° and kept under nitrogen atmosphere. *n*-Butyllithium (0.8 ml. of 1.6 *M* in hexane) was added by syringe through a septum and the solution was stirred for 4 hours. The reaction was quenched by adding 1 *N* hydrochloric acid and ice, and the mixture was extracted with ether. The extracts were dried over magnesium sulfate, filtered and evaporated to yield a yellow crystalline residue. The residue was chromatographed on silica gel using benzene as eluent, to give a white crystalline product. Recrystallization from isopropyl alcohol gave white plates, m.p. 165-167°; uv λ max (methanol): nm, 230, 278, 300, 362; ir ν (potassium bromide): 3450 cm^{-1} (NH); nmr (deuteriochloroform): δ 7.91 (1, s, Ar-H), 7.75 (1, s, Ar-H), 4.60 (broad, 1, s, NH), 4.02 (3, s, OCH_3), 7.91 (1, s, Ar-H), 7.75 (1, s, Ar-H), 4.60 (broad, 1, s, NH), 4.02 (3, s, OCH_3), 2.45 (6, s, CH_3), 1.20 [12, m, $(CH_2)_3$], 0.80 (6, t, CH_3); mass spectrum: m/e 387 (M.W.), m/e 330 ($-C_4H_9^-$).

Anal. Calcd. for $C_{22}H_{30}N_3ClO$: C, 68.11; H, 7.79; N, 10.83; Cl, 9.14. Found: C, 69.11; H, 7.71; N, 10.87; Cl, 9.41.

10-Chloro-3,4-dihydro-2-methoxy-4,4,7,8-tetramethylpyrimido-[5,4-*b*]quinoline (IX).

10-Chloro-2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinoline (II) (200 mg.) was dissolved in 60 ml. of freshly distilled THF (sodium hydride). After cooling the solution to 0° under a nitrogen atmosphere, 1 ml. of 2.3 *M* methyllithium in ether was added through a septum. The reaction was quenched after 40 minutes by adding water and 1 *N* hydrochloric acid until the *p*H became acidic. The orange solution was extracted with chloroform, and the extract was washed with water, then dried over magnesium sulfate. Evaporation gave pale yellow crystals that were recrystallized from either acetone or *n*-hexane, m.p. 158-160°; uv λ max (methanol): nm, 230, 272, 300, 355; ir ν (potassium bromide): 3480 and 3290 cm^{-1} (NH); nmr (deuteriochloroform); δ 7.90; (1, s, Ar-H), 7.74 (1, s, Ar-H), 4.83 (broad, 1, s, NH), 4.02 (3, s, OCH_3), 2.45 (3, s, $ArCH_3$), 2.43 (3, s, $ArCH_3$), 1.64 (6, s, CH_3); mass spectrum: m/e 303 (M.W.), m/e 288 ($-CH_3^-$).

Anal. Calcd. for $C_{16}H_{18}N_3ClO$: C, 63.26; H, 5.97; N, 13.83; Cl, 11.67. Found: C, 62.96; H, 6.01; N, 13.77; Cl, 11.68.

Thallium Salt of 2,4-Dimethoxy-7,8-dimethylpyrimido[5,4-*b*]-quinolin-10-one.

Compound III (2.85 g., 0.01 mole) was dissolved in 1 liter of absolute ethanol and then thallium ethoxide (2.49 g., 0.01 mole) was added at once to the above ethanolic solution. The yellow precipitate (which formed immediately after addition of the thallium ethoxide) was stirred for 2-3 hours, and then filtered to yield 4.56 g. (94%) of yellow crystals. This compound was used for the next reaction without purification; ir ν (potassium bromide) 1592 cm^{-1}, NH band (3400 cm^{-1}) absent; nmr (TFA): δ 7.88 (1, s, Ar-H), 7.33 (1, s, Ar-H), 4.20 (3, s, OCH_3), 4.05 (3, s, OCH_3), 2.13 (3, s, CH_3), 2.10 (3, s, CH_3).

Benzylation of the Thallium Salt of III.

A suspension of the thallium salt of III, (3 g., 0.0061 mole) and 5 ml. of benzyl bromide in DMF was stirred for 3 days at room temperature, and the reaction mixture was poured into water. The yellowish precipitate was collected by filtration and washed with hexane (b.p. 68.7°) in order to remove the residual benzyl bromide. Recrystallization from a mixture of methanol-1,2-dimethoxyethane gave 1.5 g. (65%) of the benzyl derivative of III, m.p. 165-167°; uv λ max (ethanol): nm, 264 (ε, 68,230), 324 (sh) (ε, 7,310), 340 (ε, 8,920), 375 (ε, 9,080), and 396 (ε, 7,850); ir ν (potassium bromide): 1610 cm^{-1} (C=O), NH band (3400 cm^{-1}) has disappeared; nmr (TFA): δ 7.83 (1, s, Ar-H), 7.30 (1, s, Ar-H), 6.95 (5, s, Ar-H) 4.98 (2, s, CH_2) 4.20 (3, s, OCH_3), 4.03 (3, s, OCH_3), 2.08 (6, s, CH_3).

Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.10. Found: C, 70.18; H, 5.69; N, 11.19.

Reaction of the Benzyl Derivative of III with a Grignard Reagent.

Methylmagnesium bromide (0.75 ml., 0.0015 mole, 2*M* ether solution) was added to a 1,2-dimethoxyethane solution (20 ml.) of the benzyl derivative of III (188 mg., 0.0005 mole) under nitrogen atmosphere at room temperature. The reaction mixture

was gradually warmed to 40-50° and was maintained at this temperature for 15 hours, then poured into 250 ml. of saturated ammonium chloride solution. The brownish crystals were collected, 150 mg. m.p. 152-154°; uv λ max (ethanol): nm, 267 (ε, 60,250); ir ν (potassium bromide): 1592 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (1, s, Ar-H), 7.90 (1, s, Ar-H); 7.50 (5, broad, Ar-H), 6.10 (2, s, CH_2), 4.12 (3, s, OCH_3), 3.10 (3, s, CH_3), 2.45 (6, s, CH_3).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.12; H, 6.08; N, 11.64.

REFERENCES AND NOTES

(1) This work was supported by a U. S. Public Health Service research grant (No. CA-06695) from the National Cancer Institute.

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