A Facile One-Step Synthesis of Certain 4-(4-Pyrimidinylmethyl)quinazolines

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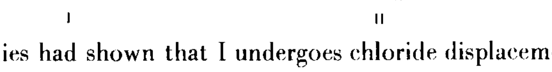
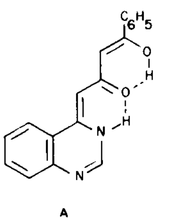
As part of a program directed toward the synthesis of potential new antimalarial agents containing both a quinazoline and a pyrimidine nucleus, we had need of a general method for the preparation of 4-(4-pyrimidinylmethyl)-quinazolines of type IV. An attractive route to this new class of compounds appeared to lie in reaction of 1,3-dialkali salts of appropriate β-diketones with 4-chloroquinazoline to form 4-quinazolinyl diketones II, which could then be cyclized with urea to form IV. Previous studies had shown that I undergoes chloride displacement with monoketone enolates (3), and we had recently (4) found that reaction of dialkali salts of benzoylacetone with 2-chloroquinoline resulted in regiospecific introduction of the 2-quinolyl moiety at the terminal methyl site of the diketone. Since the latter process represented the first reported example of the reaction of a 1,3-dicarbanion with a halogenated heterocycle, we were anxious to pursue the above approach not only as a route to compounds IV, but also to gain further insight into the generality of such reactions.

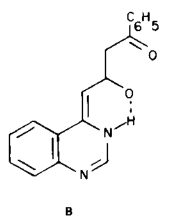


I II

Reaction of I with disodiobenzoylacetone (5) in liquid ammonia proceeded smoothly to afford diketone II in 60% yield (6). Combustion and mass spectral analyses were consistent with the gross structural features of II. However, the ^{1}H nmr spectrum indicated that II exists in deuteriochloroform solution as a mixture of two enolic tautomers, **A** and **B**, in a ratio of *ca.* 3:1. On the basis of spectral precedents established with related compounds (3,7) the major tautomer appears to be the doubly hydrogen bonded (7d) form **A**, which contributes OH absorption at 19.12, broad NH absorption at 14.68, and vinyl singlets at 6.58 and 6.36 δ. The minor tautomer, **B**, exhibits NH absorption at 14.68 overlapping with that of **A**, a vinyl singlet at 6.68 and a singlet at 4.30 δ for methylene protons. The integrated intensities of all the aforementioned peaks were consistent with these assignments. (See Experimental). Moreover, the NH and OH peaks disappeared rapidly upon addition of deuterium oxide. The absence of absorption for methylene protons at the 4-position of the β-dicarbonyl side chain (7a), and the lack of low field absorption for the proton at the 2-position of the quinazoline nucleus (3) supported the fact that C-4 of the side chain possesses exclusively vinyl character in both tautomeric forms.

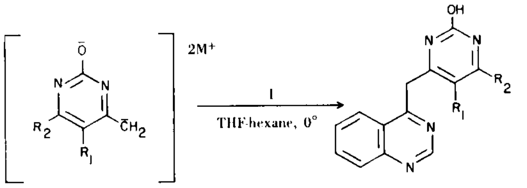


A



B

Attempts to effect acid-catalyzed cyclization of II with urea were complicated by formation of a mixture of products. Because of this, we turned our attention to approaches which would allow incorporation of the preformed pyrimidine nucleus into compounds IV. It seemed possible that dialkali salts, IIIa and IIIb, which are known (8) to react selectively with various electrophiles at the exocyclic carbanion site, might serve as a convenient source of the desired 4-pyrimidinylmethyl moieties of IVa-b. Indeed this proved to be the case, for when I was added to a solution of dilithio salts IIIa or IIIb (M = Li) in THF-hexane a 0°, displacement of chloride from I by the side chain carbanion occurred to produce IVa and IVb in yields of 66 and 46%, respectively. Similarly, disodio salts IIIa and IIIb (M = Na), prepared from the parent hydroxy pyrimidines by means of sodium amide in liquid

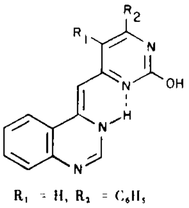


IIIa, R_1 = H, R_2 = C_6H_5
b, R_1 = C_6H_5, R_2 = CH_3

IVa, R_1 = H, R_2 = C_6H_5
b, R_1 = C_6H_5, R_2 = CH_3

ammonia, reacted with I to afford IVa and IVb in yields of 45 and 36%, respectively.

The ^1H nmr (trifluoroacetic acid) spectra of IVa-b indicate that these compounds exist entirely in the 4(3*H*)-quinazolinylidene forms **C** and **D** in this solvent. The total absence of methylene proton resonance, the presence of absorption for 1 vinyl hydrogen, and the fact that all other protons except the labile NH and OH hydrogens can be accounted for in terms of chemical shifts and intensities, (see Experimental) support these structural assignments. The appearance of resonance for the C-2 protons of the quinazoline rings of **C** and **D** at lower field than expected in a tautomer where the aromatic character of the heterocyclic ring is diminished (3), is attributed to protonation of N-1, which effects deshielding of these hydrogens (7c). The electronic spectra of IVa and IVb were characterized by intense, visible absorption bands, which are indicative of similar extended conjugation in related quinazolines (3).



C, $R_1 = H, R_2 = C_6H_5$
D, $R_1 = C_6H_5, R_2 = CH_3$

EXPERIMENTAL

Melting points were taken on a Mel-Temp melting point apparatus in sealed capillary tubes and are uncorrected. Elemental analyses were performed in this department by Q. H. Tan and T. E. Glass using a Perkin Elmer Model 240 Elemental Analyzer. Infrared spectra were taken on Beckman IR-5A and IR-20AX spectrophotometers. Uv-visible spectra were obtained with a Cary-14 spectrophotometer using 95% ethanol as the solvent. ^1H nmr spectra were determined with a JEOL JHM-PS-100 spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. Chemical shift assignments in the spectra of II and IVa-b were aided by comparisons with the spectra of freshly prepared samples of I (deuteriochloroform), 4(3*H*)quinazolinone (DMSO-d_6 and trifluoroacetic acid), 2-hydroxy-4-methyl-6-phenylpyrimidine (trifluoroacetic acid), and 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine (trifluoroacetic acid). Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer at 50 ev. *n*-Butyllithium, as a 2.04 *M* solution in hexane, was used as received from Ventrom Co., Alpha Products, Beverly, Mass. Liquid ammonia, obtained from the Matheson Co., E. Rutherford, N.J., was dried prior to use by distillation from potassium metal. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately prior to use. All other chemicals were prepared by published procedures or obtained as commercial reagent grade and used without further purification.

1-Phenyl-4-(4-quinazolinyl)-1,3-butanedione (II).

To a stirred suspension of 0.10 mole of sodium amide, prepared from 2.30 g. of sodium and a trace of hydrated ferric nitrate in 300 ml. of liquid ammonia, was added 8.12 g. (0.05 mole) of benzoylacetone as a solution in 100 ml. of anhydrous ether. After 30 minutes, the green solution was assumed to contain 0.05 mole of disodiobenzoylacetone (5). A 4.06 g. (0.025 mole) sample of I (9) in 100 ml. of ether was then added. After 1 hour the reaction was quenched by addition of 0.2 mole of solid ammonium chloride. The ammonia was evaporated (steam bath) as 100 ml. of dry ether was added. Addition of cold water (100 ml.) to the ethereal suspension, resulted in separation of a dark brown solid at the interface. This material was collected and recrystallized from 95% ethanol to afford 4.35 g. (60%) of II, m.p. 141-5-142°; ir (potassium bromide): 1660 (m), 1600 (s), 1540 (s) cm^{-1}; ^1H nmr (deuteriochloroform): δ 19.12 (s, 0.75, enol OH) 14.68 (broad s, 1, chelated NH), 8.28 (m, 10, aromatic), 6.68 (s, 0.25, vinyl proton of **B**), 6.58 (s, 0.75, vinyl proton of **A**), 6.36 (s, 0.75, vinyl proton of **A**), 4.30 (2, 0.5, diketone CH_2); mass spectrum: *m/e* 290 (M^+) with abundant peaks at 129 and 77.

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.87; N, 9.62. Found: C, 74.64; H, 4.73; N, 9.65.

When the above reaction was repeated using 0.025 mole of disodiobenzoylacetone and 0.025 mole of I the isolated yield of II was 3.8 g. (52%).

4-(2-Hydroxy-6-phenyl-4-pyrimidinylmethyl)quinazoline (IVa).

To a stirred suspension of 0.56 g. (3 mmoles) of 2-hydroxy-4-methyl-6-phenylpyrimidine (10) in 35 ml. of anhydrous THF at 0° under nitrogen was added 5.1 ml. (8 mmoles) of *n*-butyllithium in hexane. The dark red-brown solution of dilithio salt IIIa (8) was stirred for 30 minutes before addition of 0.54 g. (3.3 mmoles) of I in 10 ml. of THF. The reaction mixture was stirred at 0° for 2 hours and then 100 ml. of cold water was added. The organic phase was separated and discarded. The remaining aqueous layer was neutralized (*p*H 6.5) with 6*N* hydrochloric acid. The resulting brown precipitate was collected by filtration and recrystallized from dimethylformamide to give 0.62 g. (66%) of IVa, m.p. 310° dec.; ir (potassium bromide): 3340 (m), 1640 (s) cm^{-1}; λ max ($\epsilon \times 10^{-3}$): 428 (97.5), 445 nm (112); ^1H nmr (trifluoroacetic acid): δ 9.04 (s, 1, quinazoline H_2), 8.20 (d, 1, J = 5 Hz, quinazoline H_5), 7.90 (m, 8, aromatic), 7.21 (s, 1, pyrimidine H_5), 6.85 (s, 1, vinyl); mass spectrum: *m/e* 314 (M^+) with abundant fragment peaks at 185 and 129.

Anal. Calcd. for $C_{19}H_{14}N_4O$: C, 72.61; H, 4.46; N, 17.83. Found: C, 72.81; H, 4.16; N, 17.92.

When the above reaction was repeated using 6 mmoles of IIIa (M = Li) the isolated yield of IVa dropped to 33% because of difficulty in removing unreacted starting material from the curde product.

Dianion IIIa (M = Na) was prepared by adding 5.2 g. (28 mmoles of the hydroxy pyrimidine as a solid to 56 mmoles of sodium amide in 700 ml. of anhydrous ammonia. After being stirred for 30 minutes, the dark red solution was assumed to contain 28 mmoles of IIIa (M = Na). A solution of 4.2 g. (28 mmoles) of I in 100 ml. of ether was added and the mixture stirred for 1 hour. The reaction was neutralized with solid ammonium chloride and processed as in the reaction of disodiobenzoylacetone described above. The crude product, which appeared at the ether-water interface, was collected and recrystallized from dimethylformamide to give 3.6 g. (45%) of IVa.

4-(2-Hydroxy-6-methyl-5-phenyl-4-pyrimidinylmethyl)quinazoline (IVb).

This compound was prepared from dilithio salt IIIb and I as described above for IIIa. Recrystallization (95% ethanol) of the crude product, which precipitated upon acidification of the aqueous layer, afforded 0.45 g. (46%) of IVb, m.p. 320-321° dec.; ir (potassium bromide): 3330, 1640 cm^{-1}; λ max ($\epsilon \times 10^{-3}$): 400 (24), 420 (42.7), 442 nm (46.3); ^{1}H nmr (trifluoroacetic acid): δ 8.92 (s, 1, quinazoline H_2), 7.69 (m, 9, aromatic), 6.35 (s, 1, vinyl), 2.37 (s, 3, pyrimidine CH_3); mass spectrum: *m/e* (M$^+$) with abundant fragment peaks at 198 and 129.

Anal. Calcd. for $C_{20}H_{16}N_4O$: C, 73.17; H, 4.84; N, 17.07. Found: C, 73.43; H, 4.95; N, 17.02.

Reaction of dianion IIIb (M = Na) in liquid ammonia with I gave IVb in 36% yield.

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