Benzo[*h*]-1,6-naphthyridines by Ynamine-Isocyanate Addition (1)

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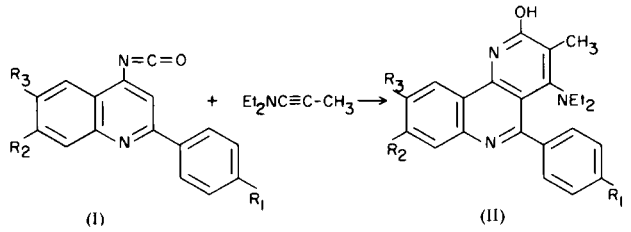
Interest in various benzonaphthyridines as potential anti-parasitic agents has stimulated synthetic efforts in this area (2,3). Since an aryl group alpha to nitrogen in quinoline-based antimalarials is known to enhance anti-parasitic activity--presumably by blocking *in vivo* oxidative metabolism at C-2, it therefore appears a desired structural feature in higher homologs (4). However, in our laboratory and at the hands of other (2) considerable difficulty has been experienced in cyclizing 2-aryl-4-amino-quinolines by Conrad-Limpach, Knorr, or Gould-Jacobs methods to 5-arylbenzo[*h*]-1,6-naphthyridines. The low yields and unsuccessful condensations appear to be the result of the bulky aryl moiety since 4-aminoquinolines, unsubstituted at C-2, are known to cyclize readily (5).

Ficini has shown that a direct and high yield synthesis of quinolines results from the condensation of aryl isocyanates and ynamines (6). Applied to 4-quinoline isocyanates, the Ficini reaction yielded us 2-hydroxy-3-methyl-4-diethylamino-5-arylbenzo[*h*]-1,6-naphthyridines (IIa-d) in one step. Furthermore, it was not necessary to isolate the requisite 4-quinoline isocyanates for these could be generated *in situ* by thermal rearrangement of the cinchoninyl azides in refluxing anhydrous benzene. The azides displayed an intense band at 2140 ± 10 cm^{-1} in the infrared spectra and the progress of their rearrangement to the isocyanates could be monitored by the diminution of this absorption. The 3 hour reflux suggested in the general experimental procedure appears more than sufficient to rearrange fully the azides studied.

Evaluation of the benzonaphthyridines (IIa-d) in mice infected with *P. berghei* (7) revealed only modest activity for IIc at 640 mg./kg., the highest dose employed. A slight prolongation of life, 3.3 days, was observed in the treated-infected mice compared to the untreated-infected controls which expired in 6.5 days. All other benzonaphthyridines were totally inactive.

TABLE

Benzonaphthyridines



(I) (II)

Compound Number	R_1	R_2	R_3	Yield %	M.p. °C	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	H	H	H	68 (a)	269-270	$C_{23}H_{23}N_3O$	77.28	6.48	11.76	77.47	6.49	11.85
IIb	H	H	Br	61 (b)	327-329	$C_{23}H_{22}BrN_3O$	63.31	5.08	9.63	63.20	5.29	9.66
IIc	Cl	Cl	OMe	62	344-346	$C_{24}H_{23}Cl_2N_3O_2$	63.16	5.08	----	63.43	5.07	----
IId	Br	H	OMe	54	332-334	$C_{24}H_{24}BrN_3O_2$	61.81	5.19	9.01	62.08	5.12	8.87

(a) Azide precursor prepared as described by H. John, *Ber.*, 59B, 1447 (1926). (b) Azide synthesized as reported by K. Feist and M. Kuklinsk, *Arch. Pharm.*, 274, 244 (1936).

EXPERIMENTAL

Melting points were obtained in capillaries in a Mel-temp apparatus and are reported uncorrected. Combustion analyses were provided by Dr. George I. Robertson, Florham Park, New Jersey.

Preparation of 2-(4′-Bromophenyl)-6-methoxycinchoninic Acid.

A mixture of 5-methoxyisatin (27.0 g., 153 mmoles), *p*-bromoacetophenone (33.0 g., 166 mmoles), 90 ml. of 33% aqueous potassium hydroxide and 190 ml. of ethanol was stirred at reflux for 7 hours. The medium was cooled, adjusted to *p*H 1 with 6*N* hydrochloric acid, and the precipitated acid collected. Recrystallization from methanol gave 8.84 g. (16%) of the desired acid, m.p. 265-283°. The analytical sample was prepared by a second recrystallization from ethyl acetate, m.p. 282.0-282.5°.

Anal. Calcd. for $C_{17}H_{12}BrNO_3$: C, 57.00; H, 3.38; N, 3.91. Found: C, 57.21; H, 3.62; N, 3.69.

The crude cinchoninyl chloride (prepared by a 2 hour reflux of 17.0 mmoles of the acid in 50 ml. of thionyl chloride) was suspended in 150 ml. of acetone, treated with 20.0 mmoles of sodium azide in 60 ml. of 1:5 water:acetone, and the precipitated azide filtered off after 4 hours of stirring at room temperature. Yields from acids to azides averaged 65 to 80%. The azides were washed with 50 ml. of chilled acetone, air-dried, and used directly. The known 2-(4′-chlorophenyl)-6-methoxy-7-chlorocinchoninyl chloride was converted to its azide in 71% yield by the above procedure (8).

General Procedure for 2-Hydroxy-3-methyl-4-diethylamino-5-arylbenzo[*h*]-1,6-naphthyridines (IIa-d).

The cinchoninyl azides (10 mmoles) in 250 ml. of anhydrous benzene were refluxed for 3 hours, filtered while hot to remove traces of insoluble material, and treated to the dropwise addition of 11 mmoles of 1-diethylamino-1-propyne in 40 ml. of benzene (9). After the reaction mixture was stirred for 12 hours at ambient temperatures it was concentrated to approximately 30 ml., chilled and filtered. The resulting benzonaphthyridines were purified by recrystallization from benzene (see Table).

REFERENCES

(1) This work, supported by contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command, is publication number 925 in the Army Research Program on Malaria.

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(5) C. R. Hauser and G. A. Reynolds, *J. Org. Chem.*, 15, 1224 (1950).

(6) J. Ficini and A. Krief, *Tetrahedron Letters*, 947 (1968).

(7) Testing carried out by Dr. L. Rane by the method reported in T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

(8) A generous sample of this chloride was provided by Dr. Edward E. Hamel who prepared it as described by R. E. Lutz, *et al.*, in *J. Am. Chem. Soc.*, 68, 1817 (1946).

(9) This ynamine is now commercially available from Columbia Organic Chemicals and freshly opened bottles may be used directly without distillation.