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1,3-BRIDGED AROMATIC SYSTEMS. IV. SYNTHESIS OF QUINOLINES[1]

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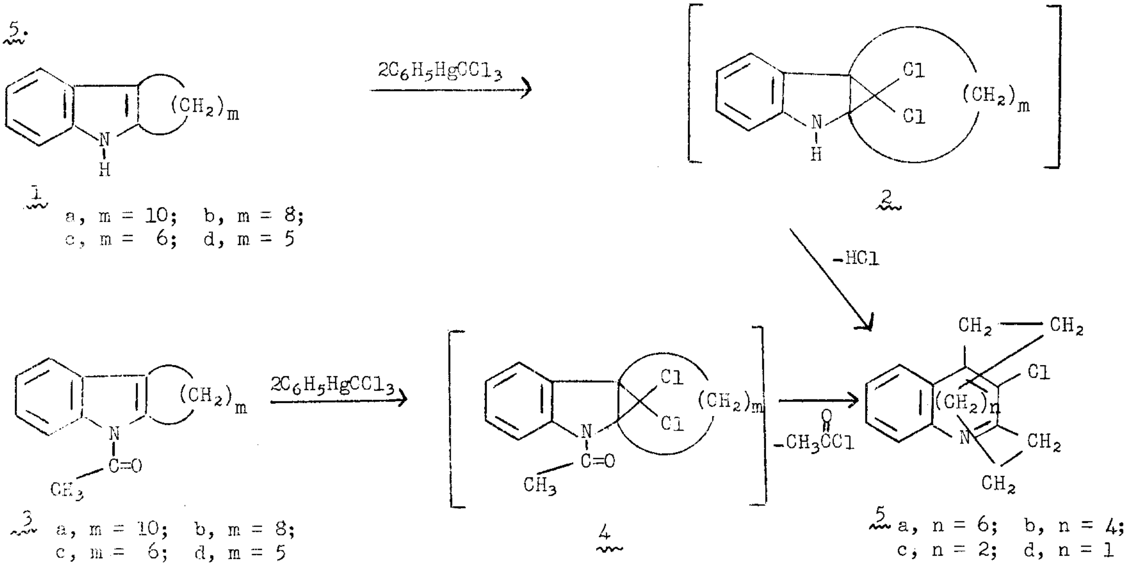
We have previously reported[2] the synthesis and some reactions of a series of 1,3-bridged naphthalenes, which were prepared in high yield by reaction of fused indenes with the elements of dihalocarbene. The ready availability of fused indoles of type 1[3], by the Fischer indole synthesis, has now made possible a convenient synthesis of the corresponding quinolines of type 5.

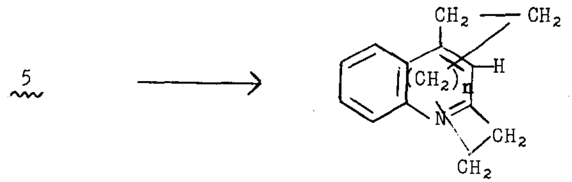


In view of the known complexity of the reaction of dihalocarbenes with indoles[4], and the competition that exists for the electrophilic dichlorocarbene by the basic nitrogen atom[5] and the olefinic bond in 1, our initial work was carried out with the derived amide 3. Thus, in a typical experiment, 3a (4.0 g) was heated 48 hours in benzene with two equivalents of phenyl(trichloromethyl)mercury. Chromatography of the crude product on neutral alumina (200 g) gave, subsequent to elution with petroleum ether (bp 60-68°), 3.09 g (76%, mp 80.5-81.5°) of 5a which was purified to mp[6] 81.5-82.5° [$\lambda_{max}^{95\%\ EtOH}$ (log ε): 235 (4.64), 285 (3.62), 296 (3.62), 309 (3.60), 323 (3.62); nmr (30% CCl_4): aromatic H (m, 4, τ 1.90-2.76) and CH_2 (very complex, 20, τ 6.04-10.39); picrate mp[6] 176-178°]. The yield of 5a was 69% (mp 75-78°) when the free base 1a was employed. The yield of 5b from 1b was 53.5% (yellow oil) which was purified to mp[6] 64.5-66° [$\lambda_{max}^{95\%\ EtOH}$ (log ε): 237 (4.65), 239 (sh) (4.63), 288 (3.79), 298 (3.78), 312 (3.62), 327 (3.61); nmr (20% in CCl_4): aromatic H (m, 4, τ 1.91-2.84) and CH_2 (very complex, 16, τ 6.05-10.59); picrate mp[6] 201-203°]; the yield of 5c from 1c was 48.6% (mp 56.5-63.0°) which was purified to mp[6] 67.0-68.0° [$\lambda_{max}^{95\%\ EtOH}$ (log ε): 241 (4.47), 293 (3.61), 320 (sh) (3.26), 336 (3.22); nmr (30% CCl_4): aromatic H (m, 4, τ 2.05-3.00) and CH_2 (very complex, 12, τ 6.08-9.53); picrate mp[6] 192.5-193.5°].

As is evident from the formula 5, the methylene bridge is tightly packed over the face of the pyridine ring to which it is attached; the chlorine atom further restricts the rotational movement of the methylene groups which leads to considerable non-equivalence of the methylene hydrogen atoms, as is evidenced by the nmr spectra. Thus, the nmr spectrum of 5a shows complex methylene hydrogen absorption between τ 6.04 and τ 10.39. The central hydrogen atoms of the methylene chain, which are tightly packed over the aromatic ring, are severely shielded and appear near τ 10. The ultraviolet spectrum of 5a is quite similar to that of the model compound 3-chloro-2,4-dimethylquinoline[4] (prepared in 49% yield by a related reaction using 2,3-dimethylindole). As the value of n is reduced to 4 (i.e., 5b) the constraint is more severe; the nmr spectrum of 5b shows a similar complexity, with the methylene hydrogen absorption between τ 6.05 and τ 10.59.

The nmr spectrum of 5c is similar to that of 5a and 5b; however, the ultraviolet spectrum of 5c shows complete loss of fine structure. As n is decreased, a shift to longer wavelength is observed. Preliminary chemical evidence supports the conclusion that the strain in 5c has perturbed and distorted the aromatic system.

Both 5a and 5b are reduced with hydrazine and palladium on charcoal[7] in high yield to the corresponding dechlorinated quinolines 6: 6a [88%; mp[6] 62-63°; $\lambda_{max}^{95\%\ EtOH}$ (log ε): 229 (4.65), 232 (sh) (4.61), 279 (3.69), 289 (sh) (3.67), 302 (3.60), 3.16 (3.64); nmr (30% CCl_4):

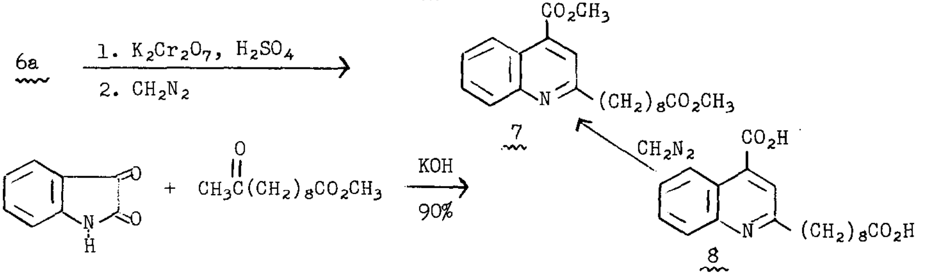


6 a, n = 6
b, n = 4
c, n = 2

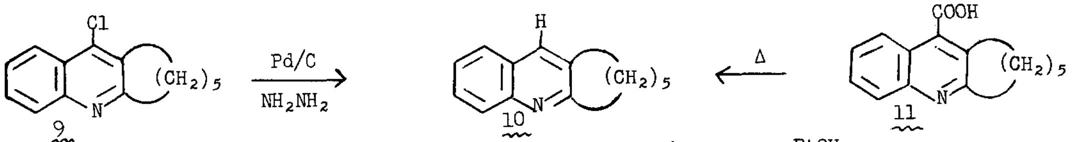
aromatic H (m, 4, τ 1.87-2.88; s, 1, τ 2.98), benzylic CH$_2$ (m, 4, τ 6.87-7.22), and CH$_2$ (m, 16, τ 7.88-9.40); hydrochloride mp[6] 230-234°]; 6b [96%; hydroscopic, mp 64-66°, dried to mp 44-45°; $\lambda_{max}^{95\%\ EtOH}$ (log ε): 229 (4.62), 278 (3.65), 292 (sh) (3.61), 304 (3.49), 317 (3.48); nmr (20% CDCl$_3$): aromatic H (m, 4, τ 1.73-2.58; s, 1, τ 2.70), benzylic CH$_2$ (m, 4, τ 6.90-7.17), CH$_2$ (m, 12, τ 8.08-9.77); picrate mp[6] 166.5-167.5°]. It can be seen from the nmr spectra of 6a and 6b that removal of chlorine in 5 eliminates the constraint of the ring methylene protons, leading to greater equivalence of the hydrogen atoms.

Reduction of 5c under identical conditions does not give 6c, but a mixture which is thought to contain products which involve reduction of the pyridine ring [nmr spectrum: methylene/aromatic H = 4.0; ir: 1624 cm^{-1} (aryl-N=C)].

The structure of 6a was confirmed by its oxidation with potassium dichromate to give in low yield, subsequent to methylation, the ester 7. The ester 7 [5% yield from 6a; mp[6] 46.5-47.5°; ir: 1725 cm^{-1}, 1740 cm^{-1}; nmr (30% CDCl$_3$): aromatic H (m, 1, τ 1.25-1.41; m, 1, τ 1.80-1.98; m, 3, τ 2.17-2.70), CH$_3$ (s, 3, τ 6.09; s, 3, τ 6.36), CH$_2$ (rough t, 2, τ 6.86-7.13; m, 14, τ 7.68-8.88)] was synthesized independently by well known methods[8], as shown in the accompanying equation [8, 90%; mp[6] 221-222°; ir: 1723, 1642 cm^{-1}].



The reaction of 1d with two equivalents of phenyl(trichloromethyl)mercury gave a tarry mixture containing no 5d (n = 1); the only product isolated was 9 (11.6%, mp 79-88°) which was purified to mp[6] 96.5-97.5° (lit.[9] mp 96-98°) [$\lambda_{max}^{95\%\ EtOH}$ (log ε): 230 (4.88), 235 (sh) (4.76), 277 (3.87), 293 (sh) (3.80), 305 (3.79), 310 (sh) (3.60), 319 (3.89); nmr (20% in DCCl$_3$): aromatic H (m, 4, τ 1.65-2.73), benzylic CH$_2$ (m, 4, τ 6.55-6.91) and CH$_2$ (broad s, 6, τ 8.12)]. This result clearly defines the lower limit of n as 2 in the synthesis of 5. The structure of 9 was established by its conversion to 10 [94%; mp[6] 93-95°; picrate, mp[6] 200.5-202°] which proved to be identical with



2:3-cycloheptenoquinoline (10), obtained in 74% yield [mp[6] 93-95°; λ_{max}^{EtOH} (log ε): 227 (4.66), 232 (4.69), 235 (4.71), 269 (3.68), 284 (sh) (3.64), 290 (3.66), 296 (3.62), 303 (3.79), 309 (3.66); 316 (3.95); nmr (20% in $DCCl_3$): aromatic H (m, 5, τ 1.84-2.79), benzylic CH_2 (m, 4, τ 6.64-7.31), CH_2 (broad s, 6, τ 8.21); picrate mp[6] 200.5-202.5°] by decarboxylation of 2:3-cycloheptenocinchoninic acid (11)[3c]. Formation of 9 from 1d can be rationalized by phenyl migration during the decomposition of the proposed intermediate 2d or by rearrangement of a related zwitterionic intermediate, and will be discussed in more detail in a subsequent paper.

The chemistry of the derived quinolines 5 and 6, and extension of the synthesis to substituted pyridines is presently under investigation.

References

1. Supported by the National Science Foundation, Grant GP-6169X.
2. W. E. Parham and J. K. Rinehart, J. Am. Chem. Soc., 89, 5668 (1968). For the previous article in this series see W. E. Parham and J. F. Dooley, J. Org. Chem., 33, 1476 (1968).
3. a) Ng.Ph. Buu-Hoï, J. Chem. Soc., 2882 (1949); b) L. M. Rice, E. Hertz and M. E. Freed, J. Med. Chem., 7, 313 (1964); c) Ng.Ph. Buu-Hoï, P. Jacquignon and T. B. Loc, J. Chem. Soc., 738 (1958).
4. C. W. Rees and C. E. Smithen, J. Chem. Soc., 928 (1964).
5. a) W. E. Parham and J. R. Potoski, Tetrahedron Letters, 21, 2311 (1966); b) W. E. Parham and J. Potoski, J. Org. Chem., 32, 275 (1967); c) W. E. Parham and J. Potoski, ibid., 32, 278 (1967); d) D. Seyferth, M. E. Gordon and R. Damrauer, J. Org. Chem., 32, 469 (1967).
6. All compounds for which a melting point or boiling point are reported have composition (C, H, N) in agreement (± 0.30) with calculated values.
7. W. L. Mosby, Chem. and Ind., 1348 (1959).
8. Ng.Ph. Buu-Hoï and R. Royer, J. Chem. Soc., 106 (1948).
9. M. U. Signal, Jr., B. J. Brent, and P. Marchini, U. S. Patent 3232945 (1966); Chem. Abstr., 64, 14175b (1966).