

SYNTHESIS OF BENZANNELATED CYCL[3.2.2]AZINE:

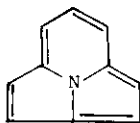
BENZO[a]CYCL[3.2.2]AZINE

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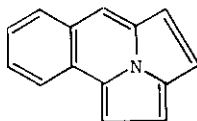
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Abstract—Benzo[a]cycl[3.2.2]azine (3) was synthesized from 6-cyanobenzo[a]indolizine (4) and dimethyl acetylene-dicarboxylate.

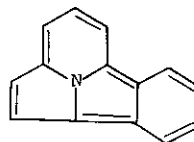
Recently, we prepared some benzannelated cycl[3.2.2]azines in order to study the effects of benzo-fusion on cycl[3.2.2]azines.¹⁻³ There are two possible isomers of benzannelated cycl[3.2.2]azine derivatives, benzo[g]cycl[3.2.2]azine (2)² and benzo[a]cycl[3.2.2]azine (3). The former compound 2 has already been reported in the literature.² However, isomer 3 is a new compound. As a continuation of the work currently in progress in this laboratory, we now report the facile synthesis of 3 according to a modification of Matsumoto's method for the synthesis of cycl[3.2.2]azine. The Matsumoto procedure has also been found to be applicable to the preparation of other cyclazine derivatives.⁴⁻⁶



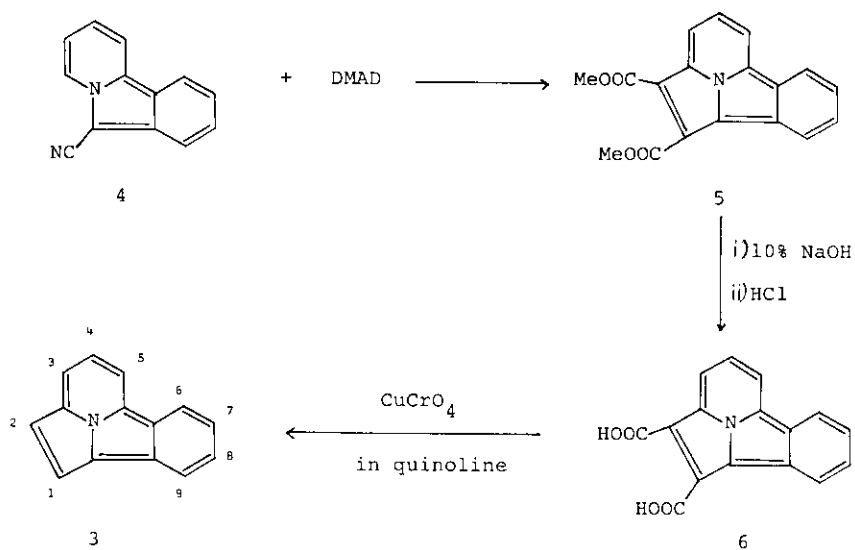
1



2



3



DMAD= dimethyl acetylenedicarboxylate

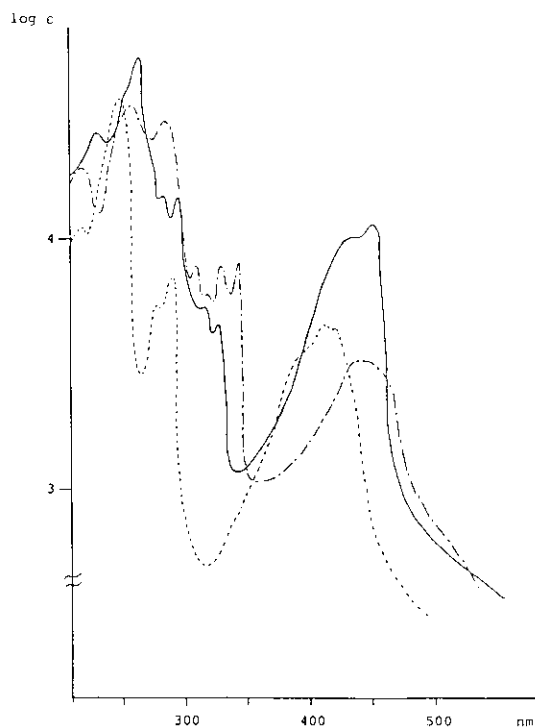


Fig. 1. UV spectra of 1, 2, and 3 in ethanol
1;..... 2;--- 3;—

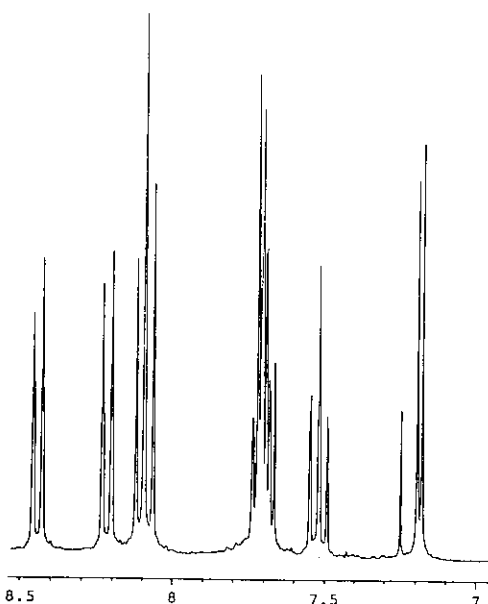


Fig. 1. ^1H -NMR spectrum (270 MHz) of
benzo[a]cycl[3.2.2]azine in CDCl_3

The [12+2]cycloaddition reaction of 4 with dimethyl acetylenedicarboxylate (DMAD) under refluxing for 20 h in toluene gave the expected product, dimethyl benzo[a]cycl[3.2.2]azine-1,2-dicarboxylate (5)⁷, in 54% yield. Hydrolysis of the diester 5 with 10% sodium hydroxide proceeded essentially quantitatively to give the diacid 6. Finally, decarboxylation of the diacid using copper chromite in quinoline occurred smoothly to produce the desired benzo[a]cycl[3.2.2]azine (3)⁸ in 49% yield.

The benzocyclazine 3 has a sweet smell like 2 and is a stable crystalline solid, and recrystallized from methanol, yielding bright yellow leaflets, mp 75°C. The complex of this compound with 2,4,7-trinitro-9-fluorenone gave dark brown needles, mp 218°C. The UV spectrum of 3 is shown in Fig. 2 along with cycl[3.2.2]azine (1)⁹, benzo[g]cycl[3.2.2]azine (2)², and dibenzo[a,d]cycl[3.2.2]azine⁵. The major bands of 3 at 260, 315, and 430 nm are bathochromocally shifted from those of the parent 1 at 255, 308, and 390 nm, respectively, consistent with the longer conjugated aromatic system in the former. ¹H-NMR spectrum of 3 is shown in Fig. 1. A proton absorbs at 7.20 ppm (J=3.84 Hz) which is more upfield than that found in the parent compound 1 (7.40 ppm)¹⁰. The coupling constant of this proton with 1-position is recognized typical aromatic character, and is smaller than that of benzo[g]cycl[3.2.2]azine (2).

REFERENCES AND NOTES

1. K.Kurata, H.Awaya, H.Gotou, Y.Tominaga, Y.Matsuda, and G.Kobayashi, Chem. Pharm. Bull., 1985, 33, 3034.
2. Y.Tominaga, H.Gotou, Y.Oniyama, Y.Nishimura, and Y.Matsuda, Chem. Pharm. Bull., 1985, 33, 3038.
3. Y.Tominaga, Y.Shiroshita, K.Kawabe, H.Gotou, Y.Oniyama, and Y.Matsuda, Heterocycles, 1985, 23, 2531.
4. T.Uchida and K.Matsumoto, Chem. Lett., 1980, 149.
5. K.Matsumoto, T.Uchida, T.Sugi, and Y.Yagi, Chem. Lett., 1982, 869.
6. K.Matsumoto, T.Uchida, T.Sugi, and T.Kobayashi, Heterocycles, 1983, 20, 1525.
7. 5, yellow needles, mp 176°C. MS m/z: 307(M⁺, 100). UV λ_{max}(EtOH)nm(log ε): 223 (4.69), 241(4.53), 256(4.46), 271(4.58), 304(4.14), 314(4.17), 428(4.06), 454 (4.04). IR ν_{max}(KBr)cm⁻¹: 1735, 1700(CO). ¹H-NMR δ (CDCl₃)(90MHz)ppm: 4.04(3H, s, OCH₃), 4.16(3H, s, OCH₃), 7.58-8.10(4H, m, aromatic-H), 8.28-8.49(3H, m,

aromatic-H).

8. 3, bright yellow leaflets, mp 75°C. MS m/z: 191(M⁺, 100). UVλ_{max}(EtOH)nm(log): 231(4.40), 260(4.70), 279(4.16), 291(4.16), 314(3.73), 326(3.66), 424(4.02), 450(4.06). ¹H-NMR δ (CDCl₃)(270MHz)ppm: 7.16(1H, d, J=3.8 Hz, 2-H), 7.50(1H, m, 7-H), 7.65-7.72(3H, m, 1, 4, 8-H), 8.06(1H, d, J=8.2 Hz, 3-H), 8.09(1H, d, J=6.6 Hz, 5-H), 8.19(1H, d, J=8.2 Hz, 9-H), 8.42(1H, d, J=8.2 Hz, 6-H).
9. R.J.Windgassen, Jr., W.H.Saunders, Jr., and V.Boekelheide, J. Am. Chem. Soc., 1959, 81, 1459.
10. M.Pompei and W.Paudler, J. Org. Chem., 1976, 41, 1661.

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