1,3-DIPOLAR CYCLOADDITION OF PYRAZOLO[1,2-a]INDAZOLES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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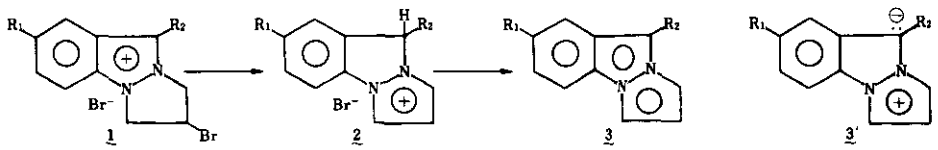
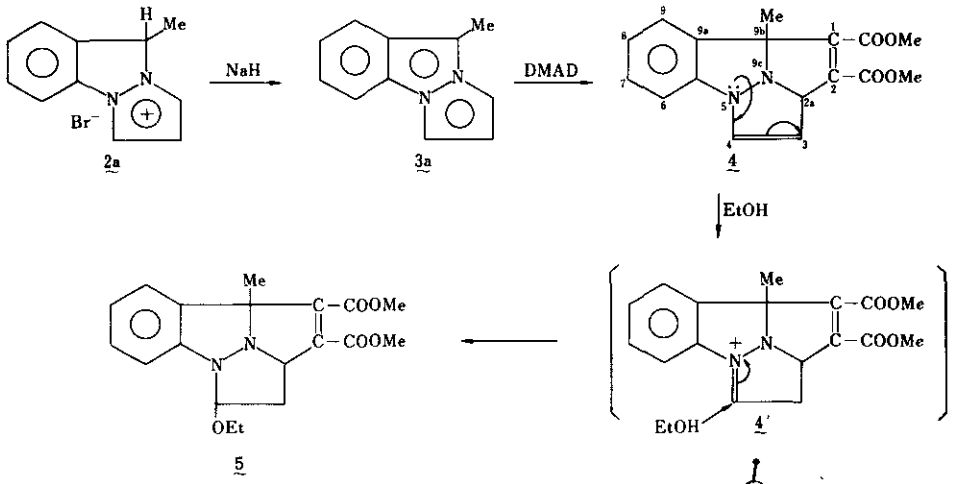
Abstract ——— Pyrazolo[1,2-a]indazoles (3a and 3b) obtained from 9H-pyrazolo[1,2-a]indazolium bromides (2a and 2b) and sodium hydride readily react with dimethyl acetylenedicarboxylate to give 1,3-dipolar cycloadducts (4 and 8). Products 4 and 8 are hydrogenated to the 3,4-dihydro derivatives (6 and 10) and converted into their 4-alkoxy derivatives (5,7 and 9) with alcohols under acidic conditions.

We recently reported that the reaction of 2-bromo-2,3-dihydro-1H-pyrazolo-[1,2-a]indazolium bromides (1) with alkaline solution initially affords 9H-pyrazolo[1,2-a]indazolium bromide (2) which are convertible by dehydrobromination into pyrazolo[1,2-a]indazoles (3), a new benzodiazapentalene ring system, and the contribution of the betain structure (3') in which a negative charge located at the 9-position is significantly large in the ground state of 3.[1]



This finding suggests that the pyrazolo[1,2-a]indazole system (3) might show a higher reactivity toward 1,3-dipolar cycloaddition[2] as compared with other 3a,6a-diazapentalene derivatives.[3] In order to explore this prediction, we investigated the reaction with dimethyl acetylenedicarboxylate and found that

the expected 1,3-dipolar cycloaddition occurred under mild conditions. Dimethyl acetylenedicarboxylate (DMAD) was added to an ice-cooled solution of 9-methyl-9H-pyrazolo[1,2-a]indazolium bromide (2a) and NaH in DMF-DMSO under nitrogen atmosphere, and the reactants were stirred for 1 h. The occurrence of reaction was apparently noticed. Products were extracted with benzene and chromatographed on silica gel to give 4-ethoxy-3,4-dihydro-1,2-dimethoxycarbonyl-9b-methyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (5) as an oil in 43% yield. The structure of 5 was deduced from elemental analysis of its oxalate and spectral (ms, pmr, cmr) examinations and finally established by X-ray analysis of the oxalate (Fig.). The formation of 5 may be rationalized by following course. The 9-methyl-pyrazolo[1,2-a]indazole (3a) formed from 2a and NaH reacts with DMAD to give a 1,3-dipolar cycloadduct (4). During chromatography on silica gel, the enamine moiety of 4 was protonated to delete to offer an immonium salt (4') which was attacked in turn by ethanol contained in $CHCl_3$[4] to give the 4-ethoxy derivative 5.



2a 3a 4 4' 5

Proof of the initial formation of 4 was provided by the ms, pmr and cmr spectra of an oily residue directly obtained from the above-mentioned benzene extract without chromatographic purification. The spectral data were fully consistent with the sturcture of 4 in spite of apparent contamination with some impurities.

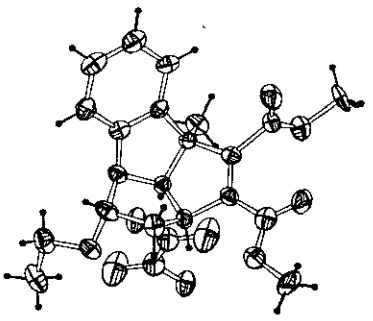
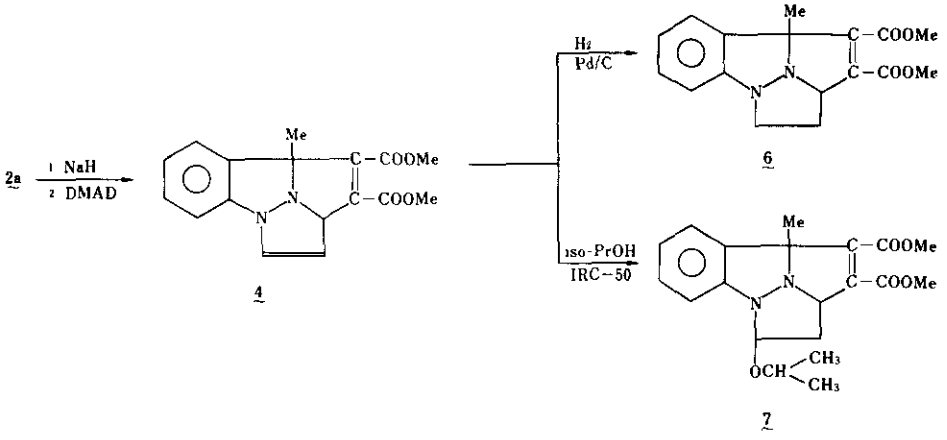


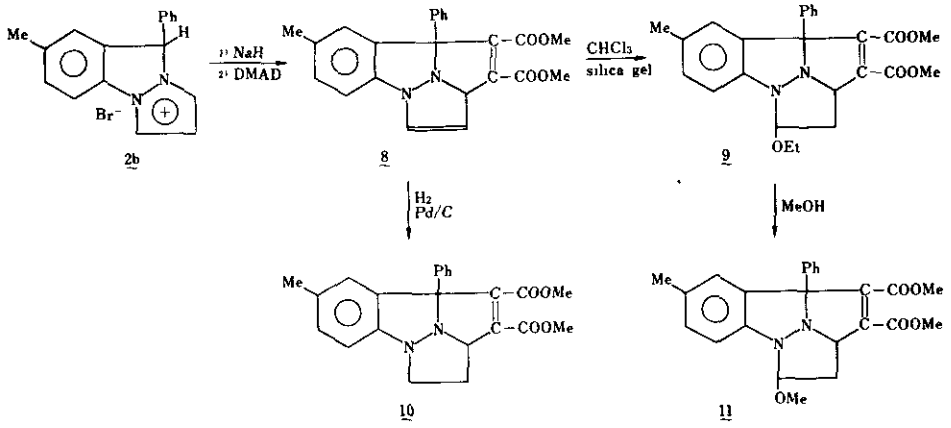
Fig. ORTEP drawing of 5 (oxalate)

Hydrogenation of 4 over palladium-charcoal in THF gave 3,4-dihydro-1,2-dimethoxycarbonyl-9b-methyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (6) as an oil in 45% overall yield from 2a. Further it was found that treatment of 4 with iso-PrOH at room temperature in the presence of a cation exchange resin (Amberlite IRC-50) resulted in the formation of 3,4-dihydro-1,2-dimethoxycarbonyl-9b-methyl-4-iso-propoxy-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]-indazole (7). Transformation of 4 into 7 was also effected in the presence of silica gel instead of IRC-50, whereas 4 was inert in the absence of silica gel or IRC-50. Apparently acidic conditions are neccessary to the transformation of 4 into 5 and 7 in accord with the proposed mechanism.



In a similar manner, 7-methyl-9-phenyl-9H-pyrazolo[1,2-a]indazolium bromide (2b) was treated successively with NaH and DMAD, and the crude 1,3-dipolar cycloadduct (8) was subjected separately to silica gel chromatography and hydrogenation to afford 4-ethoxy-3,4-dihydro-1,2-dimethoxycarbonyl-8-methyl-9b-phenyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (9) and 3,4-dihydro-1,2-dimethoxycarbonyl-8-methyl-9b-phenyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (10) in good yields of 69 and 89%, respectively.

When a solution of 9 in MeOH was left alone at room temperature for 2 d 4-methoxy derivative (11) was obtained by exchange of alkoxyl group of the aminoacetal moiety.



The reaction of 9H-pyrazolo[1,2-a]indazolium bromide, having no substituent at the 9-position, with NaH and DMAD was also attempted, but no definite product was obtained owing to the complicated reaction.

The structure assignment of 6, 7, 9, 10 and 11 were based on the satisfactory elemental analyses and spectral examinations.

EXPERIMENTAL

All melting points are uncorrected. Pmr and cmr spectra were measured on a JEOL JNM-FX200, with tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 instrument. X-Ray diffraction data were obtained from a Enraf-Nonius CAD4 diffractometer.

4-Ethoxy-3,4-dihydro-1,2-dimethoxycarbonyl-9b-methyl-2aH,9bH-5,9c-diaza-pentaleno[1,7,6-ab]indazole (5) ——— An ice-cooled solution of 9-methyl-9H-pyrazolo 1,2-a indazolium bromide (2a, 1.26 g) and 60% NaH (0.24 g) in DMF (10 ml) - DMSO (10 ml) was stirred for 10 min under nitrogen atmosphere. To the solution was added DMAD (0.85 g), and the reaction mixture was stirred for 1 h and then extracted with benzene. The benzene solution was washed with H_2O, dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$ to give 5 (0.77 g, 43%) as an oil. Ms m/z: 358 (M^+), pmr ($CDCl_3$) δ: 1.30 (3H, t, $-CH_2CH_3$), 1.75 (3H, s, $-CH_3$), 1.77-1.91 (1H, m, H_3), 2.40 (1H, dd, J=12.9 and 7.3 Hz, H_3), 3.55-3.64 (1H, m, $-OCH_2$), 3.75 (3H, s, $-OCH_3$), 3.87 (3H, s, $-OCH_3$), 3.98-4.07 (1H, m, $-OCH_2$), 4.84

(1H, dd, J=10.2 and 7.3 Hz, H_{2a}), 5.01 (1H, d, J=5.1 Hz, H_4), 6.75-7.26 (4H, m, Ar-H), cmr ($CDCl_3$) δ: 14.83 (q, $-CH_2\underline{C}H_3$), 27.96 (q, $-CH_3$), 38.73 (t, C_3), 52.28 (q, $-OCH_3$), 52.40 (q, $-OCH_3$), 63.45 (t, $-OCH_2$), 70.23 (d, C_{2a}), 80.42 (s, C_{9b}), 98.61 (d, C_4), 111.49 (d), 122.48 (d), 123.24 (d), 128.86 (d), 132.15 (s), 136.70 (s), 141.52 (s), 147.69 (s), 163.56 (s, -C=O), 164.08 (s, -C=O). Oily 5 was converted to crystalline oxalate, mp 114-116°C (EtOH). Anal. Calcd for $C_{19}H_{22}N_2O_5$ 1/2$(COOH)_2$: C, 59.55; H, 5.75; N, 6.94. Found: C, 59.27; H, 5.84; N, 6.72. Crystal data: a=18.309 (3); b=8.025 (1); c=14.627 (2) Å; β=106.13 (1); U=2064.6 ($Å^3$); space group=$P2_1/a$ (monoclinic); Z=4; D=1.294 g cm^{-3}; linear absorption coefficient=8.306 cm^{-1} (CuKα). Observed data (above 2σ level): 1216. Final R value=4.8%.

4-Ethoxy-3,4-dihydro-1,2-dimethoxycarbonyl-8-methyl-9b-phenyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (9) ——— In a similar manner, 9 was obtained from 7-methyl-9-phenyl-9H-pyrazolo[1,2-a]indazolium bromide (2b) in 69% yield, pale yellow powder, mp 110-112°C (hexane). Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.38; H, 6.08; N, 6.46. Ms m/z: 434 (M^+), pmr ($CDCl_3$) δ: 1.24 (3H, t, $-CH_2\underline{C}H_3$), 1.83-1.97 (1H, m, H_3), 2.33 (3H, s, Ar-CH_3), 2.38 (1H, dd, J=12.7 and 7.3 Hz, H_3), 3.50-3.64 (1H, m, $-OCH_2$), 3.70 (3H, s, $-OCH_3$), 3.79 (3H, s, $-OCH_3$), 3.89-4.01 (1H, m, $-OCH_2$), 4.97 (1H, dd, J=10.2 and 7.3 Hz, H_{2a}), 5.03 (1H, d, J=5.1 Hz, H_4), 6.74 (1H, d, Ar-H), 7.06-7.36 (7H, m, Ar-H), cmr ($CDCl_3$) δ: 14.83 (q, $-CH_2\underline{C}H_3$), 21.03 (q, $-CH_3$), 38.03 (t, C_3), 52.28 (q, $-OCH_3$), 52.37 (q, $-OCH_3$), 63.39 (t, $-OCH_2$), 70.65 (d, C_{2a}), 86.28 (s, C_{9b}), 99.28 (d, C_4), 111.37 (d), 126.29, 127.09, 127.76, 128.37, 129.62, 129.95, 131.91, 139.26 (s), 140.00 (s), 142.50 (s), 147.17 (s), 163.77 (s, -C=O), 163.83 (s, -C=O).

3,4-Dihydro-1,2-dimethoxycarbonyl-9b-methyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab] indazole (6) ——— Treatment of 2a (1.26 g) with NaH and DMAD as mentioned above and the benzene extract was concentrated to give 4 as an oily product. Ms m/z: 312 (M^+), pmr ($CDCl_3$) δ: 1.85 (3H, s, $-CH_3$), 3.75 (3H, s, $-OCH_3$), 3.79 (3H, s, $-OCH_3$), 5.31-5.37 (2H, overlapping multiplets, H_{2a}, H_3), 6.38 (1H, dd, J=3.9 and 1.5 Hz, H_4), 6.87-7.22 (4H, m, Ar-H), cmr ($CDCl_3$) δ: 27.25 (q, $-CH_3$), 52.25 (q, $-OCH_3$), 52.31 (q, $-OCH_3$), 74.59 (d, C_{2a}), 82.83 (s, C_{9b}), 108.04 (d), 112.86(d), 123.03 (d), 123.76 (d), 129.01 (d),

133.65 (s), 135.26 (d) 139.57 (s), 145.46 (s), 146.34 (s), 163.53 (s, -C=O), 164.72 (s, -C=O).

A solution of 4 in THF (40 ml) was hydrogenated at ordinary temperature and pressure over 10% Pd/C (0.40 g). After uptake of 1 equiv. hydrogen the filtered solution was concentrated, and the residue was chromatographed on silica gel with $CHCl_3$ to afford 6 (0.70 g, 45%) as an oil. Ms m/z: 314 (M^+), pmr ($CDCl_3$) δ: 1.74 (3H, s, $-CH_3$), 1.78-1.86 (1H, m, H_3), 2.23-2.34 (1H, m, H_3), 3.45-3.66 (2H, m, H_4), 3.75 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.62 (1H, dd, J=9.0 and 7.1 Hz, H_{2a}), 6.76-7.23 (4H, m, Ar-H), cmr ($CDCl_3$) δ : 26.80 (q, $-CH_3$), 32.41 (t, C_3), 52.28 (q, $-OCH_3$), 52.34 (q, $-OCH_3$), 54.66 (t, C_4), 71.29 (d, C_{2a}), 80.42 (s, C_{9b}), 111.76 (d), 122.29 (d), 122.84 (d), 128.98 (d), 132.58 (s), 136.33 (s), 142.59 (s), 150.19 (s), 163.80 (s, -C=O), 163.98 (s, -C=O). Oxalate: mp 113-115°C (acetone-hexane), Anal. Calcd for $C_{17}H_{18}N_2O_4 \cdot (COOH)_2$: C, 56.43; H, 5.25; N, 6.93. Found: C, 56.64; H, 5.14; N, 7.13.

3,4-Dihydro-1,2-dimethoxycarbonyl-8-methyl-9b-phenyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (10) ——— In a similar manner, 10 was obtained from 2b in 89% yield, yellow needles, mp 62-65°C (THF-hexane). Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.65; H, 5.70; N, 7.11. Ms m/z: 390 (M^+), pmr ($CDCl_3$) δ: 1.73-1.90 (1H, m, H_3), 2.18-2.35 (1H, m, H_3), 2.32 (3H, s, $-CH_3$), 3.46-3.60 (2H, m, H_4), 3.69 (3H, s, $-OCH_3$), 3.78 (3H, s, $-OCH_3$), 4.74 (1H, dd, J=9.3 and 7.1 Hz, H_{2a}), 6.74 (1H, d, Ar-H), 7.05-7.37 (7H, m, Ar-H), cmr ($CDCl_3$) δ: 21.03 (q, $-CH_3$), 31.71 (t, C_3), 52.25 (q, $-OCH_3$), 52.37 (q, $-OCH_3$), 55.27 (t, C_4), 71.81 (d, C_{2a}), 86.34 (s, C_{9b}), 111.46 (d), 125.90, 126.99, 127.79, 128.40, 130.11, 131.69, 138.99 (s), 140.85 (s), 142.07 (s), 149.49 (s), 163.65 (s, -C=O), 164.01 (s, -C=O).

3,4-Dihydro-1,2-dimethoxycarbonyl-9b-methyl-4-iso-propoxy-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (7) ——— A mixture of 4 and Amberlite IRC-50 (15 ml) in iso-PrOH (30 ml) was stirred at room temperature for 2 h. The reaction mixture was filtered, concentrated and the residue was chromatographed on silica gel with 3% acetone-benzene to give 7 as an oil. Ms m/z: 372 (M^+), pmr ($CDCl_3$) δ: 1.28 (3H, d, $-CHCH_3$), 1.29 (3H, d, $-CHCH_3$), 1.74 (3H, s, $-CH_3$), 1.78-1.87 (1H, m, H_3), 2.33 (1H, dd, J=12.7 and 7.3 Hz, H_3), 3.74 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.15-4.24 (1H, m, -OCH-), 4.82 (1H, dd,

J=10.0 and 7.3 Hz, H_{2a}), 5.15 (1H, d, J=4.9 Hz, H_4), 6.75-7.22 (4H, m, Ar-H), cmr ($CDCl_3$) δ: 21.15 (q, $-CH\underline{C}H_3$), 23.26 (q, $-C\underline{H}CH_3$), 27.93 (q, $-CH_3$), 38.91 (t, C_3), 52.25 (q, $-OCH_3$), 52.40 (q, $-OCH_3$), 68.36 (d, -OCH), 70.38 (d, C_{2a}), 80.33 (s, C_{9b}), 96.14 (d, C_4), 111.37 (d), 122.42 (d), 123.30 (d), 128.86 (d), 132.24 (s), 136.88 (s), 141.43 (s), 147.78 (s), 163.65 (s, -C=O), 164.11 (s, -C=O).

3,4-Dihydro-4-methoxy-1,2-dimethoxycarbonyl-8-methyl-9b-phenyl-2aH,9bH-5,9c-diazapentaleno[1,7,6-ab]indazole (11) ——— A solution of 9 (0.20 g) in MeOH (10 ml) was left at room temperature for 2 d. After concentration in vacuo, the residue was recrystallized from acetone-hexane to give 11 (0.10 g), yellow needles, mp 135-138°C. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.58; H, 5.78; N, 6.68. Ms m/z: 420 (M^+), pmr ($CDCl_3$) δ: 1.89-1.98 (1H, m, H_3), 2.34 (3H, s, $-CH_3$), 2.40 (1H, dd, J=12.9 and 7.6 Hz, H_3), 3.50 (3H, s, $-OCH_3$), 3.70 (3H, s, $O=C-OCH_3$), 3.79 (3H, s, $O=C-OCH_3$), 4.91 (1H, d, J=4.9 Hz, H_4), 4.95 (1H, dd, J=10.5 and 7.4 Hz, H_{2a}), 6.75 (1H, d, Ar-H), 7.08-7.34 (7H, m, Ar-H), cmr ($CDCl_3$) δ: 21.03 (q, $-CH_3$), 37.88 (t, C_3), 52.28 (q, $O=C-OCH_3$), 52.40 (q, $O=C-OCH_3$), 55.78 (q, $-OCH_3$), 70.50 (d, C_{2a}), 86.28 (s, C_{9b}), 100.69 (d, C_4), 111.31 (d), 126.32, 127.05, 127.79, 128.37, 129.62, 129.98, 132.00, 139.08 (s), 140.12 (s), 142.35 (s), 147.01 (s), 163.70 (s, -C=O), 163.83 (s, -C=O).

REFERENCES AND NOTES

1. Y. Fujimura, Y. Nawata, and M. Hamana, Heterocycles, 1986, 24, 2771.
2. R. Huisgen, Angew. Chem., 1963, 75, 604.
3. a) V. Boekelheide and N.A. Fedoruk, Proc. Natl. Acad. Sci. U.S., 1966, 55, 1385; b) O. Tsuge and H. Samura, Tetrahedron Lett., 1973, 597; Heterocycles, 1974, 2, 27; c) K.T. Potts and J.L. Marshall, J. Org. Chem., 1976, 41, 129; d) C.A. Ramsden, Tetrahedron, 1977, 33, 3203; e) H. Koga, M. Hirobe, and T. Okamoto, Tetrahedron Lett., 1978, 1291; f) K. Matsumoto, T. Uchida, and R.M. Acheson, Heterocycles, 1981, 16, 1367.
4. Chloroform contains 0.8% EtOH as a stabilizer.

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