PYRAZOLO[1,2-a]INDAZOLE AND ITS REACTION WITH DIMETHYL ACETYLENEDICARBOXYLATE

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Abstract - Pyrazolo[1,2-a]indazole (**2**) is prepared by dehydrohalogenation of 2-bromo-2,3-dihydro-1H-pyrazolo[1,2-a]indazolium bromide (**7**). This diazapentalene **2** reacts with dimethyl acetylenedicarboxylate (DMAD) at room temperature. The main products in aprotic solvents are 10cH-1,2-dimethoxycarbonyl-10c-(1',2'-dimethoxycarbonylethenyl)-1,2-diazocino-[1,2,3-ab]indazole (**15**) and 11H-2,3-dimethoxycarbonyl-11-(1',2'-dimethoxy-carbonylethenyl)pyrazolo[1,2,3-ab]1,2-benzodiazocine (**16**) arising from a stepwise process involving addition of two molecules of DMAD and rearrangement. A minor product is 1,2-dimethoxycarbonyl-5,9c-diazapentaleno-[1,7,6-ab]indazole (**9**). In methanol 1 to 2 addition and proton shift leads to 2,3-dihydro-1,2,3,4-tetramethoxycarbonyl-7,11c-diazaazuleno[1,9,8-ab]indazole (**19**) as the main reactions product. These processes are discussed in the frame of the general mechanism for heteropentalene addition reactions.

We have been interested since some years in the chemistry of polyazapentalenes,[1] i.e. heterocyclic mesoionic betaines, which are isoelectronic analogues of the pentalene dianion, and particularly of derivatives having two nitrogen atoms at the bridged positions. These compounds pertain to class B in Ramsden's classification of heteropentalenes[2] and class C in Elguero's classification.[3] Within this class, many derivatives carrying one or two further nitrogen atoms at other positions are known including benzo and dibenzo derivatives, whereas, as far as compounds having the bridged nitrogens as the only heteroatoms are concerned,[4,5] literature reports are limited to the parent compound, pyrazolo[1,2-a]pyrazole (**1**), and some of its simple derivatives.[4,5] In the present paper, the synthesis of pyrazolo[1,2-a]indazole (**2**) and the elucidation of its chemistry with dimethyl acetylenedicarboxylate are reported.

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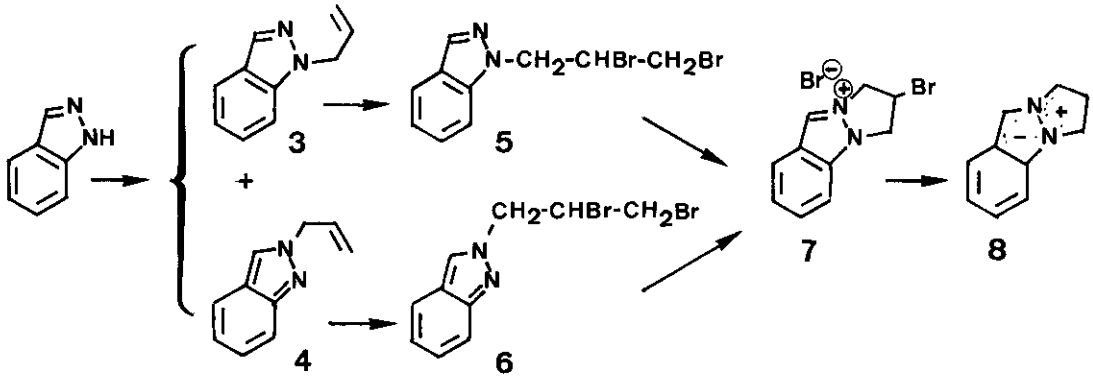
In the mean time, a paper by Fujimura concerning heterocycle **2** appeared reporting in situ preparation and reaction of this compound. No definite results were obtained for the reaction between heteropentalene **2** and dimethyl acetylenedicarboxylate, although adducts were obtained from the corresponding 5-phenyl and 5-methyl derivatives.[6]

In the present paper, we report different techniques for both the preparation and the reaction of heterocycle **2**.

RESULTS AND DISCUSSION

For the synthesis of compound **2** we put to use the same strategy employed for the synthesis of compound **1**. Thus, indazole was alkylated to yield the two isomeric allylindazoles **3** and **4**. These have been separately converted to the dibromides **5** and **6** and cyclized to the iminium salt **7** (Scheme I). There is no substantial difference in reactivity between the isomers, and for the present purpose it is convenient to carry out these steps on the isomeric mixture.



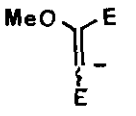
Scheme 1

The bromide **7** obtained in an overall yield of 74% (45 %)[7] is readily dehydrohalogenated by strong bases in different solvents, e.g. by adding lithium hydride or litium methoxide to a deaerated dimethyl sulfoxide (or methanol) solution of compound **7** at room temperature. Under these conditions a ^{1}H-nmr spectrum fully compatible with structure **2** was obtained (see Experimental) but we were unable to isolate pure sample of this compound in the solid state. Dehydrohalogenation with KOH in methanol gives bad results, with precipitation of a tarry material.

This heteropentalene **2** is easily oxidized in the presence of air (compare ref. 4-6) but can be conserved for several hours in degassed solution (~ 0.5M). The rate of decomposition is higher at higher concentration and a polymerization reaction leads to tars when concentration of the solution is attempted. At any rate there was no indication for the formation of other products during the dehydrohalogenation.

In order to obtain further evidence for the formation of compound **2** under these conditions and some

idea of its chemistry , the reaction with dimethyl acetylenedicarboxylate (DMAD) was investigated. Dehydrohalogenation by LiH or LiOMe proceeded in several minutes and upon addition of DMAD new products were formed. In the latter case, we found that a better yield of the same products can be obtained by changing the order of addition of the reagents, viz. by adding lithium methoxide to a deaerated solution of **7** and DMAD in N,N-dimethylformamide (DMF). The methoxide ion reacts instantaneously with DMAD and thus the active base under these conditions is anion **8** (indeed, after work up, methoxy maleate and fumarate were isolated). Dehydrohalogenation of **7** and following addition between **2** and excess DMAD are then faster and more effective than by the alternative procedure (see the Table).



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E = COOMe

Table. Preparative Results from the Reaction of Heteropentalene **2** with DMAD

Solvent	Ratio	Products (% Yield)			
	7/DMAD	**15**	**16**[d]	**9**	**19**
DMF[a]	1:4	28	16	1	1
DMF[a]	1:2	26	11	1	1
DMF[b]	1:2	15	4	-	2
MeOH[a]	1:4	10	1	1	13
MeOH[b]	1:2	10	1	1	20
Benzene[c]	1:2	1	-	-	5

[a] The bromide **7** is dehydrohalogenated in situ in the presence of DMAD by reaction with 2 moles of LiOMe.

[b] As above; DMAD is added 30 min after the addition of the base.

[c] Two phases reaction; the bromide is dehydrohalogenated by NaOH while stirring with benzene containing DMAD.

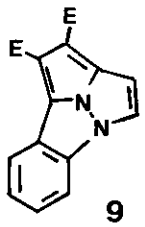
[d] Yield of product **16** refers to the present isolation procedure. Due to the scarce stability of this compound, yields may change greatly under different conditions. It appears likely that products **15** and **16** are found in roughly the same amounts.

Four products were separated from the reaction mixture and characterized. The two main products are both 1 to 2 adducts between DMAD and pentalene **2**. Of the two minor products, the red crystalline material is again a 1 to 2 adduct and the other one, a colourless material, was shown by analysis and mass spectrum to arise from the addition of one molecule of DMAD to **2** with loss of two hydrogen atoms. Other spectroscopical evidence including strong fluorescence indicating that the molecular frame is rigid, ascertained that this product is the fully aromatized diazapentaleno[1,7,6-ab]indazole **9**.

The structure of the two main adducts is not straightforward. In the first eluting product (**A**), the three protons in positions 1,2,3 in the starting material remain in the same arrangement, as shown by the coupling pattern in the ^{1}H-nmr spectrum, and are strongly shielded compared with the starting material. In the slower eluting product (**B**), the yield of which is strongly dependent on the isolation method, only two protons remain coupled and are not substantially shifted.

The simplest rationalization would be that two molecules of DMAD are successively added to yield either a seven-membered ring (as in formula **10**, for compound **A**) or a double adduct to two different sites (as in formula **11**, for compound **B**). Both modes of addition have precedents in the literature[1,8] but in the present case the following experimental evidence, valid for both compounds, militates against this hypothesis: i. the ^{13}C-nmr spectra show no sp^3 carbon atoms, except for the ester methyl groups; ii. there is a ^{13}C absorption at ca 95 δ, which fits for a N-C(COOMe)=CHCOOMe group; iii, both compounds absorbed one molecule of hydrogen on catalytic hydrogenation and yielded products containing a -N-CH_2-CH_2- group (as shown by ^{1}H and ^{13}C nmr) and showing uv spectra similar to products **15** and **16**, thus indicating that there is a N-vinyl group, the hydrogenation of which does not interrupt conjugation of the main chromophore.

Although point iii would per se be acceptable for formula **10**, all three points together exclude



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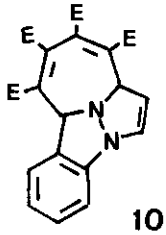

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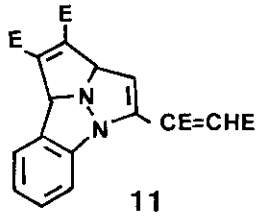

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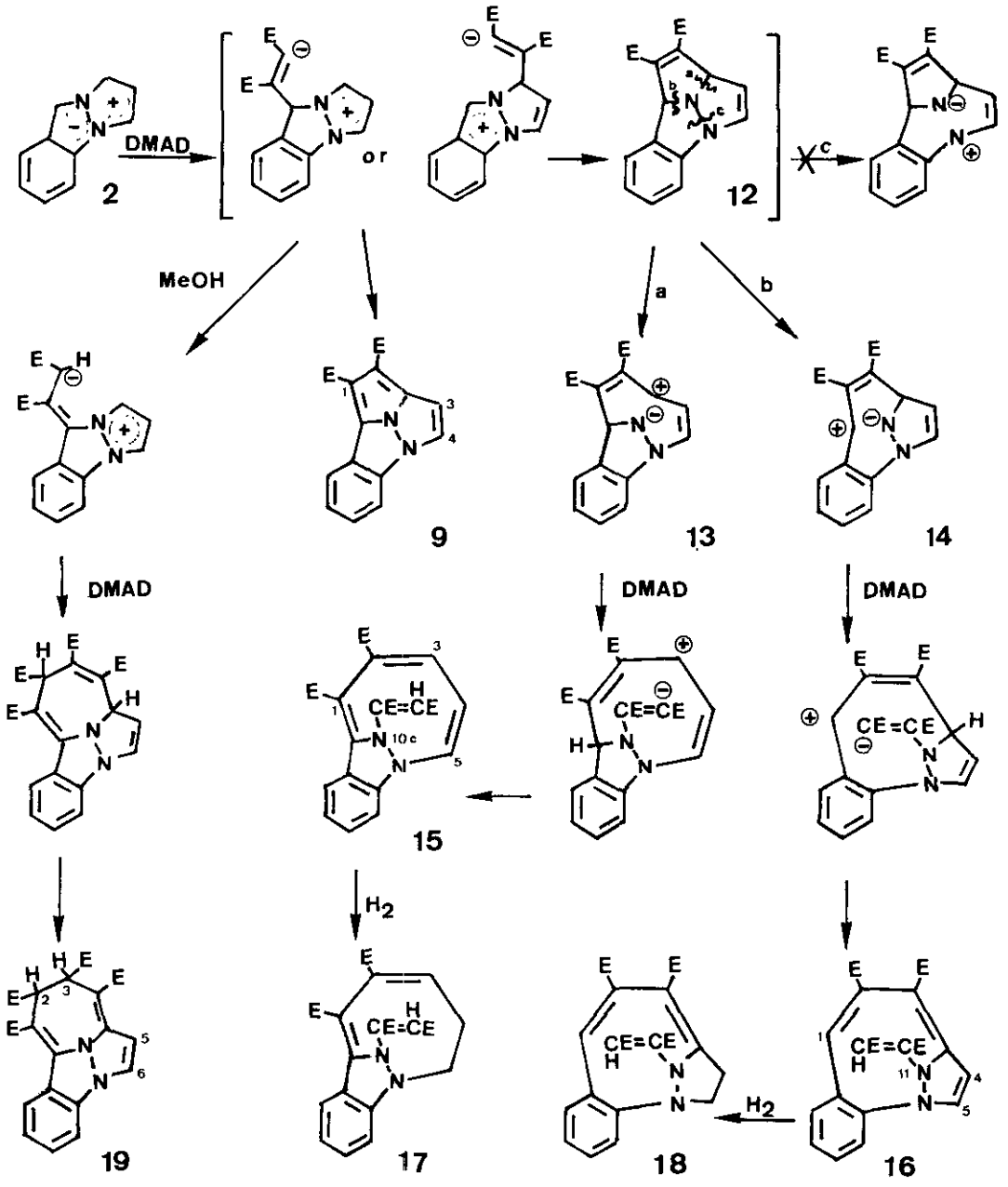
these attributions and lead to the conclusion that products **A** and **B** are formed via an addition-rearrangement process rather than simple addition.

The correct formulae can be arrived at with the following considerations. Formation of the dehydro cycloadduct **9** may be taken as an indication of the intermediate cycloadduct **12** (vide infra). Cleavage of one of the central bonds along paths a or b (path c is thermodynamically excluded since it brings a positive charge on a nitrogen atom) leads to mesomeric zwitterions **13** and **14**. These are trapped by a second molecule of DMAD, and subsequent proton shift leads to the 1 to 2 adducts **15** and **16**. The spectroscopic and chemical characteristics observed for products **A** and **B** are in fact those expected for formulae **15** and **16**, respectively (see Experimental for spectral attribution). In both cases hydrogenation involves the only enamine double bond not carrying an electron withdrawing group and yields the dihydro derivative **17** and **18** respectively.

When the reaction was carried out in methanol product distribution changed, with a drop in the yield of the above mentioned products. The main product was the red material obtained only in traces in DMF. This shows an AB system centered at 5.8 and 6 δ attributable to strongly deshielded

coupled tertiary protons (the corresponding carbon absorptions are at 46.21 δ and 48.07), besides two coupled olefinic protons at 6.25 and 7.6 and the aromatic protons, one being strongly deshielded. Formula **19** arising from sequential addition to form a seven-membered ring and hydrogen shift well accounts for these properties. The rigid conjugated structure of the chromophore



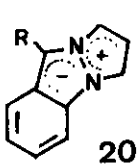
Scheme 2

explains the red colour and the fluorescence. The AB aliphatic system corresponds to the shifted hydrogen atoms.

The types of products obtained are different from what reported by Fujimura[6] on the 5-substituted diazapentalene **20** (R=Me, Ph). In that case 1 to 1 cycloadducts **21** were obtained and underwent catalytic hydrogenation or protonation onto the enamine double bond. In our case there is no indication that a similar adduct is formed as a discrete intermediate, and formula **12** is indicated in Scheme 2 only as an aid for understanding the pathways followed to the final products. In order to check whether the different results could be due to a difference in the experimental approach, the reaction was carried under conditions more similar to those of Fujimura, viz. via two phases reaction by adding aqueous NaOH to a stirred mixture of **7** in water and DMAD in benzene. However, the previously mentioned 1 to 2 adducts were again obtained (see the Table), although in much lower yields due to extensive polymerization. Apparenlty, the presence of a substituent is required for making 1 to 1 adducts isolable.

As discussed above, the addition reaction of heteropentalene **2** takes an unexpected course, in that the "normal" cycloadducts such as **21** (R=H) or **10** (analogous to the products reported from the reaction of other heteropentalenes with DMAD)[2,3,6,8] were not found among the products despite accurate investigation. The formation of the actual products rather involves complex rearrangements: thus, products **15** and **16** arise from the trapping of unprecedented mesomeric betaines **13** and **14**. However, when the broad features of the process are considered, it can be seen that the present reactions can be discussed within the general frame we had previously proposed for the reactivity of heteropentalenes.[1]

First, the great reactivity of diazapentalene **2** is due to its high-lying HOMO. From PES measurements on triaza and tetrazapentalenes[1] the ionization potential of **2** is expected to be ca 5.5 eV, i.e. 1 eV lower than that of **22**. Therefore, addition to an electron poor alkyne is expected to be easier, and indeed the reaction with DMAD is complete in minutes in the case of **2**, in 4 h in the case of triazapentalene **22** and in weeks in the case of tetraazapentalenes.[1] The greater electron availability likewise causes the easier oxidation by air and the easier polymerization of compound **2** compared with its aza analogues. Second, two azomethin ylide sites are individuated in diazapentalene **2**, and we observe addition across positions 3 and 5 but not onto the alternative 1,3-dipole (across positions 1 and 9a). This is expected since the last process involves loss of the benzene aromaticity.



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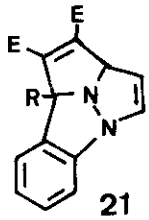

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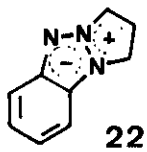

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Third we had rationalized DMAD addition with related heteropentalenes as a two steps reaction involving discrete diradical or zwitterionic intermediates rather than a concerted cycloaddition.[1] This holds also in the present case and is apparent in the reaction in methanol. Notice that product **19** does not arise by proton shift from the preformed cycloadduct **10**, but proton shift takes place at an early stage of the reaction (see Scheme **2**), as shown by the fact that product **10** is not found even in aprotic solvent and formation of products **15** and **16** is quenched in methanol. The driving force for proton shift is probably formation of a more conjugated intermediate. We previously reported both proton shift and solvent addition with related zwitterions in methanol,[1] but the course of the present reaction is different, since it involves a further addition step.

In conclusion the chemical behaviour of benzodiazapentalene **2** follows the same trend as the previously studied benzotriaza- and tetraazapentalenes.[1] The rate of the first step, a Michael type addition onto the electron poor alkyne, depends on the ionization potential of the electron rich pentalene. The following course of the reaction is however peculiar for diazapentalene **2**, in the almost exclusive propensity to skeleton rearrangement (although rearrangement of a different type had been previously observed with polyazapentalenes)[1] and to double rather than simple addition. The latter property reflects a greater reactivity of the primary adducts, in comparison with the greater stability imparted by multiple aza substitution to similar structures obtained from the polyazapentalenes.

EXPERIMENTAL

The UV-visible spectra were recorded on a Perkin-Elmer 200 spectrophotometer, the nmr spectra on a Perkin-Elmer R12 or a Brucker WP80 instrument with $(CH_3)_4Si$ as an internal standard, ir spectra on a Perkin Elmer 197 spectrophotometer, and mass spectra on a Du Pont 492 spectrometer. Melting points are uncorrected. Spectroscopic grade solvents and dimethyl acetylenedicarboxylate (DMAD) were freshly distilled before use.

Synthesis of 2-bromo-2,3-dihydro-1H-pyrazolo[1,2-a]indazolium bromide (**7**). To a solution of sodium ethoxide (from 1.52 g of sodium and 45 ml of anhydrous ethanol), 3.6 g of indazole was added at room temperature. To the clear solution, 14.25 g of allyl bromide was quickly added at 7°C while stirring and cooling with ice. After the end of the addition cooling was dismissed. The temperature rised to 38°C, and the solution was refluxed for 14 h. No starting material remains under these conditions. Work up and chromatography on silica gel eluting with cyclohexane-ethyl acetate 9:1 mixture, yielded 1-allylindazole (**3**) (3 g, 63% yield) as an oil (picrate mp 112.5-113.5°C, see ref. 9) and 2-allylindazole (**4**) (1.3 g, 28% yield) as an oil (picrate mp 125-6°C, see ref. 9). The isomers could also be easily distinguished by uv spectroscopy, see ref. 10.

Product **3** (1.58 g) was suspended in 10 ml of conc. HBr at -10°C, and Br_2 (1.6 g) in 0.5 ml of HBr was slowly added while stirring. After 1 h at -10°C dilution with water, neutralization with

Na_2CO_3 and work up yielded 1-(1,2-dibromopropyl)indazole (**5**) 2.85 g, 90% yield) as an orange oil. Product **4** was analogously brominated to yield **6**, an oil, in 90% yield.

Product **5** (2.7 g) in 50 ml of acetone was refluxed and stirred for 7 days to yield 2.03 g (75% yield) of product **7**, mp 172-173°C ^{1}H nmr (CD_3OD), δ 9.3 s, 7.5-8.3 m (4H, arom.), 5.8 m (1H, CHBr), 5.35 m (4H, CH_2); ir, 3130, 1620, 1530 cm^{-1}. Anal. calcd for $C_{10}H_{10}N_2Br_2$: C 37.76%; H, 3.17; N, 8.81. *Found:* C, 37.79%; H, 3.15; N, 8.78.

Product **6** was analogously cyclized to **7** in 80% yield in 5 days. When the three steps (allylation, bromination and cyclization) were carried out without intermediate separation of the 1- and 2-substituted isomers, the bromide **7** was obtained in 74% overall yield.

Dehydrohalogenation of bromide **7**, in an nmr tube. Two solutions, one containing bromide **7** (85 mg) in 0.5 ml of CD_3OD and the other LiH (25 mg) in 0.5 ml of CD_3OD were deaerated by argon flushing and mixed in an nmr tube. The ^{1}H nmr spectrum of the green solution showed a spectrum attributable to *pyrazolo[1,2-a]indazole* (**2**), δ 9.1 d (J=3.5 Hz) and 8.8 d (H1 and H3), 7.17 t (H2), 7.15 s (H5). The spectrum did not show appreciable change during several hours. Similar results were obtained in DMSO.

Dehydrohalogenation of bromide **7** in the presence of DMAD. Reaction of Pyrazolo[1,2-a]indazole **2** formed in situ.

Procedure a (see corresponding note in the Table). Bromide **7** (1.9 g) and DMAD (3.68 g) were dissolved in DMF or CH_3OH (150 ml) and deaerated by flushing with argon for 30 min. Lithium methoxide (0.45 g) was added in portions while maintaining the temperature under 20°C. After 15 min the solution was poured in 600 ml of H_2O and extracted with benzene (in the DMF case) or directly evaporated and the residue treated with benzene-water (in the methanol case). Evaporation of the benzene layer and chromatography on silica gel (eluting with benzene-ethyl acetate 8:2 mixture) gave products **9-19** with the yields reported in the Table, accompanied with considerable amounts of unreacted DMAD and dimethyl 2-methoxy fumarate and maleate. The characteristics of the new products are reported in the following according to the elution order. Further spectroscopic data (ir, mass spectra, COOMe and quaternary carbon absorptions in ^{13}C nmr) are in accord and are not reported for the sake of brevity.

10cH-1,2-dimethoxycarbonyl-10c-(1',2'-dimethoxycarbonylethenyl)-1,2-diazocino[1,2,3-ab]indazole (**15**), yellow crystals, mp 140-141°C (MeOH); ^{1}H nmr (C_6D_6), δ 8.05 dd (1H) and 7.4-7.2 m (3H, aromatic protons), 7.1 d (J=7 Hz) and 6.65 d (J=9, H5 and H3), 5.3 s (chain proton), 5.2 dd (H4); ^{13}C nmr ($CDCl_3$), δ 96.08 d, 109.80 d, 115.71 d, 126.28 d, 130.24 d, 130.82 d, 136.31 d, 148.06 d; Anal. calcd for $C_{22}H_{20}N_2O_8$: C, 60.00%; H, 4.58; N, 6.36. Found: C, 59.93%; H, 4.48; N, 6.29.

11H-2,3-dimethoxycarbonyl-11-(1',2'-dimethoxycarbonylethenyl)pyrazolo[1,2,3-ab]1,2-benzodiazocine (**16**), yellow crystals, mp 130-131°C (after treatment with MeOH in the cold); this product is not very stable in solution, and undergoes extensive decomposition during chromatographic work up; thus yields reported refer only to the conditions adopted; ^{1}H nmr (C_6D_6), δ 7.6 s (H1), 7.47 d (J=4 Hz) and 6.8 d (H4 and H5), 7.1-7.4 m (4H, aromatic protons), 5.35 (chain proton); ^{13}C nmr ($CDCl_3$), δ 94.20 d, 118.07 d, 122.55 d, 124.94 d, 129.97 d, 138.76 d, 142.48 d, 153.90 d. Anal.:

C, 59.84%; H, 4.63; N, 6.22.

1,2-Dimethoxycarbonyl-5,9c-diazapentaleno[1,7,6-ab]indazole (**9**), colourless crystals, mp 187°C (MeOH); ^{1}H nmr ($CDCl_3$),δ 8.1 d (J=3 Hz) and 7.05d (H3 and H4), 8.4 dd (1H) and 8-7.5 m (3H, aromatic protons). Anal. calcd for $C_{16}H_{12}N_2O_4$: C, 64.86%; H, 4.08; N, 9.46. Found: C, 65.11%, H,3.91; N, 9.26.

2,3-Dihydro-1,2,3,4-tetramethoxycarbonyl-7,11c-diazaazuleno[1,9,8-ab]indazole (**19**) red crystals, mp 190°C (MeOH); ^{1}H nmr ($CDCl_3$), δ 8.7 d (J=8 Hz, H6), 7.4 d (H5), 7.8-7.4 m (4H, aromatic protons) 5.55 (AB system, H2 and H3); ^{13}C nmr ($CDCl_3$),δ 46.21 d, 48.07 d, 107.46 d, 107.13 d, 123.00 d, 122.73 d, 128.55 d, 131.21 d. Anal.: C, 59.91%; H, 4.52, N, 6.55.

Procedure b. Bromide **7** (1.9 g) in 150 ml of the solvent of choice was deaerated by flushing with argon for 30 min. Solid lithium methoxide (0.45 g) was added as above. The colour of the solution turned to wine-red. After 30 min 1.89 g of DMAD was added and the colour turned to brown-red. After 2 h work up followed as above.

Procedure c. A two phases mixture of bromide **7** (1.9 g) in 80 ml of water and 80 ml of benzene was deaerated by flushing with argon for 3 h. DMAD (1.89 g) was added and argon flushing pursued for 40 min, 5.5 ml of a 3 M deaerated aqueous solution of NaOH was added while stirring. The benzene layer turned to yellow and then brown-red. After 3 h work up followed as above.

Catalytic hydrogenation of compounds **15** and **16**. Samples (100 mg) of the title compounds in 10 ml of solvent (ethanol for **15** and benzene for **16**) were hydrogenated at room temperature and normal pressure. 1 Mole of hydrogen was absorbed yielding products **17** and **18** respectively. These were purified by chromatography and recrystallization.

10cH-4,5-dihydro-1,2-dimethoxycarbonyl-10c-(1',2'-dimethoxycarbonylethenyl)-1,2-diazocino[1,2,3-ab]indazole (**17**), yellow crystals, decomp 75°C (after treatment with hexane), 60% yield from **15**; ^{1}H nmr (C_6D_6),δ 6.45-7.2 m (5H, aromatic and olefinic protons), 5.65 (chain proton), 3.4-3.6 m (two CH_2 groups); ^{13}C nmr (C_6D_6),δ 26.38 t, 27.65 t, 91.44 d, 115.59 d, 124.31 d, 126.46 d, 131.43 d, 146.39 d. Anal. calcd for $C_{22}H_{22}N_2O_8$: C, 59.72%; H, 5.01; N, 6.33. Found: C, 59.62%; H, 4.80; N, 6.20. M^+, 442 m/z.

11H-4,5-dihydro-2,3-dimethoxycarbonyl-11-(1',2'-dimethoxycarbonylethenyl)pyrazolo[1,2,3-ab]1,2-benzodiazocine (**18**), light yellow crystals mp 154°C (from benzene), 65% yield from **16**; ^{1}H nmr ($CDCl_3$),δ 6.9-7.3 m (4H, aromatic protons) 7.65 s (H1), 5.15 s (chain proton), 3-3.2 m (two CH_2 group); ^{13}C nmr (C_6D_6), δ 30.13 t, 61.91 t, 91.68 d, 121.88 d, 122.91 d, 129.70 d, 134.64 d, 143.18 d. Anal.: C, 59.73%, H, 4.75; N 6.14. M^+, 442 m/z.

AKNOWLEDGMENT. This work was supported in part by the Italian Ministry of Education.

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Received, 9th December, 1987