Vilsmeier–Haack–Arnold and Bromination Reactions of 4*H*-Pyrazolo[1,5-*a*]indole Derivatives[1)]

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As typical electrophilic substitution reactions of the 4*H*-pyrazolo[1,5-*a*]indole derivatives, the Vilsmeier–Haack–Arnold (V.H.A.) and bromination reactions were investigated in detail and mechanisms involving the 1*H*-pyrazolo[1,5-*a*]indoles as reaction intermediates are proposed. The V.H.A. reaction products were subjected to oxidative and reductive reactions, and a novel reduction of the conjugated system involving a double bond in the aromatic (pyrazole) ring was observed. Reaction pathways for these reactions are also proposed.

Keywords Vilsmeier–Haack–Arnold reaction; 4*H*-pyrazolo[1,5-*a*]indole; bromination; mechanism; 1*H*-pyrazolo[1,5-*a*]-indole; AM1 calculation

Among three annular tautomers[2)] of pyrazolo[1,5-*a*]indole,[3a)] the 4*H*-isomer has been best studied so far, and several methods are available for the preparation of this derivative.[3)] However, few studies have been done on the chemical behavior of these compounds.[3c,3d,4)] In this article, we describe typical electrophilic reactions of the 4*H*-isomers, notably the Vilsmeier–Haack–Arnold[5)] (V.H.A.) and bromination reactions of the pyrazolo[1,5-*a*]indole derivatives.

When the 4*H*-isomer **1** was reacted with the Vilsmeier reagent (2.2 eq) prepared from $POCl_3$ and dimethyl formamide (DMF), the reaction was slow at room temperature (r.t.) but was completed within 2 h at 60 °C to give two products, **3** (92%) and **4** (3%) (Chart 1). This reaction condition is milder than that reported for the pyrazole derivative, 1,3-dimethyl-5-methylpyrazole (95—100 °C/2 h).[6)] The minor colorless product was assigned the expected structure **4**, based on the following observations. The formyl group of **4** (M^+: *m/z* 260 from MS) was detected both in the IR (1669 cm^{-1}) and ^{1}H-NMR (δ 10.07, s) spectra. Absence of 3-H and the presence of 4-H_2 (δ 4.18, s) and the same number of aromatic protons as in **1** were apparent in the ^{1}H-NMR spectrum. In the NOESY spectrum, NOEs were detected between 3-CHO and *o*-H of the 2-phenyl substituent, as well as between 4-H and 5-H. These observations exclude the possibility of the alternative 3*H*-isomeric structure for **4**, *i.e.*, 4-formyl-2-phenyl-3*H*-pyrazolo[1,5-*a*]indole. The long-range C–H COSY spectrum and the absence of IR absorption around 1610 cm^{-1} characteristic of the hydrazone part of the 3*H*-isomer[7a)] also support this assignment. For the major yellow product the presence of the formyl group was supported by the IR (2810, 1642 cm^{-1}) and ^{1}H-NMR (δ 9.81, s) analyses. In addition, the introduction of a dimethylaminomethylene unit was deduced from the ^{1}H-NMR signals of NMe_2 (δ 3.45, s) and one vinyl proton (δ 9.51, s). The 4-H_2 was no longer present in this product. The introduction of a dimethylaminomethylene unit is the general outcome when an active methylene compound is subjected to the V.H.A. reaction,[5)] so the structure **3** was considered for the major product, though the alternative structure **5** could not be excluded at this stage. The signal of the formyl group of the major product **3** appeared at higher magnetic field than those of the minor product **4** in both the ^{1}H-(Δ 0.26 ppm) and ^{13}C-NMR (Δ 1.6 ppm) spectra. These diamagnetic shifts are caused by the conjugation of CHO with NMe_2. In the IR spectrum the CHO absorption band was at a lower frequency (Δ 27 cm^{-1}) than that of **4**. The final distinction between the structures **3** and **5** for the major product was accomplished by NOESY (^{1}H nuclear Overhauser enhancement and exchange spectroscopy) experiments. Strong NOEs were observed between 5-H/NMe_2 and CHO/*o*-H of the phenyl group. These observations are consistent with the structure **3** and not with **5**. When the V.H.A. reaction of the 4*H*-isomer **1** was continued at r.t. for 24 h without warming, the product **4** was no longer detected and **3** was obtained as a sole product (64%) together with the recovered starting material (31%). Warming seems to be prerequisite for the formation of the product **4**, *vide infra*. The same reaction of the 4*H*-isomer **2** was smooth at r.t., being completed within 4 h to give the single product **6** in 91% yield. In the ^{1}H-NMR spectrum of the product **6**, long-range

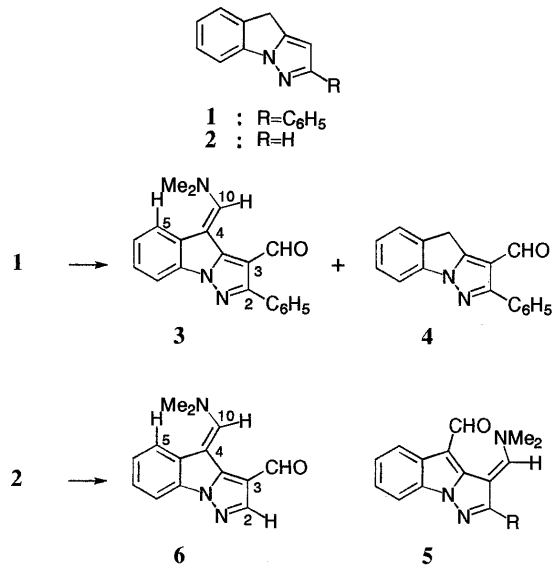


Chart 1

coupling between 3-CHO and 2-H ($J=1.2$ Hz) was detected. The structure **6** was also supported by the NOESY spectra, in which NOEs between 5-H and NMe_2, and between CHO and 2-H were seen.

The V.H.A. reaction of indene was reported to give the salt **i** as the initial product, from which the product **ii** was obtained after hydrolysis with sodium carbonate (Chart 2).[8] In contrast to this report, the V.H.A. reaction product **3** resisted further hydrolysis with aqueous 10% NaOH at refluxing temperature and was recovered without change. In order to examine the details of the formation of **ii**, Arnold prepared the enamine **iii** and found that the V.H.A. reaction of **iii** did not yield the product **ii**, but **iv**, excluding the enamine **iii** as a reaction intermediate.[8] Following this experiment, the 4*H*-isomer **1** was transformed into the enamine **7** by reaction with DMF dimethylacetal (Chart 2).[9] The geometry of NMe_2 in the product **7**, although opposite to that of the product **3**, was determined from the NOESY spectrum, which showed distinct NOEs between 5-H/10-H, NMe_2/3-H, and 3-H/*o*-H of the phenyl group. This geometry is a stable one, since NMe_2 in the products, **3**, **6** and **7** is at less crowded sites according to molecular model inspections. When the enamine **7** was subjected to the V.H.A. reaction, the reaction was completed within 30 min at r.t., and the product **3** was obtained in almost quantitative yield. Thus, the following reaction pathway is proposed for the V.H.A. reaction of the 4*H*-isomers (Chart 3).

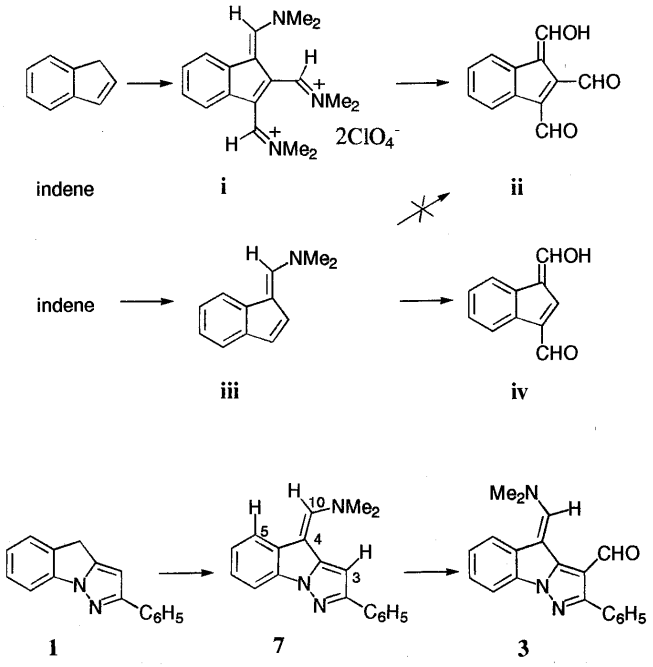


Chart 2

The reaction pathway (A) affords the minor product **4**. In this mechanism the Vilsmeier reagent (V.R.) directly attacks C-3 of the 4*H*-isomer **1**, as in the reaction of 1,3-diphenyl-5-methylpyrazole,[6] to give the unstable salt **8**. The isomerization of **8** into the stable 4*H*-isomeric form, but not into the less stable 3*H*-isomeric form, and the following elimination of HX affords the product salt **9**, whose work-up gives the minor product **4**. Since C-3 of the 4*H*-isomer is not so reactive as C-4 of the 1*H*-isomer, *vide infra*, route (A) becomes a side process and is operative only under forcing condition (warming). The involvement of the enamine **7** as a reactive intermediate for the major product formation seems reasonable, as demonstrated above in the quick reaction with V.R. leading to the major product **3**. However, the formation of the enamine **7** from the 4*H*-isomer **1** through a carbanionic species seems unreasonable due to the poor acidity of the 4-H_2,[10] as demonstrated by the rather harsh reaction conditions required for the preparation of the enamine **7**. Thus the

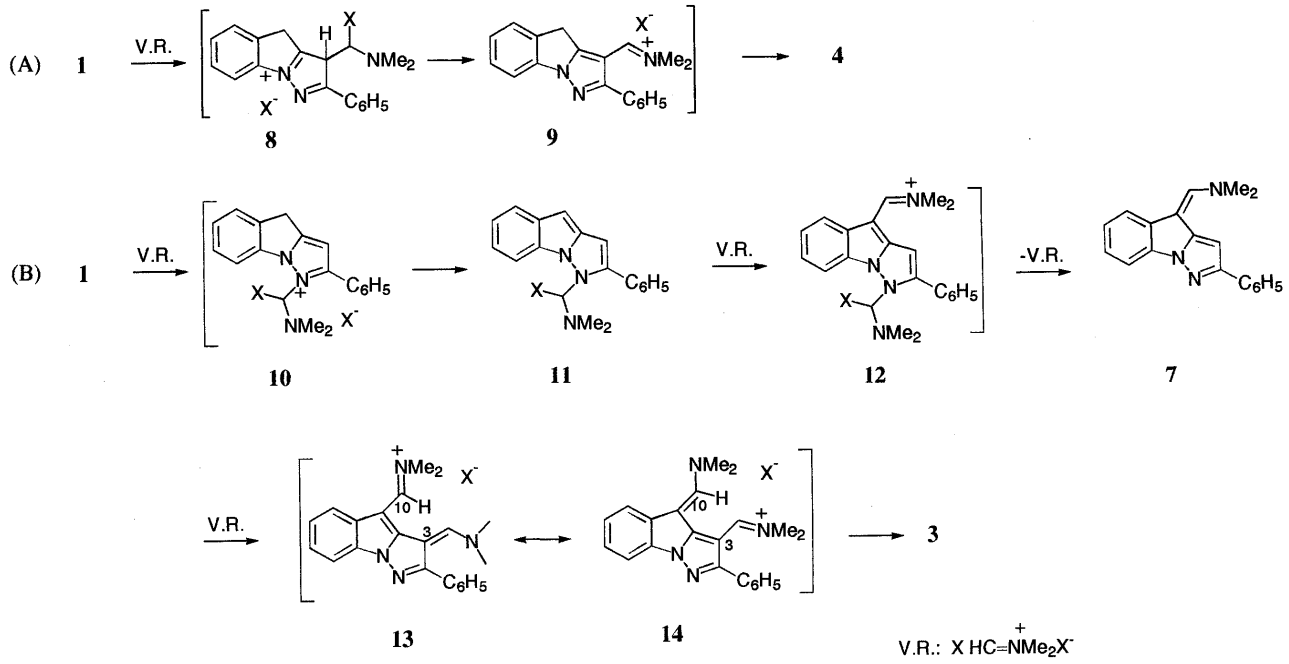


Chart 3

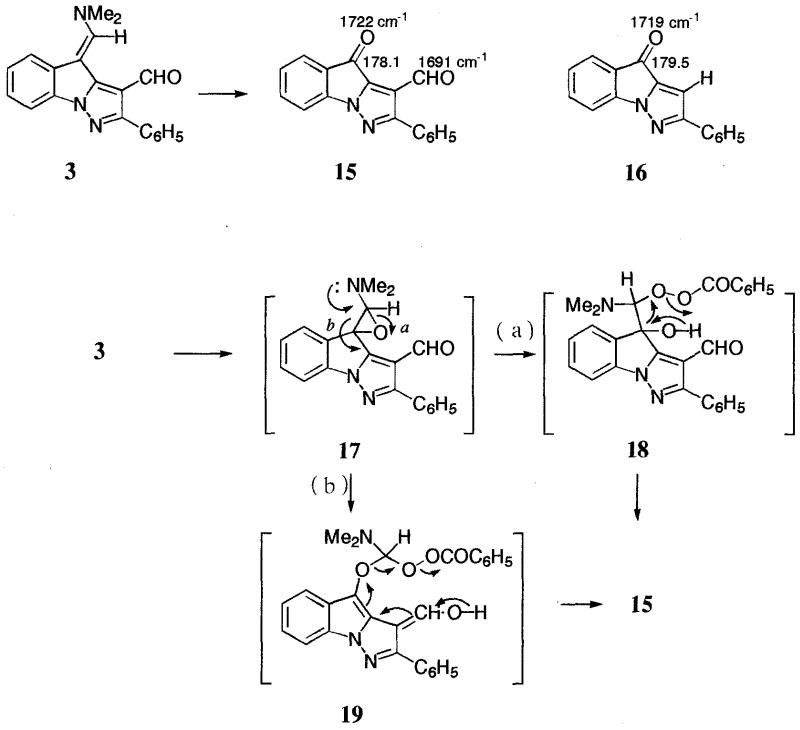


Chart 4

formation of **7** may occur through the reaction pathway (B) in Chart 3.

In route (B), V. R. attacks N-1 first to form the salt **10**. The subsequent elimination of HX and isomerization yield the highly reactive 1*H*-isomer **11**.[10] The reaction of **11** with V.R. should be smooth and departure of V.R. from the salt **12**, which is assisted by the conjugative electron-attraction from the C-4 substituent, allows the formation of the enamine **7** through simultaneous isomerization. A similar reaction mechanism was postulated for the introduction of a dimethylaminomethylene unit at the methyl group of 4-methylpyrimidine and related compounds.[11] The reaction of **7** with V.R. is fast as demonstrated in the separate experiment above. The product salt **13** thus formed has the 3*H*-isomeric form, and is in resonance with the more stable 4*H*-isomeric form **14**. The resonance stabilization among **13** and **14** allows NMe_2 at C-10 to take the more stable geometry. Since the 4*H*-isomer (*i.e.*, **14**) is more stable than the 3*H*-isomer (*i.e.*, **13**),[7a] the hydrolysis of the product salt yields the 4*H*-isomer **3** but not the 3*H*-isomer **5**. The reaction pathway (B) becomes exclusive at r.t. but increase of the reaction temperature (to 60 °C) accelerates pathway (A) as well, affording the minor product **4** (3%). The V.H.A. reaction of the 4*H*-isomer **1** was somewhat slower than that of the 2-unsubstituted 4*H*-isomer **2**, because the 2-phenyl substituent of **1** disturbs the attack of V.R. at N-1 and C-3 by deactivation of the pyrazole nucleus and steric crowding.

Since the chemical behavior of the V.H.A. reaction product with a dimethylaminomethylene unit has been little studied,[5] the product **3**, which resisted basic hydrolysis, was subjected to oxidative and reductive reactions. The oxidation of the aldehyde **3** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the orange product **15** in 52% yield (Chart 4). Two equivalents of the oxidant were required for this oxidation. Loss of a dimethylaminomethylene unit (C_3H_7N), as well as the incorporation of one oxygen atom, were indicated from the MS and NMR spectra. The formyl group (δ 10.25, s) remained intact and the formation of the C-4 keto-group was deduced from the IR and NMR spectra in comparison with those of the 4-keto compound **16** (Chart 4). These observations allowed the unequivocal assignment of the structure **15** for the orange oxidation product. Following the reports that the enamine double bond was cleaved by hydrogen peroxide and peracid,[12] and 3-methylindole was oxidized with perbenzoic acid into 2-acetylformanilide,[13] the reaction pathways for this oxidation are postulated to be as shown in Chart 4. The first step is the conjugative addition of peracid to the enamine double bond, *vide infra*, to afford the epoxide **17**. As a next step, two pathways, (a) and (b) are possible for ring-opening of the epoxide. Route (a) is initiated with C–O bond-cleavage. The subsequent reaction with a second molecule of peracid leads to the formation of the perester **18**, whose fragmentation (shown by the arrows) results in the production of the ketone **15**. The alternative pathway (b) is started by C–C bond-breaking, which is assisted by conjugative electron attraction with 3-CHO, *vide infra*. The perester **19** thus formed is fragmented as shown by the arrows to give the ketone **15**. The role of 3-CHO in this oxidation was checked by the reaction of the enamine **7**, which lacks 3-CHO. The enamine **7** was found to be too reactive for selective oxidation with *m*-CPBA, and gave an intractable mixture. The presence of 3-CHO, *i.e.*, a deactivating factor, seems to be essential for the selective oxidation of **3**. The formation of the perester **19** requires

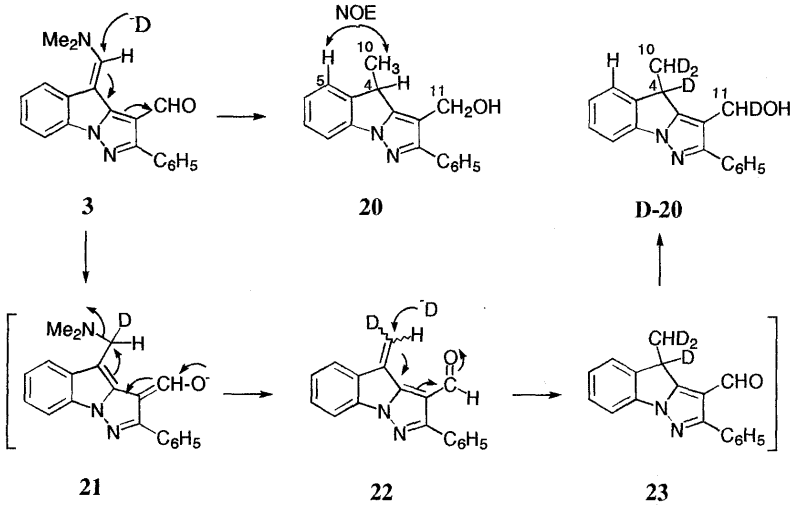


Chart 5

isomerization of the stable 4*H*-isomeric form into the less stable 3*H*-isomer, although no such isomerization is involved in the transformation of **17** into **18**, but such isomerization was found to play some role in the conjugative reduction of **3** with $NaBH_4$, *vide infra*. Therefore it is not possible to rule out either pathway at present.

In the reduction of **3** with $NaBH_4$, two reaction sites are available to the reductant, the formyl and enamine residues. The enamine double bond is in general not reduced with hydride reagent unless it takes the iminium form.[14] When **3** was exposed to $NaBH_4$ in dichloromethane–methanol (1 : 1), the alcohol **20** was obtained as a sole product in 69% yield (Chart 5). The reduction of CHO to CH_2OH was readily detected in both the ^{1}H-NMR (δ 4.73 and 4.78, AB type, J=12.2 Hz) and IR (3323 cm^{-1}) spectra. The dimethylamino group was no longer present, but the secondary methyl group (CH–C<u>H</u>$_3$) was observed at δ 1.59 (J=7.3 Hz) in the ^{1}H-NMR spectrum. From these observations, together with the molecular weight (M^+: m/z 276) from the MS, the structure **20** was assigned to the alcoholic product. The NOE detected between 5-H and 4-Me (10-H) and between C<u>H</u>$_2$OH and *o*-H of the phenyl substituent in the NOESY spectrum are consistent with this structure. The final structural proof was obtained when the same alcohol **20** was prepared from the 4-methyl aldehyde **29** by reduction with $NaBH_4$, *vide infra*. In order to see the positions of deuterium in this reduction, **3** was reduced with the deuterated reagent ($NaBD_4$) and the four-deuterated product, D-**20** (M^+: m/z 280) was obtained in 47% yield. The deuterated positions were determined by ^{1}H-NMR analyses of the product D-**20** in comparison with the non-deuterated product **20**. In the ^{1}H-NMR spectrum of D-**20** no 4-H signal was detected, and the Me (10-H) and C<u>H</u>$_2$OH (11-H) signals of **20** both changed into singlets with an integration decrease equivalent to one proton. To our surprise, the reduction of **3** with $LiAlH_4$ in ether was ineffective and **3** was recovered intact. The 3-CHO moiety is not accessible to the reductant, probably due to the deactivation caused by vinylogous conjugation with NMe_2 and steric crowding. The reaction pathway with D-incorporation is depicted in Chart 5. Reduction is initiated by the conjugative nucleophilic attack of deuteride at C-10 (not at CHO) of **3** and results in the formation of the mono-deuterated product **22** by the replacement of NMe_2 with deuterium through **21**. Similar attack of deuterium at C-10 (again, not at CHO) of the initial product **22** gives the di-deuterated enol, whose enol-keto isomerization in MeOD yields the tri-deuterated product **23**. The final deuteride reduction of CHO of **23** gives the tetra-deuterated product D-**20**. This reduction is novel because the double bond conjugating with CHO through the aromatic ring, in this case the pyrazole ring, was saturated with hydride reagent prior to aldehyde reduction.

Further studies on the V.H.A. reaction were carried out with the 4*H*-isomers, which have either one of two reaction sites (C-3 and C-4) blocked by the substituent (Chart 6). At first the 4*H*-isomer **24**, derived from the corresponding phenol[7] by methylation with dimethyl sulfate, was subjected to the V.H.A. reaction. When **24** was reacted with V.R. at 80 °C for 2 h, the aldehyde **25** was obtained in 37% yield and no other product was isolated. According to the ^{1}H-NMR spectra, both formyl (δ 9.99, s) and dimethylaminomethylene (δ 3.42, s, NMe_2; 7.31, s, =C<u>H</u>NMe_2) groups were formed in the product at the expense of 4-H_2 and one aromatic proton. However, the 2-phenyl group stayed intact. Although the product **25** had a sharp melting point (mp 165.5—166.5 °C) and showed a single spot on TLC, contamination with its atropisomer (7%) was detected at δ 3.34 ppm as a small singlet (NMe_2) in the ^{1}H-NMR spectrum. The position of CHO was determined by detailed ^{1}H-NMR analyses. In a series of the 4*H*-isomers, the 8-H signal generally appears at low magnetic field, but not as separate signals from other aromatic protons. However, 8-H is readily distinguished from the other aromatic protons by the selective coupling with C-8 that appears at the highest magnetic field region among the aromatic carbons in the ^{13}C-NMR spectra. Although the starting material **24** showed 8-H at δ 7.64 as a broad doublet (J=7.8 Hz), 8-H of the product appeared at δ 8.18 as a sharp doublet with

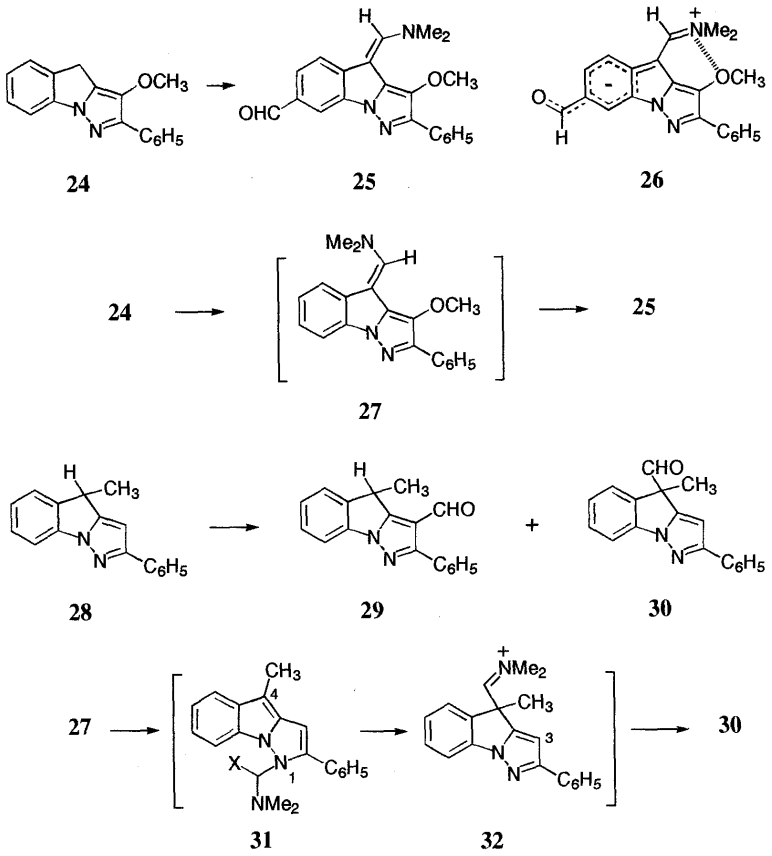


Chart 6

meta coupling ($J=1.2$ Hz). This *meta* coupling allowed us to assign the position C-7 for CHO. From these observations, the structure **25** was assigned to the major component of the product (93%). In the NOESY spectrum two NOEs were detected, CHO/8-H and OMe/NMe_2, and these observations are consistent with the structure **25**, including the stereochemistry of NMe_2, *vide infra*. In the IR spectrum the CHO absorption of **25** (1674 cm^{-1}) was detected at a higher frequency region than those of the aldehydes **3** (1642 cm^{-1}), *p*-dimethylaminobenzaldehyde (1663 cm^{-1}) and the aldehyde **4** (1669 cm^{-1}), but lower than that of benzaldehyde (1698 cm^{-1}), suggesting a smaller contribution of NMe_2 in the conjugation with CHO as compared with the aldehyde **3**. The preferential formylation at C-7 is explained by introducing the enamine **27** as a reaction intermediate, in which C-7, by vinylogous conjugation with NMe_2, is better activated toward the electrophile than C-5, which receives *peri*-steric hindrance. The formation of **27** can be understood in terms of the pathway shown for the enamine **7**, but the geometry of NMe_2 is not appropriate to avoid unfavorable space interaction with 3-OMe. This sterically unfavorable direction can be explained as follows. The long-range resonance between 7-CHO and NMe_2 as depicted in formula **26** allows the induction of a cationic center at the nitrogen atom of NMe_2 and this cationic center is responsible for an attractive interaction between NMe_2 and OMe through space. This minute attractive force could control the stereochemistry of the NMe_2 group.

Then the 4-methyl 4*H*-isomer **28**, which was prepared from the 4*H*-isomer **1** by 4-H abstraction with *n*-BuLi followed by methylation with iodomethane, was subjected to the V.H.A. reaction. When the reaction was carried out at 60 °C, two products, **29** (20%) and **30** (61%), were obtained (Chart 6). These two products possessed the same molecular composition ($C_{18}H_{14}N_2O$ from HRMS), so they are regio-isomers of the mono-formylated products. According to ^{1}H-NMR analyses, the minor product **29** still has the secondary methyl group (δ 1.74, d, $J=7.5$ Hz) but no 3-H was detected. The major product **30** has no 4-H but retains 3-H (δ 6.69, s) and 4-Me appears as a singlet (δ 1.75). In the IR spectrum, the CHO absorption band (1724 cm^{-1}) was comparatively high compared with that of **29** (1667 cm^{-1}) and close to the aliphatic aldehyde region, supporting the C-4 position for CHO. These observations are consistent with the structures assigned to the products, **29** and **30**. The spectral behavior of CHO of **29** was well correlated with that of the product **4** in the IR (1667 *vs.* 1669 cm^{-1}), ^{1}H-NMR (δ 10.05 *vs.* 10.07 ppm) and ^{13}C-NMR (δ 185.7 *vs.* 185.7 ppm) spectra. As the reaction pathway for these products, the direct attack of V.R. at C-3 of the 4*H*-isomer **28** is considered for the minor product **29**, as in the case of the production of **4**. For the major product **30**, the participation of the 1*H*-isomer **31** is taken into account as in the case of the V.H.A. reaction of the 4*H*-isomer **1**, *vide supra*. Once the reactive 1*H*-isomer **31** is formed, V.R. attacks C-4 preferably over C-3 because C-3 is deactivated by the participation of *meso*-ionic form in the resonance of the 1*H*-isomer **31**.[10] The subsequent departure of V.R. from

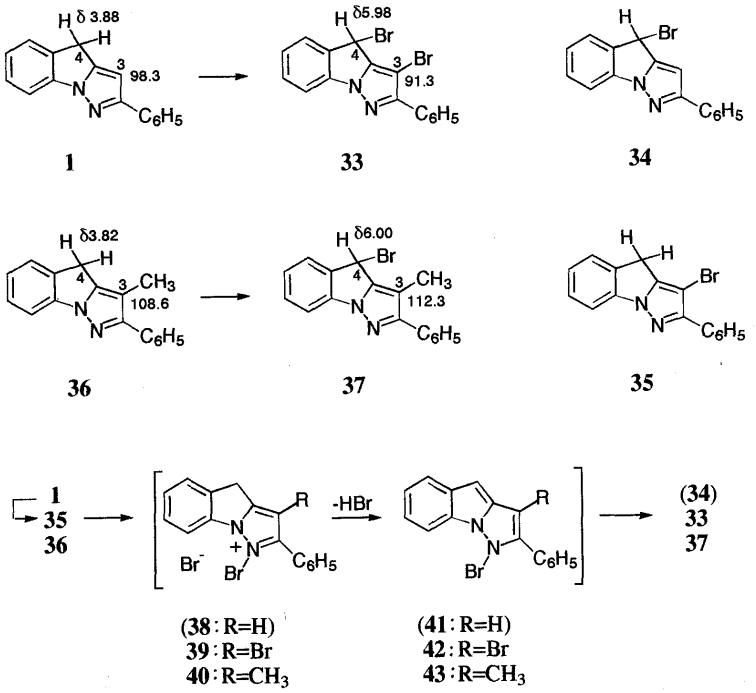
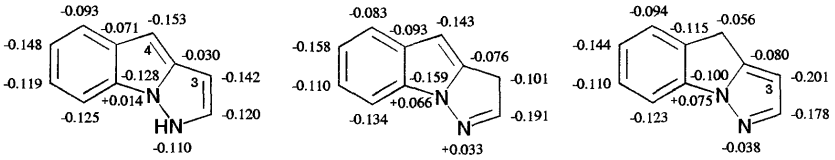


Chart 7

N-1 gives the product salt **32**, which yields the product **30** after hydrolytic work-up. Further reaction of the product salt **32** with V.R. is not possible due to the C-4 cationic substituent, which reduces the reactivity at C-3 for both electronic and steric reasons. The relative reaction rate of the two pathways is reflected in the product ratio of **29** and **30**.

As another typical electrophilic reaction, the 4*H*-isomer was subjected to the bromination reaction. When the reaction of the 4*H*-isomer **1** with bromine (2 eq) was conducted in wet CCl_4 under ice-cooling with exclusion of light in order to avoid radical involvement, the dibromide **33** was obtained in 77% yield (Chart 7). The incorporation of two bromine atoms was revealed by the isotopic ratio of the product [$M^+ : (M^+ + 2) : (M^+ + 4) = 1 : 2 : 1$ from MS]. In the ^{1}H-NMR spectrum, 3-H was no longer detectable but 4-H was observed at rather low magnetic field (δ 5.98 ppm) compared with that of the starting material **1** (δ 3.88 ppm), and its integration value was reduced to one proton. These spectral observations implied the bromine incorporations at both C-3 and C-4, and thus the structure **33** was assigned to the dibromide. The similar bromination of the 3-methyl-4*H*-isomer **36**[3b] afforded the monobromide **37** in 80% yield. Monobromination was supported by the MS [$M^+ : (M^+ + 2) = 1 : 1$]. In the ^{1}H-NMR spectrum, the 3-Me signal remained (δ 2.35, s) but one 4-H was lost and the remaining 4-H (δ 6.00, s) was detected at as low a position as in the dibromide **33**. Therefore, the structure **37** was assigned to the monobromide. The 4-Br of these bromides shifts 4-H to low magnetic field ($\Delta\delta$ 2.1 ppm). In the ^{13}C-NMR spectrum, the signal of C-3 of **37** was also moved to low magnetic field ($\Delta\delta$ 3.7 ppm) compared with **36**, although it is remote from the bromine-bearing C-4. The remote paramagnetic shift is comparatively large when the similar shift of *ipso*-C of bromobenzene from benzene ($\Delta\delta$ 5.8 ppm) is considered.[15] In contrast to this paramagnetic shift of bromobenzene, the introduction of Br at C-3 of **1** resulted in an up-field shift of C-3 in the ^{13}C-NMR spectrum. The C-3 signal of **33** appeared at higher magnetic field than that of **1** ($\Delta\delta$ 7.0 ppm) (Chart 7). Since 4-Br of **37** can cause a downfield shift of the C-3 signal ($\Delta\delta$ 3.7 ppm) as mentioned above, the total C-3 upfield shift for **33** should be (3.7 + 7 =) 10.7 ppm, which corresponds well with the upfield shift value (11.8 ppm) reported for 4-bromo-1-phenylpyrazole.[16] When the 4*H*-isomer **1** was brominated with one equivalent of bromine, the products were solely composed of the starting material **1** and the dibromide **33**, and no monobromide corresponding to either **34** or **35** was detected by detailed TLC and ^{1}H-NMR spectral analyses of the products. The C-4 brominations of these 4*H*-isomers under ionic condition can again be rationalized in terms of the participation of the 1*H*-isomers as in the V.H.A. reaction of the 4*H*-isomer **1** described above. Since the sp^2 nitrogen of the phyrazole ring was reported to complex with bromine,[17] the first step in the bromination of the 4*H*-isomer **36** could be the formation of the complex **40** (Chart 7). The following isomerization of **40** with elimination of HBr gives the reactive intermediate, the 1*H*-isomer **43**, that can react quickly with bromine accompanied with bromine departure from N-1 to yield the monobromide **37**. Since no 4,4-dibromide was formed in these brominations, the C-4 bromination *via* the 1*H*-isomer does not take place more than once. In bromination of the 4*H*-isomer **1**, two monobromides **34** and **35** are possible as an initial product leading to the dibromide **33**. The bromination of the 4*H*-isomer **1** *via* **38** and **41** gives the 4-monobromide **34** and direct bromination of **1** at C-3 affords the 3-monobromide **35**. If the 4-monobromide **34** is the initial product, its C-3



1*H*-pyrazolo[1,5-*a*]indole 3*H*-pyrazolo[1,5-*a*]indole 4*H*-pyrazolo[1,5-*a*]indole

Chart 8

bromination has to compete with the C-3 bromination of **1** at some stage of the reaction. The relative availability of **34** and **1** for C-3 bromination would be reflected in the C-3 electron densities of these compounds, which could be detected in the C-3 chemical shifts of their ^{13}C-NMR spectra (Chart 7). As observed in **37**, the introduction of 4-Br resulted in a paramagnetic shift of C-3 ($\Delta\delta$ 3.7 ppm), so the C-3 bromination of **34** should be more difficult than that of **1**. This difference of the reactivity at C-3 between **34** and **1** should allow the accumulation of the 4-monobromide **34**, when 1 eq of bromine is employed. But this was not the case. When the 3-monobromide **35** is obtained as an initial product by the direct C-3 bromination of **1**, the following C-4 bromination of **35** *via* **39** and **42** would give the dibromide **33**, the observed product, provided that the second C-4 bromination is faster than the first C-3 bromination. This is quite probable, because the reactive 1*H*-isomer **42** is involved in the second bromination. The possible reaction pathways for these brominations are summarized in Chart 7.

The involvement of the 1*H*-isomer as a reaction intermediate in both the V.H.A. reaction and bromination of the 4*H*-isomers is also supported by the following experiment. When the 4*H*-isomer **1** was exposed to AcOD–D_2O for 40 days at r.t., parts of 4-H_2 (91%) and 3-H (31%) were exchanged with deuterium according to ^{1}H-NMR analysis. The C-4 deuteration is explicable in terms of the participation of the 1*H*-isomer formed by the initial N-deuteration at N-1 and the subsequent isomerization. For C-3 deuteration, two pathways are possible, *i.e.*, C-3 deuteration of the 4*H*-isomer **1** and the 1*H*-isomer (**41** with N–D bond). Actually no electrophilic reaction at C-3 of the 1*H*-isomers has been observed so far.[10]

The relative availabilities at C-4 and C-3 of the pyrazolo[1,5-*a*]indoles toward electrophiles were evaluated from AM1 calculations[18] of the three isomers, 1*H*-, 3*H*- and 4*H*-pyrazolo[1,5-*a*]indoles. The collected atomic charges are summarized in Chart 8. In the 1*H*-isomer, the atomic electron density at C-4 is larger than that at C-3. This difference may allow the electrophilic reaction to occur preferentially at C-4 over C-3. The calculation also revealed the high reactivity at C-3 of the 4*H*-isomer toward electrophiles. But in the 3*H*-isomer, the electron density at C-6 is greater than that at C-4. However, the reaction of the 3*H*-isomers with mild electrophiles was found to occur selectively at C-4 to give the 4-substituted 4*H*-isomers after isomerization.[7a]

In summary, the reactions of the 4*H*-pyrazolo[1,5-*a*]-indole derivatives with the Vilsmeier and bromine reagents, as typical electrophilic substitution reactions, were found to involve the 1*H*-pyrazolo[1,5-*a*]indoles as reaction intermediates and to give the selective reaction products. The Vilsmeier–Haack–Arnold reaction products were subjected to oxidative and reductive reactions and a novel type of reduction of the conjugated system involving the aromatic (pyrazole) ring was observed.

Experimental[19]

4-((*E*)-Dimethylaminomethylene)-3-formyl-2-phenyl-4*H*-pyrazolo-[1,5-*a*]indole (3) and 3-Formyl-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (4) 1) A solution of **1** (929 mg, 4.00 mmol) in DMF (4 ml) was added to the Vilsmeier reagent, prepared by stirring a mixture of $POCl_3$ (0.82 ml, 8.80 mmol) and dry DMF (1 ml) at r.t. for 1 h after mixing at ice-cooling temperature in a nitrogen atmosphere. The resulting reaction mixture was further stirred at r.t. for 1 h then at 60 °C for 2 h. After quenching of the reaction with aqueous 10% NaOH, the solution was extracted with dichloromethane. The extracts were washed with brine and dried. Flash column chromatography (petroleum ether–ethyl acetate, 3 : 2) gave the product **3** (1.164 g, 92%) and **4** (35 mg, 3%). **3**, yellow needles, mp 197.5—198.0°C (from ethyl acetate). MS *m/z*: 315 (M^+, 100), 272 (92), 271 (72), 244 (21), 243 (20), 158 (15), 140 (19), 128 (13), 84 (27), 77 (18). HRMS: Calcd for $C_{20}H_{17}N_3O$: 315.1370. Found M^+: 315.1357. UV $\lambda_{max}^{CH_3CN}$ nm (log ε): 253 (4.21), 277 (4.11), 298 (sh, 3.98), 387 (4.02). IR: 2952, 2810, 1642, 1601, 1520, 1360, 1138, 1057, 947, 860, 744, 712 cm^{-1}. ^{1}H-NMR δ: 3.45 (6H, s, 2 × CH_3), 7.25 (1H, td, J=7.9, 1.1 Hz, 6-H), 7.32 (1H, td, J=7.8, 1.0 Hz, 7-H), 7.44—7.52 (3H, m, Ar-H), 7.69 (1H, d, J=7.9 Hz, 5-H), 7.75 (2H, m, 2′,6′-H), 7.86 (1H, d, J=7.8 Hz, 8-H), 9.51 (1H, s, 10-H), 9.81 (1H, s, CHO). ^{13}C-NMR δ: 44.9 ($N(CH_3)_2$), 95.2 (C-4), 110.4 (C-3), 111.2 (C-8), 122.6 (C-5), 123.4 (C-6), 124.0 (C-7), 126.9 (C-4a), 128.6 (C-3′, 5′), 128.8 (C-4′), 129.7 (C-2′, 6′), 132.8 (C-1′), 134.7 (C-8a), 148.9 (C-3a), 151.0 (C-10), 160.3 (C-2), 184.1 (CHO). *Anal.* Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.30; H, 5.25; N, 13.28. **4**, colorless needles, mp 162.0—162.5 °C (from ethyl acetate). MS *m/z*: 260 (M^+, 100), 259 (36), 232 (16), 231 (32), 204 (4), 155 (5), 129 (26), 102 (7), 101 (8), 77 (11). IR: 3056, 2919, 2852, 1669, 1542, 1472, 1377, 872, 768, 752, 692 cm^{-1}. ^{1}H-NMR δ: 4.18 (2H, s, 4-H_2), 7.32 (1H, td, J=7.5, 1.1 Hz, 6-H), 7.45—7.54 (4H, m, Ar-H), 7.57 (1H, d, J=7.5 Hz, 5-H), 7.78 (3H, m, 2′,6′,8-H), 10.07 (1H, s, CHO). ^{13}C-NMR δ: 30.1 (C-4), 111.6 (C-8), 116.1 (C-3), 125.9 (C-6), 126.2 (C-5), 128.4 (C-7), 128.9 (C-3′, 5′), 129.1 (C-2′, 6′), 129.2 (C-4′), 131.9 (C-1′), 133.4 (C-4a), 139.5 (C-8a), 149.0 (C-3a), 158.6 (C-2), 185.7 (CHO). *Anal.* Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.73; H, 4.51; N, 10.66. The similar reaction of **1** (232 mg, 1.00 mmol) with the Vilsmeier reagent prepared from $POCl_3$ (0.12 ml, 1.29 mmol) and DMF (1 ml) at r.t. for 24 h yielded **3** (203 mg, 64%) and the recovered starting material **1** (72 mg, 31%). The product **4** was not detected by TLC. 2) In a nitrogen atmosphere, a solution of **7** (86 mg, 0.30 mmol) in DMF (0.2 ml) was introduced into the Vilsmeier reagent prepared from $POCl_3$ (0.03 ml, 0.32 mmol) and DMF (0.10 ml), and the solution was stirred at r.t. for 30 min, then quenched with aqueous 10% NaOH. Work-up and purification as described above yielded the product, yellow needles (94 mg, 100%), which was identical with **3**.

4-((*E*)-Dimethylaminomethylene)-3-formyl-4*H*-pyrazolo[1,5-*a*]indole (6) Under a nitrogen atmosphere, a solution of **2** (156 mg, 1.00 mmol) in DMF (0.4 ml) was introduced into the Vilsmeier reagent prepared from $POCl_3$ (0.20 ml, 2.15 mmol) and DMF (0.2 ml), and reaction was continued at r.t. for 4 h to give, after work-up, **6** (218 mg, 91%) as pale yellow plates, mp 171.0—172.0 °C (from ethyl acetate). MS *m/z*: 239 (M^+, 100), 196 (79), 195 (39), 183 (12), 182 (6), 169 (16), 168 (35), 155 (6), 140 (13), 139 (12), 119 (9), 44 (48). UV $\lambda_{max}^{CH_3CN}$ nm (log ε): 252 (4.11), 267.5 (sh, 4.00), 296 (4.02), 385 (4.04). IR: 3056, 2972, 2761, 2730, 1662, 1616, 1520, 1422, 1375, 1171, 806, 756, 743 cm^{-1}. ^{1}H-NMR δ: 3.44 (6H, s, $N(CH_3)_2$), 7.24 (1H, td, J=7.8, 1.3 Hz, 6-H), 7.31 (1H, td, J=7.7, 1.2 Hz, 7-H), 7.69 (1H, d, J=7.8 Hz, 5-H), 7.80 (1H, d, J=7.7 Hz, 8-H),

8.09 (1H, d, J=1.2 Hz, 2-H), 9.30 (1H, s, 10-H), 9.74 (1H, d, J=1.2 Hz, CHO). ^{13}C-NMR δ: 44.8 ($N(CH_3)_2$), 94.9 (C-4), 111.2 (C-8), 112.9 (C-3), 122.6 (C-5), 123.5 (C-6), 124.0 (C-7), 127.0 (C-4a), 134.9 (C-8a), 147.7 (C-3a), 148.5 (C-2), 150.7 (C-10), 182.5 (CHO). *Anal.* Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.24; H, 5.31; N, 17.48.

4-((*Z*)-Dimethylaminomethylene)-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (7) A solution of **1** (464 mg, 2.00 mmol) in toluene (50 ml) was heated and a portion of the solvent (*ca.* 10 ml) was removed. *N,N*-Dimethylformamide dimethylacetal (1.00 ml, 7.53 mmol) and molecular sieves 4A (5 g) were added to the resulting anhydrous solution at 100 °C, and the mixture was refluxed for 20 h with constant removal of the volatile distillate. Flash column chromatography of the residue (petroleum ether–ethyl acetate, 85 : 15) gave **7** (223 mg, 38%), pale yellow needles, mp 204.5—205.5 °C (from ethanol). MS *m/z*: 287 (100), 245 (25), 244 (11), 243 (11), 231 (7), 183 (27), 169 (53), 143.5 (12), 143 (18), 141 (10), 128 (14), 115 (8), 83 (12), 81 (9), 77 (15). UV $\lambda_{max}^{CH_3CN}$ nm (log ε): 213 (4.02), 258 (4.10), 286 (3.87), 293 (sh, 3.86), 366 (4.09). IR: 3056, 2910, 1646, 1637, 1384, 750, 737, 706 cm^{-1}. ^{1}H-NMR δ: 3.32 (6H, s, $N(CH_3)_2$), 6.52 (1H, s, 3-H), 7.04 (1H, s, 10-H), 7.13 (1H, td, J=7.5, 1.2 Hz, 6-H), 7.21 (1H, td, J=7.6, 1.2 Hz, 7-H), 7.31 (1H, tt, J=7.3, 1.2 Hz, 4′-H), 7.41 (3H, m, Ar-H), 7.73 (1H, d, J=7.6 Hz, 8-H), 7.92 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 43.0 ($N(CH_3)_2$), 94.0 (C-4), 94.5 (C-3), 110.1 (C-8), 116.6 (C-5), 123.0 (C-6), 123.5 (C-7), 125.8 (C-2′, 6′), 127.5 (C-4′), 128.6 (C-3′, 5′), 133.3 (C-4a), 134.2 (C-8a), 134.4 (C-1′), 139.3 (C-10), 142.5 (C-3a), 155.0 (C-2). *Anal.* Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.68; H, 5.85; N, 14.66.

3-Formyl-4-oxo-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (15) *m*-Chloroperbenzoic acid (204 mg, 1.18 mmol) was added, in portions, to a solution of **3** (149 mg, 0.47 mmol) in CH_2Cl_2 (10 ml) at 0 °C and the resulting mixture was stirred for 1 h. The reaction was quenched with aqueous 10% NaOH (2 ml) and extracted with ether. After usual work-up, the chromatographic purification of the crude product yielded **15** (68 mg, 52%), orange needles, mp 189.5—190.0 °C (from ethyl acetate). MS *m/z*: 274 (M^+, 100), 245 (72), 218 (21), 217 (13), 190 (13), 189 (20), 141 (11), 115 (18), 114 (21), 83 (14), 77 (32), 69 (19). UV $\lambda_{max}^{CH_3CN}$ nm (log ε): 255 (4.01), 268 (sh, 3.94), 276 (sh, 3.92), 332 (sh, 3.15). IR: 3093, 2835, 2746, 1722, 1691, 1623, 1596, 1538, 1477, 1462, 1434, 1411, 1171, 1091, 1079, 902, 796, 755, 689 cm^{-1}. ^{1}H-NMR δ: 7.34 (1H, td, J=7.4, 1.2 Hz, 6-H), 7.50 (3H, m, Ar-H), 7.58 (1H, d with small splits, J=7.6 Hz, 8-H), 7.63 (1H, td, J=7.6, 1.2 Hz, 7-H), 7.73 (1H, d with small splits, J=7.4 Hz, 5-H), 7.90 (2H, m, 2′,6′-H), 10.25 (1H, s, CHO). ^{13}C-NMR δ: 111.9 (C-8), 118.9 (C-3), 125.7 (C-5), 127.4 (C-4a), 127.8 (C-6), 128.7 (C-3′,5′), 128.9 (C-2′,6′), 129.9 (C-4′), 130.7 (C-1′), 136.1 (C-7), 140.3 (C-3a), 143.6 (C-8a), 158.5 (C-2), 178.1 (C-4), 183.0 (CHO). *Anal.* Calcd for $C_{17}H_{10}N_2O_2$: C, 74.45; H, 3.67; N, 10.21. Found: C, 74.62; H, 3.44; N, 10.19.

3-Hydroxymethyl-4-methyl-2-phenyl-4*H*-phrazolo[1,5-*a*]indole (20) Under an argon atmosphere, $NaBH_4$ (38 mg, 1.00 mmol) was added to a solution of **3** (68 mg, 0.22 mmol) in a mixed solvent of CH_2Cl_2 (5 ml) and MeOH (5 ml). The solution was stirred at r.t. for 4 h and concentrated *in vacuo*. The residual solution was diluted with water and extracted with CH_2Cl_2. Flash column chromatography of the crude product (petroleum ether–ethyl acetate, 4 : 1) gave **20** (41 mg, 69%), white crystals, mp 143.5—144.0 °C (from ethyl acetate). MS *m/z*: 276 (M^+, 81), 259 (28), 245 (100), 143 (28), 130 (18), 116 (9), 115 (12), 77 (24). UV $\lambda_{max}^{CH_3CN}$ nm (log ε): 288 (4.45). IR: 3323, 3061, 2897, 1624, 1597, 1568, 1474, 1452, 1305, 1020, 1004, 771, 747, 699 cm^{-1}. ^{1}H-NMR δ: 1.59 (3H, d, J=7.3 Hz, CH_3), 2.18 (1H, br s, OH), 4.06 (1H, q, J=7.3 Hz, 4-H), 4.73 (1H, AB type, J=12.2 Hz, C<u>H</u>HOH), 4.78 (1H, AB type, J=12.2 Hz, CH<u>H</u>OH), 7.19 (1H, t, J=7.5 Hz, 6-H), 7.31—7.42 (5H, Ar-H), 7.64 (1H, d, J=7.9 Hz, 8-H), 7.77 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 17.4 (CH_3), 35.3 (C-4), 55.3 (CH_2OH), 110.5 (C-8), 113.4 (C-3), 124.6 (C-6, 7), 128.0 (C-2′, 6′, 5), 128.2 (C-4′), 128.6 (C-3′, 5′), 133.4 (C-1′), 139.3 (C-8a), 139.5 (C-4a), 150.0 (C-3a), 155.0 (C-2). *Anal.* Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.14; H, 5.77; N, 10.16. The alcohol **20** was also obtained quantitatively from the aldehyde **29** (15 mg, 0.05 mmol) by the similar reduction with $NaBH_4$ (3 mg, 0.08 mmol) in methanol (1 ml) at r.t. for 1 h.

3-Hydroxy[$^2H_1$]methyl-4-[$^2H_2$]methyl-[4-$^2H_1$]-4*H*-pyrazolo[1,5-*a*]-indole (D-20) Compound **3** (72 mg, 0.23 mmol) was reduced similarly with $NaBD_4$ (42 mg, 1.00 mmol) in a mixture of dry CH_2Cl_2 and MeOD (1 : 1, 2 ml) to give the tetradeuterio compound D-**20** (30 mg, 47%) and the starting material **3** (15 mg, 21%). D-**20**, white crystals, mp 141.0—142.0 °C (from ethyl acetate–pentane). MS *m/z*: 280 (M^+, 87), 263 (17), 262 (6), 248 (100), 146 (25), 132 (14), 117 (12), 77 (13). IR: 3339, 3060, 2890, 2140, 1627, 1598, 1565, 1474, 1452, 1307, 1025, 1016, 1001, 751, 697 cm^{-1}. ^{1}H-NMR δ: 1.59 (1H, s, $CDC\underline{H}D_2$), 1.86 (1H, br s, OH), 4.77 (1H, d, J=7.6 Hz, C<u>H</u>DOH, singlet by D_2O exchange), 7.21 (1H, td, J=7.5, 1.0 Hz, 6-H), 7.31—7.49 (5H, Ar-H), 7.66 (1H, d, J=7.8 Hz, 8-H), 7.80 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 16.9 (CHD_2, with small splittings), 35.2 (C-4, with small splittings), 55.1 (CHDOH, t), 110.5 (C-8), 113.3 (C-3), 124.6 (C-6, 7), 128.0 (C-2′, 6′, 5), 128.2 (C-4′), 128.6 (C-3′, 5′), 133.4 (C-1′), 139.2 (C-8a), 139.7 (C-4a), 150.0 (C-3a), 155.0 (C-2).

3-Methoxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (24) Dimethyl sulfate (0.86 ml, 9.09 mmol) was added to a suspension of 3-hydroxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (997 mg, 4.02 mmol), powdered KOH (663 mg, 10.04 mmol) and tetra-*n*-butyl ammonium bromide (TBAB, 65 mg, 0.20 mmol) in CH_2Cl_2 (50 ml) containing water (2 ml) and the mixture was stirred at r.t. for 10 min in a nitrogen atmosphere. After dilution with CH_2Cl_2, the solution was washed, dried and evaporated. Recrystallization of the residue gave **24** (948 mg, 90%), colorless needles, mp 112.5—113.0 °C (from methanol). MS *m/z*: 262 (M^+, 53), 247 (19), 144 (48), 130 (14), 116 (100), 89 (26). IR: 3058, 2934, 2827, 1625, 1601, 1476, 1298, 1256, 1092, 1031, 747, 699 cm^{-1}. ^{1}H-NMR δ: 4.00 (3H, s, OCH_3), 4.08 (2H, s, 4-H), 7.15 (1H, td, J=7.5, 1.1 Hz, 6-H), 7.29 (1H, tt, J=7.1, 1.5 Hz, 4′-H), 7.34—7.46 (4H, m, Ar-H), 7.64 (1H, d, J=7.8 Hz, 8-H), 8.04 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 29.3 (C-4), 59.4 (OCH_3), 110.1 (C-8), 124.1 (C-6), 125.7 (C-5), 126.4 (C-2′, 6′), 127.4 (C-4′), 128.2 (C-7), 128.4 (C-3′, 5′), 129.4 (C-3), 132.6 (C-1′), 133.0 (C-4a), 139.4 (C-3a), 140.5 (C-8a), 143.7 (C-2). *Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.93; H, 5.25; N, 10.73.

4-(Dimethylaminomethylene)-7-formyl-3-methoxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (25) Compound **23** (262 mg, 1.00 mmol) was allowed to react at r.t. for 2 h, then at 80 °C for 2 h with the Vilsmeier reagent prepared from $POCl_3$ (0.24 ml, 2.57 mmol) and DMF (1.00 ml). Quenching of the reaction with aqueous 10% NaOH and work-up as described above gave the crude product, and chromatography (petroleum ether–ethyl acetate, 65 : 35) yielded **25** (127 mg, 37%), yellow crystals, mp 165.5—166.5 °C (from ethyl acetate). MS *m/z*: 345 (M^+, 59), 330 (100), 227 (39), 171 (44), 149 (51), 141 (56), 129 (40), 97 (55). IR: 3066, 2927, 2810, 1674, 1641, 1600, 1474, 1407, 1367, 1341, 1279, 1172, 1126, 1105, 1058, 1002, 772, 699 cm^{-1}. ^{1}H-NMR δ (major isomer: 93%): 3.42 (6H, s, $N(CH_3)_2$), 3.71 (3H, s, OCH_3), 7.31 (1H, s, $CHNMe_2$), 7.32—7.52 (4H, m, Ar-H), 7.67 (1H, dd, J=8.3, 1.3 Hz, 6-H), 8.06 (2H, m, 2′,6′-H), 8.18 (1H, d, J=1.3 Hz, 8-H), 9.99 (1H, s, CHO). ^{1}H-NMR δ (minor isomer: 7%): 3.34 (s, $N(CH_3)_2$), 3.79 (s, OCH_3). ^{13}C-NMR δ (major isomer): 43.1 ($N(CH_3)_2$), 62.1 (OCH_3), 93.4 (C-4), 111.4 (C-8), 116.4 (C-5), 124.7 (C-6), 126.8 (C-2′, 6′), 127.7 (C-4′), 128.5 (C-3′, 5′), 132.2 (s), 132.3 (s), 133.1 (s), 134.1 (s), 134.3 (s), 139.8 (s), 141.8 ($\underline{C}HNMe_2$), 146.8 (s), 191.2 (CHO). ^{13}C-NMR δ (minor isomer): 44.7 ($N(CH_3)_2$), 61.4 (OCH_3). *Anal.* Calcd for $C_{21}H_{19}N_3O_2$: C, 73.02; H, 5.54; N, 12.17. Found: C, 73.13; H, 5.58; N, 12.02.

4-Methyl-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (28) The 4*H*-isomer **1** (997 mg, 4.29 mmol) was dissolved in dry THF (50 ml) and the solution was cooled to −78 °C under dry argon, then 0.82 M *n*-BuLi in hexane (5.75 ml, 4.72 mmol) was slowly added over 5 min. The resultant pink solution was stirred for 15 min, then iodomethane (0.60 ml, 9.64 mmol) was added and the reaction was continued at the same temperature for 1 h. After addition of aqueous ammonium chloride and water, the solution was extracted with ether. The crude product was purified by flash column chromatography (petroleum ether–ethyl acetate, 97 : 3) to give **28** (980 mg, 93%) and the 4,4-dimethylated product (55 mg, 5%). **28**, colorless oil. MS *m/z*: 246 (M^+, 100), 231 (14), 143 (40). HRMS: Calcd for $C_{17}H_{14}N_2$: 246.1111. Found M^+: 246.1133. IR (neat): 3060, 2971, 2930, 1624, 1596, 1545, 1473, 1455, 1303, 767, 728, 694 cm^{-1}. ^{1}H-NMR δ: 1.57 (3H, d, J=7.3 Hz, CH_3), 4.08 (1H, br q, J=7.3 Hz, 4-H), 6.58 (1H, d, J=1.2 Hz, 3-H), 7.20 (1H, td, J=7.5, 1.1 Hz, 6-H), 7.32 (1H, tt, J=7.2, 1.3 Hz, 4′-H), 7.37—7.48 (4H, m, Ar-H), 7.67 (1H, dd, J=7.6, 1.0 Hz, 8-H), 7.90 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 18.0 (CH_3), 35.1 (C-4), 97.4 (C-3), 110.4 (C-8), 124.4 (C-6), 124.6 (C-5), 125.8 (C-2′, 6′), 127.9 (C-4′), 128.1 (C-7), 128.6 (C-3′, 5′), 133.9 (C-1′), 139.3 (C-4a), 139.8 (C-8a), 151.5 (C-3a), 156.3 (C-2).

3-Formyl-4-methyl-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (29) and 4-Formyl-4-methyl-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (30) A solution of **28** (259 mg, 1.05 mmol) in DMF (0.5 ml) was added to the Vilsmeier reagent prepared from $POCl_3$ (0.15 ml, 1.61 mmol) and DMF (1.0 ml)

at r.t., and the resulting solution was kept at 45 °C for 6 h. After addition of aqueous 10% NaOH and extraction as described above, the crude product was flash-chromatographed (petroleum ether–ethyl acetate, 9 : 1) to give **29** (59 mg, 20%) and **30** (177 mg, 61%). **29**, colorless crystals, mp 115.0—116.0 °C (from ethyl acetate–pentane). MS *m/z*: 274 (M^+, 100), 273 (72), 246 (27), 245 (87), 231 (7), 229 (10), 218 (7), 217 (6), 202 (6), 143 (33), 142 (20), 140 (6), 128 (19), 115 (24), 101 (15), 77 (29). HRMS: Calcd for $C_{18}H_{14}N_2O$: 274.1105. Found M^+: 274.1093. IR: 3058, 2942, 2845, 1667, 1542, 1471, 860, 755, 704 cm^{-1}. ^{1}H-NMR δ: 1.74 (3H, d, J=7.5 Hz, CH_3), 4.35 (1H, q, J=7.5 Hz, 4-H), 7.33 (1H, td, J=7.6, 1.0 Hz, 6-H), 7.44—7.54 (5H, m, Ar-H), 7.74—7.77 (3H, m, 2′,6′,8-H), 10.05 (1H, s, CHO). ^{13}C-NMR δ: 15.3 (CH_3), 37.3 (C-4), 111.5 (C-8), 116.2 (C-3), 125.0 (C-5), 126.1 (C-6), 128.4 (C-7), 128.9 (C-3′, 5′), 129.1 (C-2′, 6′), 129.2 (C-4′), 132.0 (C-1′), 138.8 (C-8a), 139.5 (C-4a), 153.8 (C-3a), 159.0 (C-2), 185.7 (CHO). *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.90; H, 5.43; N, 10.20. **30**, colorless syrup. MS *m/z*: 274 (M^+, 21), 246 (53), 245 (100), 218 (7), 217 (9), 143 (24), 142 (20), 140 (8), 116 (8), 115 (19), 105 (8), 91 (5), 77 (13). HRMS: Calcd for $C_{18}H_{14}N_2O$: 274.1105. Found M^+: 274.1108. IR (neat): 3061, 2981, 2932, 2818, 2715, 1724, 1620, 1543, 1476, 1455, 1381, 1341, 1300, 954, 907, 767, 697 cm^{-1}. ^{1}H-NMR δ: 1.75 (3H, s, CH_3), 6.69 (1H, s, 3-H), 7.27 (1H, td, J=7.6, 1.0 Hz, 6-H), 7.36 (2H, m, 5,4′-H), 7.44 (2H, m, 3′,5′-H), 7.51 (1H, td, J=7.7, 1.2 Hz, 7-H), 7.73 (1H, d, J=7.7 Hz, 8-H), 7.90 (2H, m, 2′,6′-H), 9.18 (1H, s, CHO). ^{13}C-NMR δ: 17.6 (CH_3), 56.6 (C-4), 99.2 (C-3), 111.0 (C-8), 125.2 (C-5), 125.3 (C-6), 125.9 (C-2′, 6′), 128.3 (C-4′), 128.8 (C-3′, 5′), 130.0 (C-7), 133.2 (C-1′), 134.7 (C-4a), 140.2 (C-8a), 147.3 (C-3a), 157.1 (C-2), 193.5 (CHO).

3,4-Dibromo-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (33) Bromine (0.1 ml, 1.94 mmol) was added to a solution of the 4*H*-isomer **1** (232 mg, 1.00 mmol) in CCl_4 (10 ml) containing a few drops of water in a flask which was wrapped with aluminum foil and cooled in an ice-bath. The resulting solution was stirred at r.t. for 1 h with exclusion of light. The reaction solution containing precipitates was briefly concentrated to *ca.* 2 ml and the precipitates were collected and recrystallized from ethyl acetate–pentane to give **33** (304 mg, 77%), yellow crystals, mp 181.5—182.5 °C (from chloroform–hexane). MS *m/z*: 392 (M^++4, 3), 390 (M^++2, 6), 388 (M^+, 3), 311 (96), 309 (100), 229 (74), 127 (36), 101 (21), 77 (51). IR: 3073, 2970, 1622, 1471, 1449, 1428, 1125, 976, 747, 722, 694 cm^{-1}. ^{1}H-NMR δ: 5.98 (1H, s, 4-H), 7.27 (1H, td, J=7.5, 1.1 Hz, 6-H), 7.46 (4H, m, Ar-H), 7.61 (2H, m, 5,8-H), 7.96 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 33.5 (C-4), 91.3 (C-3), 111.0 (C-8), 126.0 (C-6), 127.0 (C-5), 127.8 (C-2′, 6′), 128.5 (C-3′, 5′), 128.7 (C-4′), 130.5 (C-7), 131.7 (C-1′), 134.9 (C-4a), 138.9 (C-8a), 144.2 (C-3a), 153.8 (C-2). *Anal.* Calcd for $C_{16}H_{10}Br_2N_2$: C, 49.27; H, 2.58; N, 7.18. Found: C, 49.40; H, 2.46; N, 6.93.

4-Bromo-3-methyl-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (37) A solution of **36** (91 mg, 0.37 mmol) in CCl_4 (10 ml) containing a few drops of water was placed in a flask covered with aluminum foil and cooled to 0—3 °C in a nitrogen atmosphere. Then bromine (0.02 ml, 0.39 mmol) was added and the resulting solution was stirred at the same temperature for 1 h. The precipitates were recrystallized to give **37** (96 mg, 80%), yellow needles, mp 105.5—106.5 °C (from ethyl acetate–hexane). MS *m/z*: 326 (M^++2, 2), 324 (M^+, 2), 246 (31), 245 (100), 142 (27), 122 (10), 115 (15). IR: 3058, 2925, 2853, 1621, 1600, 1473, 1304, 749, 702 cm^{-1}. ^{1}H-NMR δ: 2.35 (3H, s, CH_3), 6.00 (1H, s, 4-H), 7.21 (1H, td, J=7.6, 1.1 Hz, 6-H), 7.37 (1H, tt, J=7.5, 1.3 Hz, 4′-H), 7.40 (1H, td, J=7.8, 1.1 Hz, 7-H), 7.46 (2H, m, 3′,5′-H), 7.58 (2H, m, 5,8-H), 7.73 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 9.5 (CH_3), 34.5 (C-4), 110.6 (C-8), 112.3 (C-3), 125.0 (C-6), 126.9 (C-5), 127.7 (C-2′, 6′), 127.9 (C-4′), 128.5 (C-3′, 5′), 130.3 (C-7), 133.5 (C-1′), 135.4 (C-4a), 139.3 (C-8a), 143.5 (C-3a), 155.6 (C-2). *Anal.* Calcd for $C_{17}H_{13}BrN_2$: C, 62.79; H, 4.03; N, 8.61. Found: C, 62.79; H, 3.82; N, 8.52.

Deuterium Exchange Reaction of 1 A solution of **1** (57 mg, 0.25 mmol) in a mixture of AcOD (1.0 ml) and D_2O (0.10 ml) was stirred at r.t. for 40 d. The solution was dissolved in ether and washed with 5% $NaHCO_3$ solution, water and brine successively, then dried over $MgSO_4$. Deuterium incorporation into the product (56 mg, 96%) was determined by examination of the ^{1}H-NMR spectrum, in which 8-H (δ 7.69) was used as a reference signal. The replacement of 4-H with deuterium was 91% and that of 3-H was 31%.

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References and Notes

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19) For general directions see ref. 7*a*.