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STUDIES ON THE SYNTHESIS OF INDOLE ALKALOIDS OF CONDYLOCARPINE TYPE. C-4 ALKYLATION OF THE 1-ALKYL-3-(HYDRAZONO)-2-PIPERIDONE SYSTEM.

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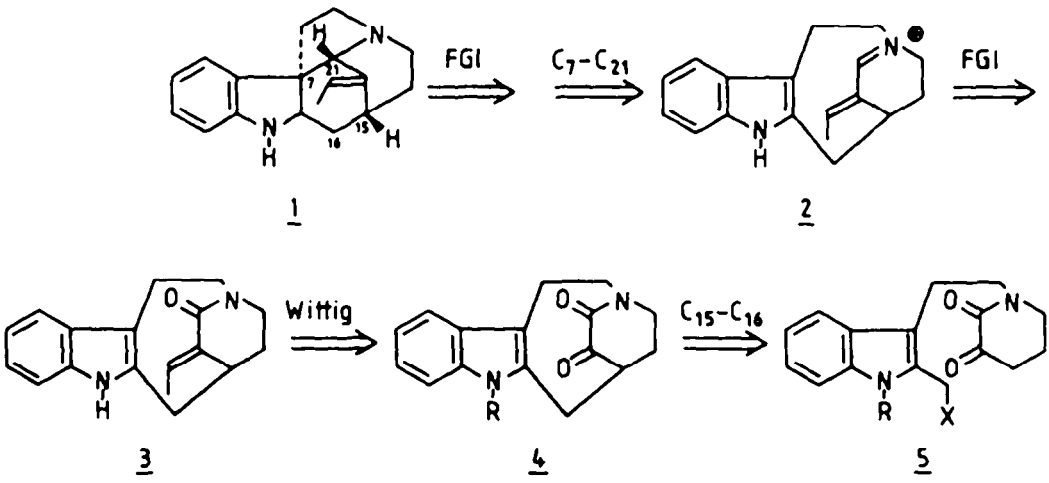
Abstract: A method for C-4 alkylation of the 1-alkyl-3-(hydrazono)-2-piperidone system (α-ketoamide hydrazone) is described. Attempts to apply it to an intramolecular alkylation for the creation of a condylocarpine alkaloid intermediate failed.

INTRODUCTION

The aim of the work was to develop an intramolecular alkylation method applicable to a general synthesis of condylocarpine type indole alkaloids keeping the stereoselectivity in mind; aspidospermatidine 1 was chosen as the final target molecule and Ender's chiral hydrazone method[1] for introduction of the desired stereoselectivity.

A retrosynthetic analysis[2] (Scheme 1) of 1, by oxidation and disconnection of the C_7-C_{21} bond gives the iminium compound 2. This might be generated from the amide 3 in analogy to the synthesis described by Harley-Mason.[3] The ethylidene fragment might be added by Wittig reaction, which usually takes place at a keto carbonyl group in preference to an amide carbonyl group (compound 4). The E-olefin is more stable than the Z-isomer and should be the major product. Uskokovic et al.[4] have shown that iminium compounds like 2 are in the E-configuration. The indole nitrogen in compound 4 should be protected. Disconnection of the C_{15}-C_{16} bond gives the ketoamide 5 with a leaving group X at C-16.



1 2 3 4 5

Scheme 1. Retrosynthesis of aspidospermatidine 1.
FGI = Functional Group Interconversion.

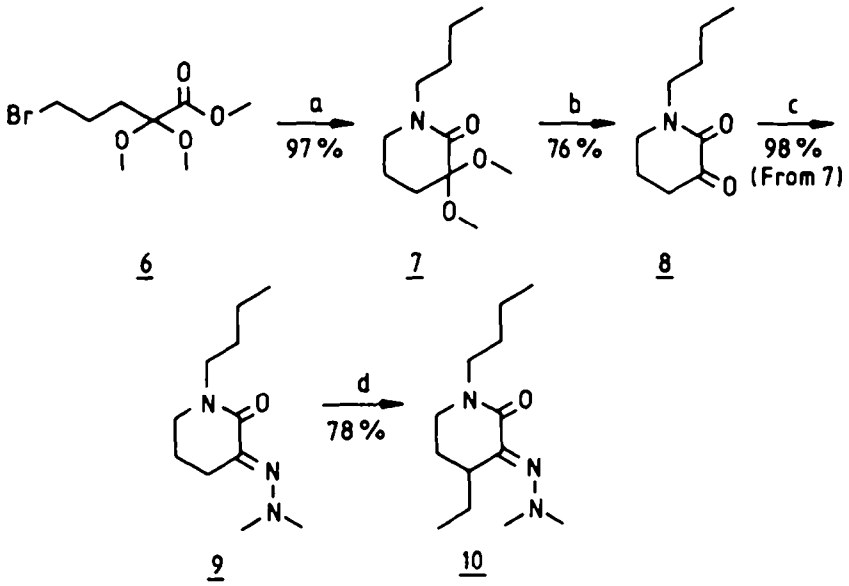
RESULTS AND DISCUSSION

The synthetic strategy adopted required, as first step, creation of the C_{15}-C_{16} bond by intramolecular alkylation using a suitable 1-indolylethyl-3-(hydrazono)-2-piperidone, and then if this proved successful, to procede further according to the lines depicted in the retrosynthetic analysis.

We decided first to test the feasibility of our synthetic strategy by applying it to an intermolecular alkylation using a simple 1-alkyl-3-(hydrazono)-2-piperidone. For that purpose a new route to 1-alkyl-2,3-piperidinediones was developed.

The bromoester 6 was prepared in four steps from γ-butyrolactone.[5,6] n-Butylamine[7] was treated with bromoester 6 in basic conditions to give the ketal 7. Deprotection of this afforded the desired 1-butyl-2,3-piperidinedione 8.

Condensation of 8 with 1,1-dimethylhydrazine yielded the corresponding 1-butyl-3-(dimethylhydrazono)-2-piperidone 9.[8] Lithiation of this (cf. ref. 9), followed by alkylation with ethyl bromide afforded 1-butyl-3-(dimethylhydrazono)-4-ethyl-2-piperidone 10 in good yield[10] (Scheme 2).



Scheme 2. Synthesis of 1-butyl-3-(dimethylhydrazono)-4-ethyl-2-piperidone 10. a) $BuNH_2$, b) TsOH, AcMe, c) NH_2NMe_2, d) 1. LDA, 2. EtBr.

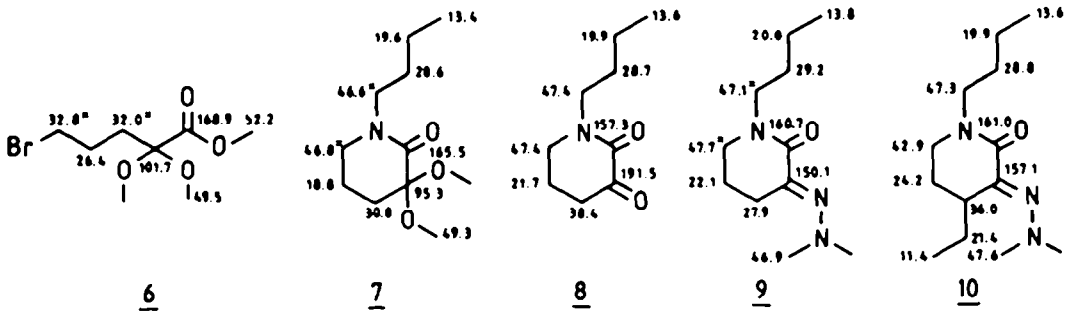
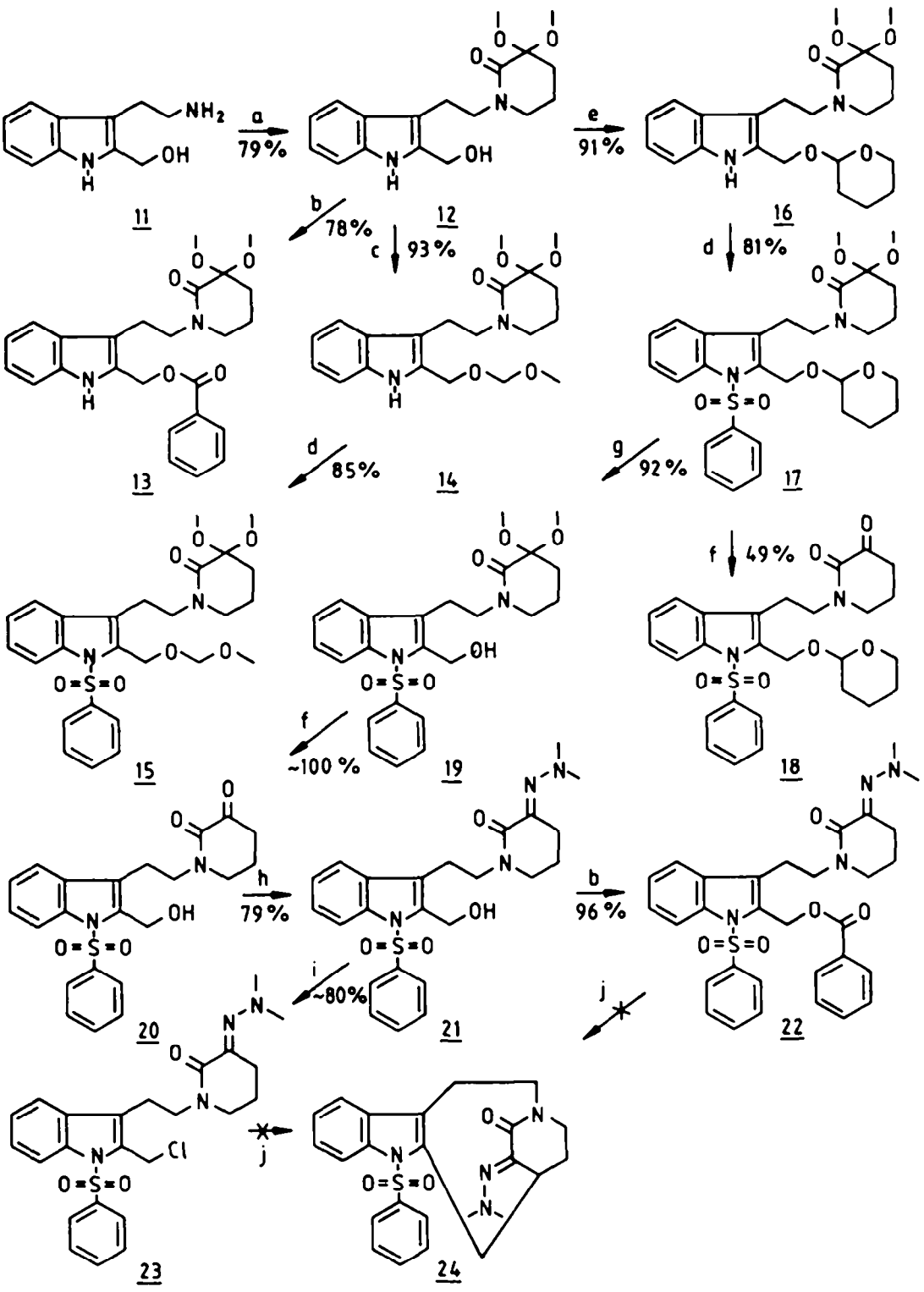


Fig. 1. ^{13}C NMR data of compounds 6-10. All the spectra were recorded in $CDCl_3$

With an effective alkylation method using an intermediate of desired type in hand, we turned our efforts to the application of the method to the intramolecular alkylation of a suitable 1-indolylethyl-3-(hydrazono)-2-piperidone. Scheme 3 depicts the experiments made.



Scheme 3. Elaboration of indolic compounds and attempted cyclizations.
a) 6, $NaHCO_3$, KI, b) PhCOCl, Pyr, c) MOMCl, i-Pr_2EtN, d) 1. LDA, 2. $PhSO_2Cl$, e) THPCl, i-Pr_2EtN, f) TsOH, AcMe, g) TsOH, MeOH, h) NH_2NMe_2, i) MsCl, 2,6-diMe Pyr, j) LDA

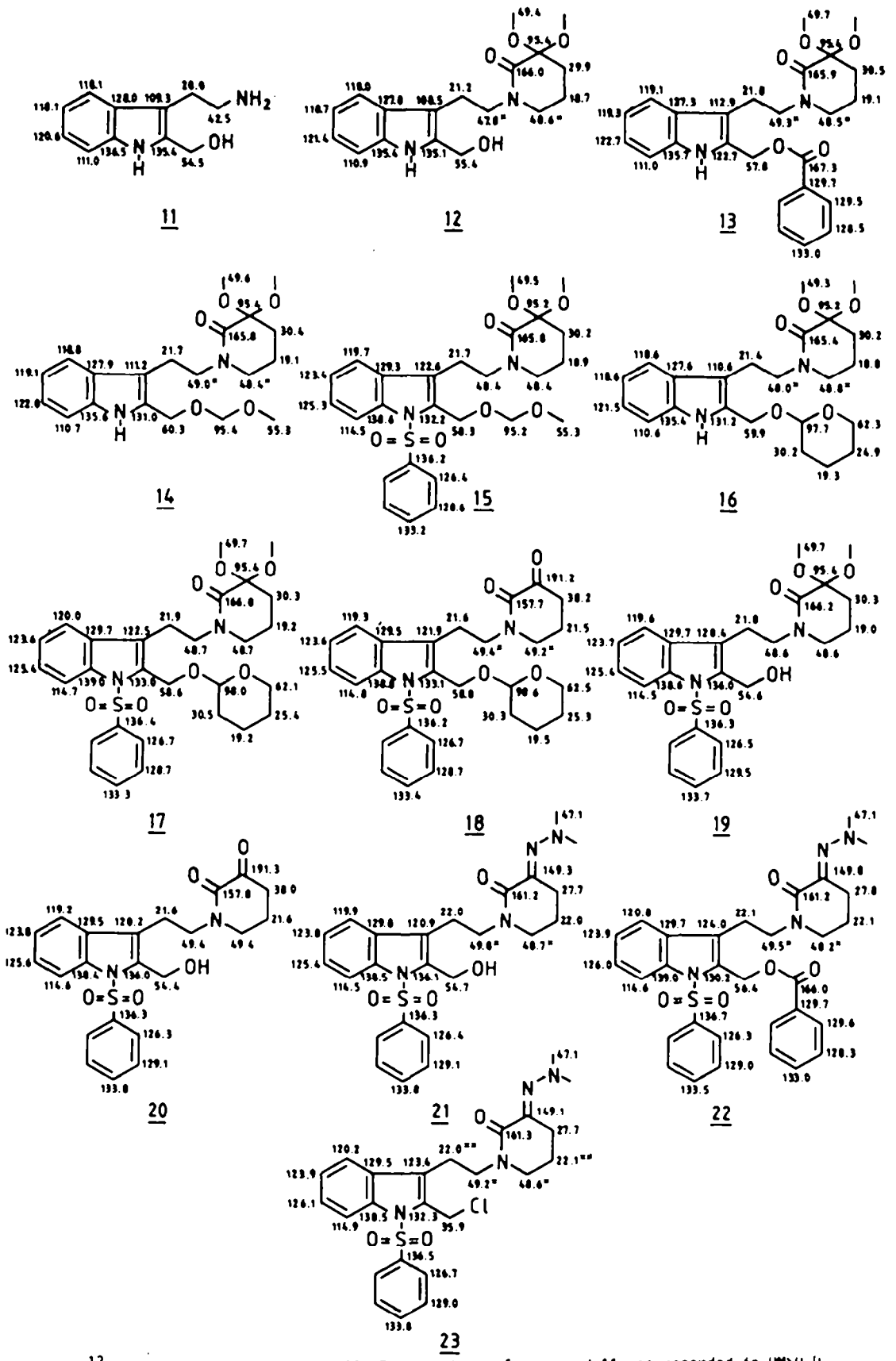


Fig. 2. ^{13}C NMR data of compounds 11-23. The spectrum of compound 11 was recorded in DMSO-D_6. All the other spectra were recorded in $CDCl_3$.

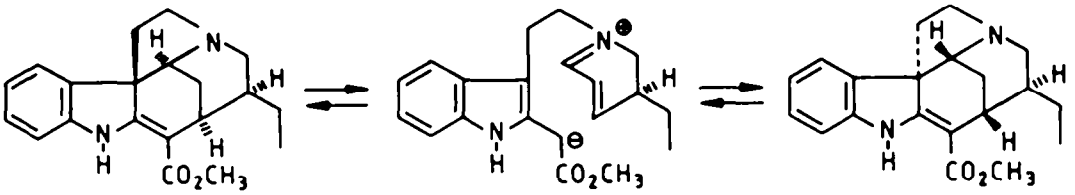
Reaction between 3-(2-aminoethyl)-2-hydroxymethylindole 11 (prepared according to Brieskorn and Wittig[11]) and bromoester 6 gave the lactam 12, which was benzoylated to yield ester 13. As the keto function could not be successfully unveiled (compound 13 was too acid labile), we were forced to modify our strategy.

The hydroxyl group in the lactam 12 was methoxymethylated to yield compound 14, and the indole nitrogen was protected with benzenesulfonyl chloride[12] to afford the amide 15. When the phase transfer procedure of Illi[13] was used, the reaction gave besides the desired amide 15 a considerable amount of starting material (~2/5). Since the methoxymethyl group could not be successfully removed, we again had to modify our synthetic strategy.

Tetrahydropyran protection of the hydroxyl group in the lactam 12 led to compound 16, and protection of the indole nitrogen with benzenesulfonyl chloride yielded compound 17. Stepwise deprotection of compound 17 (17→19→20) turned out to be more economical than its direct deprotection to 20 (or via 18). Condensation of compound 20 with 1,1-dimethylhydrazine afforded the corresponding hydrazone alcohol 21, which was benzoylated to compound 22. Unfortunately, compound 22 could not be intramolecularly alkylated to yield the desired compound 24; starting material and hydrazone alcohol 21 were obtained instead.

An alternative route to the desired cyclization was investigated as well. Reaction of the hydrazone alcohol 21 with methanesulfonyl chloride gave the chloride 23 (cf. ref. 14). However, when this was treated with LDA no intramolecular alkylation (23→24) took place: only unidentified highly polar material and a small amount of the starting chloride 23 were isolated.

The desired cyclizations (22→24 and/or 23→24) thus could not be realized and the planned aspidospermatidine synthesis was not achieved. Examination of Dreiding models shows that the system would be somewhat strained, evidently enough to defeat our strategy. Nevertheless, approximately the same steric conditions are met in the proposed intermediate 26 (Scheme 4) in the inversion of the cage structure of (-)-19,20-dihydroakuammicine 25 to its diastereoisomer 27.[15]



25 26 27

Scheme 4. Proposed racemization of 19,20-dihydroakuammicine 25.[15]

CONCLUSIONS

Although the desired cyclizations (22→24) and/or 23→24) failed, apparently because of steric reasons, the method described to alkylate the 1-alkyl-3-(hydrazono)-2-piperidone system is valuable. With the use of chiral hydrazones, functional groups might be stereoselectively introduced to the 4-position of a 2,3-piperidinedione ring. Besides this, the present investigation provided valuable information about the selective protection/deprotection of synthetically interesting indole derivatives.

EXPERIMENTAL

THF ja DME were distilled from $LiAlH_4$, CH_2Cl_2 and amines from CaH_2. Reactions were performed in argon atmosphere. Preparative column chromatography was done with Silica Woelm TSC (act III) or Alumina Woelm TSC (act III) or in the case of flash chromatography (Still *et al.*[16]) with Silica gel 60 $PF_{254-366}$ (for preparative layer chromatography from Merck). The same gel was used on glass plates in preparative thin layer chromatography.

The IR spectra were recorded with a Perkin-Elmer Infrared Spectrophotometer 700 in 1/cm using KBr tablets or NaCl crystals. The ^1H NMR spectra were recorded with a Jeol JNM-FX 60 spectrometer at 59.80 MHz in parts per million (δ) downfield from Me_4Si in $CDCl_3$. The ^{13}C NMR spectra were recorded at 15.04 MHz and relative to $CDCl_3$ at 77.0 ppm. The spectral data obtained are presented in Figs. 1 and 2 (*vide supra*). The mass spectra were recorded with a Jeol-DX 303/DA 5000 spectrometer using electron ionization unless otherwise stated.

1-Butyl-3,3-dimethoxy-2-piperidone (7)

A mixture of 5-bromo-2,3-dimethoxypentanoic acid methyl ester (6) (1.80 g, 7.06 mmol, made by the method of Yates and Schwartz[8]), butylamine (3.9 ml, 40 mmol) and KI (1.2 g, 7.2 mmol) in methanol (10 ml) was refluxed overnight. The solvent was evaporated, CH_2Cl_2 was added and the mixture filtered. The filtrate was extracted from aqueous NH_4Cl (50%, saturated, 20 ml) with CH_2Cl_2 (10 ml + 4x4 ml). The extracts were dried with $MgSO_4$ and chromatographed (alumina, MeOH:CH_2Cl_2 = 1:99) to give an oil (1.48 g, 6.9 mmol, 97%).
IR: 2970, 1660.
^1H NMR: 0.9-2.1 (m, 11H), 3.1-3.5 (m, 4H), 3.34 (s, 6H).
MS (m/z) CI (CH_4): 216 (M^+ +1, 15%), 184 (100%), 97 (22), 56 (59); Exact mass (EI): 215.1526 (calc. for $C_{11}H_{21}NO_3$: 215.1522).

1-Butyl-2,3-piperidinedione (8)

A solution of ketal 7 (100 mg, 0.465 mmol) and p-toluenesulfonic acid monohydrate (285 mg, 1.5 mmol) in acetone (3 ml) was stirred at room temperature for 30 min. $NaHCO_3$ (300 mg, 3.5 mmol) was added and stirring was continued for ten min. The mixture was filtered, the filtrate concentrated *in vacuo* and the residue chromatographed (flash, silica, AcMe:CH_2Cl_2 = 12:88) to give an oil (60 mg, 0.355 mmol, 76%).
IR: 2970, 1730, 1660.
^1H NMR: 0.9-1.8 m (m, 7H), 2.1-2.4 (m, 2H), 2.6-2.9 (m, 2H), 3.3-3.7 (m, 4H).
MS (m/z): 169 (M^+, 92%), 140 (15), 127 (32), 126 (100), 98 (62), 70 (26): Exact mass: 169.1099 (calc. for $C_9H_{15}NO_2$: 169.1103).

1-Butyl-3-(dimethylhydrazono)-2-piperidone (9)

Ketal 7 (625 mg, 2.90 mmol) was deprotected in acetone (6 ml) and p-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol) during 20 min. The solution was made basic with $NaHCO_3$ (0.5 g, 6 mmol), filtered and the solvent evaporated. CH_2Cl_2 was added, the mixture filtered again and the solvent evaporated. The residue was dissolved in methanol (5 ml) and 1,1-dimethylhydrazine (0.455 ml, 6 mmol) was added. After stirring for 40 min at room temperature, the solvent was evaporated and the residue filtered through alumina (CH_2Cl_2:MeOH = 99:1) to give an oil (610 mg, 2.9 mmol, 98%).
IR: 2970, 2880, 1650, 1580, 1450.
^1H NMR: 0.9-1.8 (m, 7H), 1.7-2.1 (m, 2H), 2.4-2.7 (m, 2H), 2.76 (s, 6H), 3.2-3.6 (m, 4H).
MS (m/z): 211 (M^+, 100%), 169 (49), 168 (42), 140 (33), 126 (33), 125 (93), 101 (62), 97 (36), 86 (46); Exact mass: 211.1691 (calc. for $C_{11}H_{21}N_3O$: 211.1685).

1-Butyl-3-(dimethylhydrazono)-4-ethyl-2-piperidone (10)

Hydrazone 9 (50 mg, 0.234 mmol) in THF (1 ml) was added to a solution of LDA [made by adding BuLi (93.9 µl of 2.5 M in hexane, 0.235 mmol) to an ice/acetone-cooled solution of diisopropylamine (36 µl, 0.258 mmol) in THF (1 ml)]. After stirring for 10 min the solution was further cooled (-83°C, ethyl acetate bath), bromoethane (18 µl, 0.24 mmol) was added and the solution was left to warm to room temperature in 1.5 hr. The solvent was evaporated and the residue extracted from aqueous NH_4Cl (saturated, 10 ml) with CH_2Cl_2 (5x5 ml). The organic extracts were dried with $MgSO_4$. The solvent was evaporated and the residue chromatographed (alumina, CH_2Cl_2: MeOH = 99:1) to give an oil (44 mg, 0.182 mmol, 78%).
IR: 2980, 1660, 1460.
^1H NMR: 0.8-1.7 (m, 12H), 1.8-2.2 (m, 2H), 2.4-2.7 (m, 1H), 2.69 (s, 6H), 3.1-3.6 (m, 4H).
MS (m/z): 239 (M^+, 85%), 197 (97), 196 (48), 195 (67), 181 (45), 168 (50), 153 (43), 125 (60), 112 (36), 101 (100), 98 (46), 97 (37), 86 (72); Exact mass: 239.1982 (calc. for $C_{13}H_{25}N_3O$: 239.1998).

3-[2-(3,3-Dimethoxy-2-oxopiperidino)ethyl]-2-hydroxymethyl indole (12)

A mixture of 5-bromo-2,2-dimethoxypentanoic acid methyl ester (1.34 g, 5.25 mmol), KI (1.32 g, 5.3 mmol), $NaHCO_3$ (0.89 g, 10.6 mmol) and 3-(2-aminoethyl)-2-hydroxymethylindole (11) (1.01 g, 5.31 mmol, made by the method of Brieskorn and Wittig[11]) was refluxed in methanol (10 ml) overnight. Methanol was evaporated and the residue extracted from water (50 ml) with CH_2Cl_2 (20 ml +

3x10 ml). The extracts were dried with $MgSO_4$, the solvent was evaporated, and the residue chromatographed (silica, CH_2Cl_2:MeOH:Et_3N = 95:5:0.2) to yield an oil (1.40 g, 4.2 mmol, 79%).
IR: 3300, 2960, 1640, 1460.
^1H NMR: 1.6-1.9 (m, 4H), 2.9-3.8 (m, 4H), 3.12 (s, 6H), 4.76 (br s, 2H), 6.94-7.62 (m, 4H), 8.92 (br s, 1H).
MS (m/z): 332 (M^+, 11%), 300 (13), 285 (11), 173 (100), 160 (23), 156 (22), 145 (31), 142 (34), 128 (25), 115 (31); Exact mass: 332.1734 (calc. for $C_{18}H_{24}N_2O_4$: 332.1736).

2-(Benzoyloxymethyl)-3-[2-(3,3-dimethoxy-2-oxopiperidino)ethyl]indole (13)

Benzoyl chloride (0.49 ml, 4.2 mmol) was added to an ice-cooled solution of alcohol 12 (1.16 g, 3.50 mmol) in pyridine (7 ml). The ice bath was removed and the mixture stirred overnight. Pyridine was evaporated and the residue extracted from water (30 ml) with CH_2Cl_2 (10 ml + 2x7 ml). The extracts were dried with $MgSO_4$, the solvent evaporated, and the residue chromatographed (silica, MeOH:CH_2Cl_2:Et_3N = 2:98:0.2) to give a foam (1.20 g, 2.7 mmol, 78%).
IR: 3300, 2960, 1720, 1640, 1460.
^1H NMR: 1.86 (m, 4H), 3.0-3.7 (m, 6H), 3.35 (s, 6H), 5.51 (s, 2H), 7.0-8.1 (m, 9H), 9.07 (br s, 1H).
MS (m/z): 436 (M^+, 5%), 277 (71), 156 (21), 155 (57), 142 (21), 122 (57), 105 (100), 77 (64); Exact mass: 436.1970 (calc. for $C_{25}H_{28}N_2O_5$: 436.1998).

3-[2-(3,3-Dimethoxy-2-oxopiperidino)ethyl]-2-(2,4-dioxapentyl)indole (14)

Chloromethyl methyl ether (0.58 ml, 7.65 mmol) was injected to an ice-cooled solution of alcohol 12 (1.70 g, 5.10 mmol) and N,N-diisopropylethylamine (1.5 ml, 8.4 mmol, triethylamine reacted only with the chloride producing a quaternary ammonium salt) in CH_2Cl_2 (30 ml). The cooling bath was removed and the solution stirred overnight. The solvent was evaporated and the residue extracted from water (20 ml) with CH_2Cl_2 (15 ml + 2x7 ml). The organic phases were washed with aqueous NH_4Cl (saturated, 20 ml) and dried with Na_2SO_4. After evaporation an oil (1.70 g, 4.8 mmol, 93%) was obtained.
IR: 3300, 2970, 1650, 1460.
^1H NMR: 1.89 (m, 4H), 3.0-3.8 (m, 6H), 3.34 (s, 6H), 3.39 (s, 3H), 4.66 (s, 2H), 4.76 (s, 2H), 7.0-7.8 (m, 4H), 8.57 (br s, 1H).
MS (m/z): 376 (M^+, 11%), 283 (12), 217 (100), 172 (19), 157 (30), 156 (26), 155 (27), 144 (31), 142 (29), 115 (30); Exact mass: 376.2012 (calc. for $C_{20}H_{28}N_2O_5$: 376.1998).

1-Benzenesulfonyl-3-[2-(3,3-dimethoxy-2-oxopiperidino)ethyl]-2-(2,4-dioxapentyl)indole (15)

Indole 14 (39.5 mg, 0.105 mmol) in DME (0.7 ml) was added to a cooled (bath temperature ~ -57°C, $CHCl_3$+N_2) solution of LDA [made from diisopropylamine (35 µl, 0.25 mmol) and BuLi (125 µl, 1.7 M in hexane, 0.21 mmol) in DME (2 ml)]. A precipitate was formed, which dissolved when the mixture was allowed to warm to 0°C. The solution was cooled (~ -57°C) benzenesulfonyl chloride (27 µl, 0.21 mmol) was added, and the mixture was stirred overnight to room temperature. The solvent was evaporated and the residue extracted from water (15 ml) with CH_2Cl_2 (3x7 ml). The extracts were dried with $MgSO_4$, the solvent removed and the residue chromatographed (silica, MeOH:CH_2Cl_2:Et_3N = 3:97:0.2) to give an oil (46 mg, 0.089 mmol, 85%).
IR: 2980, 1650, 1450, 1370.
^1H NMR: 1.84 (m, 4H), 2.9-3.6 (m, 6H), 3.34 (s, 6H), 3.43 (s, 3H), 4.65 (s, 2H), 4.98 (s, 2H), 7.0-8.2 (m, 9H).
MS (m/z): 516 (M^+, 5%), 485 (22), 484 (71), 357 (22), 343 (23), 281 (64), 186 (26), 184 (23), 156 (47), 144 (53), 115 (100), 114 (53), 101 (54), 77 (57); Exact mass (CI, NH_3, M+1): 517.2003 (calc. for $C_{26}H_{33}N_2O_7S$: 517.2009).
With BuLi as base only 57% of indole 15 was obtained.
The methoxymethyl group could not be removed with 1M toluenesulfonic acid in methanol. In refluxing ethanol with H_2SO_4 the starting material was destroyed. The method by Monti et al.[17] using pyridinium p-toluenesulfonate in refluxing ethyl methyl ketone was inconvenient because the large amount of pyridine made it difficult to follow the reaction by TLC.

3-[2-(3,3-Dimethoxy-2-oxopiperidino)ethyl]-2-[(2-tetrahydro-2H-pyranyl)oxymethyl]indole (16)

2-Chlorotetrahydro-2H-pyran (0.65 g, 5.4 mmol) in CH_2Cl_2 (9 ml) was injected to an ice/acetone -cooled solution of alcohol 12 (897 mg, 2.7 mmol) and N,N-diisopropylethylamine (1.03 ml, 5.94 mmol) in CH_2Cl_2 (10 ml). The cooling bath was removed and stirring was continued overnight. The solvent was evaporated and the residue extracted from aqueous NH_4Cl (saturated, 30 ml) with CH_2Cl_2 (15 ml + 2x5 ml). The extracts were washed twice with the salt solution to remove traces of the amine. The extracts were dried with $MgSO_4$. Evaporation of the solvent gave an oil (1.03 g, 2.5 mmol, 91%).
IR: 3300, 2970, 1650.
^1H NMR: 1.2-2.1 (m, 10H), 2.8-3.8 (m, 8H), 3.33 (s, 6H), 4.63 (br s, 1H), 4.79 (s, 2H), 6.9-7.8 (m, 4H), 9.00 (br s, 1H).
MS (m/z): 416 (M^+, 4%), 332 (12), 300 (17), 257 (17), 173 (100), 160 (26), 156 (23), 144 (27), 143 (23), 142 (22), 85 (30); Exact mass: 416.2271 (calc. for $C_{23}H_{32}N_2O_5$: 416.2311).
The reaction of alcohol 12 with 3,4-dihydro-2H-pyran and an acid catalyst (p-toluenesulfonic acid or its pyridinium salt) was complicated by the acid lability of the alcohol.

1-Benzenesulfonyl-3-[2-(3,3-dimethoxy-2-oxopiperidino)ethyl]-2-[(tetrahydro-2H-pyranyl)oxymethyl]-indole (17)

Indole 16 (46 mg, 0.11 mmol) in THF (1 ml) was added to a cooled (AcOEt-bath, -83°C) solution of LDA [2.9 ml, 0.12 mmol of a solution made of diisopropylamine (62 µl, 0.44 mmol), BuLi (200 µl, 2.1 M in hexane, 0.42 mmol) and THF (9.8 ml)]. The cooling bath was removed and the solution was allowed to reach room temperature. The solution was cooled (-83°C), benzenesulfonyl chloride (17 µl, 0.13 mmol) was added and the solution was allowed to reach room temperature overnight. The solvent was evaporated and the residue extracted from aqueous NH_4Cl (saturated 30 ml) with CH_2Cl_2 (10 ml + 4x5 ml). The extracts were dried with $MgSO_4$. The solvent was evaporated and the residue chromatographed (flash, silica MeOH:CH_2Cl_2:Et_3N = 3:97:0.2) to give an oil (49.5 mg, 89 mmol, 81%).
IR: 2980, 1650, 1450.
^{1}H NMR: 1.3-2.0 (m, 10H), 2.9-3.8 (m, 8H), 3.34 (s, 6H), 4.77 (br s, 1H), 5.03 (d, J = 7.6 Hz, 2H), 7.1-8.2 (m, 9H).
MS (m/z): 472 (M^+ -84, 6%), 454 (11), 440 (51), 299 (64), 281 (60), 156 (40), 144 (50), 115 (100), 114 (54), 101 (50), 85 (81), 77 (54); The use of the desorption chemical ionization probe, combined with the EI ion source, permits the detection of the molecular ion peak at m/z 556 (2%) corresponding to $C_{29}H_{36}N_2O_7S$.

1-Benzenesulfonyl-3-[2-(2,3-dioxopiperidino)ethyl]-2-[(2-tetrahydro-2H-pyranyl)oxymethyl]indole (18)

In an attempt to remove both the ketone- and the alcohol- protecting groups a solution of ketal 17 (114 mg, 0.205 mmol) and p-toluenesulfonic acid monohydrate (200 mg, 1 mmol) in acetone (7 ml) was stirred at room temperature for 10 min. $NaHCO_3$ (200 mg, 2.3 mmol) was added, acetone was removed, CH_2Cl_2 was added, and the mixture was filtered. The filtrate showed two spots on TLC (silica, MeOH:CH_2Cl_2 = 10:90) so the deprotecting procedure was repeated, but there was no significant change of the product on TLC. The obtained filtrate was concentrated and chromatographed (silica, AcMe:CH_2Cl_2:Et_3N = 10:90:0.2) to give two fractions: oil 18 (51 mg, 0.10 mmol, 49%) and oil 20 (15.5 mg, 0.036 mmol, 18%, much destroyed during chromatography judging from the TLC product distribution).
IR: 2970, 1730, 1665, 1450.
^{1}H NMR: 1.2-2.1 (m, 8H), 2.3-2.7 (m, 2H), 2.7-4.0 (m, 8H), 4.77 (br s, 1H), 5.03 (d, J = 7 Hz, 2H), 7.2-8.2 (m, 9H).
MS (m/z): 510 (M^+, 5%), 426 (52), 409 (26), 408 (26), 313 (30), 296 (32), 286 (40), 285 (100), 268 (40), 267 (95), 239 (36), 172 (40), 156 (70), 155 (42), 154 (57), 144 (95), 142 (62), 141 (66), 126 (90), 85 (93), 77 (67); Exact mass: 510.1855 (calc. for $C_{27}H_{30}N_2O_6S$: 510.1825).

1-Benzenesulfonyl-3-[2-(3,3-dimethoxy-2-oxopiperidino)ethyl]-2-hydroxymethylindole (19)

Tetrahydropyranyl ether 17 (200 mg, 0.36 mmol) and p-toluenesulfonic acid monohydrate (380 mg, 2 mmol) were stirred in methanol (2 ml) for 20 min. $NaHCO_3$ (400 mg, 4.7 mmol) was added and stirring was continued for 10 min. The solvent was evaporated, CH_2Cl_2 added, the mixture filtered and the solvent evaporated. Chromatography (silica, MeOH:CH_2Cl_2:Et_3N = 3:97:0.2) gave an oil (157 mg, 0.33 mmol, 92%).
IR: 3400, 2980, 1640.
^{1}H NMR: 1.8 (m, 4H), 2.8-3.8 (m, 6H), 3.22 (s, 6H), 4.94 (br s, 2H), 7.2-8.2 (m, 9H).
MS (m/z): 472 (M^+, 3%), 454 (11), 441 (18), 440 (60), 425 (28), 313 (78), 299 (91), 281 (75), 172 (56), 154 (47), 144 (93), 141 (68), 115 (100), 114 (64), 101 (71), 77 (60); Exact mass: 472.1667 (calc. for $C_{24}H_{28}N_2O_6S$: 472.1668).

1-Benzenesulfonyl-3-[2-(2,3-dioxopiperidino)ethyl]-2-hydroxymethyl indole (20)

A solution of ketal 19 (526 mg, 1.1 mmol) and p-toluenesulfonic acid monohydrate (475 mg, 2.5 mmol) in acetone (5 ml) was stirred for 15 min. $NaHCO_3$ (0.5 g, 6 mmol) was added. After stirring for 10 min the solvent was evaporated, CH_2Cl_2 was added and the mixture was filtered. Evaporation of the filtrate gave a foam (495 mg ~100%).
IR: 3400, 1740, 1660, 1460, 1370.
^{1}H NMR: 1.8 (m, 2H), 2.2-2.7 (m, 2H), 3.0-3.8 (m, 6H), 4.88 (br s, 2H), 7.0-8.3 (m, 9H).
MS (m/z): 426 (M^+, 6%), 313 (17), 285 (35), 267 (43), 172 (40), 144 (85), 142 (82), 126 (82), 77 (100), 70 (55); Exact mass: 426.1261 (calc. for $C_{22}H_{22}N_2O_5S$: 426.1250).

1-Benzenesulfonyl-3-[2-(3-dimethylhydrazono-2-oxopiperidino)ethyl]-2-hydroxymethyl indole (21)

1,1-Dimethylhydrazine (114 µl, 1.5 mmol) and acetic acid (two drops) were added to a solution of ketone 20 (440 mg, 1 mmol) in methanol (6 ml) and the solution was stirred for an hour. The solvent was evaporated and the residue extracted from salt water [$NaHCO_3$ (saturated 5 ml) + NH_4Cl (saturated, 5 ml)] with CH_2Cl_2 (10 ml + 2x5 ml). The extracts were dried with $MgSO_4$. Chromatography (alumina, MeOH:CH_2Cl_2 = 1:99) gave a foam (371 mg, 79%).
IR: 3400, 2970, 1640, 1580, 1450.
^{1}H NMR: 1.6 (m, 8H), 2.4-3.8 (m, 8H), 2.76 (s, 6H), 4.92 (s, 2H), 7.1-8.2 (m, 9H).
MS (m/z): 468 (M^+, 11%), 298 (14), 297 (47), 266 (23), 173 (27), 157 (33), 156 (75), 153 (35), 144 (59), 143 (34), 142 (54), 125 (39), 91 (50), 77 (100); Exact mass: 468.1820 (calc. for $C_{24}H_{28}N_4O_4S$: 468.1831).

1-Benzenesulfonyl-2-(benzoyloxymethyl)-3-[2-(3-dimethylhydrazono-2-oxopiperidino)ethyl]indole (22)

Benzoyl chloride (50 µl, 0.43 mmol) was added to a cooled (ice/acetone-bath) solution of alcohol 21 made from protected compound 17 (200 mg, 0.359 mmol) in pyridine (4 ml). The cooling bath was removed and the solution stirred for 37 hr at room temperature. Pyridine was evaporated and the residue extracted from salt water [$NaHCO_3$ (saturated, 5 ml) + NaCl (saturated, 10 ml)] with CH_2Cl_2 (3x5 ml). The extracts were dried with $MgSO_4$, the solvent was evaporated and the residue chromatographed (silica, MeOH:CH_2Cl_2:Et_3N = 3:97:0.2) to yield a foam (154 mg, 0.27 mmol, 96%).
IR: 1720, 1640, 1450.
^1H NMR: 1.8 (m, 2H), 2.4-3.7 (m, 8H), 2.77 (s, 6H), 5.81 (s, 2H), 7.1-8.3 (m, 14H).
MS (m/z): 572 (M^+, 20%), 408 (20), 298 (30), 297 (76), 266 (54), 156 (65), 154 (39), 125 (39), 105 (100), 97 (34), 77 (90); Exact mass: 572.2068 (calc. for $C_{31}H_{32}N_4O_5S$: 572.2094).
In an attempt to cyclisize the indole compound, ester 22 (24.5 mg, 0.0427 mmol) in THF (1/2 ml) was added to a cooled (AcOEt-bath, -83°C) solution of LDA [from diisopropylamine (7.2 µl, 0.051 mmol) and BuLi (22 µl, 2.3 M in hexane, 0.051 mmol) in THF (1 ml)]. The solution was stirred and allowed to reach room temperature overnight. TLC showed two spots. The solvent was evaporated and the residue chromatographed (preparative TLC, silica, CH_2Cl_2:MeOH:Et_3N = 96:4:0.2) to give starting material 22 and the alcohol 21 (~1:1).

1-Benzenesulfonyl-2-chloromethyl-3-[2-(3-dimethylhydrazono-2-oxopiperidino)ethyl]indole (23) and attempted cyclizations

Methanesulfonyl chloride (10 µl, 0.13 mmol) in 2,6-dimethylpyridine (250 µl) was added to cooled (ice/acetone-bath) alcohol 21 (31 mg, 0.066 mmol). The mixture was stirred to dissolve the alcohol and the solution stored at -2°C for 17 hr. TLC (alumina, MeOH:CH_2Cl_2 = 1:99) showed that the alcohol had disappeared and a new less polar compound had formed. The solvent and the unreacted methanesulfonyl chloride were removed in vacuo at room temperature. THF (1 ml) was added and the mixture was cooled (-83°C). LDA [0.15 mmol from diisopropylamine (25 µl, 0.18 mmol) and BuLi (75 µl, 2.1 M in hexane, 0.15 mmol)] in THF (1 ml) was added to the mixture and the temperature was allowed to rise to 15°C in three hours. The mixture was extracted from aqueous NH_4Cl (saturated, 20 ml) with CH_2Cl_2 (20 + 2x5 ml) and the extracts were dried with $MgSO_4$. Chromatography (alumina, MeOH:CH_2Cl_2 = 1:99) gave a foam (14.5 mg, 0.030 mmol) of 23.
IR: 2980, 1650, 1580, 1460.
^1H NMR: 1.6 (m, 2H), 2.4-3.7 (m, 8H), 2.78 (s, 6H), 5.19 (s, 2H), 7.2-8.2 (m, 9H).
MS (m/z): 486 (M^+, <1%), 451 (14), 297 (38), 296 (23), 199 (25), 186 (31), 157 (28), 156 (100), 153 (36), 144 (25), 143 (23), 142 (28), 91 (28), 77 (57); Exact mass: 486.1513 (calc. for $C_{24}H_{27}ClN_4O_3S$: 486.1492).
In a further attempt to effect the ring closure, the chloride 23 (14 mg, 0.029 mmol) was dissolved in THF (1 ml), cooled (-83°C bath temperature) and treated with LDA (0.030 mmol), and the solution was stirred overnight with warming to room temperature. TLC showed highly polar material and a trace of the starting chloride 23. The solvent was evaporated and the residue chromatographed (preparative TLC, silica MeOH:CH_2Cl_2 = 5:95) to yield the chloride 23 (less than 2 mg).

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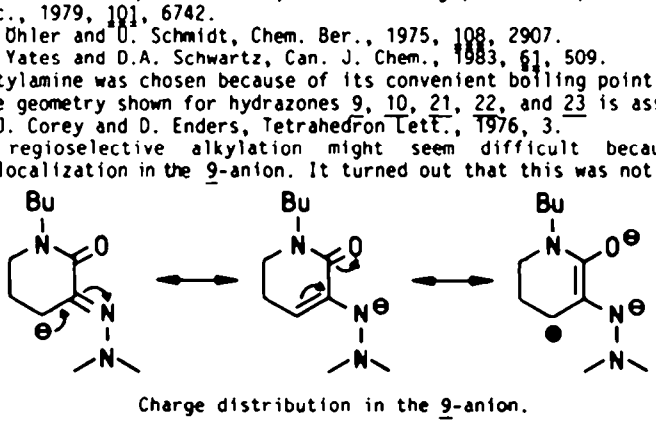

Charge distribution in the 9-anion.

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