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# Some Observations on the Brunner Reaction

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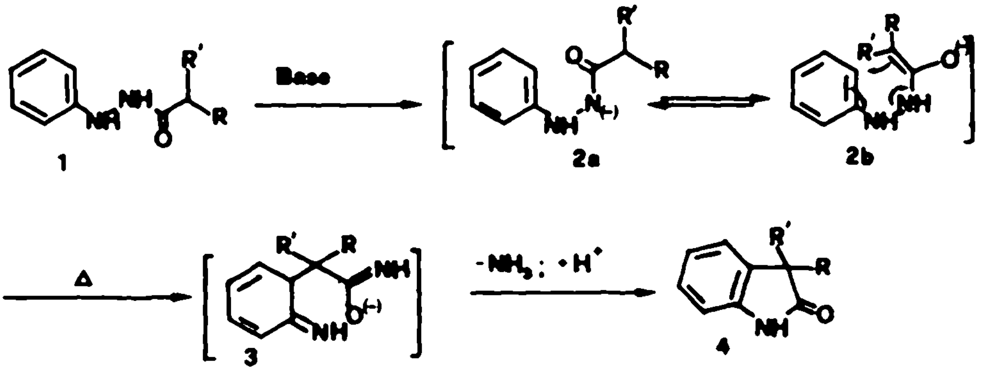
Summary: Elucidation of the stereochemical course of the Brunner reaction is described. A slight modification in the procedure gives better yields and seems very promising for a more general application of this reaction.

The Brunner reaction [1], an analogue to the Fischer indole synthesis, opens an attractive pathway to various oxindoles (Scheme 1).
The pratical application, however, is limited as the cyclisation is typically performed at high temperatures ( ca. 230°C ) in presence of a large excess of a strong base such as calcium hydride, thus giving moderate yields of the oxindole derivative ( 4 ) ( 41-44% ) even when an optimized procedure is followed[2].

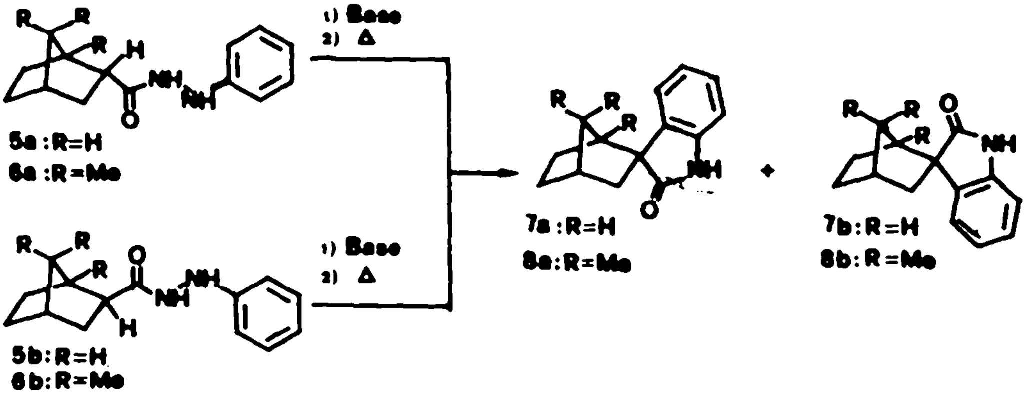


Scheme 1.

In addition the stereochemical course in the pericyclic step leading from the proposed intermediate 2b to 3 [1] has hiterto not been investigated,only the existence of 3 has been supported by definitely identifying the nitrogen atom lost as ammonia to be the one adjacent to the carbonyl group [1,3].
Because this reaction might be used in a total synthesis of Gelsemine[4] we have attempted a further insight in its stereochemical outcome and the realisation of a more general and high yielding synthetic procedure than those reported previously.
To elucidate the stereochemical course we pyrolyzed the phenylhydrazides of pure endo- or exo-norbornane carboxylic acid ( 5a ) (5b ) with nearly stoichiometric amounts of a strong base.Different bases such as BuLi ,MeONa and tBuOK were employed to check their influence on the stereochemistry and the yields of the reaction.The results are reported in Table I.
Changing the counterion from lithium, sodium to potassium we found that the yields were considerably lowered and the temperature needed to induce the evolution of ammonia was increased , although the stereoselectivity in favour of 7a became slightly but reproducibly better[5] ( Table I ). These results were virtually independent from the stereochemistry of the starting material which provides evidence for the existence of the planar intermediate of type 2b[6] shown in Scheme 1.

TABLE I

Effect of the base on the stereochemistry and the yields of the Brunner reaction.



| Phenylhydrazide | Base | Pyrolysis temp. °C | % Yield | GLC ratio a : b |
|---|---|---|---|---|
| 5a | BuLi | 210 | $78^a$ (1) | 75 : 25 |
| 5a | MeONa | 240 | $55^a$ - | 80 : 20 |
| 5a | tBuOK | 250 | $38^a$ (17) | 83 : 17 |
| 5b | BuLi | 210 | $(85)^b$ | 75 : 25 |
| 5b | MeONa | 240 | $(80)^b$ | 81 : 19 |
| 5b | tBuOK | 250 | $(80)^b$ | 83 : 17 |
| 6a+6b | BuLi | 220 | $49^c$ | 60 : 40 |
| 6a+6b | MeONa | 220 | $45^c$ | 48 : 52 |
| 6a+6b | tBuOK | 230 | $32^c$ | 62 : 38 |

a) Optimized yields of isolated products ; in brackets percentage of recovered starting material. b) Gas chromatographic yields calculated for the crude mixture. c) Non optimized yields of isolated products.

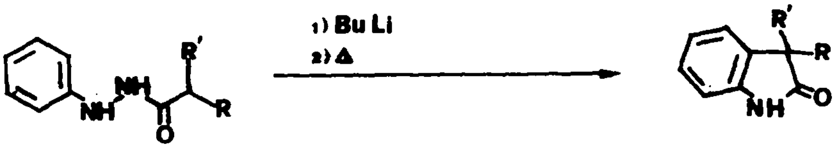
The major product ( 7a ), identified by comparison with an authentic sample[7] is derived from an attack of the phenyl ring to the exo surface of the norbornyl system in agreement with corresponding nucleophilic[8], electrophilic[9] and pericyclic[10] reactions.

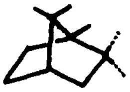
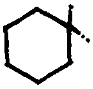
In the Brunner reaction,performed as previously described,using now a mixture of exo- and endo- camphoric acid phenylhydrazides (6a+6b ) , we found that together with reduction in selectivity, the major product was 8b corresponding to an attack to the exo surface. Although the selectivity was low , this result is unexpected considering the" normal" behaviour of the attack to camphor derivatives[12].

The previously reported experiments indicate a reasonable improve in the yields of the oxindole system.A confirm of the generality of the reaction using a stoichiometric amount of a lithium base was shown by pyrolysis of the phenylhydrazides of propionic- , phenylacetic- and cyclohexylcarboxylic- acids ( 9, 10, 11 ). The corresponding oxindoles ( 12 , 13 , 14 in Table 2 ) were obtained in quite acceptable yields, thus allowing application of this modified Brunner reaction in synthesis of natural compounds containing the oxindole moiety.

TABLE II

Oxindole synthesis by pyrolysis of the lithium salts of phenylhydrazides.



| Oxindole | R ; R' | % yield | m.p.(°C) | lit. m.p. | lit. yield |
|---|---|---|---|---|---|
| 7a+7b | R = R'=  | 78 (1)[a] | 142-160 | -- | -- |
| 8a+8b | R = R'=  | 49 (10)[a] | 186-192 | -- | -- |
| 12 | R =Me , R'=H | 64 (12)[a] | 118-120 | 122-123[2] | 44[2] |
| 13 | R =Ph , R'=H | 48 | 180-187 | 183[13] | 85[b] |
| 14 | R = R'=  | 51 (8)[a] | 119-121 | 124[14] | 35 |

a) Yields of isolated products ; in brackets percentage of recovered starting material. b) Only crude product specified. In our case, the crude yields were almost quantitative.

## Experimental

GLC analyses were carried out in a Carlo Erba 4200 equipped with a 15 m SE 54 capillary column; areas were determined by averaging the weight of cut peaks obtained from several runs.

NMR spectra were recorded in CDCl$_3$ solution on a Varian EM 390 (90 MHz) and a Bruker WM 250 (250 MHz) , values are given in ppm (δ) downfield to TMS.

IR spectra were recorded on a Perkin Elmer 983.Melting points are uncorrected .

THF was distilled from Na and LiAlH$_4$,t-BuOH was dried over molecular sieves.

Propionic acid phenylhydrazide (**9** ).

Phenylhydrazine (1.08 g,10 mmol) and triethylamine (1.02 g,10 mmol) in dry Et$_2$O (20 ml) were added dropwise to propionyl chloride (0.92 g,10 mmol) in dry Et$_2$O(20 ml) at 0°C under stirring.The mixture was then warmed to r.t. and boiled for 1 h. After evaporation of the solvent in vacuo,the remaining solid was treated with boiling water (20 ml) and filtered.The residue was recrystallized from EtOH-H$_2$O 8-1,giving **9** , 1.3 g, 72% yield, m.p. 154-156 °C, (lit[2] 158-159°C).

Phenylacetic acid phenylhydrazide(**10**).

From phenylacetyl chloride (1.5 g, 10 mmol) and following an analogous procedure to **9**, after recrystallization from EtOH-H$_2$O 8-1, **10** was obtained, 1.6g 70% yield,m.p. 167-168°C (lit[15] 168-169°C).

Cyclohexancarboxylic acid phenylhydrazide (11 ).
From cyclohexanoyl chloride (1.46 g, 10 mmol ) and following an analogous procedure to 10, after crystallization from $MeOH-H_2O$ 6-1, 11 was obtained, 1.6 g, 75 % yield,m.p. 160-163°C, (lit.[16] 164°C).

Bicyclo [2.2.1] heptane,2-exo-carboxylic acid phenylhydrazide (5b).
2-Exo-norbornyloyl chloride was prepared trating 2-exo-norbornylic acid[17] ( 1.4 g, 10 mmol )and oxalyl chloride ( 12.6 g, 100 mmol) for 2 h. at 60°C.After distillation of the excess of oxalyl chloride, norbornyloyl chloride was obtained as a viscous yellow oil, to which, in dry $Et_2O$ (20 ml) at 0°C, the mixture of phenylhydrazine (1.08 g, 10 mmol) and triethylamine (1.06g, 10 mmol) in dry $Et_2O$ (10 ml) was carefully added.After warming to r.t. and boiling for 1 h. , evaporation of the solvent gave a solid which was treated with boiling water (20 ml) and filtered.The residue was recrystallized from $EtOH-H_2O$ 8-1 giving 5b, 1.26 g, 55% Yield. m.p. 162-163°C.
$\nu_{max}$ 3320, 3236, 3035, 2955, 2872, 1660, 1601, 1495, 1451 $cm^{-1}$.
NMR $\delta(CDCl_3)$ 1.19 ( m, 3H ), 1.63 ( m, 4H ), 1.89 ( m, 1H ), 2.18 ( m, 1H), 2.31 ( m, 1H ), 2.42 ( m, 1H, CHCO ), 5.80 ( b, 1H, CONH ), 6.80 ( m, 2H, Arom ), 6.92 ( m, 1H, Arom ), 7.21 ( m, 2H Arom ), 7.76 ( b, 1H, NHPh) .
Calcd. for $C_{14}H_{18}N_2O$. C 73.01, H 7.88, N 12.16 ; Found C 73.22, H 7.92, N 12.14.

Bicyclo [2.2.1] heptane,2-endo-carboxylic acid phenylhydrazide (5a).
Starting from 2-endo-norbornylic acid[18] (1.4 g, 10 mmol) an analogous procedure to 5b gave 5a,after crystallization from $EtOH-H_2O$, 1.49 g, 65 % Yield , m.p. 156.5-157.5°C.
$\nu_{max}$ 3429, 3340, 3092, 2954, 2874, 1680, 1602, 1494, 1464. $cm^{-1}$.
NMR $\delta$ $(CDCl_3)$ : 1.57 ( m, 4H ), 1.85 ( m, 2H ), 2.44 ( m, 1H ), 2.65 ( m, 1H ), 2.85 ( m, 1H, CHCO ), 6.41 ( b, 1H, CONH ), 6.95 ( m, 2H, Arom ), 7.01 ( m, 1H, Arom ), 7.37 ( m, 2H, Arom ), 7.79 ( b, 1H, NHPh).
Calcd. for $C_{14}H_{18}N_2O$ . C 73.01, H 7.88, N 12.16 : Found C 73.16, H 7.86 ,N 12.80

1-Methyl,7,7-dimethyl,bicyclo [2.2.1]heptane,2-carboxylic acid phenylhydrazide (6a+6b).
Starting from 1-methyl,7,7-dimethyl,bicyclo [2.2.1] heptane,2-carboxilic acid[18] (1.8 g, 10 mmol) (a 75-25 mixture of exo-endo isomers),the corresponding hydrazide was prepared following the same procedure described for 5b, giving ,after crystallization from $MeOH-H_2O$ 6-1, 6a+6b, 1.4 g, 52 % yield as a mixture of exo-endo isomers in an approximatively 3:1 ratio (NMR).Data are given for this mixture.
m.p. 153-158°C. $\nu_{max}$ 3430, 3331, 3097, 2952, 2872, 1689, 1602, 1494, 1464 $cm^{-1}$.
NMR $\delta(CDCl_3)$ : 0.99 ( s, 3H, Me ), 1.1 ( s, 6H, Me ), 1.7 ( m, 7H, CH and $CH_2$ ), 2.31 ( m, 1H, CHCO ), 6.3 ( b, 1H, CONH ), 6.84 ( m, 3H, Arom ), 7.2 ( m, 2H, Arom ), 7.7 ( b, 1H, NHPh ).
Calcd for $C_{17}H_{24}N_2O$. C 74.96 H 8.88 N 10.28 ; Found C 75.00, H 8.83, N 10.26 .

General procedure for pyrolyses of lithium salts of phenylhydrazides.
n-Butyllithium (0.4 ml of a 1.36 M solution in hexane,0.54 mmol),was added slowly,under nitrogen at -78°C to a solution of 0.5 mmol of the phenylhydrazide in THF (1.5 ml),whereupon the mixture turned deep red.The solvent was carefully evaporated in a Kugelrohr apparatus,always under nitrogen and the red residue pyrolysed at 205-210°C.The solid decoloured and ammonia was liberated.After a further heating of 90 min.,the residue was cooled,dissolved in methanol,acidified with conc.HCl and the solvent evaporated in vacuo.The residue was treated with sat. $Na_2CO_3$ solution ( 2 ml ) to achieve a pH of 7-8. and with half-saturated brine ( 4 ml ). After extraction with $Et_2O$(four times with 5 ml) and

drying with anhydrous $Na_2SO_4$ the solvent was evaporated to give the oxindole as a solid which can be purified or by crystallization or by column chromatography on silica gel.

3-Norbornyloxindoles(**7a+7b**).
Following the general procedure, a solid containing **7a+7b** in a GLC ratio of 25 to 75 was obtained. Further purification by column chromatography gave this mixture in the same ratio, pure up to 98% at GLC. Data are given for this mixture. 84.4 g , 79% yield m.p. 142-146°C. $\nu_{max}$ (Nujol) 3150, 1700, 1610 cm $^{-1}$. NMR $\delta$ ($CDCl_3$) 1.3-1.5 (m, 2H ), 1.9 (m, 2H 9, 2.2 (m, 2H ), 2.2-2.4 (br., 2H ), 2.6 (m, 1H ), 6.8-7.3 (m, 4H, Arom), 7.8 (br., 1H, NH).
Compounds 7a and 7b were not isolated but monitored by comparison of their GLC retention times with those of authenthic samples[7,11].

3-Camphoroxindole ( **8a+8b**)
Starting from a ca. 3:1 exo-endo mixture of the hydrazides (**6a+6b**) , pyrolyses of the lithium salt gave (8a+8b) in a GC ratio of 38:62 ( 49% yield). Data are given for this mixture m.p. 186-192°C . $\nu_{max}$3420, 3175, 2980, 1710, 1635, cm$^{-1}$. NMR $\delta$($C_6D_6$) : 0.53 ( s, 3H, Me ), 1.01 ( s, 3H, Me ), 1.32 ( s, 3H, Me ), 1.42 ( m, 1H, $CH_{Ha}H_b$-C ), 1.61 ( b.s., 2H, $CH_2$ ), 1.78 ( b.t., 1H, $CH_aH_b$-C ), 1.95 ( m, 2H, $CH_2$ ), 2.25 ( m, 1H, CH), 6.79 ( d, 1H, Arom ), 6.95 ( t, 1H, Arom ), 7.14 ( t, 1H, Arom ), 7.31 ( b, 1H, NH), 7.53 ( d, 1H, Arom).Taking nuclear Overhouse difference spectra on the mixture, irradiation of the methyl at 1.32 ppm gave a strong enhancement at the doublet at 7.14 ppm.
Calcd for $C_{17}H_{21}NO$. C 79.06, H 8.29, N 5.49 ; Found C 79.56, H 8.33, N 5.39.
**7b** was then purified by several PTLC eluted with n-hexane:$Et_2O$ 2:3 (GLC purity up to 90% ) m.p. 191-193°C. NMR $\delta$($CDCl_3$) 0.53 (s, 3H, Me ), 1.01 ( s, 3H, Me), 1.27 (bs., 1H, CH), 1.32 (s, 3H, Me), 1.45 (m, 1H, CH), 1.61 (bs., 2h, CH ), 1.91 (t, 1H, CH, J = 3 Hz), 1.95 (m, 2H, CH+CH), 6.78 (d, 1H, J = 7Hz, $H_{Oxind.7}$), 6.95 (t, 1H, J = 7Hz, $H_{Oxind.5}$) 7.14 (t, 1H, J = 7Hz, $H_{Oxind.6}$), 7.21 (br,., 1H, NH), 7.53 (d, 1H, $H_{Oxind.4}$).Nuclear Overhouse difference spectra did not show any enhancement on the aromatic ring signals irradiating the methyl groups, identifying this isomer as the exo. From its GLC retention times the analysis of the mixture was performed.

3-Methyloxindole 12
$\nu_{max}$ (Nujol) 3160, 1735, 1620, 740 cm$^{-1}$. NMR $\delta$ ($CDCl_3$) 1.50 (d, 3H, J = 7.5Hz), 3.52 (q, 1H, J = 7.5Hz, CHCO), 6.9-7.4 (m, 4H, Arom), 8.2 (br,. 1H, NH).

3-Phenyloxindole 13
$\nu_{max}$ (Nujol) 3130, 1708, 1615, 1325, 742, 700 cm$^{-1}$.NMR $\delta$ ($CDCl_3$) 4.6 (s, 1H, CH), 6.9-7.2 (m,4H, Arom. Oxinnd.), 7.2-7.5 (m, 6H, Ph and NH).

2-Oxospiro- [ cyclohexane.3.indole] 14.
$\nu_{max}$ (Nujol) 3140, 1710, 1620, 1340, 735 cm$^{-1}$. NMR $\delta$($CDCl_3$) 1.3-2.1 (m, 10H, Cyclohexane), 7.0-7.6 (m, 4H, Arom.), 8.0 (br., 1H, NH).

Pyrolyses of sodium and potassium salts.
In this case, the hydrazides were dissolved under nitrogen at r.t. in dry t-BuOH containing ca. 1.05 eq. of sodium methoxide or potassium t-butoxide, respectively, and further treated in the same manner described above .

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5 . A possible influence of the corresponding anions was excluded by adding the bases to a solution of the phenylhydrazides in tBuOH, evaporation of the solvent and subsequent pyrolysis.

6 . Further support results from the observation that the recovered starting material is always a diasteromeric mixture of **5a** and **5b**.

7 . Autenthic samples of **7a** and **7b** were kindly provided by I.Fleming( Cambridge University ).

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