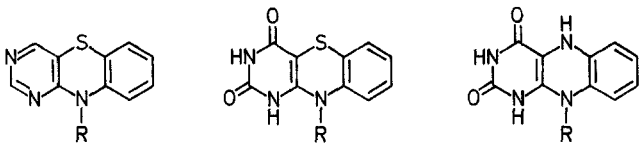
A Convenient Method for Indole *N*-Alkylation in Substituted Pyrazino[2′,1′:6,1]pyrido[3,4-*b*]indoles[1]

Shiv K. AGARWAL, Anil K. SAXENA*, Nitya ANAND

Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226001, India

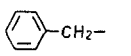
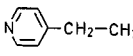
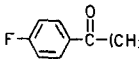
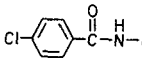
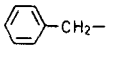
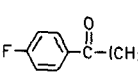
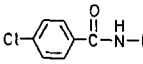
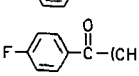
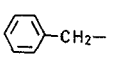
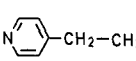
The indole *N*-alkylation in polyfunctional condensed indoles is a field of considerable interest because of the biological activity exhibited by many of these compounds[2-6]. The difficulty encountered in indole *N*-alkylation in substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indoles **1** by the classical method of generating an anion with sodium hydride or thallium(II) ethoxide followed by alkyl halide treatment, namely the simultaneous quaternisation at N-5, led to a search for alternative methods.

We now report a convenient method for the synthesis of the *N*-alkylindole derivatives **3**, by the reaction of **1** with 1-methyl-2,2-dialkoxypyrrolidine[7] **(2)** in dry tetrahydrofuran.



1 **2** **3**

Table 1. 2,7-Disubstituted 1,2,3,4,6,7,12,12a-Octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indoles **3**

Substrate **1** No.	R^1	R^2 in **2**	Product No.	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
1a		CH_3	**3a**	88	see experimental procedure and Ref.[2]			
1b		CH_3	**3b**	72	203° ($CHCl_3$/CH_3OH)	$C_{22}H_{26}N_4$ (346.5)	2950–2800, 1610, 760	(CF_3COOH): 2.6–4.7 (m, 18H); 6.4–7.1 (m, 4H); 7.5–7.7 (m, 2H); 8.1–8.3 (m, 2H)
1c		CH_3	**3c**	90	174–176° ($CHCl_3$/CH_3OH)	$C_{25}H_{28}FN_3O$ (405.5)	2970–2760, 1680, 1600, 840, 750	(DMSO-d_6): 2.2–4.2 (m, 20H); 6.8–7.2 (m, 6H); 7.7–8.2 (m, 2H)
1d		CH_3	**3d**	83	144–145° ($CHCl_3$/ether)	$C_{24}H_{27}ClN_4O$ (423.0)	2930–2800, 1640, 745	($CDCl_3$): 2.1–3.6 (m, 18H); 6.7–7.6 (m, 8H)
1a		C_2H_5	**3e**	79	198° ($CHCl_3$/CH_3OH)	$C_{23}H_{27}N_3$ (345.5)	3000–2850, 1630, 755, 710	($CDCl_3$/DMSO-d_6): 1.10 (t, 3H); 2.2–4.1 (m, 15H); 6.7–7.4 (m, 9H)
1c		C_2H_5	**3f**	85	180° ($CHCl_3$/CH_3OH)	$C_{26}H_{30}FN_3O$ (419.5)	2970–2800, 1675, 1600, 700	($CDCl_3$/DMSO-d_6): 1.15 (t, 3H); 1.7–6.0 (m, 19H); 6.8–7.3 (m, 6H); 7.7–8.0 (m, 2H)
1d		C_2H_5	**3g**	80	155° ($CHCl_3$/ether)	$C_{25}H_{29}ClN_4O$ (437.0)	2950, 2300, 1640, 745	($CDCl_3$): 1.20 (t, 3H); 2.3–4.0 (m, 17H); 6.9–7.9 (m, 8H)
1c		n-C_3H_7	**3h**	90	186° ($CHCl_3$/CH_3OH)	$C_{27}H_{32}FN_3O$ (433.6)	2900–2800, 1680, 1600, 745	(DMSO-d_6): 1.10 (t, 3H); 1.8–4.2 (m, 21H); 6.7–7.5 (m, 6H); 7.7–7.9 (m, 2H)
1a		n-C_3H_7	**3i**	90	222° ($CHCl_3$/CH_3OH)	$C_{24}H_{29}N_3$ (359.5)	2960–2800, 1610, 755, 710	(CF_3COOH): 0.9 (t, 3H); 2.5–5.0 (m, 17H); 6.8–7.2 (m, 9H)
1b		n-C_3H_7	**3j**	74	215° ($CHCl_3$/CH_3OH)	$C_{24}H_{30}N_4$ (374.5)	2950–2800, 1615, 755	(CF_3COOH): 1.10 (t, 3H), 2.3–4.8 (m, 19H), 6.3–6.8 (m, 4H); 7.2–7.4 (m, 2H); 7.8–8.1 (m, 2H)

[a] Satisfactory microanalyses obtained: C ±0.47, H ±0.37, N ±0.32.

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Table 2. 2-Substituted 1,2,3,4,6,7,12,12a-Octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indoles **1a–d**

Compound 1[a]	Yield [%]	m.p. [°C] (solvent)	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
1a	57	200–202° ($CHCl_3$/*i*-C_3H_7OH)	$C_{21}H_{23}N_3$ (317.4)	3140–3020, 2940–2790, 1450, 740, 700	(DMSO-d_6): 2.3–5.0 (m, 13H); 6.7–7.5 (m, 8H); 8.2 (m, 1H); 15.6 (br. s, 1H)
1b	90	205° ($CHCl_3$/*i*-C_3H_7OH)	$C_{21}H_{24}N_4$ (332.5)	3250, 2900–2730, 1615, 727	($CDCl_3$); 2.4–3.8 (m, 14H); 4.0 (m, 1H); 7.2–7.8 (m, 9H)
1c	53	187–189° ($CHCl_3$/*i*-C_3H_7OH)	$C_{24}H_{26}FN_3O$ (391.5)	3300, 2950–2750, 1684, 1600, 835, 742, 705	(DMSO-d_6): 1.7–3.9 (m, 17H); 6.7–7.0 (m, 2H); 7.1–7.3 (m, 4H); 7.8–8.0 (m, 2H); 10.55 (s, 1H)
1d[b]	75	209° ($CHCl_3$/ether)	$C_{23}H_{25}ClN_4O$ (408.9)	3400–3250, 2920–2800, 1640, 745	($CDCl_3$); 1.8–3.5 (m, 16H); 6.7–7.8 (m, 8H); 8.43 (br. s, 1H)

[a] For R^1, see Table 1.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.11, N ±0.40.

The yields obtained were in the range of 72–90% depending upon the substituted pyrazinopyridoindoles **1** used. The yields, reaction times, and physical data for compounds **1** and **3** are given in Tables 1 and 2.

2-Benzyl-1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (1a; $R^1 = C_6H_5CH_2$); Typical Procedure:

Benzyl bromide (9.4 g, 0.055 mol) is added dropwise to the stirred mixture of 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (**1**; R = H[1]; 11.35 g, 0.05 mol) and freshly baked sodium carbonate (5.83 g, 0.055 mol) in dry dimethylformamide (100 ml). The reaction mixture is stirred at 76 °C for 48 h, cooled and poured into water (200 ml). The separated solid is filtered, washed with water (500 ml), and dried at 30 °C under reduced pressure. The crude product is dissolved in chloroform (200 ml), cooled at 25 °C, and filtered from insoluble materials. The filterate is eluted through a column of 100–200 mesh florisil (50 g) and more chloroform (1500 ml) is eluted through the column. The eluted solvent is concentrated under reduced pressure to 100 ml. At this point the distillation is continued at atmospheric pressure and isopropanol is added slowly until the vapour temperature rises to 70–72 °C. The residue is cooled at 5 °C and filtered. The solid is washed with isopropanol/hexane (40:60, 3 × 20 ml) and dried at 80 °C under reduced pressure; yield: 9.0 g (57%); m.p. 200–202 °C.

$C_{21}H_{23}N_3$	calc.	C 79.49	H 7.26	N 13.25
(317.4)	found	79.32	7.21	13.02

I.R. (KBr): ν = 3140–3020; 2940–2760; 1450; 740; 700 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 2.3–5.0 (m, 13H); 6.7–7.5 (m, 8H); 8.2 (m, 1H); 15.6 ppm (br s, 1H).

2-Benzyl-7-methyl-1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (3a; $R^1 = CH_2C_6H_5$, $R^2 = CH_3$); Typical Procedure:

1-Methyl-2,2-dimethoxypyrrolidine (**2**; $R^2 = CH_3$; 4.35 g, 0.03 mol) is added dropwise to a stirred suspension of 2-benzyl-1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (**1a**; 6.47 g, 0.0204 mol) in dry tetrahydrofuran (100 ml). The reaction mixture is stirred at 35 °C for 6 h, concentrated, triturated with ether (25 ml) to remove 1-methyl-2-pyrrolidone, and filtered to give **3a**; yield: 6.0 g (88%); m.p. 207–208 °C (from chloroform/methanol).

$C_{22}H_{25}N_3$	calc.	C 79.77	H 7.55	N 12.69
(331.2)	found	79.23	7.33	12.48

I.R. (KBr): ν = 2950–2850; 1600; 750; 700 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 2.6–4.8 (m, 15H); 4.9–5.3 (m, 1H); 6.9–7.7 ppm (m, 9H).

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[1] CDRI Communication No. 2861.

[2] A. K. Saxena, P. C. Jain, N. Anand, P. R. Dua, *J. Med. Chem.* **16**, 560 (1973).

[3] A. K. Saxena et al., *Indian Patent* 131367 (1976), *German Patent* 2333929 (1975); *U.S. Patent* 3917599 (1975); *Canadian Patent* 982132 (1976); *French Patent* 7409968 (1974); *C.A.* **82**, 156373 (1975); **84**, 164842 (1976); **85**, 5673 (1976); **82**, 171057 (1975).

[4] N. Kumar, P. C. Jain, *Progr. Drug. Res.* **21**, 409 (1977).

[5] J. W. Schulenberg, D. F. Page, *J. Med. Chem.* **13**, 145 (1970).

[6] J. W. Schulenberg, *U.S. Patent* 3644384 (1969), 3717638, (1969); *C.A.* **76**, 140890 (1972); **78**, 147995 (1973).

[7] H. Bredereck, F. Effenberger, H. P. Beyerlin, *Chem. Ber.* **97**, 3081 (1964).

[8] A. K. Saxena et al., *Indian J. Pharm Sci.* **40**, 222 (1978).

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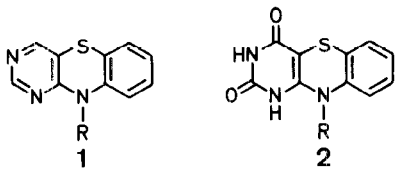
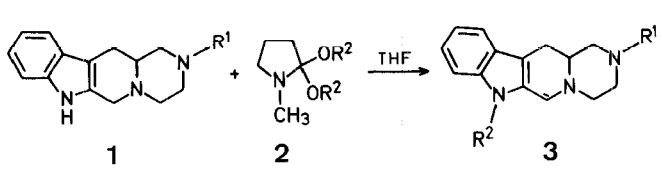
Errata

Y. Maki, M. Sako, M. Tanabe, M. Suzuki, *Synthesis* **1981** (6), 462-464: The first formula scheme (p. 462, left-hand column) should be:

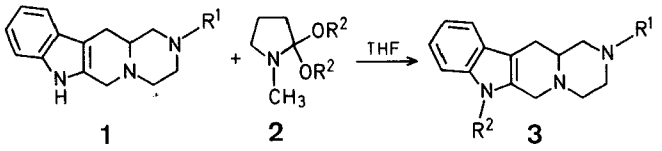


S. K. Agarwal, A. K. Saxena, N. Anand, *Synthesis* **1981** (6), 465-466: The formula scheme (p. 465, right-hand column) should be:



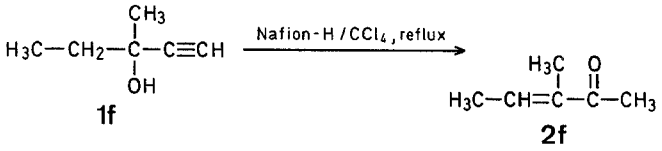
0039-7881/81/0932-0748 $ 03.00

S. K. Agarwal, A. K. Saxena, N. Anand, *Synthesis* **1981** (6), 465-466:
The formula scheme (p. 465) should be:



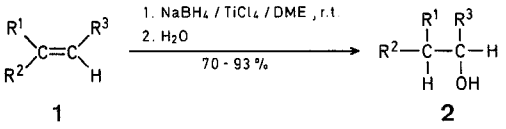
1 2 3

G. A. Olah, A. P. Fung, *Synthesis* **1981** (6), 473-474:
The reaction scheme **1f→2f** should be:



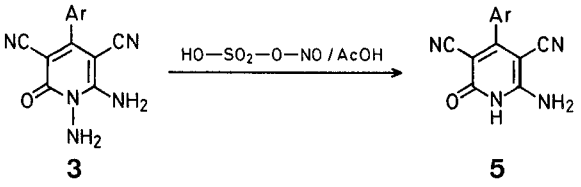
1f 2f

Abstract 6127, *Synthesis* **1981** (6), 498:
The formula scheme **1→2** should be:



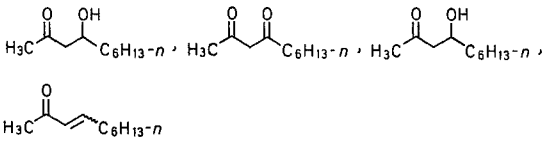
1 2

J. L. Soto, C. Seoane, P. Zamorano, F. J. Cuadrado, *Synthesis* **1981** (7), 529-530:
The reaction scheme **3→5** (p. 529) should be:

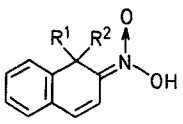


3 5

A. B. Smith, III, P. A. Levenberg, *Synthesis* **1981** (7), 567-570:
The heading for Table 1 (p. 567) should be Oxidation of 4-Hydroxy-2-decanone **(3a)** under various conditions. The structure given in the first column of Table 1 should be, respectively:

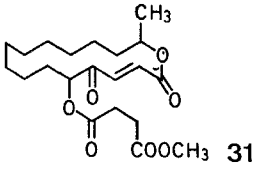


G. Bartoli, M. Bosco, A. C. Boicelli, *Synthesis* **1981** (7), 570-572:
The structure of products **4aa-cd** (p. 571) should be:



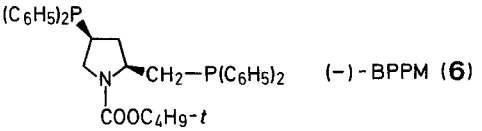
4aa-cd

Y.-H. Lai, *Synthesis* **1981** (8), 585-604:
The structure of compound **31** (p. 588) should be:



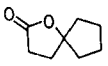
M. R. H. Elmoghayar, M. K. A. Ibraheim, A. H. H. Elghandour, M. H. Elnagdi, *Synthesis* **1981** (8), 635-637:
The title compounds **5** are thiazolo[3,2-*a*]pyridine derivatives.

A. Kleemann, J. Martens, M. Samson, W. Bergstein, *Synthesis* **1981** (9), 740-741:
The structure of compound **6** should be:



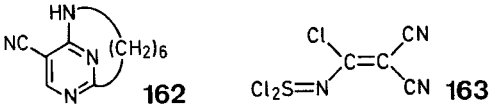
(-)-BPPM (6)

Abstract 6236, *Synthesis* **1981** (11), 922:
The structure of product **3** should be:



3

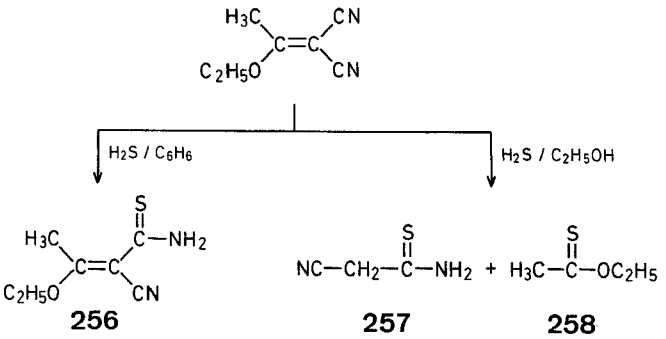
F. Freeman, *Synthesis* **1981** (12), 925-954:
The structures of compounds **162** and **163** (p. 937) should be:



162 163

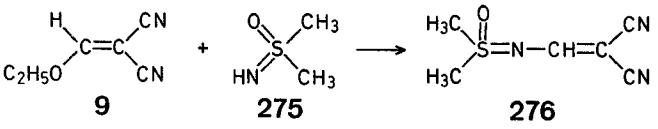
The text of the first paragraph starting on p. 943 (right-hand column) should be: Hydrogen sulfide reacts with 1-ethoxyethylidenemalononitrile, the methyl homolog of **9**, to give different products depending on the solvent used[293].

The following formula scheme should be:



256 257 258

The first formula scheme on p. 944 (right-hand column) should be:

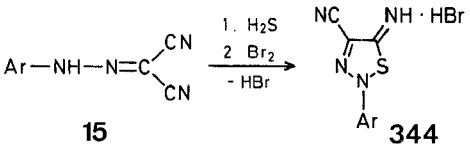


9 275 276

The last sentence on page 946 (left-hand column) should be: An analogous reaction with cyclopentadiene leads to the 2-azabicyclo[2.2.1]heptene **(299)** and with cyclohexadiene to 2-azabicyclo[2.2.2]octene **(301)** derivatives[317].

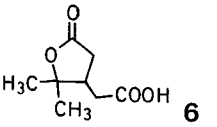
The correct names for compounds **336** and **337** (p. 949) are 5-hydroxy-2-oxo-3-phenylazo-1,2,3,7-tetrahydropyrazolo[1,5-*a*]pyrimidine **(336)** and α-(*N*-methylphenylhydrazono)-cyanoacetamidrazone **(337)**.

The formula scheme **15→344** (p. 950) should be:



15 344

A. Guzmán, S. Mendoza, E. Diaz, *Synthesis* **1981** (12), 989-991:
The structure of compound **6** (p. 990) should be:



6

Abstract 6269, *Synthesis* **1981** (12), 1015:
The legend under the formula scheme should read: n = 1, 2, 3.