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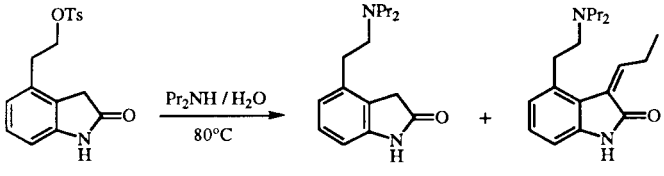
Received November 28, 1994
Revised November 21, 1995

New 2-oxoazepino[3,4,5-*cd*]indole derivatives were formed by the reaction of the tosylate SK&F 98339 with *N*-alkyl and *N*-arylidenepropylamines in moderate yield.

J. Heterocyclic Chem., **33**, 209 (1996).

Ropinirole (SK&F 101468) is currently in phase III clinical trials for the treatment of Parkinson's disease. The final step of our synthesis of SK&F 101468 involves the reaction of the tosylate, SK&F 98339, with di-*n*-propylamine. Interestingly, a significant quantity of a propylidene impurity, SK&F 98959, is formed during the reaction (Scheme 1).

Scheme 1

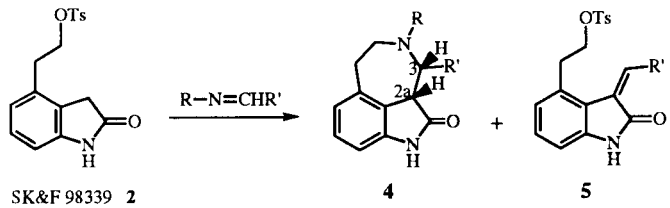


SK&F 98339 **2** SK&F 101468 **1** SK&F 98959 **3**

The propylidene derivative **3** can be formed from the condensation of SK&F 101468 with propionaldehyde. However, as propionaldehyde was neither detectable nor likely to exist in the dipropylamine used in the process, it was assumed a propionaldehyde equivalent was responsible for the formation of **3**. As a working hypothesis, it was predicted that one such propionaldehyde equivalent might be *N*-propylidenepropylamine, a potential impurity in di-*n*-propylamine. This might condense with SK&F 98339 to give a propylidene derivative which after displacement of the tosylate group with diisopropylamine would give SK&F 98959. Alternatively it might condense directly with SK&F 101468.

When the reaction of SK&F 98339 with *N*-propylidenepropylamine (R = Pr, R' = Et) **1** was subsequently attempted, unexpectedly, the major product was not a propylidene derivative **3** but a 2-oxoazepino[3,4,5-*cd*]indole **4** (Scheme 2). The product was isolated in 58% yield.

Scheme 2

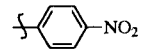
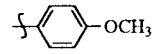
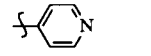
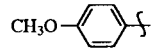
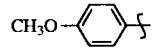
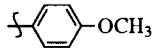
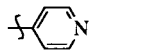
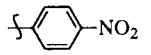
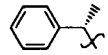


SK&F 98339 **2** **4** **5**

$RNH_2 + R'CHO \longrightarrow R{-}N{=}CHR'$

Table 1

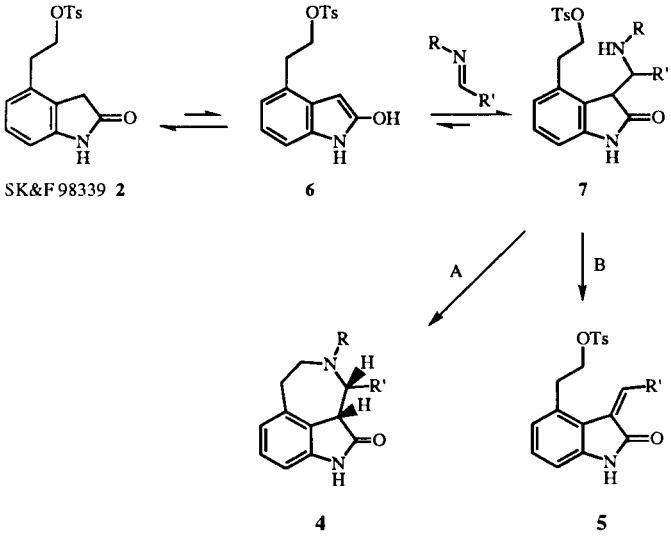
Preparation of Substituted Azepine Derivatives

Entry	R	R'	4	5
1	*n*-Pr	Et	58	-
2	*n*-Pr	Ph	53	30
3	*n*-Pr		32	40
4	*n*-Pr		47	28
5	*n*-Pr		52	17
6	*n*-Pr		-	63 [1]
7	Ph	Et	-	- [2], [3]
8		Et	-	- [2], [3]
9		Ph	11	45
10	Ph		-	61
11	Ph		-	39
12	$PhCH_2$		36	31
13		Ph	-	30

The scope of the reaction of SK&F 98339 with imines was therefore explored further. SK&F 98339 was treated with a series of imines (prepared in high yield by the reaction of different aldehydes with the appropriate amines in toluene at room temperature) in boiling THF. The results are illustrated in Table 1 which lists the percentage weight yields of **4** and **5** after isolation by chromatography.

Clearly azepine **4** is formed only when R = primary alkyl or electron rich aryl. A possible mechanism to explain these results is shown in Scheme 3. Nucleophilic attack by the 2-oxindole *via* its enol form **6** on the imine carbon gives intermediate **7**. Subsequent intramolecular S_N2 displacement of the tosylate group by the flanking amine side chain gives the azepine *via* path A. Presumably

Scheme 3



when R or R' = branched alkyl (compare entry 1 with 6 and entry 12 with 13) the amine side chain is too sterically hindered to act as a nucleophile and elimination occurs to give the olefin. When R = aryl the amine is a weaker nucleophile and a good leaving group and again the elimination pathway B is preferred. The electron donating 4-methoxy substituent in entry 9 would render the amine a better nucleophile and a poorer leaving group which could explain the formation of some cyclised azepine product. The relative stereochemistry about the two chiral centres at C-2a and C-3 has been assigned as syn with the substituent at C-3 in a pseudo axial position for each of the azepines prepared. This assignment was based on nuclear Overhauser enhancement difference experiments.

In conclusion, we have prepared new azepino[3,4,5-*cd*]-indole derivatives simply by the reaction of a 2-oxindole (SKF 98339) with imines.

EXPERIMENTAL

Melting points were measured with a Buchi MP apparatus and are uncorrected. Elemental analyses were performed using a Control Equipment Corporation 440 instrument. The ir spectra were recorded on a Perkin Elmer 781 spectrophotometer. The 270 MHz ^{1}H nmr spectra were recorded on a Jeol JNM-GX 270 FT spectrometer. The 400 MHz ^{1}H nmr and ^{13}C nmr spectra were recorded on a Jeol JNM-GX 270 FT spectrometer. Chemical shifts are reported as parts per million downfield shift from TMS as internal standard. Mass spectra and accurate mass measurements were recorded on a VG 70-250-SEQ mass spectrometer.

General Procedure for the Preparation of Imines.

To a solution of aldehyde (47 mmoles) in toluene (2 ml per gram of substrate) was added the amine (47 mmoles). The reaction mixture became warm during the addition and water formed typically within 10 minutes. After 60 minutes the water was separated and the toluene layer was concentrated *in vacuo* to give the pure imine in almost quantitative yield. The product was used without further purification in the next reaction.

3-Ethyl-2-oxo-4-propyl-2,2a,3,4,5,6-hexahydro-1*H*-azepino[3,4,5-*cd*]indole.

A mixture of SK&F 98339 (5 g, 0.015 mole) and *N*-propylidenepropylamine (5 g, 0.05 mole) was stirred at 80° for 20 minutes. The cooled mixture was poured into water (25 ml) and extracted with dichloromethane (3 x 25 ml). The combined organic extracts were washed with 2 *M* hydrochloric acid (3 x 25 ml) and the organic phase discarded. The aqueous solution was basified to *p*H 12 with 2 *M* sodium hydroxide (75 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic parts were washed with water (3 x 75 ml), saturated brine (25 ml), dried (magnesium sulfate) and evaporated under reduced pressure to give an orange gum (4.77 g). Chromatography over silica gel, eluting with ethyl acetate:hexane 1:3-1:1 afforded the title compound as a white solid 2.27 g (58%), mp 133.5-135.0° (from ethyl acetate); ir (chloroform): 3420, 2960, 2925, 2865, 1710, 1615, 1460, 1305, and 1055 cm^{-1}; pmr (270 MHz, deuteriochloroform): 0.85 (t, 3H, J = 7 Hz, 11-CH_3), 0.95 (t, 3H, J = 7 Hz, 14-CH_3), 1.18, 1.39 (2 x m, 2 x 1H, 10-CH_2), 1.58 (m, 2H, 13-CH_2), 2.18 (dd, 1H, J = 4, 15 Hz, 6-H), 2.95 (m, 3H, 5-H, 12-CH_2), 3.20 (m, 2H, 3-H, 5-H), 3.39 (dd, 1H, J = 13, 13 Hz, 6-H), 4.22 (d, 1H, J = 4 Hz, 2a-H), 6.72 (d, 2H, J = 8 Hz, 7-H, 9-H), 7.05 (t, 1H, J = 8 Hz, 8-H), and 9.08 (s, 1H, 1-H); cmr (400 MHz, deuteriochloroform): 10.5 (q, C-11), 11.8 (q, C-14), 19.6 (t, C-10), 21.2 (t, C-13), 31.2 (t, C-6), 44.6 (t, C-5), 48.3 (d, C-2a), 53.9 (t, C-12), 61.0 (d, C-3), 116.2 (d, C-9), 122.1 (d, C-7), 137.3 (d, C-8), 138.0 (s, C-6a), 140.2 (s, C-9b), 142.7 (s, C-9a), and 179.0 (s, C-2); ms: m/z 258 (19.2), 229 (66.9), 186 (10.6), 149 (11.9), 130 (17.9), and 112 (100).

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.61; H, 8.57; N, 10.89.

General Procedure for the Reaction of Imines with SK&F 98339.

A solution of SK&F 98339 (6.04 mmoles) and imine (6.04 mmoles) in THF (5 ml per gram of SK&F 98339) was heated under reflux for 18 hours. The reaction mixture was then concentrated to dryness and the residue was chromatographed on silica gel using the indicated eluant to give the azepine and the olefin.

2-Oxo-3-phenyl-4-propyl-2,2a,3,4,5,6-hexahydro-1*H*-azepino-[3,4,5-*cd*]indole.

Elution with dichloromethane:acetone, 95:5 gave the title compound (2.47 g, 53%) as a pale yellow crystalline solid, mp 158-159° (from methanol); pmr (270 MHz, deuteriochloroform): δ 0.95 (t, 3H, J = 7 Hz), 1.65 (m, 2H), 2.60 (m, 2H), 2.80 (m, 1H), 2.95 (m, 2H), 3.35 (m, 1H), 4.40 (d, 1H, J = 5 Hz), 4.60, (d, 1H, J = 5 Hz), 6.70 (d, 1H, J = 7 Hz), 6.85 (d, 1H, J = 8 Hz), 6.90 (m, 2H), 7.10-7.20 (m, 4H) and 7.90 (br s, 1H, NH); hrms: Calcd. for $C_{20}H_{22}N_2O$: 306.1810. Found: 306.1786.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.18; H, 7.24 ; N, 9.06.

Further elution gave 3-benzylidene-4-[2'-(*p*-toluenesulphonyloxy)ethyl]-2-oxindole (1.73 g, 30%) as a yellow crystalline solid mp 162-163° (from methanol); ir (potassium bromide): 1697,

1360, 1175 and 1095 cm^{-1}; pmr (400 MHz, DMSO-d_6): 2.25 (s, 3H), 3.30 (t, 2H, J = 7 Hz), 4.35 (t, 2H, J = 7 Hz), 6.70 (d,1H, J = 7 Hz), 6.75 (d, 1H, J = 7 Hz), 7.10 (t, 1H, J = 7 Hz), 7.25 (d, 2H, J=8 Hz), 7.4 (m, 3H), 7.50 (s, 1H), 7.55 (d, 2H, J = 7 Hz), 8.00 (m, 2H) and 10.50 (s, 1H); hrms: Calcd. for $C_{24}H_{21}NO_4S$: 419.1192. Found: 419.1193.

Anal. Calcd. for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.72; H, 5.17; N, 3.53.

2-Oxo-3-(4-nitrophenyl)-4-propyl-2,2a,3,4,5,6-hexahydro-1*H*-azepino[3,4,5-*cd*]indole.

Elution with dichloromethane:acetone - 98:2-90:10 gave 3-(4-nitrobenzylidene)-4-[2'-(*p*-toluenesulphonyloxy)ethyl]-2-oxindole (1.68 g, 40%) as a bright orange crystalline solid, mp 176-178° (from methanol); ir (potassium bromide): 3200, 1682, 1522, 1346 and 1174 cm^{-1}; pmr (400 MHz, DMSO-d_6): 2.40 (s, 3H), 3.35 (t, 2H, J = 8 Hz), 4.35 (t, 2H, J = 8 Hz), 6.70 (d, 1H, J = 8 Hz), 6.80 (d, 1H, J = 8 Hz), 7.15 (t, 1H, J = 7 Hz), 7.30 (d, 2H, J = 9 Hz), 7.50 (d, 1H, J = 9 Hz), 7.60 (s, 1H), 8.00 (d, 2H, J = 9 Hz), 8.25 (d, 2H, J = 9 Hz) and 10.60 (s, 1H, NH); hrms: Calcd. for $C_{24}H_{20}N_2O_6S$: 464.1042. Found: 464.1041.

Anal. Calcd. for $C_{24}H_{20}N_2O_6S$: C, 62.06; H, 4.34; N, 6.03. Found: C, 61.92; H, 4.56; N, 6.14.

The title compound was also obtained the as a pale orange crystalline solid (1.02 g, 32%), mp 140-142° (from ether-hexane); pmr (400 MHz, deuteriochloroform/DMSO-d_6, 4:5): 0.95 (t, 3H, J = 7 Hz), 1.60 (m, 2H), 2.60 (m, 1H), 2.75 (m, 2H), 2.90 (m, 1H), 3.10 (m, 1H), 3.30 (m, 1H), 4.50 (d, 1H, J = 6 Hz), 4.55 (d, 1H, J = 6 Hz), 6.60 (d, 1H, J = 8 Hz), 6.75 (d, 1H, J = 8 Hz), 7.15 (m, 3H), 7.50 (s, 1H) and 8.00 (d, 2H, J = 9 Hz); hrms: Calcd. for $C_{20}H_{21}N_3O_3$: 351.1583. Found: 351.1582.

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 67.95; H, 6.05; N, 11.46.

2-Oxo-3-(4-methoxyphenyl)-4-propyl-2,2a,3,4,5,6-hexahydro-1*H*-azepino[3,4,5-*cd*]indole.

Elution with ethyl acetate:hexane, 1:1 gave the title compound (2.30 g, 47%) as a pale yellow crystalline solid mp 138-140° (from ether); pmr (400 MHz, deuteriochloroform): 0.95 (t, 3H, J = 9 Hz), 1.60 (m, 2H), 2.60 (m, 2H), 2.75 (m, 1H), 2.90 (m, 2H), 3.35 (m, 1H), 3.70 (s, 3H), 4.35 (d, 1H, J = 5 Hz), 4.55 (d, 1H, J = 5 Hz), 6.65 (m, 3H), 6.80 (m, 3H), 7.15 (t, 1H, J = 9 Hz) and 8.60 (s, 1H); hrms: Calcd. for $C_{21}H_{24}N_2O_2$: 336.1838. Found: 336.1838.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.55; H, 7.00; N, 8.42.

Further elution gave 3-(4-methoxybenzylidene)-4-[2'(*p*-toluenesulphonyloxy)ethyl]-2-oxindole (1.88 g, 28%), mp 166-167° (from methanol); ir (potassium bromide): 3195, 1688, 1590, 1512 and 1171 cm^{-1}; pmr (400 MHz, DMSO-d_6): 2.35 (s, 3H), 3.30 (t, 2H, J = 7 Hz), 3.85 (s, 3H), 4.30 (t, 2H, J = 7 Hz), 6.70 (d, 1H, J = 8 Hz), 6.75 (d, 1H, J = 8 Hz), 7.00 (d, 2H, J = 9 Hz), 7.10 (t, 1H, J = 7 Hz), 7.30 (d, 2H, J = 8 Hz), 7.45 (s, 1H), 7.55 (d, 2H, J = 9 Hz), 8.15 (d, 2H, J = 10 Hz), and 10.50 (s, 1H); hrms: Calcd. for $C_{25}H_{23}NO_5S$: 449.1297. Found: 449.1299.

Anal. Calcd. for $C_{25}H_{23}NO_5S$: C, 66.80; H, 5.16; N, 3.12. Found: C, 66.55; H, 5.19; N, 3.20.

(*R*)-(*Z*)-9-(1-{2-*p*-Toluenesulphonyloxy} ethyl)-3-(2-methyl)-butylidenyl-2-oxindole.

Elution with ethyl acetate:hexane, 1:1 gave the title compound as a beige solid (0.64 g, 63%) mp 124-125° (from ether-hexane); ir (sodium chloride): 2900, 1700, 1450, 1380, and 1180 cm^{-1}; pmr (270 MHz, deuteriochloroform) 0.95 (t, 3H, J = 8 Hz), 1.10 (d, 3H, J = 7 Hz), 1.36-1.60 (m, 2H), 2.40 (s, 3H), 3.20 (t, 2H), 4.05 (m, 1H), 4.25 (t, 2H, J = 7 Hz), 6.60 (d, 1H, J = 12 Hz), 6.70 (d, 1H, J = 7 Hz), 6.80 (d, 1H, J = 7 Hz), 7.10 (t, 1H, J = 7 Hz), 7.25 (d, 2H, J = 9 Hz), 7.65 (d, 2H, J = 9 Hz) and 9.50 (s, 1H); hrms: Calcd. for $C_{22}H_{25}NO_4S$: 399.1583. Found: 399.1589.

2-Oxo-3-phenyl-4-(4-methoxyphenyl)-2,2a,3,4,5,6-hexahydro-1*H*-azepino[3,4,5-*cd*]indole.

Elution with dichloromethane:acetone, 98:2-95:5 gave 3-benzylidene-4-[2'-(*p*-toluenesulphonyloxy)ethyl]-2-oxindole (2.85 g, 45%) which had identical physical and spectroscopic properties to the sample previously prepared. The title compound was also obtained (0.61 g, 11%) as a pale yellow crystalline solid, mp 193-198° (from methanol); pmr (400 MHz, deuteriochloroform and a few drops of DMSO-d_6 to solubilise): 2.65 (m, 1H), 3.40 (m, 2H), 3.75 (s, 3H), 3.80 (m, 1H), 4.35 (d, 1H, J = 5 Hz), 5.65 (d, 1H, J = 5 Hz), 6.75 (d, 2H, J = 8 Hz), 6.85-7.05 (m, 6H), 7.05-7.20 (m, 4H) and 10.00 (s, 1H, NH); hrms: Calcd. for $C_{24}H_{22}N_2O_2$: 370.1681. Found: 370.1682.

Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 6.10; N, 7.58.

2-Oxo-3-(4-nitrophenyl)-4-benzyl-2,2a,3,4,5,6-hexahydro-1*H*-azepino[3,4,5-*cd*]indole.

Elution with dichloromethane:THF, 100:0-90:10 gave the title compound (1.30 g, 36%) as a pale yellow crystalline solid, mp 188° (from methanol); pmr (400 MHz, deuteriochloroform): 2.70 (m, 1H), 2.90 m, 1H), 3.05 (m, 1H), 3.30 (m, 1H), 3.85 (AB quartet, 2H, J = 14 Hz), 4.50 (d, 1H, J = 6 Hz), 4.70 (d, 1H, J = 6 Hz), 6.70 (d, 1H, J = 8 Hz), 6.85 (d, 1H, J = 8 Hz), 7.10-7.50 (m, 8H), 7.80 (s, 1H) and 8.00 (d, 2H, J = 8 Hz); hrms: Calcd. for $C_{24}H_{21}N_3O_3$: 399.1583. Found: 399.1583. Further elution gave 3-(4-nitrobenzylidene)-4-[2'-(*p*-toluenesulphonyloxy)ethyl]-2-oxindole (1.30 g, 36%) which had identical physical and spectroscopic properties to the sample previously prepared.

2-Oxo-3-(4-pyridyl)-4-propyl-2,2a,3,4,5,6-hexahydro-1*H*-azepino[3,4,5-*cd*]indole.

Elution with dichloromethane:acetone, 8:2 as eluant gave 3-(4'-pyridylmethylidene)-4-[2'-(*p*-toluenesulphonyloxy)ethyl]-2-oxindole (0.44 g, 17%) as an orange crystalline solid), mp 152-154° (from methanol); ir (potassium bromide): 1705, 1589, 1362 and 1172 cm^{-1}; pmr (400 MHz, DMSO-d_6, 40°): 2.35 (s, 3H), 3.25 (m, 2H), 4.30 (m, 2H), 6.70 (d, 1H, J = 9 Hz), 6.75 (d, 1H, J = 9 Hz), 7.15 (t, 1H, J = 8 Hz), 7.30 (d, 2H, J = 6 Hz), 7.45 (s, 1H), 7.50 (d, 2H, J = 7 Hz), 7.60 (d, 2H, J = 7 Hz), 8.60 (d, 2H, J = 7 Hz) and 10.50 (s, 1H, NH); hrms: Calcd. for $C_{23}H_{20}N_2O_4S$: 420.1222. Found: 420.1232.

The title compound was also obtained (0.96 g, 52%) as a yellow crystalline solid, mp 132-135° (from ether); pmr (270 MHz, deuteriochloroform): 1.00 (t, 3H, J = 8 Hz), 1.65 (m, 2H), 2.75 (m, 2H), 2.85 (m, 1H), 3.05 (m, 1H), 3.30 (m, 2H), 4.50 (AB quartet, 2H, J = 6 Hz), 6.75 (d, 1H, J = 8 Hz), 6.85 (d, 1H, J = 8 Hz), 6.95 (d, 2H, J = 7 Hz), 7.20 (t, 1H, J = 7 Hz) 8.1 (s, 1H, NH) and 8.40 (d, 2H, J = 7 Hz); hrms: Calcd. for $C_{19}H_{21}N_3O$: 307.1685. Found: 307.1685.

Acknowledgement.

We are grateful to Dr. J. Wright and Mr. J. Richards for helpful discussions concerning the structure of the new azepines.

REFERENCES AND NOTES

[1] This compound was prepared using the Campbell modification of the Chancel procedure; M. F. Chancel, *Bull. Soc. Chim. France,* **11**, 933, (1884); B. K. Campbell, K. N. Campbell, and A. H. Sommers, *J. Am. Chem. Soc.*, *66*, 82 (1944).

[2] It was not possible to isolate the required imine, probably due to its propensity to self condense.

[3] M. S. Kharasch, I. Richlin and F. R. Mayo, *J. Am. Chem. Soc.*, **62**, 494 (1940).