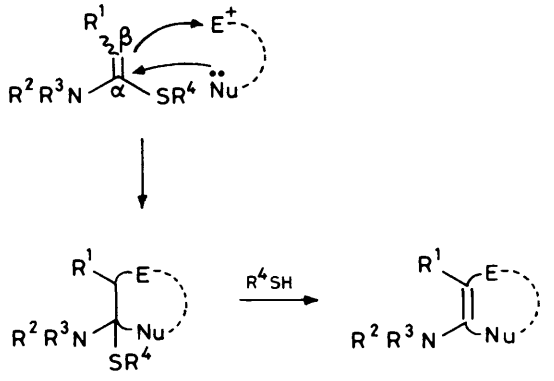
Ketene *S,N*-Acetals as Synthetic Intermediates for Heterocycles. Reaction of Ketene *S,N*-Acetals with 1,4-Quinones[1]

Hiroki Takahata,* Akira Anazawa, Keiko Moriyama, and Takao Yamazaki*
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama, 930-01, Japan

Annelation of ketene *S,N*-acetals with 1,4-quinones is found to give benzo[*b*]- and naphtho[1,2-*b*]-furans bearing enamine groups. Subsequent enamine reaction allows the formation of 1-benz- and naphtho[1,2-*b*]oxepines and benzofuran-2-ones.

Enamines are an important group of synthetic intermediates,[2] ketene *S,N*-acetals being regarded as α-alkylthio derivatives.[3,4] So far we have explored the potentials of the latter as intermediates in the synthesis of nitrogen heterocycles such as uracils,[5] pyrimidines,[6] pyrazoles,[6] and pyridines.[7] In these reactions, ketene *S,N*-acetals are allowed to react with a variety of electrophiles to form a carbon–carbon bond at the β-position, the compound so formed then being susceptible to attack by nucleophiles at the α-position. Subsequent, selective elimination of an alkanethiol entity regenerates the enamine (Scheme 1), so



Scheme 1.

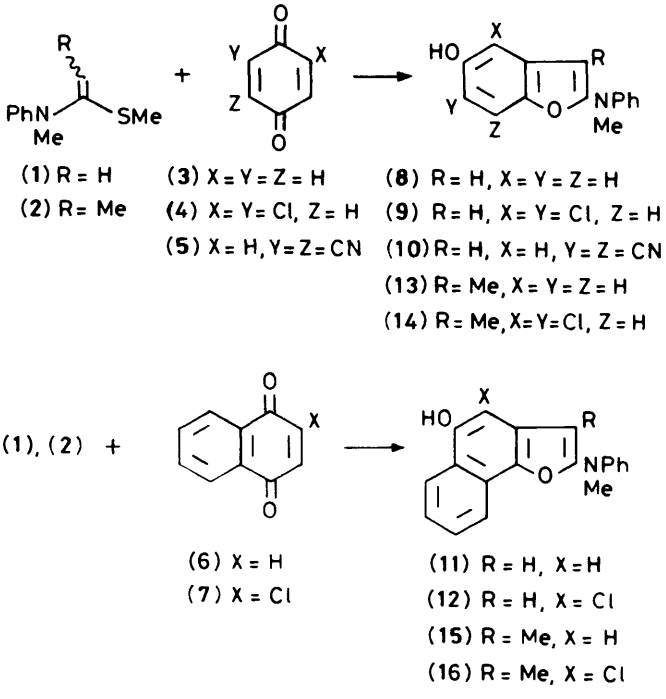
making it available for further manipulation. We now describe a new synthesis of some oxygen heterocycles following this route.

First cycloaddition of ketene *S,N*-acetals with 1,4 quinones was investigated.[8] Ketene *S,N*-acetals (**1**) and (**2**) were prepared from *N*-methyl-*N*-phenylthioacetamide in good yields according to the method of Gompper.[9] Annelation of (**1**) with 1,4-benzoquinone (**3**) under reflux in several kinds of solvent proceeded to give the selectively demethanethiolated 2-amino-benzofuran (**8**) in yields as shown in Table 1. The use of tetrahydrofuran (THF) or toluene as solvents gave good results in comparison with other solvents. Similar reaction of (**1**) with (**4**)—(**7**) provided the corresponding benzofurans (**9**) and (**10**) and naphtho[1,2-*b*]furans (**11**) and (**12**), respectively (Table 1).† Treatment of (**2**) with (**3**), (**4**), or (**6**) in boiling toluene gave 3-methylbenzofurans (**13**) and (**14**) and 3-methylnaphtho[1,2-*b*]furan (**15**) (Table 1). The use of a solvent with a lower boiling point such as THF gave none of the desired product. The reaction between (**7**) and (**2**) failed to give the expected compound (**16**) even under drastic conditions (xylene, reflux)

† Chromatography of the annelation reactions gave furans and some unidentified side-products.

Table 1. Annelation of ketene *S,N*-acetals with 1,4-quinones

Compd.	Reaction solvent	Yield (%)	Compd.	Reaction solvent	Yield (%)
(**8**)	Toluene	45	(**11**)	Toluene	26
	THF	44		THF	35
	Benzene	33	(**12**)	Toluene	16
	DME	21		THF	29
	MeCN	20	(**13**)	Toluene	38
(**9**)	Toluene	51	(**14**)	Toluene	46
	THF	25	(**15**)	Toluene	8
(**10**)	THF	10			



Scheme 2.

and leading instead to intractable mixtures and the recovery of (**7**) (32%).

We next turned our attention to the further role of the enamine component of the accessible furans. Ring-expansion of cyclic enamine with dimethyl acetylenedicarboxylate (DMAD) has already been described.[10] Reaction of the 3-unsubstituted furans (**8**), (**9**), and (**11**) with DMAD in boiling dioxane gave rise to the ring enlarged oxepines (**17**) (62%), (**18**) (42%), and (**19**) (57%) respectively. However, reaction of 3-methylfuran (**13**) led

Table 2. Benzo- and naphtho[1,2-*b*]-furans

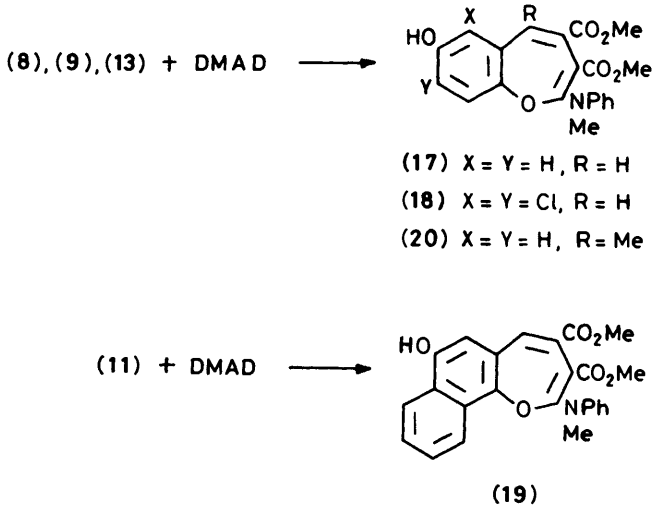
Compd.	M.p. (°C) (solvent)	$\nu_{max.}$/cm^{-1} (Nujol)	δ(CDCl$_3$)	Formula	Analysis (%)* C	H	N
(**8**)	75—77 (cyclohexane-Pr$^i_2$O)	3 300, 1 590	3.40 (3 H, s, NMe) 5.70 (1 H, s, 3-H)	$C_{15}H_{13}NO_2$	75.3 (75.3)	5.5 (5.4)	5.85 (5.9)
(**9**)	113—114 (cyclohexane-Pr$^i_2$O)	3 400, 1 590	3.47 (3 H, s, NMe) 5.70 (1 H, s, 3-H)	$C_{15}H_{11}C_{12}NO_2$	58.5 (58.6)	3.6 (3.5)	4.55 (4.5)
(**10**)	274—277 (CH_2Cl_2)	3 320, 2 210 1 600	3.60 (3 H, s, NMe) 5.55 (1 H, s, 3-H)	$C_{17}H_{11}N_3O_2$	70.6 (70.3)	3.8 (3.9)	14.5 (14.6)
(**11**)	138—140 (cyclohexane)	3 250, 1 590	3.54 (3 H, s, NMe) 6.00 (1 H, s, 3-H)	$C_{19}H_{15}NO_2$	78.9 (79.15)	5.2 (5.3)	4.8 (5.0)
(**12**)	100—103 (cyclohexane)	3 420, 1 590	3.54 (3 H, s, NMe) 6.03 (1 H, s, 3-H)	$C_{19}H_{14}ClNO_2$	70.5 (69.7)	4.4 (4.35)	4.3 (4.2)
(**13**)	137—140 (cyclohexane)	3 370, 1 600	2.00 (3 H, s, Me) 3.40 (3 H, s, NMe)	$C_{16}H_{15}NO_2 \cdot \frac{1}{4}H_2O$	74.5 (74.65)	5.9 (5.9)	5.4 (5.4)
(**14**)	104—107 (cyclohexane)	3 430, 1 600	2.24 (3 H, s, Me) 3.40 (3 H, s, NMe)	$C_{16}H_{13}C_{12}NO_2$	59.65 (59.7)	4.1 (4.2)	4.35 (4.3)
(**15**)	180—183 ($CHCl_3$)	3 400, 1 600	2.60 (3 H, s, Me) 3.42 (3 H, s, NMe)	$C_{20}H_{17}NO_2 \cdot \frac{1}{4}H_2O$	78.0 (77.8)	5.7 (5.45)	4.55 (4.4)

* Found values in parentheses.

Table 3. Oxepines

Compd.	Yield (%)	M.p. (°C) (solvent)	$\nu_{max.}$/cm^{-1} (Nujol)	δ(CDCl$_3$)	Formula	Analysis (%)* C	H	N
(**17**)	62	186—187 (Pr$^i_2$O–CH_2Cl_2)	3 350, 1 720, 1 705	3.45 (3 H, s, NMe), 3.52 (3 H, s, CO_2Me) 3.85 (3 H, s, CO_2Me), 6.15 (1 H, s, 5-H)	$C_{21}H_{19}NO_6$	66.1 (65.9)	5.0 (5.05)	3.7 (3.6)
(**18**)	42	209—212 (Pr$^i_2$O–CH_2Cl_2)	3 350, 1 730, 1 700	3.48 (3 H, s, NMe), 3.88 (6 H, s, 2CO_2Me) 6.61 (1 H, s, 5-H)	$C_{21}H_{17}Cl_2NO_6$	56.0 (55.95)	3.8 (3.8)	3.1 (3.3)
(**19**)	57	(210—214 (CH_2Cl_2–EtOH)	3 300, 1 720, 1 700	3.40 (3 H, s, NMe), 3.46 (3 H, s, CO_2Me) 3.85 (3 H, s, CO_2Me), 6.83 (1 H, s, 5-H)	$C_{25}H_{21}NO_6$	69.6 (69.8)	4.9 (4.9)	3.25 (3.4)

* Found values in parentheses.



Scheme 3.

only to the recovery of unchanged material (Scheme 3). Michael addition to the 3-position of (**8**) was now pursued. Addition of (**8**) to Michael acceptors (**20a**—**c**) at 150 °C in a sealed tube gave as expected the 3-substituted benzofurans (**21a**) (77%), (**21b**) (67%), and (**21c**) (59%), respectively. In turn, (**8**) and the compounds (**21a**—**c**) thus prepared were transformed into the biologically interesting[11] benzofuran-2-ones (**22**) (**23a**), (**23b**), and (**23c**) in moderate yields (78, 53, 30, and 45%, respectively) by hydrolysis with 10% hydrochloric acid in THF at room temperature (Scheme 4). In these reactions, (**1**) is synthetically equivalent to (**24**). In addition, annelation of (**8**) with 2 equivalents of phenyl isocyanate was performed.[5] However, the expected compound (**25**) was not obtained but a 1:1 adduct (**26**) was isolated in quantitative yield (Scheme 5). In contrast, compound (**8**) preferentially underwent *O*-acetylation instead of C-3 acetylation with acetyl chloride in the presence of pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give (**27**) (61%) (Scheme 6). Finally, treatment of (**1**) with the 1,4-bisiminoquinone (**28**)[12] in boiling THF effected similar cyclization, to give the corresponding indole (**29**) (82%) (Scheme 7). Michael addition of (**29**) was unsuccessful, owing to the electron withdrawing tendency of the sulphonyl substituent and the high aromaticity of the indole; thus the enamine character of (**29**) may be weakened compared with (**8**).

Experimental

^{1}H N.m.r. spectra were measured with a JEOL PMX-60 instrument in deuteriochloroform (tetramethylsilane as internal reference), mass spectra with a JEOL JMS-D200 machine,

Table 4. Michael adducts (**21a—c**)

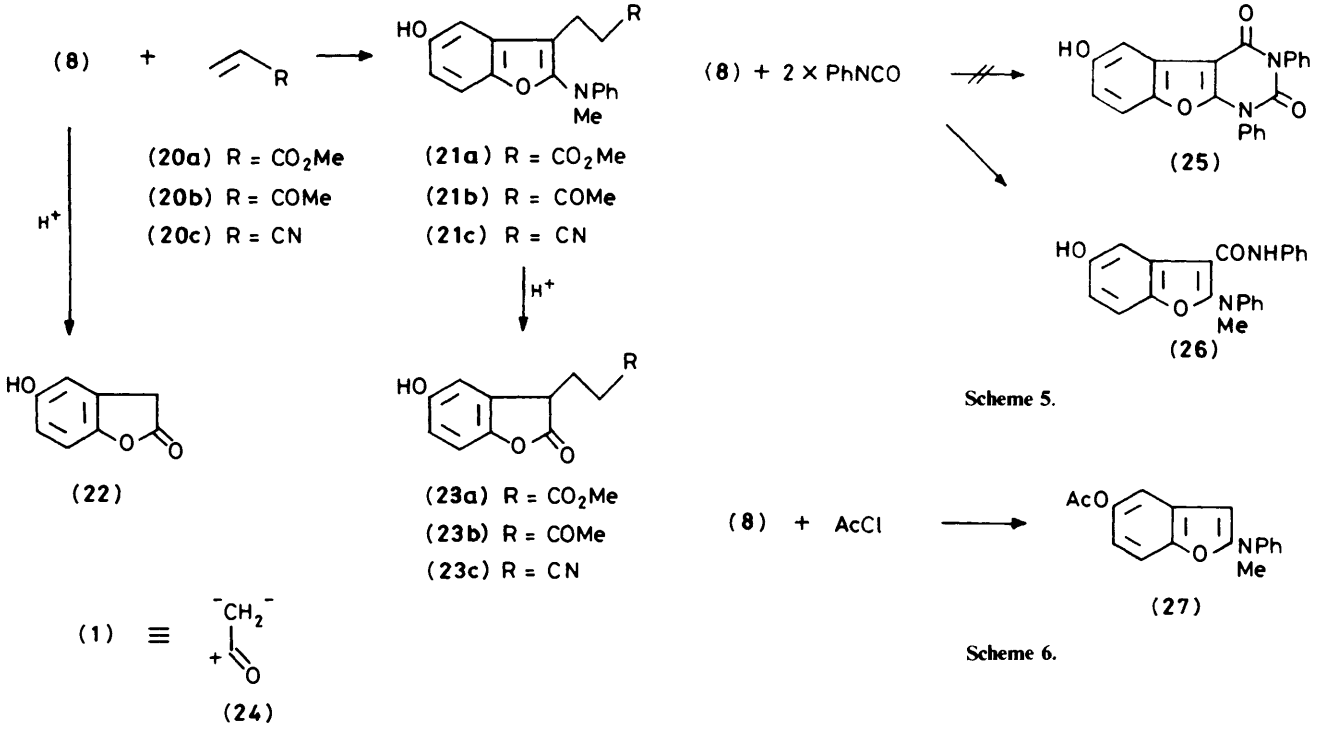
Compd.	Yield (%)	M.p. (°C) (solvent)	$\nu_{max.}$/cm^{-1} (Nujol)	δ($CDCl_3$)	Formula	Analysis (%)* C	H	N
(**21a**)	77	85—86 (hexane-Pr^i_2O)	3 350, 1 720	3.36 (3 H, s, NMe), 3.62 (3 H, s, CO_2Me)	$C_{19}H_{19}NO_4$	70.1 (70.25)	5.9 (5.8)	4.3 (4.45)
(**21b**)	67	79—82 (hexane-Pr^i_2O)	3 350, 1 700	2.04 (3 H, s, COMe), 3.31 (3 H, s, NMe)	$C_{19}H_{19}NO_3$	73.8 (73.5)	6.2 (6.3)	4.3 (4.6)
(**21c**)	59	126—130 (CH_2Cl_2–Pr^i_2O–light petroleum)	3 350, 2 270	3.34 (3 H, s, NMe)	$C_{18}H_{16}N_2O_2$	73.95 (74.05)	5.5 (5.6)	9.6 (9.1)

* Found values in parentheses.

Table 5. Benzofuran-2-ones

Compd.	Yield (%)	M.p. (°C) (solvent)	$\nu_{max.}$/cm^{-1} (Nujol)	δ($CDCl_3$)	Formula	Analysis (%)* C	H	N
(**22**)	78	190—194 (lit.,[13] 190 °C)	3 340, 1 760	3.75 (2 H, s, CH_2)				
(**23a**)	53	Oil	3 310, 1 800, 1 730†	3.69 (3 H, s, CO_2Me), 3.78 (1 H, t, *J* 6 Hz, CH)	$C_{12}H_{12}O_5$	61.0 (60.8)	5.1 (5.2)	
(**23b**)	30	114—117 (CH_2Cl_2-Pr^i_2O)	3 235, 1 785, 1 690	2.14 (3 H, s, COMe), 3.75 (1 H, t, *J* 6 Hz, CH)	$C_{12}H_{12}O_4$	65.4 (65.4)	5.5 (5.5)	
(**23c**)	45	122—124 (CH_2Cl_2–CCl_4)	3 355, 2 280, 1 790	3.80 (1 H, t, *J* 6 Hz, CH)	$C_{11}H_9NO_2$	65.0 (64.3)	4.5 (4.6)	6.9 (6.7)

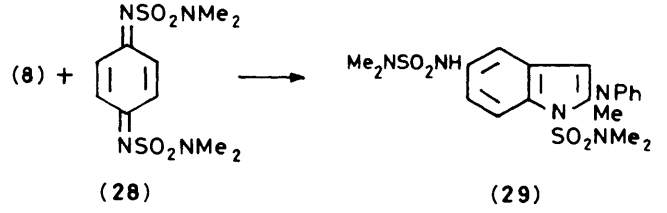
* Found values in parentheses. † Taken in neat.



Scheme 4.

Scheme 5.

Scheme 6.



Scheme 7.

and i.r. spectra in Nujol unless otherwise noted, on a JASCO A-102 spectrophotometer. M.p.s were determined on a Yanaco micro-melting point apparatus and are uncorrected. Column chromatography was performed on silica gel 60 (230—400 mesh) with medium pressure, hexane–ethyl acetate being used as eluant.

N-Methyl-N-phenyl-1-(methylthio)vinylamine (**1**) *and N-methyl-N-phenyl-1-(methylthio)prop-1-enylamine* (**2**).—According to Gompper's method,[9] methylation of *N*-methyl-*N*-phenylthioacetamide (36.3 g) with methyl iodide (46.3 g) in dry ether (200 ml) followed by dehydroiodination with potassium t-butoxide (36.5 g) in dry ether (400 ml) gave the ketene *S,N*-acetal (**1**) (20.1 g, 63%), b.p. 115—116 °C/3.5 mmHg; $\nu_{max.}$(film) 1 590 cm^{-1}; δ 2.14 (3 H, s, SMe), 3.14 (3 H, s, NMe), 4.87 (2 H, d, *J* 4.5 Hz, =CH_2) (Found: M^+, 179.075. $C_{10}H_{13}NS$ requires *M*, 179.077). Analogous to the procedure described for (**1**), from *N*-methyl-*N*-phenylthiopropionamide (40 g) the ketene *S,N*-acetal (**2**) (30.3 g, 74.3%) was prepared, b.p. 71—73 °C/0.3 mmHg; $\nu_{max.}$(film) 1 600 cm^{-1}; δ 1.56 (0.8 H, d, *J* 7 Hz, Me), 1.85 (1.2 H, d, *J* 7 Hz, Me), 2.00 (1.8 H, s, SMe), 2.10 (1.2 H, s, SMe), 3.19 (3 H, s, NMe), and 5.62 (1 H, m, =CH) (Found: M^+, 193.092. $C_{11}H_{15}NS$ requires *M*, 193.092).

General Procedure for Annelation of the Ketene S,N-*Acetal* (**1**) *with* 1,4-*Quinones* (**3**)—(**7**) *or* (**2**) *with* (**3**), (**4**), *and* (**6**).—A mixture of compound (**1**) (1.1 mmol) and compounds (**3**), (**4**), (**6**), and (**7**) (1 mmol) in a solvent (5 ml) shown in Table 1 was refluxed for 15 h. Reaction using (**5**) was carried out at room temperature. After evaporation, the residue was chromatographed to give 2-(N-*methylanilino*)*benzofuran*-5-*ol* (**8**), 4,6-*dichloro*-2-(N-*methylanilino*)*benzofuran*-5-*ol* (**9**), 5-*hydroxy*-2-(N-*methylanilino*)*benzofuran*-6,7-*dicarbonitrile* (**10**), 2-(N-*methylanilino*)*naphtho*[1,2-b]*furan*-5-*ol* (**11**), and 4-*chloro*-2-(N-*methylanilino*)*naphtho*[1,2-b]*furan*-5-*ol* (**12**) in the yields shown in Table 1. In the same manner, annelation of compound (**2**) (1.1 mmol) with compounds (**3**), (**4**), and (**6**) (1 mmol) gave 3-*methyl*-2-(N-*methylanilino*)*benzofuran*-5-*ol* (**13**), 4,6-*dichloro*-3-*methyl*-2-(N-*methylanilino*)*benzofuran*-5-*ol* (**14**), and 3-*methyl*-2-(N-*methylanilino*)*naphtho*[1,2-b]*furan*-5-*ol* (**15**), respectively (Table 2).

General Procedure for the Ring Expansion of Compounds (**8**), (**9**), or (**11**) *with* DMAD.—A mixture of compounds (**8**), (**9**), or (**11**) (0.5 mmol) and DMAD (0.55 mmol) in dioxane (5 ml) was refluxed for 15 h. After evaporation, the residue was chromatographed to give *dimethyl*-7-*hydroxy*-2-(N-*methylanilino*)-1-*benzoxepine*-3,4-*dicarboxylate* (**17**), *dimethyl* 6,8-*dichloro*-7-*hydroxy*-2-(N-*methylanilino*)-1-*benzoxepine*-3,4-*dicarboxylate* (**18**), or *dimethyl*-7-*hydroxy*-2-(N-*methylanilino*)-*naphtho*[1,2-b]*oxepine*-3,4-*dicarboxylate* (**19**), respectively (Table 3).

General Procedure for Michael Addition of (**8**) *with Michael Acceptors* (**20a**—**c**).—A mixture of compounds (**8**) (0.5 mmol) and (**20**) (0.55 mmol) in a sealed tube was heated at 150 °C for 15 h. The mixture was then subject to chromatography to afford 3-(2-*methoxycarbonylethyl*)-2-(N-*methylanilino*)*benzofuran*-5-*ol* (**21a**), 2-(N-*methylanilino*)-3-(3-*oxobutyl*)*benzofuran*-5-*ol* (**21b**), and 3-(2-*cyanoethyl*)-2-(N-*methylanilino*)*benzofuran*-5-*ol* (**21c**), respectively (Table 4).

General Procedure for Hydrolysis of Compounds (**8**) *and* (**21a**—**c**).—A solution of compound (**8**) or compounds (**21a**—**c**) (0.5 mmol) in a mixture of 10% HCl (2 ml) and THF (4 ml) was stirred at room temperature for 5 h. Water (10 ml) was then added and the mixture extracted with dichloromethane. The extract was washed (brine), dried ($MgSO_4$), evaporated and the residue was chromatographed to provide 2,3-*dihydro*-5-*hydroxybenzofuran*-2(3H)-*one* (**22**), 2,3-*dihydro*-5-*hydroxy*-3-(2-*methoxycarbonylethyl*)*benzofuran*-2(3H)-*one* (**23a**), 2,3-*dihydro*-5-*hydroxy*-3-(3-*oxobutyl*)*benzofuran*-2(3H)-*one* (**23b**), and 3-(2-*cyanoethyl*)-2,3-*dihydro*-5-*hydroxybenzofuran*-2(3H)-*one* (**23c**), respectively (Table 5).

2-(N-*Methylanilino*)-3-(N-*phenylcarbamoyl*)*benzofuran*-5-*ol* (**26**).—A mixture of compound (**8**) (0.5 mmol) and phenyl isocyanate (1 mmol) in toluene (10 ml) was refluxed for 15 h. After cooling, the precipitate was filtered off. The solid was washed with dichloromethane and recrystallized with hexane–THF to give (**26**) (178 mg, 99%), m.p. 195—200 °C; $\nu_{max.}$ 1 730 and 1 640 cm^{-1}; δ 3.60 (3 H, s, NMe) and 8.98 (1 H, br s, NH) (Found: C, 73.4: H, 4.9; N, 8.2. $C_{22}H_{18}N_2O_3$ requires C, 73.7; H, 5.1; N, 7.8%).

5-*Acetoxy*-2-(N-*methylanilino*)*benzofuran* (**27**).—Acetyl chloride (0.55 mmol) was injected into a mixture of compound (**8**) (0.5 mmol), 4-dimethylaminopyridine (0.05 mmol), and pyridine (5 ml). The mixture was refluxed for 15 h, evaporated and the residue chromatographed to give (**27**) (86 mg, 61%), m.p. 89—90 °C (hexane–di-isopropyl ether); $\nu_{max.}$ 1 760 cm^{-1}; δ 2.30 (3 H, s, COMe), 3.40 (3 H, s, NMe), and 5.73 (1 H, s, 3-H) (Found: C, 72.8; H, 5.4; N, 5.1. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%).

N-1-*Dimethylsulphamoyl*-5-*dimethylsulphamoylamino*-2-(N-*methylanilino*)*indole* (**29**).—A mixture of *p*-quinone bis-(dimethylaminosulphonimide[14] (1 mmol) and compound (**1**) (1.1 mmol) in THF (5 ml) was refluxed for 15 h. After evaporation, the residue was chromatographed to give compound (**29**) (370 mg, 82%), m.p. 165—169 °C ($CHCl_3$–CCl_4); $\nu_{max.}$ 3 260 and 1 595 cm^{-1}; δ 2.62 (6 H, s, NMe_2), 2.85 (6 H, s, NMe_2), 3.33 (3 H, s, NMe), and 6.42 (1 H, s, 3-H) (Found: C, 50.45; H, 5.6; N, 15.2. $C_{19}H_{25}N_5O_4S_2$ requires C, 50.5; H, 5.6; N, 15.5%).

Acknowledgements

The authors thank the Ministry of Education, Sciences, and Culture (Japan) for a research grant.

References

1 Preliminary communication, H. Takahata, A. Anazawa, K. Moriyama, and T. Yamazaki, *Chem. Lett.*, 1986, 5.
2 A. G. Cook, 'Enamines: Synthesis, Structure, and Reaction,' Marcel Dekker, New York, 1969; P. W. Hickmott, *Tetrahedron*, 1982, **38**, 1975; *ibid.*, 1982, **38**, 3363; *ibid.*, 1984, **40**, 2989.
3 T. Mukaiyama, S. Azisawa, and T. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2641.
4 R. Gompper and W. Elser, *Justus Liebigs Ann. Chem.*, 1969, **725**, 73.
5 H. Takahata, T. Nakajima, and T. Yamazaki, *Synth. Commun.*, 1984, **14**, 675; H. Takahata, T. Nakajima, M. Nakano, A. Tomiguchi, and T. Yamazaki, *Chem. Pharm. Bull.*, 1985, **33**, 4299.
6 H. Takahata, T. Nakajima, K. Matoba, and T. Yamazaki, *Synth. Commun.*, 1984, **14**, 1257.
7 H. Takahata, T. Nakajima, and T. Yamazaki, *Chem. Pharm. Bull.*, 1984, **32**, 1658.
8 K. C. Brannock, R. D. Burpitt, H. E. Davis, H. S. Pridgen, and J. G. Thweatt, *J. Org. Chem.*, 1964, **29**, 2579.
9 R. Gompper and W. Elser, 'Organic Synthesis,' Coll. Vol. V, John Wiley and Sons, Inc., New York, 1970, 780.
10 M. S. Lin and V. Snieckus, *J. Org. Chem.*, 1971, **36**, 645; R. M. Acheson, N. D. Wright, and P. A. Tasker, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2918; D. N. Reinhoudt and C. G. Kouwenhoven, *Tetrahedron Lett.*, 1972, 5203.
11 K. Krohn, *Tetrahedron Lett.*, 1975, 4667.
12 G. Domschke, G. Heller, and U. Natzeck, *Chem. Ber.*, 1966, **99**, 939.
13 S. B. Bostock and A. H. Renfrew, *Synthesis*, 1978, 66.
14 R. Adams and R. P. Shafer, *J. Am. Chem. Soc.*, 1953, **75**, 667.

Received 26*th June* 1986; *Paper* 6/1286