Anal. Calcd. for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; H, 4.32. Found: C, 63.80; H, 4.40.

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NUTLEY 10, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE, DUBLIN]

Synthesis of Heterocyclic-Substituted Chromones and Chalcones

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The preparation of eleven new 2-heterocyclic-substituted chromones and of five new related chalcones is reported. Condensation of 2′-hydroxyacetophenones with heterocyclic acid chlorides, Baker-Venkataraman rearrangement of the products, followed by dehydration gave the chromones III. Base-catalyzed condensation of 2′-hydroxyacetophenones with heterocyclic aldehydes yielded the chalcones IV.

In recent years increasing attention has been directed to the biological activity of chromones and chalcones. Broncho-dilatory[1] and coronary spasmolytic[2] properties have been reported for various chromones, especially those having heterocyclic substituents in the 2-position, while related chalcones have exhibited bacteriostatic,[3] tuberculostatic,[4] and insecticidal[5] activity.

This paper describes the preparation of a number of new heterocyclic-substituted chromones and some of the corresponding chalcones, together with some previously reported in the literature but now synthesized by a different method. All the compounds reported have been tested for antitumor activity by the National Institutes of Health, Bethesda, Md., and some for cardiovascular activity by the Lilly Research Laboratories, Indianapolis, and the Smith Kline & French Laboratories of Philadelphia.

Synthesis of chromones of this type has most frequently been accomplished by a Claisen condensation of 2′-hydroxyacetophenones with the ethyl esters of heterocyclic acids, followed by dehydration.[2] Oxidative ring-closure of 2′-hydroxychalcones with selenium dioxide has also been employed.[6] A further method[7] adopted in the present work has

TABLE I

2′-ACYLOXYACETOPHENONES

Compound	M.P.	Yield, %	Calcd., %	Found, %
2′-Nicotinyloxyacetophenone	88–89	90	C, 69.7; H, 4.6; N, 5.8	C, 69.4; H, 4.6; N, 5.2
2′-Isonicotinyloxyacetophenone	80–81	30	C, 69.7; H, 4.6; N, 5.8	C, 69.5; H, 4.8; N, 5.8
4′-Methoxy-2′-nicotinyloxyacetophenone	89–90	20	C, 66.4; H, 4.8; N, 5.2	C, 66.6; H, 4.8; N, 5.4
2′-Isonicotinyloxy-4′-methoxyacetophenone	75–76	15	C, 66.4; H, 4.8; N, 5.2	C, 66.5; H, 5.0; N, 4.9
5′-Methoxy-2′-nicotinyloxyacetophenone	78–80	91	C, 66.4; H, 4.8; N, 5.2	C, 66.8; H, 4.9; N, 5.1
2′-Isonicotinyloxy-5′-methoxyacetophenone	84–85	81	C, 66.4; H, 4.8; N, 5.2	C, 66.4; H, 4.8; N, 5.1
4′,6′-Dimethoxy-2′-nicotinyloxyacetophenone	123–124	83	C, 63.8; H, 5.0; N, 4.6	C, 63.5; H, 5.3; N, 4.4
2′-Isonicotinyloxy-4′,6′-dimethoxyacetophenone	121–122	79	C, 63.8; H, 5.0; N, 4.6	C, 63.5; H, 5.2; N, 4.9
3′,4′-Dimethoxy-2′-nicotinyloxyacetophenone	118–119	71	C, 63.8; H, 5.0; N, 4.6	C, 63.9; H, 5.0; N, 4.7
2′-Isonicotinyloxy-3′,4′-dimethoxyacetophenone	120–121	52	C, 63.8; H, 5.0; N, 4.6	C, 63.8; H, 4.9; N, 4.8
2′-Quinaldyloxyacetophenone	140–141	47	C, 74.2; H, 4.5; N, 4.8	C, 74.2; H, 4.7; N, 4.6
2′-(2-Furoyloxy)-4′-methoxyacetophenone	113–114	95	C, 64.6; H, 4.7	C, 64.3; H, 4.6
2′-(2-Furoyloxy)-5′-methoxyacetophenone	70–71	77	C, 64.6; H, 4.7	C, 64.4; H, 4.5
2′-(2-Furoyloxy)-6′-methoxyacetophenone	87–89	84	C, 64.6; H, 4.7	C, 64.6; H, 4.7
2′-(2-Thenoyloxy)acetophenone	112–114	83	C, 63.4; H, 4.1; S, 13.0	C, 63.1; H, 4.2; S, 12.6
4′-Methoxy-2′-(2-thenoyloxy)acetophenone	88–89	94	C, 60.9; H, 4.4; S, 11.6	C, 60.4; H, 4.2; S, 12.0
5′-Methoxy-2′-(2-thenoyloxy)acetophenone	75–77	95	C, 60.9; H, 4.4; S, 11.6	C, 60.9; H, 4.6; S, 11.3
6′-Methoxy-2′-(2-thenoyloxy)acetophenone	90–91	96	C, 60.9; H, 4.4; S, 11.6	C, 61.0; H, 4.4; S, 11.0

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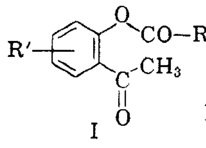
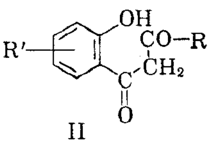
involved three stages: (1) condensation of various 2′-hydroxyacetophenones with the appropriate heterocyclic acid chloride to give the keto esters I(R = 3-pyridyl, 4-pyridyl, 2-quinolyl, 2-furyl, 2-thienyl; R′ = H, methoxyl); (2) Baker-Venkataraman rearrangement to the 1,3-diketones II, followed by (3), dehydration to the chromones III.



I



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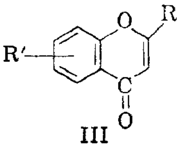
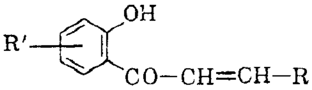


III

Heterocyclic hydroxychalcones have been prepared by condensation of 2′-hydroxyacetophenones with heterocyclic aldehydes using aqueous alkali,[3-8] sodium methoxide,[9] piperidine[7] or mineral acid[7] as the condensing agent. In the present work, five of the chalcones IV (R = 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl; R′ = H, methoxyl) were synthesized using aqueous alkali; in the other cases sodium methoxide was employed.



IV

TABLE II

1,3-Diketones

Compound	M.P.	Yield, %	Calcd., %	Found, %
1-(2-Hydroxyphenyl)-3-(3-pyridyl)propane-1,3-dione	145–146	87	C, 69.7; H, 4.6; N, 5.8	C, 69.6; H, 4.5; N, 5.7
1-(2-Hydroxyphenyl)-3-(4-pyridyl)propane-1,3-dione	144–145	40	C, 69.7; H, 4.6; N, 5.8	C, 69.4; H, 4.7; N, 6.0
1-(2-Hydroxy-4-methoxyphenyl)-3-(3-pyridyl)propane-1,3-dione	145–146	27	C, 66.4; H, 4.8; N, 5.2	C, 66.1; H, 4.9; N, 5.1
1-(2-Hydroxy-4-methoxyphenyl)-3-(4-pyridyl)propane-1,3-dione	143–144	50	C, 66.4; H, 4.8	C, 66.1; H, 4.9
1-(2-Hydroxy-5-methoxyphenyl)-3-(3-pyridyl)propane-1,3-dione	143–144	68	C, 66.4; H, 4.8; N, 5.2	C, 66.3; H, 4.9; N, 5.2
1-(2-Hydroxy-5-methoxyphenyl)-3-(4-pyridyl)propane-1,3-dione	117–119	52	C, 64.8; H, 5.3; N, 4.9[a]	C, 64.4; H, 5.3; N, 4.8
1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3-pyridyl)propane-1,3-dione	127–128	28	C, 63.8; H, 5.0; N, 4.6	C, 63.8; H, 5.0; N, 4.5
1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-pyridyl)propane-1,3-dione	155–156	47	C, 63.8; H, 5.0; N, 4.6	C, 63.8; H, 5.1; N, 5.0
1-(2-Hydroxy-3,4-dimethoxyphenyl)-3-(3-pyridyl)propane-1,3-dione	122–124	35	C, 63.8; H, 5.0; N, 4.6	C, 63.5; H, 5.0; N, 5.1
1-(2-Hydroxy-3,4-dimethoxyphenyl)-3-(4-pyridyl)propane-1,3-dione	150–152	60	C, 63.8; H, 5.0; N, 4.6	C, 64.2; H, 5.0; N, 4.9
1-(2-Hydroxyphenyl)-3-(2-quinolyl)propane-1,3-dione	148–149	33	C, 74.2; H, 4.5; N, 4.8	C, 74.4; H, 4.7; N, 4.8
1-(2-Furyl)-3-(2-hydroxy-4-methoxyphenyl)propane-1,3-dione	94–95	75	C, 64.6; H, 4.7	C, 64.1; H, 4.6
1-(2-Furyl)-3-(2-hydroxy-5-methoxyphenyl)propane-1,3-dione	93–94	50	C, 64.6; H, 4.7	C, 65.0; H, 4.6
1-(2-Furyl)-3-(2-hydroxy-6-methoxyphenyl)propane-1,3-dione	114–117	70	C, 64.6; H, 4.7	C, 64.9; H, 4.4
1-(2-Hydroxyphenyl)-3-(2-thienyl)propane-1,3-dione	80–81	75	C, 63.4; H, 4.1; S, 13.0	C, 63.6; H, 4.3; S, 13.4
1-(2-Hydroxy-4-methoxyphenyl)-3-(2-thienyl)propane-1,3-dione	112–114	70	C, 60.9; H, 4.4; S, 11.6	C, 60.7; H, 4.1; S, 11.7
1-(2-Hydroxy-5-methoxyphenyl)-3-(2-thienyl)propane-1,3-dione	82–84	60	C, 60.9; H, 4.4; S, 11.6	C, 60.9; H, 4.3; S, 10.9
1-(2-Hydroxy-6-methoxyphenyl)-3-(2-thienyl)propane-1,3-dione	99–100	62	C, 60.9; H, 4.4; S, 11.6	C, 60.9; H, 4.3; S, 11.0

[a] $C_{15}H_{13}NO_4 \cdot {}^1/_2CH_3OH$.

EXPERIMENTAL

Microanalyses were carried out by Mrs. E. M. Carey of the Chemistry Department, University College, Dublin, and by Drs. Weiler and Strauss, Analytical Laboratory, Oxford, England. All melting points are uncorrected

Materials. Substituted 2′-hydroxyacetophenones were prepared by conventional methods: 2′-hydroxy-4′-methoxyacetophenone[10] had m.p. 60°; 2′-hydroxy-5′-methoxyacetophenone[11] had m.p. 47°; 2′-hydroxy-3′,4′-dimethoxyacetophenone[12] had m.p. 77°; 2′-hydroxy-4′,6′-dimethoxyacetophenone[13] had m.p. 82–83°.

Acid chlorides also were prepared by established procedures: nicotinyl choride[14] had b.p. 102°/20 mm.; isonicotinyl chloride[14] had b.p. 95°/25 mm.; 2-furoyl chloride[15] had b.p. 77°/35 mm.; 2-thenoyl chloride[16] had b.p. 96°/15 mm.; quinaldyl chloride[17] had m.p. 96°.

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TABLE III

CHROMONES

Compound	M.P.	Yield, %	Calcd., %	Found, %
2-(3-Pyridyl)chromone[a]	128–130[b]	97	C, 75.3; H, 4.1; N, 6.3	C, 75.5; H, 4.3; N, 6.0
2-(4-Pyridyl)chromone[a]	142–143[c]	71	C, 75.3; H, 4.1; N, 6.3	C, 74.9; H, 3.8; N, 6.1
7-Methoxy-2-(3-pyridyl)chromone[a]	159–160[d]	75	C, 71.1; H, 4.3; N, 5.5	C, 71.3; H, 4.3; N, 5.2
7-Methoxy-2-(4-pyridyl)chromone[a]	192–193[e]	55	C, 71.1; H, 4.3; N, 5.5	C, 70.8; H, 4.6; N, 5.7
6-Methoxy-2-(3-pyridyl)chromone	156–158	75	C, 71.1; H, 4.3; N, 5.5	C, 71.5; H, 4.4; N, 5.0
6-Methoxy-2-(4-pyridyl)chromone[a]	182–183[f]	80	C, 71.1; H, 4.3; N, 5.5	C, 71.2; H, 4.4; N, 5.3
5,7-Dimethoxy-2-(3-pyridyl)chromone	161–162	85	C, 67.8; H, 4.6; N, 4.9	C, 67.8; H, 4.7; N, 4.4
5,7-Dimethoxy-2-(4-pyridyl)chromone	228–230	78	C, 67.8; H, 4.6; N, 4.9	C, 68.1; H, 4.8; N, 5.0
7,8-Dimethoxy-2-(3-pyridyl)chromone	170–172	63	C, 67.8; H, 4.6; N, 4.9	C, 67.4; H, 4.7; N, 4.7
7,8-Dimethoxy-2-(4-pyridyl)chromone	200–201	63	C, 67.8; H, 4.6; N, 4.9	C, 67.5; H, 4.6; N, 5.0
2-(2-Quinolyl)chromone	200–201	75	C, 79.1; H, 4.0; N, 5.1	C, 78.7; H, 4.2; N, 4.7
2-(2-Furyl)-7-methoxychromone[a]	158–159[g]	93	C, 69.4; H, 4.2	C, 69.4; H, 3.9
2-(2-Furyl)-6-methoxychromone	172–173	80	C, 69.4; H, 4.2	C, 69.4; H, 4.1
2-(2-Furyl)-5-methoxychromone	175–176	93	C, 69.4; H, 4.2	C, 69.2; H, 4.3
2-(2-Thienyl)chromone[a]	97–99[h]	88	C, 68.4; H, 3.5; S, 14.0	C, 68.3; H, 3.5; S, 14.1
7-Methoxy-2-(2-thienyl)chromone	140–141	71	C, 65.1; H, 3.9; S, 12.4	C, 65.1; H, 3.9; S, 11.9
6-Methoxy-2-(2-thienyl)chromone	130–131	87	C, 65.1; H, 3.9; S, 12.4	C, 64.7; H, 3.7; S, 11.9
5-Methoxy-2-(2-thienyl)chromone	121–122	64	C, 65.1; H, 3.9; S, 12.4	C, 64.9; H, 4.0; S, 12.0

[a] Previously reported in the literature, synthesized by a different method. [b] Reported[2b] m.p. 127–128°. [c] Reported[2b] m.p. 142–143°. [d] Reported[2c] m.p. 159°. [e] Reported[2b] m.p. 192°. [f] Reported[2b] m.p. 184°. [g] Reported[6] m.p. 160°. [h] Reported[7b] m.p. 102°.

TABLE IV

CHALCONES

Compound	M.P.	Yield, %	Calcd., %	Found, %
1-(2-Hydroxyphenyl)-3-(2-pyridyl)propenone[a]	98–99[c]	24[b]	C, 74.6; H, 4.9; N, 6.2	C, 74.2; H, 5.0; N, 6.2
1-(2-Hydroxyphenyl)-3-(3-pyridyl)propenone[a]	151–153[d]	22[b]	C, 74.6; H, 4.9; N, 6.2	C, 74.2; H, 4.7; N, 6.0
1-(2-Hydroxyphenyl)-3-(4-pyridyl)propenone	118–119	6	C, 74.6; H, 4.9; N, 6.2	C, 74.3; H, 5.0; N, 5.9
1-(Hydroxy-4-methoxyphenyl)-3-(2-pyridyl)-propenone	132–133	16	C, 70.6; H, 5.1; N, 5.5	C, 70.9; H, 5.2; N, 5.3
1-(2-Hydroxy-4-methoxyphenyl)-3-(3-pyridyl)-propenone	137–138	21	C, 70.6; H, 5.1; N, 5.5	C, 70.2; H, 5.1; N, 5.9
1-(2-Hydroxy-4-methoxyphenyl)-3-(4-pyridyl)-propenone	141–142	8	C, 70.6; H, 5.1; N, 5.5	C, 70.2; H, 5.2; N, 5.0
1-(2-Hydroxyphenyl)-3-(2-thienyl)propenone[a]	99–100[e]	38[b]	C, 62.9; H, 4.8; S, 12.9	C, 62.8; H, 5.1; S, 12.4
1-(2-Hydroxy-4-methoxyphenyl)-3-(2-thienyl)-propenone	94–95	17	C, 64.6; H, 4.6; S, 12.3	C, 64.3; H, 4.6; S, 12.0

[a] Previously reported in the literature, prepared by a different method. [b] Synthesized by sodium methoxide condensation; others prepared by aqueous alkaline condensation. [c] Reported[8] m.p. 101–102°. [d] Reported[8] m.p. 161–162°. [e] Reported[8] m.p. 99-100°, 100°.[7b]

The general method for the preparation of the chromones is illustrated by the synthesis of *6-methoxy-2-(3-pyridyl)-chromone:*

Nicotinyl chloride (5.6 g., 0.04 mole) was added dropwise to an ice-cooled, stirred solution of 5.8 g. (0.035 mole) of 2′-hydroxy-5′-methoxyacetophenone in 10 ml. of dry pyridine. The mixture was stirred for 3 hr. at room temperature and was then poured onto crushed ice and acetic acid. The solid material which separated was washed with 2% sodium hydroxide solution and with water. Crystallization from methanol gave 8.6 g. (91%) of *5′-methoxy-2′-nicotinyloxyacetophenone* as colorless needles, m.p. 78–80°.

To a solution of 8.6 g. of this keto ester in 15 ml. of dry pyridine was added 3.4 g. of dry, powdered potassium hydroxide. The mixture was shaken vigorously for 20 min. in a stoppered flask and was then set aside for 15 hr. The crude product liberated by the addition of cold, dilute acetic acid was washed with water and crystallized from methanol to give 5.8 g. (68%) of *1-(2-hydroxy-5-methoxyphenyl)-3-(3-pyridyl)propane-1,3-dione* as lemon yellow needles, m.p. 143–144°.

Ten milliliters of concd. sulfuric acid was added slowly to an ice-cooled, stirred solution of 5.8 g. of the diketone in 40 ml. of chloroform. The mixture was stirred for 30 min. at 20° and was then made alkaline by the cautious addition of cold, concentrated sodium hydroxide solution. Water was added, the organic layer was separated and the aqueous layer was extracted with further portions of chloroform. The residue after removal of the solvent and crystallization from a mixture of benzene and ligroin yielded 4.1 g. (75%) of *6-methoxy-2-(3-pyridyl)chromone* as colorless pillars, m.p. 156–158°.

In only one case was this procedure modified: *2′-quinaldyloxyacetophenone* was prepared by adding quinaldyl chloride dissolved in dry benzene to 2′-hydroxyacetophenone in dry pyridine.

Melting points, percentage yields and analytical data of the 2′-acyloxyacetophenones are recorded in Table I, those of the 1,3-diketones in Table II, and those of the chromones in Table III.

Preparation of the chalcones. (1) *1-(2-Hydroxy-4-methoxyphenyl)-3-(3-pyridyl)propenone* was prepared by aqueous alkaline condensation. To a solution of 3.32 g. (0.02 mole) of 2′-hydroxy-4′-methoxyacetophenone and 3.20 g. (0.03

mole) of pyridine-3-aldehyde in 50 ml. of ethanol was added 10 ml. of 50% potassium hydroxide solution over a period of 20 min. The mixture was stirred for 4 hr. and was then acidified with ice-cold acetic acid. Crystallization of the precipitate from ethanol gave 1.1 g. (21%) of yellow needles, m.p. 137–138°.

Four other chalcones were prepared by this method: *1-(2-hydroxyphenyl) - 3 - (4 - pyridyl)propenone, 1 - (2 - hydroxy-4 - methoxyphenyl) - 3 - (2 - pyridyl)propenone, 1 - (2 - hydroxy-4 - methoxyphenyl) - 3 - (4 - pyridyl)propenone* and *1 - (2-hydroxy - 4 - methoxyphenyl) - 3 - (2 - thienyl)propenone;* the other chalcones were prepared by the following procedure.

(2) *1-(2-Hydroxyphenyl)-3-(2-pyridyl)propenone* was prepared by sodium methoxide condensation. To a mixture of 2.72 g. (0.02 mole) of 2′-hydroxyacetophenone and 3.20 g. (0.03 mole) of pyridine-2-aldehyde in 40 ml. of methanol was added a solution of 1.1 g. of sodium in 20 ml. of methanol. The reaction mixture was kept overnight at room temperature and was then poured onto crushed ice and acetic acid. The precipitate which formed was crystallized from benzene, giving 1.1 g. (24%) of the chalcone as yellow needles, m.p. 98–99°.

Melting points, percentage yields and analytical data of the chalcones are given in Table IV.

Acknowledgment. We wish to express our thanks to the National Institutes of Health, Bethesda, Md., for the provision of a research grant.

DUBLIN, IRELAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLIX. Pyrido[2,1-b]benzo[f]-1,3-thiazepinium Salts[1]

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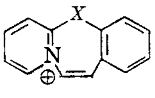
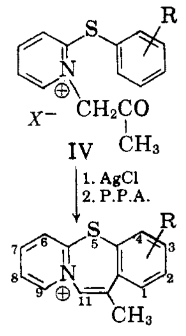
The first pyrido[2,1-b]benzo[f]-1,3-thiazepinium salts have been prepared by quaternization of suitable 2-phenylthiopyridines with iodoacetone, followed by cyclization of the quaternary salts in polyphosphoric acid at 160°. The new pyridobenzothiazepinium salts include the 12-methyl perchlorate and three of its derivatives.

The success met with[3] in the synthesis of the first morphanthridizinium salts (I) led to an extension of the general method to the preparation of the first pyridobenzoxazepinium salts (II),[4] in which the methylene bridge has been replaced by an oxygen atom. A logical sequel was an attempt to prepare the related but unknown pyrido[2,1-b]benzo[f]-1,3-thiazepinium salts (III). The nearest approach to such a system appears to be 11-phenyldibenzo-[b,f][1,4]thiazepine which was reported[5] to have been synthesized with the expectation that it might show quasi-aromatic properties. The unshared electrons on the sulfur bridge of the new pyridobenzothiazepinium salts (III) would be expected to delocalize (to a small extent) into the pyridine ring, conferring on the system a resonance stabilization which has no counterpart in the morphanthridizinium system (I). On the other hand it would not be expected that delocalization of the unshared electrons from sulfur would be so extensive as that from the oxygen bridge of the pyridobenzoxazepinium salts (II).[6]

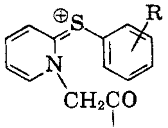
The acetonyl quaternary iodides (VI, X = I) were readily formed by the reaction of iodoacetone with the easily prepared[7] 2-arylthiopyridines(V). The quaternary iodides were converted to the corresponding chlorides (VI, X = Cl) before all cyclization attempts. It had been found earlier[3] that 1-acetonyl-2-benzylpyridinium chloride, when refluxed for five days in 48% hydrobromic acid, was cyclized to the morphanthridizinium ion (I) in 75% yield. Under the same reaction conditions the 1-acetonyl-2-phenylthiopyridinium salt (VI) was recovered unchanged (as the perchlorate).



I. $X = CH_2$
II. $X = O$
III. $X = S$



V



IVB

The great difference in ease of cyclization evidenced when the methylene bridge is replaced by sulfur can best be explained by invoking resonance. If B makes any significant contribution to the res-

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[1] For the preceding communication of this series see *J. Org. Chem.*, **26**, 3278 (1961).

[2] This research was supported by a research grant (NSF-G6215) of the National Science Foundation.

[3] K. B. Moser and C. K. Bradsher, *J. Am. Chem. Soc.*, **81**, 2547 (1959).

[4] C. K. Bradsher, L. D. Quin, and R. E. Le Bleu, *J. Org. Chem.*, **26**, 3273 (1961).

[5] C. I. Brodrick, J. S. Nicholson, and W. F. Short, *J. Chem. Soc.*, 3857 (1954).

[6] For a discussion of the effect of delocalization on the bond angles of diphenyl ether and diphenyl sulfide see R. J. Gillespie, *J. Am. Chem. Soc.*, **82**, 5978 (1960).

[7] L. G. S. Brooker, G. H. Keyes, R. H. Sprague, R. H. Van Dyke, E. Van Lane, G. Van Zandt, and F. L. White, *J. Am. Chem. Soc.*, **73**, 5329 (1951).