Rearrangement of 2-Phenacyl-1,2-benzisothiazolin-3-one to 2-Benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one

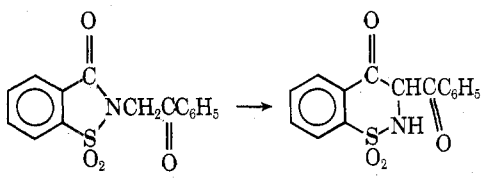
John C. Grivas

Sherwin Williams Chemicals, The Sherwin-Williams Company, Chicago, Illinois 60628

Received November 21, 1975

2-Phenacyl-1,2-benzisothiazolin-3-one (4) rearranges to 2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one (6) in good yield under mild basic conditions. Evidence supports a general-base-catalyzed mechanism initiated by abstraction of a proton from the α carbon atom, followed by attack on the sulfur atom, and opening of the S–N bond. Compound 6 rearranges to a yellow isomer which was not identified. Reaction of 2-mercaptobenzamide with phenylglyoxal gave 2-benzoyl-4*H*-3,1-benzoxathiin-4-one (13) instead of the expected 6.

The presence of an active hydrogen adjacent to nitrogen in 2-phenacylsaccharin (1) presents the opportunity for a base-catalyzed ring expansion and the formation[1-3] of 1,2-benzothiazine dioxide 2. In contrast, 2-(α-phenylethoxycarbonylmethyl)saccharin has been reported[4] to give a 1,3-benzothiazine. In this report the rearrangement of 2-phenacyl-1,2-benzisothiazolin-3-one (4) to 2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one (6) under mild base-catalyzed conditions is presented.



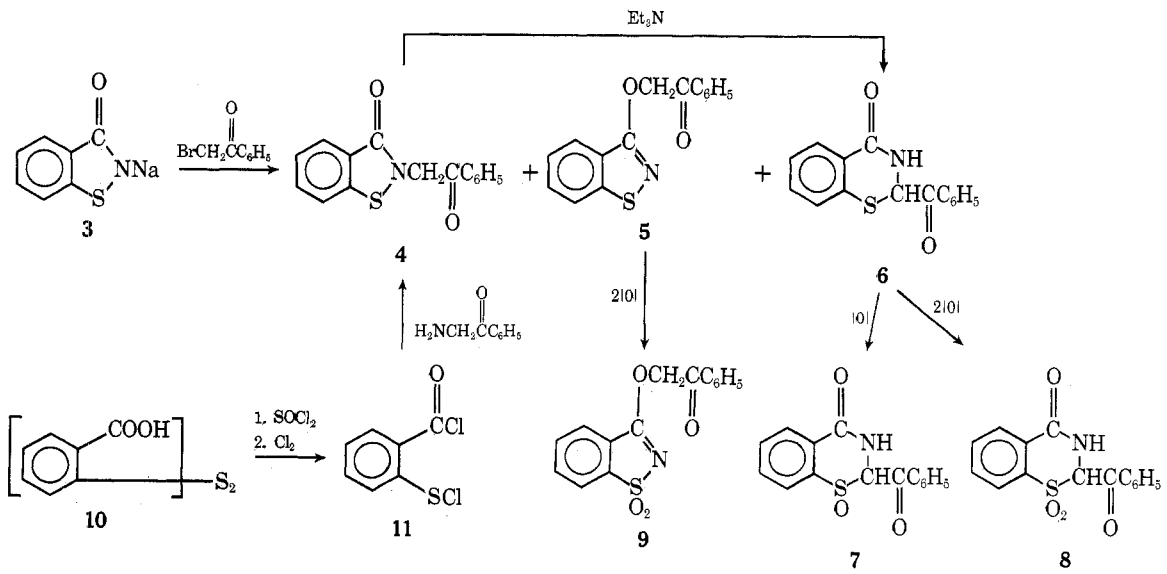
1 2

Results and Discussion

The rearrangement was first observed during a brief study of the alkylation of 3 by α-bromoacetophenone. Unexpectedly, this reaction yielded 6, in addition to products 4 and 5 from N- and O-alkylation of 3 (Scheme I). The isolation of pure 4, 5, and 6 was greatly facilitated by good separation on TLC silica gel plates with chloroform–methanol (99:1). Structure 4 was proven unequivocally by oxidation to the known dioxide 1 and synthesis (10 → 11 → 4). Oxidation of 5 gave dioxide 9, both 5 and 9 exhibiting ir and NMR spectra consistent with their assigned structures. The ketone absorption[5] appeared near 1700 cm^{-1}, while the characteristic amide band[6] of 2-substituted 1,2-benzisothiazolin-3-ones near 1660 cm^{-1} was absent. It is on this basis that the 1705- and 1660-cm^{-1} absorptions of 4 were assigned to the ketone and amide vibrations, respectively.

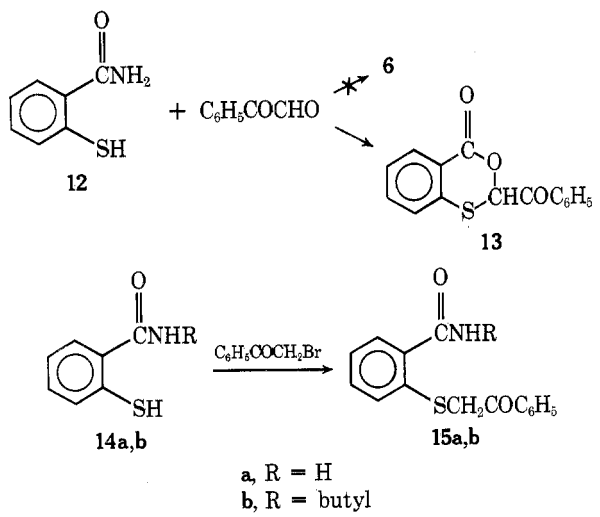
The ir spectrum of 6 showed the ν(NH) absorption at 3200 cm^{-1} in Nujol mull, in addition to the strong ketone and amide absorptions at 1688 and 1656 cm^{-1}, respectively. In chloroform solution the NH vibration appeared as a very sharp band of medium intensity at 3340 cm^{-1} definitely indicating a secondary amino grouping. Additional evidence for 6 was provided by the NMR spectra in DMF-d_6, which showed two doublets at 8.44 and 6.62 ppm for the NH and CH groups, respectively. Upon deuteration, the NH proton exchanged and the 6.62-ppm CH doublet collapsed into a singlet indicating coupling between the two groups and, thus, firmly establishing the existence of the –CHNH– moiety. Oxidation of 6 by hydrogen peroxide gave oxide 7, but attempts to effect conversion to dioxide 8 resulted in overoxidation. On the other hand, oxidation of 6 with *m*-chloroperbenzoic acid provided 8 (mp 217–218 °C), and not the known 2 (mp 163–164.5 °C). The spectral behavior of 8 and 2 is also substantially different. The latter is actually a completely enolized β-diketone[2,7] showing a positive ferric chloride test, an enolic hydroxy group, and no carbonyl absorption. In contrast, compounds 6 and 8 exhibited none of those properties. Subsequently, evidence to substantiate the possibility that 6 was formed by ring expansion of pre-

Scheme I



cursor 4 and not by any other plausible route was sought. When pure 4 was treated with 1–2 equiv of sodium methoxide in methanol a fast rearrangement (4 → 6) occurred accompanied by substantial decomposition (TLC). Compound 4 remained unchanged after 10-h reflux in toluene, but in the presence of 1 equiv of triethylamine, a smooth, nearly quantitative (TLC) rearrangement took place which yielded pure 6, identical in all respects with the alkylation product. Therefore, on the basis of the aforementioned results, structure 6 was assigned to the rearrangement product of 4.

In an attempt to synthesize 6, the procedure[8] for the preparation of 2-substituted 1,3-benzothiazin-4-ones by passing hydrogen chloride into an ethanolic solution of 2-mercaptobenzamide (12) and an aldehyde was tested. Surprisingly, treatment of 12 with phenylglyoxal hydrate under the same conditions yielded 2-benzoyl-4*H*-3,1-benzoxathiin-4-one (13) in 28% yield but none of the expected 6 (TLC).



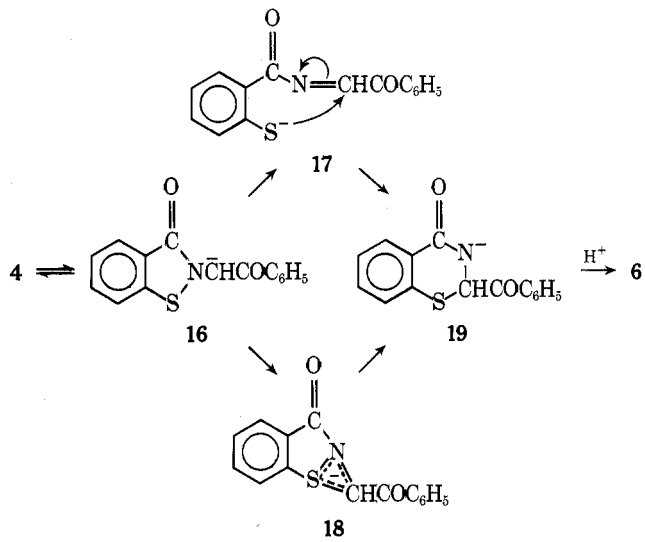
The assignment of structure 13 was based on the lack of nitrogen (microanalysis) and ir spectra, which showed the absence of ν(NH) and amide I bands as in 6, and the presence of ketone (1697 cm^{-1}) and δ-lactone (1743 cm^{-1}) stretching vibrations in carbon disulfide solution. Possibly, this difference in behavior between an aldehyde and phenylglyoxal is due to the highly acidic hydroxyl group of the intermediate hemiacetal formed which attacks the amide carbonyl group with the expulsion of ammonia.

In another attempt to synthesize the 1,3-thiazinone ring compounds 15 were prepared by alkylation of 14. Bromination of the phenacyl moiety of 15 followed by heating in the presence of triethylamine failed to effect cyclization.

From a mechanistic point of view, the ring expansion of 4 must be initiated by abstraction of a proton and the formation of carbanion 16, which may rearrange by means of species 17.

In view of the ability of the S atom to utilize its empty d orbitals and accommodate the negative charge in the p orbitals of the carbon atom, a second path through 18 is also possible. Both paths involve the severance of the sulfenamide and not the amide bond, since the former is weaker than the latter. In contrast, the rearrangement of 2-phenacylsaccharin (1) gives[2] 1,2-benzothiazinone 2 because the amide bond is weaker than the sulfonamide bond and split preferentially.

The formation of a number of compounds during the rearrangement of 4 under strongly basic conditions has already been mentioned. In fact, such solutions turn yellow-red, mainly because of the formation of a yellow substance, which was proven to be the rearrangement product of 6. Thus, the yellow substance was isolated in 37% yield by subjecting 6 to slightly more severe conditions. It was found to be an isomer of 6, devoid of NH, enolic OH, and



ketone groups, but retaining the amide moiety (strong absorption at 1665 cm^{-1}). No additional work to identify this compound was carried out.

Experimental Section[9]

Alkylation of the Sodium Salt of 1,2-Benzisothiazolin-3-one with α-Bromoacetophenone. Isolation of 4, 5, and 6. A mixture of the sodium salt of 1,2-benzisothiazolin-3-one (3, 17.3 g, 0.1 mol) and α-bromoacetophenone (19.9 g, 0.1 mol) in benzene was refluxed with stirring for 3 h, filtered from a solid, and evaporated to dryness. The sticky residue obtained was stirred in water (200 ml), and then in acetone (300 ml) for 30 min to yield a solid, which was filtered off, taken up in boiling benzene (150 ml), and filtered hot. Upon cooling the benzene filtrate deposited almost pure **2-phenacyl-1,2-benzisothiazolin-3-one (4).** One recrystallization from benzene gave the analytical sample: mp 156–157 °C; yield 4.7 g (17.5%); ir ($CHCl_3$) 1705 (ketone) and 1660 cm^{-1} (amide); NMR ($CDCl_3$) δ 5.25 (s, 2, CH_2), 7.20–7.70 (m, 6, aromatic H), 7.90–8.10 (m, 3, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.90. Found: C, 66.91; H, 4.29; N, 5.14; S, 12.13.

The above acetone mother liquor was evaporated to dryness, and the residue was dissolved in hot benzene (50 ml), diluted with cyclohexane (30 ml) until a slight precipitation occurred, made clear by addition of acetone (2 ml), and allowed to stand at room temperature. The crystallized crude product (7.8 g, mp 128–160 °C) was found (TLC) to be a mixture of 4 (40%) and 6 (60%). The crude product was recrystallized six times from benzene to yield pure **2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one (6)** free of 4 (TLC): mp 190–192 °C; yield 2.1 g (8%); ir (Nujol mull) 3200 (NH), 1688 (ketone), and 1656 cm^{-1} (amide); NMR (DMF-d_6) δ 6.62 (d, 1, CH), 7.10–7.80 (m, 6, aromatic H), 8.00–8.30 (m, 3, aromatic H), 8.44 (d, 1, NH).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.90. Found: C, 66.92; H, 3.96; N, 5.25; S, 11.61.

All mother liquors were combined and brought to dryness and the residue was dissolved in benzene and chromatographed through silica gel. Elutions with benzene–chloroform mixtures yielded crude **3-phenacyloxy-1,2-benzisothiazole (5)** which was purified by two recrystallizations from acetone–hexane: mp 146.5–147.5 °C; yield 1.1 g (4%); ir (KBr) 1700 cm^{-1} (ketone); NMR ($CDCl_3$) δ 5.78 (s, 2, CH_2), 7.20–7.80 (m, 6, aromatic H), 7.80–8.20 (m, 3, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12, N, 5.20; S, 11.90. Found: C, 66.92; H, 3.96; N, 5.25; S, 11.61.

Additional elutions with $CHCl_3$ and $CHCl_3$–MeOH gave several fractions of crude 4 and 6 which were purified by crystallization to give additional 4 (3.1 g, 11.5%) and 6 (1.3 g, 4.8%).

2-Phenacyl-1,2-benzisothiazolin-3-one (10 → 11 → 4). To a stirred solution of 2,2′-dithiodibenzoic acid (23 g, 0.075 mol) and

dimethylformamide (4 drops) in 1,2-dichlorobenzene (125 ml) at 110–115 °C, a solution of thionyl chloride (14 ml, 0.19 mol) in the same solvent (20 ml) was added dropwise over a period of 1 h. The reaction mixture was cooled and chlorine gas (~11 g) was bubbled through at 10–15 °C for 25 min. The clear solution of sulfenyl halide **11** obtained was kept at 10–15 °C for an additional 20 min and at 60 °C under reduced pressure for 10 min, cooled, and added dropwise at 20–40 °C to a vigorously stirred mixture of α-aminoacetophenone hydrochloride (26 g, 0.15 mol), water (50 ml), and 1,2-dichlorobenzene (50 ml). During the addition, simultaneously and through a separate addition funnel, triethylamine (65 ml, 0.46 mol) was added at such a rate that a slight excess of triethylamine was present in the reaction mixture. After the additions had been completed (15 min) the mixture was heated to 60 °C, cooled, and filtered from a solid. This solid was stirred in water (100 ml), filtered off, and purified by two crystallizations from methylene chloride–benzene to yield 9.3 g (23%) of pure **4**, mp 157–158 °C.

The water layer from the filtrate of the reaction mixture was separated, and the organic layer was diluted with petroleum ether (1000 ml), cooled overnight, and filtered to give a second crop of **4**, which was purified by three crystallizations from methylene chloride–benzene; mp 155–157 °C, yield 13.2 g (32%). Total yield was 55%. The product was identical with the sample isolated from the aforementioned alkylation reaction as shown by mixture melting point, ir, NMR, and TLC.

2-Phenacyl-1,2-benzisothiazolin-3-one 1,1-Dioxide (4 → 1). A solution of **4** (0.54 g, 2 mmol) and *m*-chloroperbenzoic acid (85%, 0.9 g, 4.4 mmol) in chloroform was allowed to stand at room temperature for 4 days, extracted with aqueous $NaHCO_3$ and water, and evaporated to dryness under reduced pressure. The crude **1** obtained was purified by two recrystallizations from ethanol; mp 193–195 °C (lit.[1] mp 193–194 °C); ir (Nujol) 1735 (amide), 1697 (ketone), 1335 and 1182 cm^{-1} ($-SO_2-$); NMR (DMF-d_6) δ 8–8.5 and 7.5–7.8 (aromatic H), 5.52 (s, 2, CH_2).

3-Phenacyloxy-1,2-benzisothiazoline 1,1-Dioxide (9). A solution of **5** (0.27 g, 1 mmol) and *m*-chloroperbenzoic acid (0.45 g, 2.2 mmol) in chloroform (15 ml) was stirred at room temperature for 4 days and the crystallized product (mp 190–191 °C, 70 mg) was filtered off. The filtrate was extracted with aqueous $NaHCO_3$, then water, and the chloroform layer was evaporated to dryness to yield a second crop of crude **9**. The two crops were combined and recrystallized twice from ethanol to give pure **9**: mp 190–191 °C; yield 0.24 g (80%); ir (Nujol) 1700 (ketone), 1325 and 1173 cm^{-1} ($-SO_2-$); NMR (DMF-d_6) δ 6.25 (s, 2, CH_2), 7.50–7.90 (m, 3, aromatic H), 7.95–8.30 (m, 6, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_4S$: C, 59.79, H, 3.68; N, 4.65; O, 21.24; S, 10.65. Found: C, 59.96; H, 3.57; N, 4.54; O, 21.09; S, 10.51.

Preparation of 6 by Rearrangement of 4. To a stirred solution of **4** (1.08 g, 4 mmol) in toluene (50 ml) at 80 °C, triethylamine (0.55 ml, 4 mmol) was added and the reaction mixture was refluxed for 1 h. The solution was then concentrated to 30 ml, further concentrated in vacuo to 10 ml, cooled, and filtered to yield crude **6** (0.9 g, mp 184–189 °C). The crude product was purified by two recrystallizations from ethanol to give 0.7 g (65%) of pure **6**. This sample was identical in all respects (ir, NMR, TLC, and mixture melting point) with the sample isolated from the alkylation of **3**.

2-Benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1-Oxide (7). To a solution of **6** (2.7 g, 10 mmol) in glacial acetic acid, H_2O_2 (30%, 1.8 ml, 0.15 mmol) was added and the mixture was allowed to stand at room temperature for 5 days. The crystallized product (1.1 g, mp 222–227 °C) was recrystallized twice from ethanol to give the analytical sample; mp 235–236 °C (gas evolution); yield 1 g (33%); ir (Nujol) 3340, 3220 (NH), 1695 (ketone), 1665 (amide), 1100 cm^{-1} (S=O); NMR (DMF-d_6) δ 8.24 (s, 1, NH), 7.47 (d, 1, CH), 7.3–8.1 (m, 9, aromatic H).

Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91; O, 16.82; S, 11.24. Found: C, 62.96; H, 3.64; N, 4.78; O, 16.91; S, 11.44.

2-Benzoyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1,1-Dioxide (8). To a stirred cold solution of **6** (0.54 g, 2 mmol) in chloroform, *m*-chloroperbenzoic acid (85%, 0.9 g, 4.4 mmol) was added. The solution obtained was allowed to stand at room temperature for 3 days and evaporated to dryness under reduced pressure to give a solid, which was stirred in ether (30 ml), filtered off, and purified by two recrystallizations from ethanol: mp 217–218 °C (when placed at 170 °C, it melted, resolidified, and remelted at 212–214 °C); yield 0.2 g (33%); ir (Nujol) 3230, 3100 (NH), 1690 (ketone), 1670 (amide), 1336 and 1187 cm^{-1} ($-SO_2-$); NMR (DMF-d_6) δ 9.1 (s, 1, NH), 7.25–8.40 (m, 10, aromatic H + CH).

Anal. Calcd for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65; O, 21.24; S, 10.64. Found: C, 59.79: H, 3.59; N, 4.62; O, 21.09; S, 10.62.

2-Phenacylthiobenzamide (15a). A solution of 2-mercaptobenzamide (0.77 g, 5 mmol) and α-bromoacetophenone (1 g, 5 mmol) in pyridine (10 ml) was stirred at ambient temperature for 15 min, heated under reflux for 15 min, and evaporated in vacuo to dryness. The crystalline residue was stirred in water (100 ml), filtered off, and recrystallized from methanol to yield crude **15a** (1.15 g, mp 150–152 °C), which was purified by two recrystallizations from methanol; mp 154.5–155 °C; yield 0.95 g (70%); ir (KBr) 3350 and 3180 (NH_2), 1680 (ketone), and 1633 cm^{-1} (amide); NMR (DMF-d_6) δ 8.12 (d of d, 2, aromatic H), 7.86 (broad, 2, NH_2), 7.1–7.8 (m, 7, aromatic H), 4.65 (s, 2, CH_2).

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.67; H, 4.66; N, 5.03; S, 11.60.

***N*-Butyl-2-phenacylthiobenzamide (15b).** A solution of *N*-butyl-2-mercaptobenzamide (2.1 g, 10 mmol) and α-bromoacetophenone (2 g, 10 mmol) in pyridine (20 ml) was stirred at ambient temperature for 15 min, heated under reflux for 15 min, and evaporated to dryness. The residue was extracted with hot benzene (100 ml), diluted with cyclohexane (20 ml), concentrated, and cooled to yield 2.4 g (73%) of crude **15b**, mp 73–75 °C. A small sample was recrystallized from aqueous methanol; mp 76–78 °C; ir (KBr) 3300 (NH), 1680 (ketone), and 1625 cm^{-1} (amide); NMR (DMF-d_6) δ 8–8.25 (d of d, 3, aromatic H + NH), 7.1–7.8 (m, 7, aromatic H), 4.66 (s, 2, SCH_2) 3.33 (q, 2, NCH_2) 1.2–1.8 (m, 4, CH_2CH_2), 0.89 (t, 3, CH_3).

Anal. Calcd for $C_{19}H_{21}NO_2S$; C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.90; H, 6.56; N, 4.38; S, 9.64.

2-Benzoyl-4*H*-3,1-benzoxathiin-4-one (13). Dry hydrogen chloride was passed through a solution of 2-mercaptobenzamide (1.5 g, 10 mmol) and phenylglyoxal monohydrate (1.5 g, 10 mmol) in ethanol (4 ml) at 50 °C for 15 min to yield a crystalline precipitate. The mixture was cooled, and the crude product was filtered off and purified by two recrystallizations from ethanol: mp 126.5–127.5 °C; yield 0.75 g (28%); ir (CS_2) 1743 (lactone), 1697 cm^{-1} (ketone); NMR (DMF-d_6) δ 8.0–8.4 and 7.3–7.9 (m, 10, aromatic H + CH); mol wt 270 ($CHCl_3$).

Anal. Calcd for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73; S, 11.86. Found: C, 66.41; H, 3.65; S, 11.61.

Yellow Product by Rearrangement of 6. 1,3-Benzothiazine **6** (1.08 g, 4 mmol) was dissolved in toluene (50 ml) by brief heating under reflux. The solution was cooled to ca. 70 °C, triethylamine (1.1 ml, 8 mmol) was added, and heating at 70 °C was continued for a total of 16 h. The yellow-red solution was evaporated to dryness, the residue was stirred in acetone (3 ml), and the yellow solid was filtered off, mp 150–156 °C, yield 0.55 g (51%). The crude product was purified by two recrystallizations from methylene chloride–petroleum ether (bp 30–60 °C): mp 160–160.5 °C; yield 0.4 g (37%); ir (Nujol) 1665 cm^{-1} (amide); NMR (DMF-d_6) δ 7.50–8.10 (m, 6, aromatic H), 8.10–8.60 (m, 3, aromatic H). Mol wt: calcd, 269; found, 272 ($CHCl_3$).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; O, 11.89; S, 11.90. Found: C, 67.09; H, 4.04; N, 5.19; O, 12.12; S, 11.93.

Registry No.—**1**, 15246-95-4; **3**, 58249-25-5; **4**, 49549-92-0; **5**, 58249-26-6; **6**, 58249-27-7; **7**, 58249-28-8; **8**, 58249-29-9; **9**, 58249-30-2; **10**, 119-80-2; **11**, 3950-02-5; **12**, 5697-20-1; **13**, 58249-31-3; **14b**, 58249-32-4; **15a**, 58249-33-5; **15b**, 58249-34-6; α-bromoacetophenone, 70-11-1.

References and Notes

(1) K. Abe, S. Yamamoto, and K. Matsui, *J. Pharm. Soc. Jpn.*, **76**, 1058 (1956); *Chem. Abstr.*, **51**, 3499 (1957).
(2) H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, *J. Org. Chem.*, **30**, 2241 (1965).
(3) A. Kraaijeveld and A. M. Akkerman, U.S. Patent 3 284 450 (1966).
(4) H. Zinnes, H. A. Comes, and J. Shavel, *J. Org. Chem.*, **29**, 2068 (1964).
(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2d ed, Wiley, New York, N.Y., 1966, p 137.
(6) J. C. Grivas, unpublished data.
(7) C. R. Rasmussen, *J. Org. Chem.*, **39**, 1554 (1974).
(8) R. C. Moreau and E. Delacoux, *Bull. Soc. Chim. Fr.*, 502 (1962).
(9) Melting points were determined with a Thomas-Hoover oil bath capillary apparatus and were not corrected. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.