About 30 min was required for 2.0 g of the compound to dissolve at ambient temperature in a solution of 1 g of sodium hydroxide, 20 ml of water, and 10 ml of ethanol. When the solution was acidified after 16 hr, 1.6 g (97.5%) of benzilic acid was recovered.[5]

Thermolysis of 1-Benziloylimidazole.—The title compound (1.9 g) in a small flask was placed in an oil bath preheated to 150°. Within 5 min the sample melted and began to evolve carbon dioxide (qualitative test); the total heating time was 20 min and the final bath temperature, 145°. Water-soluble, white needles (mp 89–90°) sublimed to the cooler portion of the flask; their infrared spectrum was the same as that for imidazole. The cooled, gummy residue was triturated with ether plus water, then with ether. The small amount of poorly soluble residue was boiled with 3 ml of acetonitrile and cooled; there was recovered 0.12 g (9%) of white solid (mp 193–195°) whose infrared spectrum was the same as that for **benzilide.**

The combined ether–water extracts were separated and the ether layer washed once more with water. Cooling the ethereal solution at 5° for several days gave 0.15 g of a white solid, mp 180–190°. Two recrystallizations from absolute ethanol raised the melting point to 190.5–191.5° dec. The analyses are consistent with those required for **1,3-dibenzhydrylimidazolium benzilate.** The melting point and infrared spectrum were identical with those for the product obtained from 1,3-dibenzhydrylimidazolium chloride (mp 199–200°) and sodium benzilate in ethanol.

Anal. Calcd for $C_{43}H_{36}N_2O_3$: C, 82.14; H, 5.77; N, 4.46. Found: C, 82.39; H, 5.72; N, 4.57.

Evaporating the ether solution left 1.04 g of semisolid residue which was fractionally crystallized from cyclohexane. The less soluble material was more benzilide (0.32 g, 22%); the more soluble fraction (0.3 g, 19%) melted at 87.5–88.5° after several recrystallizations from cyclohexane. Admixture with a sample of **1-benzhydrylimidazole** made from imidazole and diphenylchloromethane did not depress the melting point; the infrared spectra of the two samples were also identical.

Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96; mol wt, 234.3. Found: C, 81.88; H, 6.05; N, 11.91; mol wt, 235.

In a related experiment, 5.15 g of benzilic acid and 3.7 g of 1,1′-carbonyldiimidazole in 50 ml of dry acetonitrile were refluxed for 2 hr; the solvent was removed and residue worked up as above. There was recovered 1.7 g (32%) of 1-benzhydrylimidazole (mp 83–86°), 0.9 g (19%) of impure 1,3-dibenzhydrylimidazolium benzilate (mp 170–180°), and 0.5 g of **polyester of benzilic acid** (carbonyl absorption 5.8 μ).

Anal. Calcd for $(C_{14}H_{10}O_2)_x$: C, 79.98; H, 4.79. Found in one experiment: C, 81.29; H, 5.86; N, 3.64. Found in a second experiment: C, 80.43; H, 5.45; N, 2.16; mol wt, 1150.

Registry No.—**1**, 15441-11-9; **3**, 7189-67-5; **4**, 15448-88-1.

(5) The formation of benzilic acid upon hydrolysis eliminates the isomeric, 1-carbodiphenylmethoxyimidazole, $R_2CHOCOIm$, as the structure of the product from the benzilic acid and 1,1′-carbonyldiimidazole reaction. The slow rate of solution of **1** in basic solution argues against **6** as a possible structure for the reaction product.

ortho Metalation of N-Substituted Benzenesulfonamides by Excess *n*-Butyllithium. Condensation with Carbonyl Compounds. Cyclizations[1]

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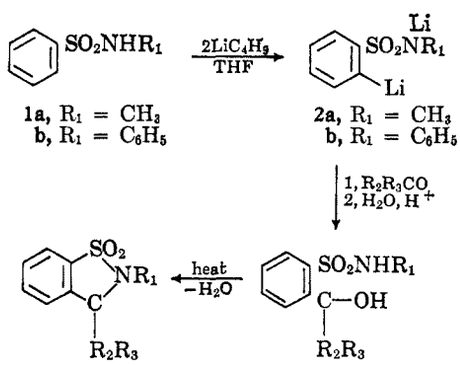
As an extension of previous work on N-methylbenzamide,[2] we have found that N-methyl- and N-phenylbenzenesulfonamides (**1**) undergo *ortho* metalation, as well as N-metalation, with excess *n*-butyllithium to form dilithiosulfonamides **2**, as evidenced by condensations with carbonyl compounds to give *ortho* derivatives (Scheme I, Table I). *ortho* Metalation was also observed with N-phenyl-*p*-tolylsulfonamide. The carbinols underwent thermal cyclodehydration at 200–230° to form the sultams (cyclic sulfonamides); this reaction was facilitated by acids (Table II). Attempts to cyclize the carbinol sulfonamide derived from cyclohexanol were unsatisfactory. In the case of the **4b**, cyclodeamination to the sultone **5** also occurred in low yield, as previously observed.[3]

SCHEME I



1a, $R_1 = CH_3$; **b**, $R_1 = C_6H_5$

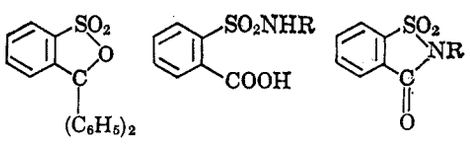
2a, $R_1 = CH_3$; **b**, $R_1 = C_6H_5$

3a, $R_1 = CH_3$, $R_2 = R_3 = C_6H_5$; **b**, $R_1 = R_2 = R_3 = C_6H_5$; **c**, $R_1 = R_2 = CH_3$, $R_3 = C_6H_5$; **d**, $R_1 = R_2 = C_6H_5$, $R_3 = CH_3$; **e**, $R_1 = CH_3$, $R_2 = H$, $R_3 = C_6H_5$

4a, $R_1 = CH_3$, $R_2 = R_3 = C_6H$; **b**, $R_1 = R_2 = R_3 = C_6H_5$; **c**, $R_1 = R_2 = CH_3$, $R_3 = C_6H_5$; **d**, $R_1 = R_2 = C_6H_5$, $R_3 = CH_3$

As indicated in the Tables, the yields of the carbinol sulfonamides and sultams were generally good to excellent. Table II further shows that all three of the methods of cyclodehydration to form sultams were suitable with the N-methyl carbinol sulfonamides, but that only the hydrobromic acid and thermal methods were satisfactory with the N-phenyl carbinol sulfonamides. The sulfuric acid method failed with the latter compounds apparently because of sulfonation of the anilino ring, since water-soluble material was produced.

The structures of the products were supported by analyses (see Tables I and II) and infrared spectra. The spectra of the carbinol sulfonamides exhibited strong peaks in the regions of 1330–1300 and 1155–1145 cm^{-1} for the SO_2 group and sharp peaks of medium strength in the regions 3520–3450 and 3400–3250 cm^{-1} for the OH group and NH group of the secondary sulfonamide, respectively. The spectra also showed peaks in the regions 780–710 and 710–670 cm^{-1} for four and five adjacent aromatic hydrogens. The



5

6a, $R = CH_3$; **b**, $R = C_6H_5$

7a, $R = CH_3$; **b**, $R = C_6H_5$

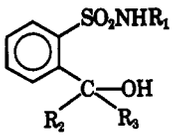
(1) Supported by the Army Research Office (Durham) and by Public Health Service Research Grant No. CA 04455-09 from the National Cancer Institute.

(2) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

(3) A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, 1339 (1952).

TABLE I

SUBSTITUTED *o*-SULFAMYLBENZYL ALCOHOLS

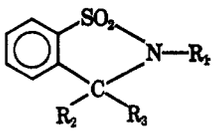


Compd	Substituent R1	Substituent R2	Substituent R3	Recryst solvent	Mp,[a] °C	Yield,[b] %	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
4a	CH_3	C_6H_5	C_6H_5	Acetone	199–200[c]	82	$C_{20}H_{19}NSO_3$	67.96	5.42	3.96	9.07	68.03	5.39	3.86	8.90
4b	C_6H_5	C_6H_5	C_6H_5	Acetone	198–199[d]	50	$C_{25}H_{21}NSO_3$	72.26	5.09	3.37	7.72	72.09	5.10	3.33	7.34
4c	CH_3	CH_3	C_6H_5	Methanol	132–133	58	$C_{15}H_{17}NSO_3$	61.83	5.88	4.81	11.01	61.57	5.83	4.88	10.54
4d	C_6H_5	CH_3	C_6H_5	Methanol	135–136	48	$C_{20}H_{19}NSO_3$	67.96	5.42	3.96	9.07	68.13	5.42	3.95	8.96
	CH_3	$-(CH_2)_5-$		Ether	126–127	72	$C_{13}H_{19}NSO_3$	57.96	7.11	5.20		57.88	7.03	5.20	

[a] Melting points of analytical samples. [b] The melting points of the materials on which these yields are based were generally 1–3° lower than those reported here. [c] Literature[4] mp 194–195° and 194°.[5] [d] Literature[4] mp 205°.

TABLE II

SUBSTITUTED 1,2-BENZISOTHIAZOLE-1,1-DIOXIDES (SULTAMS)



Compd	Substituent R1	Substituent R2	Substituent R3	Mp,[a] °C	Yield,[b] % H_2SO_4 method	Yield,[b] % HBr method	Yield,[b] % Thermal method	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
3a	CH_3	C_6H_5	C_6H_5	217–217.5[c,g]	87	98	85	$C_{20}H_{17}NSO_2$	71.61	5.11	4.18	9.56	71.32	5.08	4.20	9.31
3b	C_6H_5	C_6H_5	C_6H_5	224–224.5[h]	0[d]	94	83	$C_{25}H_{19}NSO_2$	75.54	4.82	3.52	8.07	75.63	4.75	3.55	8.05
3c	CH_3	CH_3	C_6H_5	171.5–172.5[g]	97	85		$C_{15}H_{15}NSO_2$	65.91	5.53	5.12	11.73	65.88	5.47	5.13	11.70
3d	C_6H_5	CH_3	C_6H_5	194.5–195.5[h]	0[d]	88		$C_{20}H_{17}NSO_2$	71.61	5.11	4.18	9.56	71.43	5.01	4.12	9.47
3e[e]	CH_3	H	C_6H_5	135–136[i]	72[f]			$C_{14}H_{13}NSO_2$	64.84	5.05	5.40		65.11	5.21	5.14	

[a] Melting points of analytical samples. [b] The melting points of the materials on which these yields are based were 1–3° lower than those reported here. [c] Literature[5] mp 211–212°. [d] Only water-soluble material was obtained; see Experimental Section. [e] The crude condensation product was used; see Experimental Section. [f] Over-all yield based on the starting N-methylbenzenesulfonamide (**1a**). [g] Recrystallized from ethanol. [h] Recrystallized from acetone. [i] Recrystallized from methanol.

infrared spectra of the sultams exhibited peaks at 1290–1275 and 1175–1160 cm^{-1} for the SO_2 group and at 780–710 and 710–670 cm^{-1} for four and five adjacent aromatic hydrogens, but none in the regions characteristic of the OH and NH groups.

The dilithiosulfonamides were also carbonated to form presumably the acid sulfonamides **6**, which were cyclized to give the *o*-sulfobenzoic imides **7** in over-all yields of 49 and 22%, respectively.

The present method of *ortho* lithiation–condensation could probably be extended to other electrophilic compounds and to other benzenesulfonamides. This method appears more convenient than an earlier one employed for the preparations of carbinol sulfonamides **4a–b** from the *o*-sulfobenzoic imides **7** and excess phenylmagnesium bromide[3–5] or phenyllithium.[6] Moreover, the present method is more general since it is applicable to the synthesis of carbinol sulfonamides where the two groups attached to the carbinol carbon are the same or different, whereas the earlier method is limited to the former type.

(4) F. Sachs, F. von Wolff, and A. Ludwig, *Ber.*, **37**, 3252 (1904).
(5) P. H. Cobb and G. P. Fuller, *Am. Chem. J.*, **45**, 605 (1911).
(6) A. Mustafa, W. Asher, O. H. Hishmat, A. F. A. Shalaby, and M. Kamel, *J. Am. Chem. Soc.*, **76**, 5447 (1954).

Experimental Section[7–9]

Metalation of 1a–b with *n*-Butyllithium to Form Dilithiosulfonamides 2 a–b.—A solution of 0.025 mole of N-methyl- or N-phenylbenzenesulfonamide (**1a**, bp 158–161° at 1.4–1.6 mm,[10] and **1b**, mp 109–110°,[11] respectively, in 100 ml of tetrahydrofuran[12] in a dry flask under nitrogen was cooled to 0°, and 40 ml (0.0625 mole) of a solution of 1.599 *M* *n*-butyllithium in hexane[13] was added during 10 min. After stirring for 15–20 min at 0°, the orange suspension from **1a** and the yellow suspension from **1b** was considered to contain 0.025 mole of the dilithiosulfonamides **2a** and **2b**, respectively. These suspensions were employed as described below.

Condensations of 2a–b with Ketones to Form Carbinol Sulfonamides.—These reactions were effected under nitrogen at 0° as described below. The results are summarized in Table I.

To the stirred, cold mixture containing dilithiosulfonamides **2a** or **2b** was added, during 4 min, a solution of 7.29 g (0.04 mole) of benzophenone in 40 ml of tetrahydrofuran,[12] and the stirring continued for 30 min. The orange suspension of **2a**

(7) Melting points and boiling points are uncorrected.
(8) Elemental analyses were performed by Janssen Pharmaceutica, Belgium.
(9) Infrared spectra (KBr method) were produced on a Perkin-Elmer Infracord Model 137 and 237. Nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard in deuteriochloroform.
(10) See M. H. J. Backer, *Rec. Trav. Chim.*, **24**, 485 (1905); T. L. Cairns and J. C. Sauer, *J. Org. Chem.*, **20**, 627 (1955).
(11) See R. G. Shephered, *ibid.*, **12**, 275 (1947).
(12) Freshly distilled from lithium aluminum hydride.
(13) Foote Mineral Co., New Johnsonville, Tenn.

changed into a clear orange solution, and the yellow suspension of **2b** changed into a green then into a yellow solution. To the cold solution was added with stirring 50–60 ml of 5% hydrochloric acid, and the resulting two layers were separated. After saturation with sodium chloride, the aqueous layer was thoroughly extracted with ether, and the extracts were combined with the original organic layer. The ethereal solution was dried over magnesium sulfate and the solvent was removed under reduced pressure on the steam bath. The slightly colored liquid residue was cooled in an ice bath to precipitate some fine crystals. The mixture was filtered, and the solid was washed with a little ether. The filtrate (to which the washings had been added) was evaporated to leave more crystals, which were collected. This procedure was repeated until no more crystals were obtained. The several crops of crystals were combined and recrystallized to give prismatic crystals of carbinol sulfonamide **4a** or **4b**. Condensation of **2a** and **b** with acetophenone gave **4c** and **4d**.

Dilithiosulfonamide **2a** was also condensed with cyclohexanone. The crude product was stirred with a small amount of methanol, and the mixture was allowed to stand at 0° for a few hours. The resulting crystals were collected, and washed with a little methanol to give 4.65 g (72%) of prismatic crystals of the carbinol sulfonamide, mp 124.5–125.5° (126–127° after recrystallization from ether).

Cyclodehydrations of Carbinol Sulfonamides to Form Sultams.—These reactions were effected by one or more of the methods described below; the results are summarized in Table II.

A. Sulfuric Acid Method.—A 1-g sample of the carbinol sulfonamide was dissolved in 10 ml of concentrated sulfuric acid at room temperature. After standing for 15–17 hr, the solution was poured onto crushed ice. The resulting, white precipitate was collected, washed with water, dried in air, and recrystallized from an appropriate solvent to give the sultam.

In the reactions of carbinol sulfonamides **4b** and **4d**, the pasty material on the filter dissolved on washing with water. Similar water-soluble material was obtained even when **4b** was dissolved in sulfuric acid at 0° and the solution was poured onto crushed ice after 1 hr or only 5 min.

B. Hydrobromic Acid Method.—A 1-g sample of the carbinol sulfonamide was refluxed gently with 30 ml of 48% hydrobromic acid for 4–6 hr. The reaction mixture was then filtered, and the solid was washed with water, dried in air, and recrystallized from an appropriate solvent to give the sultam.

C. Thermal Method.—A 1-g sample of the carbinol sulfonamide was heated under a slow stream of nitrogen in a round-bottomed flask at 220–230° on a Wood's metal bath for 6 hr. The flask was then removed from the bath, and the molten mass was allowed to come to room temperature. The resulting solid was recrystallized from an approprirate solvent to give the sultam.

Condensation of Dilithiosulfonamide 2a with Benzaldehyde and Cyclization of Crude Product.—This condensation was effected as described above for benzophenone to give the crude carbinol sulfonamide which was dissolved in 30 ml of concentrated sulfuric acid. After standing at room temperature for 1 hr, the solution was poured onto 200 g of crushed ice to afford solid (8.0 g) which was dissolved in hot acetone (decolorizing with charcoal). The solvent was evaporated and the residue was recrystallized from methanol to give 4.68 g (72%, over-all yield fron **1a**) of sultam **3e**, mp 133–134.5° (see Table II).

Conversion of Carbinol Sulfonamide 4b to Sultone 5.—A 1-g sample of **4b** was dissolved in 5 ml of concentrated sulfuric acid and, after standing at room temperature for 1 hr, the solution was heated on the steam bath for 1 hr. After cooling, the solution was poured onto crushed ice. The resulting mixture was saturated with sodium chloride and extracted with ether. The ethereal extract was washed with a little water and dried over magnesium sulfate. The solvent was evaporated to give 0.14 g (18%) of **5** (leaflets), mp 163–165° and at 164–165.5° after recrystallization from methanol (lit.[3,14–17] mp 162°)).

Anal. Calcd for $C_{19}H_{14}SO_3$: C, 70.79; H, 4.38; S, 9.95. Found: C, 70.48; H, 4.38; S, 10.26.

When a solution of 1 g of **4b** in 5 ml of concentrated sulfuric acid was allowed to stand at room temperature for 17 hr and then worked up in a similar manner, only 0.01 g (1%) of **5** was obtained.

Carbonations of Dilithiosulfonamides 2a–b and Cyclizations of Crude Products.—A suspension of **2a**, prepared from 0.05 mole of **1a** in 150 ml of tetrahydrofuran[12] and 80 ml of 1.599 *M* *n*-butyllithium,[13] was added slowly with stirring to a large excess of Dry Ice suspended in ether under nitrogen. After the excess Dry Ice had evaporated, the white suspension was stirred with 100 ml of 15% hydrochloric acid, and the resulting mixture was worked up to give crude product **6a** which was dissolved in 50 ml of concentrated sulfuric acid. After 10 min, the solution was poured onto crushed ice, and the precipitate was recrystallized from aqueous ethanol to give 4.84 g (49%) of N-methyl-*o*-sulfobenzoic imide (**7a**, needles), mp 131–132° and 131.5–132° after further recrystallization from ethanol (lit. mp 131–133°[18] and 132°[19]). The infrared spectrum showed peaks at 1740 (CO), 1325 and/or 1170 (SO_2), and at 751 cm^{-1} (four adjacent aromatic hydrogens).

Anal. Calcd for $C_8H_7NSO_3$: C, 48.72; H, 3.58; N, 7.10. Found: C, 48.58; H, 3.59; N, 6.96.

Similarly, a suspension of **2b**, prepared from 0.04 mole of **1b** in 160 ml tetrahydrofuran[12] and 65 ml (0.10 mole) of *n*-butyllithium in hexane,[13] was carbonated and the crude product **6b** treated with sulfuric acid for 30 min. There was obtained, on pouring the solution onto crushed ice and recrystallizing from ethanol, 2.30 g (22%) of N-phenyl-*o*-sulfobenzoic imide (**7b**, prismatic crystals), mp 191–192° and at 192–192.5° after further recrystallization (lit. mp 187–190°[20] and 190°[21]). The infrared spectrum showed peaks at 1740 and 1725 (CO), 1335 and 1180 (SO_2), and at 760, 755, 743, and 693 cm^{-1} (four and five adjacent hydrogens on *ortho* and monosubstituted benzene rings).

Anal. Calcd for $C_{13}H_9NSO_3$: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.10; H, 3.50; N, 5.41.

Lithiation of *p*-Tolylsulfonamide and Condensation with Benzophenone.—This lithiation was effected with 0.05 mole of sulfonanide in 175 ml of tetrahydrofuran[12] and 69 ml (0.105 mole) of 1.55 *M* *n*-butyllithium in hexane.[13] The resulting yellow suspension was treated with 0.06 mole of benzophenone in 55 ml of tetrahydrofuran[12] to produce a blue-green color which faded to yellow. The reaction mixture was stirred with 100 ml of water, and the solvents were stripped until the temperature of the distillate was 100°. After cooling, the residue was stirred with 100 ml of ether, and 25 ml of concentrated hydrochloric acid was then added. The resulting mixture was worked up to give 17.2 g (80%) of carbinol sulfonamide, mp 214–215° after recrystallization from acetonitrile. The infrared spectrum showed peaks at 3400 (OH), 3150 (NH), 1310 and 1140 (SO_2), 769, 760, 751 and 695 (five adjacent aromatic hydrogens), and at 880 and 830 cm^{-1} (three hydrogens on the 1,2,4-substituted benzene ring).

Anal. Calcd for $C_{26}H_{23}NSO_3$: C, 72.70; H, 5.39; N, 3.26. Found: C, 72.80; H, 5.39; N, 3.54.

5-Methyl-2,3,3-triphenyl-2,3-dihydro-1,2-benzothiazole 1,1-Dioxide.—This reaction was effected by the hydrobromic acid method, employing 1 g of carbinol sulfonamide XVI and 30 ml of this acid (refluxed 4 hr). The product was recrystallized from a mixture of methanol and acetone to give 0.89 g (93%) of the substituted sultam (fine needles), mp 220–222°. The infrared spectrum showed peaks at 1285 and 1180 and/or 1165 (SO_2), 739 and 693 (five adjacent aromatic hydrogens), and at 879, 820 and 811 cm^{-1} (three hydrogens on the 1,2,4-substituted benzene ring). No peaks appeared in the region of 3500–3100 cm^{-1}. The nmr spectrum of this compound showed a singlet signal at δ 2.33 and a multiplet signal at 6.9–7.9 ppm attributable to the ring methyl group and aromatic protons, respectively. The ratio of the protons was 3:18 in agreement with the calculated value.

Anal. Calcd for $C_{26}H_{21}NSO_2$: C, 75.88; H, 5.14; N, 3.40; S, 7.79. Found: C, 76.16; H, 5.23; N, 3.56; S, 7.76.

Registry No.—**3a**, 15449-03-3; **3b**, 15448-89-2; **3c**, 15448-90-5; **3d**, 15448-91-6; **3e**, 15448-92-7; **4a**, 15448-93-8; **4b**, 15448-94-9; **4c**, 15448-95-0; **4d**, 15448-96-1; **4**

(14) I. Remsen and A. P. Saunders, *Am. Chem. J.*, **17**, 366 (1895).
(15) P. Fritsch, *Ber.*, **29**, 2290 (1896).
(16) R. List and M. Stein, *ibid.*, **31**, 1648 (1898).
(17) P. H. Cobb, *Am. Chem. J.*, **35**, 486 (1906).
(18) E. W. McClelland, L. A. Warren, and J. H. Jackson, *J. Chem. Soc.*, 1587 (1929).
(19) E. Arndt and H. Scholz, *Ann.*, **510**, 62, 69 (1934).
(20) R. List and M. Stein, *Ber.*, **31**, 1648 (1924).
(21) I. Remsen and C. E. Coates, *Am. Chem. J.*, **17**, 320 (1895).

(R_1 = CH_3; R_2, R_3 = $-(CH_2)_5-$), 15448-97-2; **5**, 15448-98-3; **7a**, 15448-99-4; **7b**, 15449-00-0; $C_{26}H_{23}NO_3S$, 15449-0-11; $C_{26}H_{21}NO_2S$, 15449-02-2; *n*-butyllithium, 109-72-8.

O-Benzyl-N-*t*-butyloxycarbonyl-L-threonine[1]

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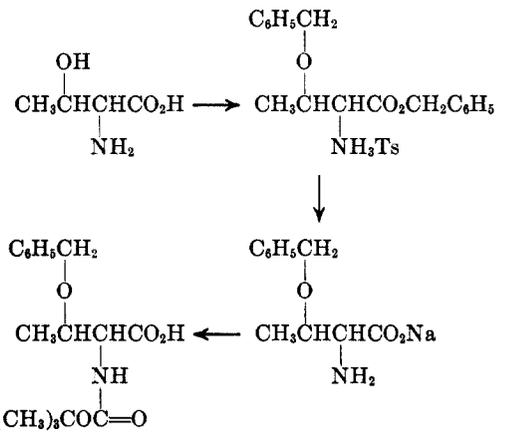
In the synthesis of threonine-containing peptides by the Merrifield solid-phase method,[4] acylation of the threonine hydroxyl was a serious side reaction.[5-7] To avoid the formation of branched-chain peptides due to such O-acylation, a suitable hydroxyl-protected derivative of threonine was needed. O-Benzylthreonine was considered to be fully compatible with the Merrifield method, but the existing synthesis[8] of this derivative (benzylation in sodium–liquid ammonia) causes racemization. A new synthesis, in which steric purity is maintained, has now been developed.



Although the yield was low, the labor required was minimal. The O-benzyl-L-threonine was converted to O-benzyl-N-*t*-butyloxycarbonyl-L-threonine, which has been used for the synthesis of several peptides by the Merrifield method.[7] With this new derivative, formation of branched-chain by-products was completely eliminated.

Experimental Section[9]

O-Benzyl-L-threonine Benzyl Ester Hemioxalate.—A mixture of 100 ml of benzyl alcohol, 200 ml of toluene, 11.9 g (0.1 mole) of L-threonine, and 24.7 g of *p*-toluenesulfonic acid monohydrate was refluxed with a Dean–Stark trap until no more water was collected (18–22 hr). The mixture was chilled, diluted with 150 ml of ethyl acetate, and shaken with sufficient cold 0.5 *M* sodium carbonate to bring the aqueous phase to pH 9. The organic phase was separated and washed once with water. The combined aqueous phase and wash were back-extracted once with 100 ml of ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered, and mixed with a solution of 12 g of oxalic acid dihydrate in 60 ml of methanol. After chilling the solution several hours, the hemioxalate salt was collected by filtration and washed with cold ethanol to yield 9.1 g (23%) of colorless crystals (mp 165–167°), $[\alpha]^{22}D$ −44.6° (*c* 1.2, methanol) not changed by recrystallization from ethanol.

Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.7; H, 6.0; N, 3.6. Found: C, 62.0; H, 5.9; N, 3.7.

In order to obtain a final product free of nonbenzylated threonine, the oxalate must be recrystallized until it is free of threonine benzyl ester, as shown by melting point (threonine benzyl ester hemioxalate, mp 135°) and by thin-layer chromatography on silica gel in the system ethanol–water–benzene–acetic acid (40:20:10:5): threonine benzyl ester hemioxalate, R_f 0.70; O-benzylthreonine benzyl ester hemioxalate, R_f 0.82.

O-Benzyl-L-threonine.—O-Benzylthreonine benzyl ester hemioxalate (3.9 g, 0.01 mole) was converted to the free base by partition between 1 *M* potassium carbonate and ethyl acetate. The ethyl acetate was dried over magnesium sulfate and evaporated under reduced pressure. The residual oil was dissolved in 50 ml of methanol and treated with 12 ml of 1 *M* sodium hydroxide. After the solution had stood 2 hr at room temperature, it was evaporated and the amino acid was isolated by chromatography on a short column of Dowex 1 ion exchange resin by adsorption to the free base of the resin and elution with 1 *M* acetic acid. The O-benzylthreonine was recrystallized from water by addition of propanol to yield 1.5 g (72%), $[\alpha]^{25}D$ −30.4 (*c* 1.1, acetic acid).[10] In paper chromatography, O-benzylthreonine showed R_f 0.89 in phenol–water; R_f 0.70 in 1-propanol–water (2:1); and R_f 0.66 in 1-butanol–acetic acid–water (4:1:5).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.4; H, 7.3; N, 6.9.

O-Benzyl-N-*t*-butyloxycarbonyl-L-threonine. A. From O-Benzylthreonine.—O-Benzylthreonine was converted to the desired product by the method of Schwyzer, *et al.*[11] (reaction with *t*-butyloxycarbonyl azide in the presence of magnesium oxide), and was recrystallized from ethyl acetate in 75% yield: mp 115–116; $[\alpha]^{22}D$ +15.8° (*c* 1.1, methanol).

Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.5; N, 4.5. Found: C, 62.4; H, 7.5; N, 4.7.

B. From O-Benzylthreonine Benzyl Ester Hemioxalate. Direct Synthesis without Isolation of O-Benzylthreonine.—To a cold stirred mixture of 6 g (0.017 mole) of O-benzylthreonine benzyl ester hemioxalate in 50 ml of methanol was gradually added a solution of 2.5 g of sodium hydroxide in 15 ml of water; stirring was continued 1 hr at room temperature. To the solution was then added a solution of 2.2 g of sodium bicarbonate in 20 ml of water and 5.4 ml (0.04 mole) of *t*-butyloxycarbonyl azide (Aldrich) in 50 ml of dioxane. Stirring was continued 22 hr at 45°. The solution was evaporated under reduced pressure to low volume to remove dioxane, diluted with water, and extracted with ether to remove unreacted azide and any remaining ester. The aqueous phase was chilled, acidified to pH 3 with solid citric acid, and extracted three times with ethyl acetate. The ethyl acetate was dried over magnesium sulfate and evaporated to yield 2.3 g (48%) of an oil which crystallized on standing in the cold. The product was homogeneous by thin layer chromatography (silica gel; chloroform–methanol–acetic acid (85:10:5); R_f 0.77). Recrystallization from ethyl acetate gave 1.8 g of colorless crystals, mp 115–116°.

Demonstration of Steric Purity.—An aliquot of O-benzyl-N-*t*-butyloxcarbonylthreonine thus prepared was dissolved in anhydrous trifluoroacetic acid and anhydrous hydrogen bromide was bubbled slowly through the solution for 90 min, with exclusion of moisture. This material after evaporation showed the same optical rotation as a sample of the starting L-threonine similarly treated, and agreed well with the theoretical value. Paper chromatography of the recovered material in the system

(1) (a) Supported in part by grant AM-1260 from the United States Public Health Service; (b) T. Mizoguchi, G. Levin, D. W. Woolley, and J. M. Stewart, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p O206.

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