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Received November 30, 1977

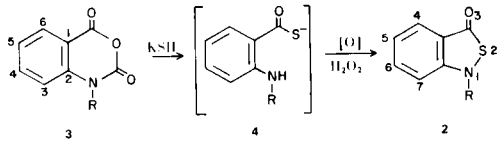
A new and general synthesis of 2,1-benzisothiazolin-3-ones (**2**) is described from the corresponding isatoic anhydride (**3**) and potassium hydrogen sulfide which gives the thioanthranilic acid (**4**) which is readily oxadized and ring closed to **2** with hydrogen peroxide. Phosphorus oxychloride converted 3-hydroxy-2,1-benzisothiazole to 3-chloro-2,1-benzisothiazole which gave a number of different 3-substituted 2,1-benzisothiazoles by nucleophilic substitution of the 3-chloro group. Electrophilic substitution of 1-methyl-2,1-benzisothiazolin-3-one (**2i**) proceeded readily to give the corresponding 5-bromo-, 5-nitro-, and 5-chlorosulfonyl-1-methyl-2,1-benzisothiazolin-3-one. This appears to be a good synthetic route to such 2,1-benzisothiazole derivatives.

J. Heterocyclic Chem., **15**, 529 (1978)

Although numerous 1,2-benzisothiazolin-3-ones (**1**) have been known for some time (1-4), there has been only one prior report (5) on the isomeric 2,1-benzisothiazolin-3-one (**2**). We have devised a general synthetic route which now makes compounds of type **2** readily available (6) from the corresponding isatoic anhydride (**3**).

1 2

The ring opening of an isatoic anhydride (**3**) with potassium hydrosulfide as described by Fanning and Roberts (7) gives the potassium salt of the corresponding thioanthranilic acid **4**, which was not isolated but converted *in situ* with hydrogen peroxide to the desired 2,1-benzisothioazolin-3-one in good yield.



3 4 2

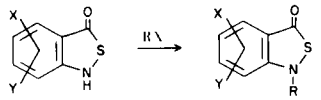
This basic procedure proved to be quite general for the preparation of 2,1-benzisothiazolin-3-ones (**2**). The isatoic anhydrides **3** (Table I) were converted to the corresponding substituted 2,1-benzisothiazolin-3-ones (Table II) in yields which were generally from 50-90%.

The first step (**3** to **4**) was run in water or methanol as a solvent containing a very nearly stoichiometric quantity of alkali metal hydroxide (in water or methanol) or carbonate (in water) and saturated with hydrogen sulfide gas. To this well stirred solution, maintained at 0-40°, was slowly added the desired isatoic anhydride (**3a-k**) and the mixture stirred until CO_2 evolution had ceased (10 minutes to 1 hour).

In the case where water was employed as the solvent, the excess hydrogen sulfide gas was removed by flushing the reaction mixture with nitrogen gas followed by treatment of the mixture with a slight excess of hydrogen peroxide at 25-50°. Neutralization with acid produced the 2,1-benzisothiazolin-3-one (**2a-k**). With methanol, it was first necessary to remove the solvent and replace it with water before oxidation could be successfully achieved.

Alkylation of 2,1-Benzisothiazolin-3-ones Unsubstituted at N_1.

Alkylation of unsubstituted-2,1-benzisothiazolin-3-ones (**2**, R = H) was readily accomplished with an excess of alkyl or aralkyl halide and sodium or potassium carbonate in refluxing acetone. The resulting 1-substituted 2,1-benzisothiazolin-3-one are listed in Table III. No *O*-alkylation



products were detected. In the case of 1-methyl-2,1-benzisothiazolin-3-one (**2i**), the product obtained by methylation of 2,1-benzisothiazolin-3-one proved to be identical to that obtained *via* ring closure of *N*-methylthioanthranilic acid (**4**, R = CH_3), see Table II. The synthesis of **2i** by these methods yielded a product with m.p. 58° which was identical to that reported (5) by an independent synthesis. That the product **2i** could *not* be 3-methoxy-2,1-benzisothiazole (**13**) was shown by an independent synthesis of **13** from 3-chloro-2,1-benzisothiazole (**10a**).

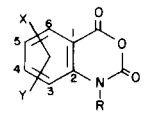
The infrared spectra of all 1-substituted 2,1-benzisothiazolin-3-ones (**2**) exhibited a strong -C(=O)-S-N absorption in the 1690-1620 cm^{-1} region, which was absent in all derivatives not containing this moiety. This characteristic could be utilized to demonstrate the position of alkylation at N_1 and readily identify this type of compound.

Electrophilic Substitution of 2-Methyl-2,1-benzisothiazolin-3-one (**2i**).

Nitration of 1-methyl-2,1-benzisothiazolin-3-one (**2i**) proved to proceed very readily and was an exothermic reaction. It was, therefore, run in a maximum of 20% nitric acid. Under these conditions, the sole product isolated was 1-methyl-5-nitro-2,1-benzisothiazolin-3-one (**5b**) in 35% yield.

Table I

Isatoic Anhydrides



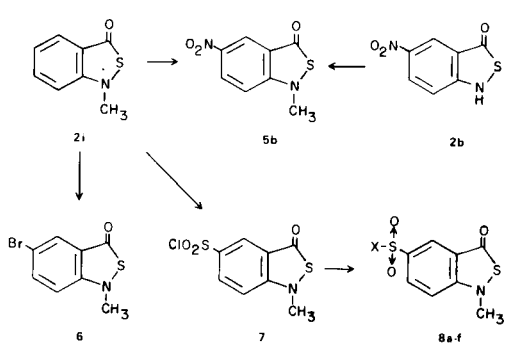
No.	R	X	Y	M.p., °C
3a	H	H	H	----- (a)
3b	H	5-NO_2	H	----- (b)
3c	H	5-Cl	H	----- (b)
3d	H	5-CH_3	H	257-261° dec. (c)
3e	H	4-Cl	H	215° dec. (d)
3f	H	5-OCH_3	H	242-244° dec. (e)
3g	H	5-Cl	3-Cl	205° dec. (f)
3h	H	4-CH_3	3-CH_3	*ca.* 292° dec. (g)
3i	CH_3	H	H	----- (a)
3j	CH_3	5-Cl	H	----- (h)
3k	$C_6H_5CH_2$	H	H	137-140° (i)

(a) Purchased from Sherwin and Williams Chemicals. (b) Purchased from J. T. Baker Chemicals. (c) Lit. 245° dec.; H. Panaotovic, *J. Prakt. Chem.*, [2] **33**, 58 (1886). (d) Lit. 278-282° dec.; S. M. Gadekar and E. Ross, *J. Org. Chem.*, **26**, 613 (1961). (e) *Anal.* Calcd. for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.98; H, 3.65; N, 7.14. (f) Lit. 251-253°; see footnote d for reference. (g) *Anal.* Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.95; H, 4.87; N, 7.34. (h) Purchased from K and K Chemicals. (i) Lit. 140-141°; W. L. F. Armarego, *J. Chem. Soc.*, 2697 (1961).

The position of nitration was established as 5- by an independent synthesis of **5b** from 5-nitro-2,1-benzisothiazolin-3-one (**2b**) by methylation with methyl iodide (Table III).

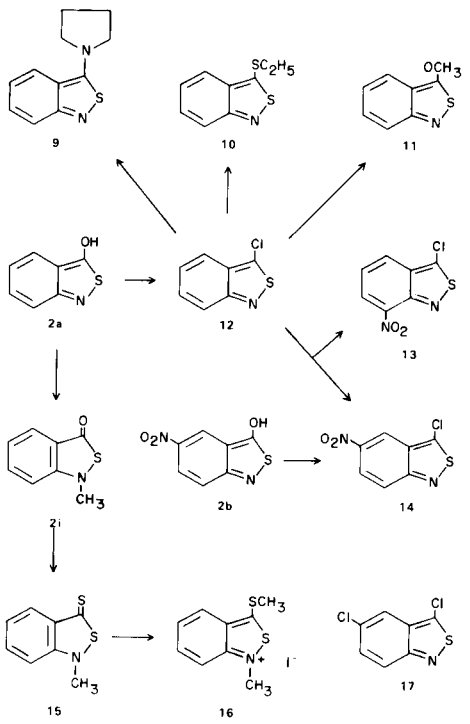
Bromination of 1-methyl-2,1-benzisothiazolin-3-one (**2i**) was accomplished with *N*-bromosuccinimide (NBS) in methylene chloride at room temperature. As shown by proton magnetic resonance (pmr), comparison with 5-chloro-1-methyl-2,1-benzisothiazolin-2-one (Table II, **2j**), the product obtained was shown to be 5-bromo-1-methyl-2,1-benzisothiozolin-3-one (**6**). Compound **6** was obtained in excellent yield as the only product.

Reaction Scheme I



Similarly, chlorosulfonation of **2i** gave an 83% yield of 5-chlorosulfonyl-1-methyl-2,1-benzisothiazolin-3-one (**7**). Treatment of **7** with ammonia gave 5-sulfonamido-1-methyl-2,1-benzisothiazolin-3-one, (**8f**) in excellent yield. A number of 5-*N*-substituted sulfonamido-1-methyl-2,1-benzisothiazolin-3-ones (**8a-g**) were prepared from **7** with the appropriate amine (Table IV).

Reaction Scheme II

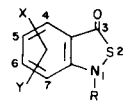


It should be considered that the compound 2,1-benzisothiazolin-3-one (**2**, R = H) may well exist as the tautomeric 3-hydroxy-2,1-benzisothiazole (**2a**) which should react with phosphorus oxychloride to give 3-chloro-2,1-benzisothiazole (**12**). Indeed this reaction was found to take place to give **12** as a yellow oil with an infrared spectrum and other properties matching those described by Buckley and coworkers (9) for **12** prepared by diazotization of 3-amino-2,1-benzisothiazole. The yield of **12** was increased from 38% to 63% by phosphorus oxychloride in the presence of pyridine.

Phosphorus oxychloride alone with 5-chloro-3-hydroxy-2,1-benzisothiazole (**2c**) gave an 88% yield of 3,5-dichloro-2,1-benzisothiazole (**17**). Similarly, 5-nitro-3-hydroxy-2,1-benzisothiazole (**2b**) with phosphorus oxychloride gave a 43% yield of 3-chloro-5-nitro-2,1-benzisothiazole (**14**), which was also obtained by the direct nitration of 3-chloro-2,1-benzisothiazole (**12**) with concentrated sulfuric and nitric acids. A second product from this nitration proved to be 3-chloro-7-nitro-2,1-benzisothiazole (**13**) which was separated from **14** by silica gel column chromatography. This distriubtion of isomers is similar to that obtained by

Table II

2,1-Benzisothiazolin-3-ones Prepared from Corresponding Isatoic Anhydride

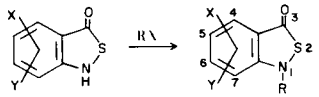


No.	R	X	Y	M.p., °C	% Yield	Empirical Formula	Elemental Analysis Calculated C	H	N	Found C	H	N
2a	H	H	H	138.0-139.5° dec.	54	C_7H_5NOS	55.61	3.33	9.27	55.64	3.35	9.34
2b	H	5-NO_2	H	dec. >208°	28	$C_7H_4N_2O_3S$	42.86	2.05	14.28	42.82	2.15	14.12
2c	H	5-Cl	H	200-206° dec.	71	C_7H_4ClNOS	45.29	2.17	7.55	45.41	2.29	7.42
2d	H	5-CH_3	H	144.5-146.0°	55	C_8H_7NOS	58.18	4.26	8.48	58.18	4.45	8.48
2e	H	6-Cl	H	*ca.* 196-200° dec. (a)	57	C_7H_4ClNOS	45.29	2.17	7.55	45.37	2.19	7.35
2f	H	5-OCH_3	H	133.0-134.5°	78	$C_8H_7NO_2S$	53.02	3.90	7.73	53.29	4.29	7.44
2g	H	5-Cl	7-Cl	231.5-233.0°	62	$C_7H_3Cl_2NOS$	38.34	1.38	6.39	38.31	1.32	6.30
2h	H	6-CH_3	7-CH_3	192-194°	74	C_9H_9NOS	60.31	5.06	7.82	60.39	5.24	7.52
2i	CH_3	H	H	57.0-58.5° (b)	53	-----	-----	-----	-----	-----	-----	-----
2j	CH_3	5-Cl	H	95-97°	89	C_8H_6ClNOS	48.13	3.03	7.02	48.40	3.16	7.16
2k	$C_6H_5CH_2$	H	H	54.0-55.5°	77	$C_{14}H_{11}NOS$	69.68	4.60	5.80	59.71	4.58	5.79

(a) Rapid heating. (b) Previously prepared by another method (5); lit. m.p. 58°.

Table III

1-Substituted 2,1-Benzisothiazolin-3-one Prepared by Alkylation

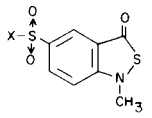


No.	RX	X	Y	M.p., °C	% Yield	Empirical Formula	Elemental Analysis Calculated C	H	N	Found C	H	N
2i	CH_3I	H	H	54.0-57.5°	86	a	-----	-----	-----	-----	-----	-----
2j	CH_3I	5-Cl	H	94-96°	96	a	-----	-----	-----	-----	-----	-----
5a	CH_3CH_2I	H	H	b.p. 121-122°/0.1 mm	50	C_9H_9NOS	60.31	5.06	7.82	60.45	5.06	7.85
5b	CH_3I	5-NO_2	H	137-138.5°	35	$C_8H_6N_2O_3S$ (b)	45.71	2.88	13.32	45.45	2.59	13.47
5c	CH_3CH_2I	5-Cl	H	75.0-76.5°	31	C_9H_8ClNOS	50.59	3.77	6.56	50.51	3.68	6.53
5d	$CH_3CH_2O_2CCH_2Br$	5-Cl	H	101.0-102.5°	Quant.	$C_{11}H_{10}ClNO_3S$	48.62	3.71	5.16	48.69	3.74	5.16
5e	$C_6H_5CH_2Cl$	5-Cl	H	66.5-68.0°	12	$C_{14}H_{10}ClNOS$	60.98	3.66	5.08	61.21	3.64	4.85
5f	CH_2=$CHCH_2Br$	5-Cl	H	44.0-46.5°	69	$C_{10}H_8ClNOS$	53.22	3.57	6.21	53.18	3.73	6.19
5g	CH_3I	5-CH	H	88.5-89.5°	Quant.	C_9H_9NOS	60.31	5.06	7.82	60.39	5.06	7.81
5h	CH_3I	6-Cl	H	109.5-110.5°	83	C_8H_6ClNOS	48.13	3.03	7.02	48.19	3.14	7.17
5i	CH_3I	5-OCH_3	H	83-84°	93	$C_9H_9NO_2S$	55.37	4.64	7.18	55.41	4.57	7.14
5j	CH_3I	5-Cl	7-Cl	120-121°	97	$C_8H_5Cl_2NOS$	41.04	2.15	5.98	41.10	2.16	5.99
5k	CH_3I	6-CH_3	7-CH_3	60.0-61.5°	90	$C_{10}H_{11}NOS$	62.15	5.74	7.25	62.08	5.56	7.21

(a) See Table II. (b) Identical to the product of nitration of 1-methyl-2,1-benzisothiazolin-3-one (**2i**).

Table IV

Sulfamoyl-1-Methyl-2,1-Benzisothiazoles



No.	X	M.p. °C (Solvent)	% Yield	Empirical Formula	Analysis Calculated C	H	N	Found C	H	N
8a		189.5-191.0° (Ethanol)	44	$C_{12}H_{14}N_2O_3S_2$	48.30	4.73	9.39	48.27	4.77	9.33
8b	$(CH_3CH_2)_2N$-	Slowly >118° (Ethanol-water)	96	$C_{12}H_{16}N_2O_3S_2$	47.98	5.37	9.32	47.99	5.45	9.39
8c	$(HOCH_2CH_2)_2N$-	148.5-150.0°	98	$C_{12}H_{16}N_2O_5S_2$	43.36	4.85	8.43	43.31	4.86	8.53
8d		201-203° (DMF-Ethanol)	63	$C_{12}H_{14}N_2O_4S_2$	45.85	4.49	8.91	45.79	4.49	8.94
8e	CH_3CH_2HN-	Slowly >173° (Ethanol)	68	$C_{10}H_{12}N_2O_3S_2$	44.10	4.44	10.28	43.92	4.63	10.11
8f	H_2N-	224-225.5° (Ethanol)	95	$C_8H_8N_2O_3S_2$	39.33	3.30	11.47	39.34	3.42	11.48

direct nitration of 2,1-benzisothiazole under similar conditions (10).

Nucleophilic displacement of the 3-chloro-group in **12** occured quite readily. Sodium methoxide in refluxing methanol converted **12** to 3-methoxy-2,1-benzisothiazole (**11**). Treatment of **12** with ethanethiol in the presence of sodium methoxide gave 3-ethylthio-2,1-benzisothiazole (**10**). Pyrrolidine and 3-chloro-2,1-benzisothiazole gave 3-pyrrolidino-2,1-benzisothiazole (**9**) in above 90% yield. Since **9** had been previously reported by Meyer and coworkers (11) by stannous chloride reduction of *o*-nitropyrrolidino thiobenzamide, we repeated this synthesis (11) and obtained a product **9** identical in all respects with that obtained from **12** and pyrrolidine. The treatment of 1-methyl-2,1-benzisothiazolin-3-one (**2i**) with phosphorus pentasulfide in pyridine gave 1-methyl-2,1-benzisothiazoline-3-thione (**15**). The melting point and other properties of **15** were similar to those reported (5) for **15** prepared from *N*-methylanthranilic acid by another route. The treatment of **15** with methyl iodide in benzene resulted in the preparation of the interesting product 1-methyl-3-methylthio-2,1-benzisothiazolinium iodide (**16**).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The spectra reported were obtained using a Perkin-Elmer 257 grating infrared spectrophotometer, a Hitachi Perkin-Elmer R-20A high resolution nmr spectrometer (internal standards: TMS for deuteriochloroform and DDS for DMSO-d_6), and a Cary 15 ultraviolet spectrophotometer. All analytical samples displayed a single spot on thin layer chromatography and were analyzed by the Heterocyclic Chemical Corporation of Harrisonville, Missouri.

2,1-Benzisothiazolin-3-ones.

General Synthetic Procedure in Methanol Solvent (Table II).

To a stirred solution of a metal hydroxide (1 equivalent) in methanol (300 ml./0.1 mole) saturated with hydrogen sulfide gas at room temperature was slowly added an isatoic anhydride (1 equivalent). After the gas (carbon dioxide) evolution had ceased, the resulting solution was filtered before the solvent removed *in vacuo*. The resulting product was dissolved or suspended in water (200 ml./0.1 mole) and cautiously treated with a slight excess of 30% hydrogen peroxide. After filtering, the reaction mixture was adjusted to *ca.* *p*H 7, the resulting product collected and purified by reprecipitation followed by recrystallization from water or ethanol.

Example I.

2,1-Benzisothiazolin-3-one (**2a**).

A solution of potassium hydroxide (15 g.) in methanol (600 ml.) was saturated with hydrogen sulfide gas. While the solution was stirred at room temperature, technical isatoic anhydride (**3a**, 36.7 g., 0.225 mole) was added portionwise followed by an additional 10 minutes of stirring. The reaction mixture was dried over sodium sulfate, filtered, and the solvent removed *in vacuo* leaving a yellow solid. This product was then suspended in water (300 ml.) and treated with 15% hydrogen peroxide (80 ml.) at such a rate as to keep the temperature below 40°. After stirring for an additional 30 minutes, the reaction mixture was filtered, and the filtrate adjusted to *ca.* *p*H 6 with 2*N* hydrochloric acid. The solid

that separated was collected and crystallized from water yielding 18.4 g. (54%) of yellow needles melting at 137.5-140° dec. Sublimation produced an analytical sample, m.p. 138-139.5° dec., positive ferric chloride test (methanol); ir (potassium bromide): 3090, 1620, 1600, 745 cm^{-1}; pmr (DMSO-d_6): δ 6.95-7.90 (m, 4), 9.80 ppm (broad, 1); ms: m/e 151, 123, 96, 83; uv (ethanol): λ max (ε) 217 (6.14 x 10^{-4}), 230 (shoulder), 243 (shoulder) 353 mμ (4.68 x 10^{-3}).

Example II.

5,7-Dichloro-2,1-benzisothiazolin-3-one (**2g**).

To a stirred solution of potassium hydroxide (13 g.) in methanol (700 ml.), saturated with hydrogen sulfide gas at ambient temperature was added 3,5-dichloroisatoic anhydride (**3g**, 46.4 g.). After the gas evolution had ceased, the mixture was filtered, and the orange filtrate taken to dryness *in vacuo*. The resulting orange solid was suspended in water (300 ml.) and cautiously treated with 30% hydrogen peroxide (30 ml.). After filtering, the filtrate was adjusted to *ca.* *p*H 7, the cream colored solid collected, washed with water, and reprecipitated from base by adjusting the *p*H to *ca.* 1. This gave 27 g. (62%) of a cream colored solid melting at 227-230°. Two recrystallizations from ethanol produced an analytical sample, light yellow needles, m.p. 231.5-233.0°; ir (potassium bromide): 1620, 875 cm^{-1}; pmr (DMSO-d_6): δ 7.68 (d, 1, J = 2 Hz), 7.88 ppm (d, 1, J = 2 Hz): uv (ethanol): λ max (ε) 202 (1.93 x 10^{-4}), 224 (2.26 x 10^{-4}), 237 (shoulder), 253 (9.65 x 10^{-3}), 262 (shoulder), 372 mμ (4.56 x 10^{-3}).

Example III.

5-Nitro-2,1-benzisothiazolin-3-one (**2b**).

A solution of sodium hydrogen sulfide (0.18 mole) in 50 ml. of methanol (prepared by bubbling hydrogen sulfide gas into a solution of 7.2 g. of sodium hydroxide in 50 ml. of methanol followed by purging with nitrogen gas) was added over a 30 minute period to a stirred suspension of 5-nitroisatoic anhydride (**3b** 37.5 g., 0.18 mole) in methanol (500 ml.) at room temperature (8). The resulting solution was filtered and the solvent removed *in vacuo* leaving a yellow-orange solid which was suspended in *N* sodium hydroxide (600 ml.) and slowly treated with 30% hydrogen peroxide (21 ml.). After 15 minutes of additional stirring, the dark red solution was filtered and the filtrate made strongly acidic with hydrochloric acid. The resulting yellow solid was collected, washed with water, and redissolved in base. After filtration, the solution was adjusted to *p*H 5.5 with acetic acid, the yellow solid that separated was collected, washed with water and crystallized from water. This gave 10 g. (28%) of a yellow-green solid melting at 204-208° dec. Recrystallization from toluene produced an analytical sample as yellow plates, m.p. dec. slowly > 208°; ir (potassium bromide): 1650, 1615, 1510, 1325, 885, 830 cm^{-1}; pmr (DMSO-d_6): δ 7.48 (d, 1, J = 9 Hz), 8.38 (dd, 1, J = 9, 2.5 Hz), 8.48 (d, 1, J = 2.5 Hz); uv (ethanol): λ max (ε) 204 (1.47 x 10^{-4}) 222 (1.55 x 10^{-4}), 228 (1.55 x 10^{-4}), 236 (inflection), 270 (1.03 x 10^{-4}), 345 mμ (1.04 x 10^{-4}).

2,1-Benzisothiazolin-3-ones.

General Synthetic Procedure in Water Solvent (Table II).

A stirred solution of a metal carbonate or metal hydroxide (1 equivalent) in water (500 ml./0.1 mole) was flushed with nitrogen gas then saturated with hydrogen sulfide gas at room temperature. To this solution was slowly added an isatoic anhydride (1 equivalent), the reaction mixture purged for 30 minutes with nitrohydrogen peroxide. After filtering, the filtrate was adjusted to *ca.* *p*H 7, the resulting product collected and purified by reprecipitation followed by recrystallization from water or ethanol.

Example I.

5-Chloro-2,1-benzisothhiazolin-3-one (**2c**).

A solution of potassium carbonate (56 g., 0.40 mole) in water (2 l.) was flushed with nitrogen gas then saturated with hydrogen sulfide gas. With the continued introduction of hydrogen sulfide, 5-chloroisatoic anhydride (**3c**, 78.8 g., 0.40 mole) was added portionwise to the stirred solution over 1 hour, followed by 30 minutes of purging with nitrogen gas. To this stirred mixture was added dropwise a solution of potassium hydroxide (40 g.) in 15% hydrogen peroxide (160 ml.) with cooling to maintain the temperature between *ca.* 25-35°. The brown solution was filtered and the filtrate adjusted to *ca.* *p*H 7 with 2*N* hydrochloric acid. The resulting tan solid was collected and dried yielding 52.8 g. (71%) of **2c**, m.p. > 200°. Recrystallization from water produced a colorless analytical sample, m.p. 200-206° dec; ir (potassium bromide): 3090, 1660, 1605, 870, 808 cm^{-1}; pmr (DMSO-d_6): δ 7.55 (d, 1, J = 5 Hz), 7.67 (d, J = 5 Hz), 7.72 (s, 1), 10.2 ppm (broad, 1); ms: m/e 185, 157, 130, 122, 95; uv (ethanol): λ max (ε) 222 (4.49 x 10^{-4}), 248 (shoulder), 256 (1.10 x 10^{-4}), 264 mμ (3.14 x 10^{-3}).

Example II.

5-Methyl-2,1-benzisothiazolin-3-one (**2d**).

To a solution of potassium hydroxide (6.6 g.) in water (250 ml.) saturated with hydrogen sulfide gas was added 5-methylisatoic anhydride (**3d**, 17.7 g., 0.10 mole) over one hour. The reaction mixture was filtered, the excess hydrogen sulfide removed by flushing with nitrogen gas, and the filtrate then treated with 30% hydrogen peroxide (14 ml.) with the occasional addition of ice to maintain the temperature below 40°. Following an additional 15 minutes of stirring, the reaction mixture was filtered through celite, and the filtrate adjusted to *p*H 7 with 2*N* hydrochloric acid. The resulting yellow solid was collected, washed with water, and dried. In this manner, 9 g. (55%) of **2d** was obtained. An analytical sample was obtained by reprecipitation of a portion of the product from base (charcoal), by adjustment of the *p*H to *ca.* 3, followed by recrystallization from ethanol-water as light-yellow needles, m.p. 144.5-146.0°; ir (potassium bromide): 1635, 865, 810 cm^{-1}; pmr (DMSO-d_6): δ 2.42 (s, 3), 7.20-7.60 ppm (m, 3); uv (ethanol): λ max (ε) 221 (2.35 x 10^{-4}), 245 (9.57 x 10^{-3}), 252 (inflection), 267 (shoulder), 358 mμ (4.47 x 10^{-3}).

1-Substituted 2,1-Benzisothiazolin-3-ones from *N*-Substituted Isatoic Anhydrides.

General Procedure (Table II).

To a stirred solution of 1 molar equivalent of sodium or potassium hydroxide in methanol (*ca.* 300 ml./0.1 mole base) saturated with hydrogen sulfide gas at room temperature was added 1 molar equivalent of an *N*-substituted isatoic anhydride portionwise over *ca.* 30 minutes. After gas evolution had ceased, the reaction mixture was filtered, and the solvent removed *in vacuo*. The resulting product was dissolved in water (*ca.* 200 ml./0.1 mole) and cautiously treated with a slight excess of 30% hydrogen peroxide, while maintaining the reaction temperature between 25-40°. The product was extracted with ether and the extracts washed with aqueous ferrous sulfatesulfuric acid, followed by water and then dried over anhydrous magnesium sulfate. After removing the solvent *in vacuo*, the resulting product, depending on its purity (tlc), was either recrystallized from cyclohexane or chromatographed over silica gel followed by recrystallization from cyclohexane.

Example I.

1-Methyl-2,1-benzisothiazoline-3-one (**2i**).

To a stirred solution of sodium hydroxide (4.5 g.) in methanol (400 ml.) saturated with hydrogen sulfide gas was added *N*-methylisatoic anhydride (**3i**, 177 g.) portionwise over 30 minutes. After addition, the reaction mixture was stirred with sodium sulfate for 15 minutes and filtered. Removal of the solvent *in vacuo* produced a yellow solid, which was dissolved in water (2 l.) and slowly treated with 15% hydrogen peroxide (40 ml.). (During the addition, the temperature was maintained near room temperature by ice cooling). The product was extracted with ether and the extracts washed with aqueous ferrous sulfate-sulfuric acid followed by water and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave 8.8 g. (53%) of a yellow oil, the majority of which slowly solidified into a low melting yellow solid. Recrystallization from cyclohexane produced yellow needles melting as 57-58° (lit. (5) 58°); ir (potassium bromide): 1645, 1600, 762 cm^{-1}; pmr (deuteriochloroform): δ 3.47 (s, 3), 6.90-7.90 ppm (m, 4); uv (ethanol): λ max (ε) 222 (2.04 x 10^{-4}), 234 (1.73 x 10^{-4}), 247 (8.71 x 10^{-3}), 253 (shoulder), 366 mμ (3.83 x 10^{-3}).

Example II.

1-Benzyl-2,1-benzisothiazolin-3-one (**2k**).

To a stirred solution of potassium hydroxide (1.5 g.) in methanol (60 ml.), saturated with hydrogen sulfide gas, was added *N*-benzylisatoic anhydride (**3k**, 6.4 g.). Sodium sulfate was added, the mixture stirred for an additional 30 minutes, filtered, and the solvent removed *in vacuo*. The resulting yellow semi-solid was suspended in water (50 ml.) and slowly treated with 7.5% hydrogen peroxide (20 ml.) while maintaining the temperature between 25-35°. After stirring for an additional 15 minutes, the reaction mixture was extracted with ether, the organic layer washed with 5*N* potassium carbonate, aqueous ferrous sulfate-sulfuric acid, water, and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave 4.7 g. (77%) of a viscous yellow liquid, which solidified on scratching, m.p. 35-40°. An analytical sample was obtained by first chromatographing this product over alumina (140 g., Baker 0539) with chloroform followed by reprecipitation from ether-petroleum ether (30-60°) as yellow needles, m.p. 54-55.5°; ir (potassium bromide): 1650, 1600, 755 cm^{-1}; pmr (deuteriochloroform): δ 4.98 (s, 2), 7.33 (s, 5), 6.90-8.00 ppm (m, 4); uv (ethanol): λ max (ε) 217 (2.15 x 10^{-4}), 247 (1.11 x 10^{-4}), 254 (shoulder), 365 mμ (5.50 x 10^{-3}).

1-Substituted 2,1-Benzisothiazolin-3-ones from 2,1-Benzisothiazolin-3-ones.

General Procedure (Table III).

A mixture of 2,1-benzisothiazolin-3-one, 1-6 molar equivalents of an alkyl or aralkyl halide, and an excess of potassium carbonate was heated under refluxing in acetone (10-20 ml./g. starting material) for 1 hour. The reaction mixture was then poured into water and extracted with ether. Removal of the solvent *in vacuo* gave the product, which was purified by one of the following methods: (a) recrystallization from cyclohexane or ethanol-water, (b) distillation followed by recrystallization, or (c) chromatography followed by recrystallization.

1-Methyl-5-nitro-2,1-benzisothiazolin-3-one (**5b**).

With rapid stirring, 1-methyl-2,1-benzisothiazolin-3-one (**2i**, 10 g.) was added to 20% nitric acid (300 ml.) maintained at 5-10°. The highly exothermic reaction was kept in check by the occasional direct addition of ice to the reaction mixture. When the reaction subsided, as noted by a drop in temperature, the resulting yellow solid was collected, dried and crystallized from toluene-heptane to yield 4.5 g. (35%) of crude product, m.p. 115-133°. Percolation through silica gel with chloroform followed by recrystallization from ethanol-water produced an analytical sample, yellow solid, m.p., 137-138.5°; ir (potassium bromide): 1680, 1605, 1520, 1330, 865, 823 cm^{-1}; pmr (deuteriochloroform): δ 3.65 (, e), 7.25 (d, 1, J = 9 Hz), 8.40 (dd, 1, J = 9, 2 Hz), 8.68 ppm (d, 1, J = 2 Hz); uv (ethanol): λ max (ε) 207 (1.53 x 10^{-4}), 225 (1.67 x 10^{-4}), 232 (1.69 x 10^{-4}), 240 (inflection), 170 (1.07 x 10^{-4}), 252 mμ (1.13 x 10^{-4}).

The product was shown, by mixture melting point (136-137°), tlc, and infrared analysis, to be identical with a sample prepared by methylation of 5-nitro-2,1-benzisothiazolin-3-one (**2b**).

5-Bromo-1-methyl-2,1-benzisothiazolin-3-one (**6**).

To a solution of 1-methyl-2,1-benzisothiazolin-3-one (**2i**, 3.3 g., 20 mmoles) in methylene chloride (50 ml.) was added NBS (3.6 g., 20.2 mmoles) and the mixture stirred at room temperature for 40 minutes. After washing well with water and drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo* giving a quantitative yield of a dark green solid melting at 80-89°. An analytical sample was obtained by crystallizing this product twice from cyclohexane (charcoal) as yellow solid, m.p. 96-98°; ir (potassium bromide): 1675, 1630, 1610, 900, 800 cm^{-1}; pmr (deuteriochloroform): δ 3.46 (s, 3), 7.05 (d, 1, J = 9 Hz), 7.60 (dd, 1, J = 9, 2 Hz), 7.89 ppm (d, 1, J = 2 Hz); uv (ethanol): λ max (ε) 203 (1.47 x 10^{-4}), 224 (2.63 x 10^{-4}), 225 (inflection), 252 (inflection, 262 (1.46 x 10^{-4}), 378 mμ (4.66 x 10^{-3}).

Anal. Calcd. for C_8H_5BrNOS: C, 39.36; H, 2.48; H, 5.74. Found: C, 39.43; H, 2.47; N, 5.73.

5-Chlorosulfonyl-1-methyl-2,1-benzisothiazolin-3-one (**7**).

To chlorosulfonic acid (15 ml.), stirred in an ice bath, was slowly added 1-methyl-2,1-benzisothiazolin-3-one (**2i**, 5.0 g.). As soon as all the solid had dissolved, the reaction mixture was removed from the ice bath, stirred at room temperature for 30 minutes, then heated on a steam bath for 10 minutes. After cooling in an ice bath, the reaction mixture was cautiously poured into ice-water. The resulting yellow solid was collected, washed with water, and dried giving 6.6 g. (83%), m.p. 131-136.5°. A single crystallization from toluene-heptane gave an analytical sample as yellow needles, m.p. 134.5-138°; ir (potassium bromide): 1660, 1595, 1370, 1180, 865, 805 cm^{-1}; pmr (deuteriochloroform): δ 3.63 (s, 3), 7.32 (d, 1, J = 9 Hz), 8.11 (dd, 1, J = 9, 2 Hz), 8.49 ppm (d, 1, J = 2 Hz); uv (ethanol): λ max (ε) 219 (2.50 x 10^{-4}), 237 (inflection), 263 (1.45 x 10^{-4}), 314 (6.81 x 10^{-3}), 364 mμ (2.72 x 10^{-3}).

Anal. Calcd. for $C_8H_6ClNO_3S_2$: C, 36.43; H, 2.29; N, 5.31. Found: C, 36.42; H, 2.38; N, 5.26.

1-Methyl-5-sulfonamido-2,1-benzisothiazolin-3-one (**8f**).

A suspension of 5-chlorosulfonyl-1-methyl-2,1-benzisothiazolin-3-one (**7**, 2.6 g.) in ethanol (100 ml.) was saturated with ammonia gas and stirred at room temperature for 1 hour. After removing the solvent *in vacuo*, the resulting product was suspended in water, collected by filtration and dried. This gave 2.3 g. (95%) of a cream colored solid melting at 216-220°. An analytical sample was obtained by recrystallization twice from ethanol, m.p. 224-225.5°; ir (potassium bromide): 1645 (shoulder), 1605, 1355, 1341, 1165, 1148, 866, 808 cm^{-1}; pmr (DMSO-d_6): δ 3.62 (s, 3), 7.40 (m, broad, 2), 7.60-8.15 ppm (m, 3); uv (ethanol): λ max (ε) 210 (i), 225 (2.52 x 10^{-4}), 237 (2.12 x 10^{-4}), 261 (1.79 x 10^{-4}), 282 (shoulder), 368 mμ (4.29 x 10^{-3}).

5-(*N*,*N*-Disubstituted sulfonamido)-1-methyl-2,1-benzisothiazolin-3-ones (**8a-e**).

General Procedure (Table IV).

To a suspension of 5-chlorosulfonyl-1-methyl-2,1-benzisothia-

zolin-3-one (**7**, 3.0 g.) in water (25 ml.) was added a disubstituted amine (5 ml.) and the reaction mixture stirred at room temperature for *ca.* 2 hours. The resulting product was collected, washed with water and dried. Recrystallization from the appropriate solvent gave an analytical sample.

Example I.

5(*N*-Ethylsulfonamido)-1-methyl-2,1-benzisothiazolin-3-one (**8e**).

A suspension of 5-chlorosulfonyl-1-methyl-2,1-benzisothiazolin-3-one (**7**, 3 g., 11.4 mmoles), 70% ethylamine (0.8 g., 12.5 mmoles), and triethylamine (2 ml.) in water (50 ml.) was stirred at room temperature for 1.5 hours. The yellow solid was collected, washed with water, and crystallized from ethanol giving 2.1 g. (68%) of **8e**, slowly melts $> 172°$. An analytical sample obtained by an additional recrystallization from ethanol to give yellow plates, slowly melts $> 173°$; ir (potassium bromide): 1650, 1610, 1320, 1135, 865, 820 cm^{-1}; pmr (DMSO-d_6): δ 1.02 (t, 3, J = 7 Hz), 2.83 (t, broad, 2 J = 7 Hz), 3.65 (s, 3), 7.64 ppm (m, 1); uv (ethanol): λ max (ϵ) 224 (2.26 x 10^{-4}), 237 (1.79 x 10^{-4}), 262 (1.59 x 10^{-4}), 262 (1.59 x 10^{-4}), 283 (shoulder), 369 mμ (2.62 x 10^{-3}).

3-Chloro-2,1-benzisothiazole (**12**).

Method (1).

To a solution of 3-hydroxy-2,1-benzisothiazole (**2a**, 5.0 g.) in pyridine (2.5 ml.) was cautiously added phosphorus oxychloride (5 ml.). After the exothermic reaction subsided, the red reaction mixture was heated at 130-140° with stirring for 1 hour. After cooling to room temperature, it was cautiously poured into ice-water with vigorous stirring. This mixture was then extracted with ether, which was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo* yielding 4.2 g. of an orange liquid. Distillation produced a light yellow analytical sample (3.5 g., 63%), b.p. 65°/0.2 mm; ir, identical to that described by Buckley, *et al.*, (10); pmr (deuteriochloroform): δ 7.05-7.88 ppm (m); uv (ethanol): λ max (ϵ) 204 (2.23 x 10^{-4}), 222 (1.86 x 10^{-4}), 291 (8.02 x 10^{-3}), 298 (shoulder), 303 (1.02 x 10^{-4}), 328 mm (5.82 x 10^{-3}).

Anal. Calcd. for C_7H_4ClNS: C, 49.57; H, 2.37; N, 8.26. Found: C, 49.61; H, 2.35; N, 8.28.

Method (2).

A suspension of 3-hydroxy-2,1-benzisothiazole (**2a**, 10 g.) in phosphorus oxychloride (100 ml.) was heated on the steam bath for 1.5 hours. After removing the excess phosphorous oxychloride *in vacuo*, the resulting dark oil was poured into ice-water, and extracted several times with ether. The combined extracts were washed with saturated sodium bicarbonate followed by water and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* left an orange liquid, which, by vacuum distillation, afforded 4.3 g. (38%) of analytical product; yellow oil, b.p. 72-75° (1 mm).

3,5-Dichloro-2,1-benzisothiazole (**17**).

5-Chloro-3-hydroxy-2,1-benzisothiazole (**2c**) was heated on a steam bath with phosphorus oxychloride (10 ml./g.) for 1-1.5 hours. After removing the excess phosphorus oxychloride *in vacuo*, the resulting dark oil was poured into ice-water and the resulting tan solid collected, washed with water and dried. The yield was 88%. Crystallization from ethanol-water followed by sublimation produced an analytical sample, m.p. 78.5-80.5°.

Anal. Calcd. for $C_7H_3Cl_2NS$: C, 41.20; H, 1.48; N, 6.86. Found: C, 41.21; H, 1.45; N, 6.84.

3-Chloro-5-nitro-2,1-benzisothiazole (**14**).

3-Hydroxy-5-nitro-2,1-benzisothiazole (**2b**) was treated with phosphorus oxychloride as in the preparation of 3,5-dichloro-2,1-benzisothiazole, above. After 2-1/2 hours, the excess phosphorus oxychloride was removed *in vacuo* and the residual dark syrup was poured into ice-water with stirring. The solid that separated was collected and washed with ice-water, dried to give, after recrystallization from aqueous ethanol, a 43% yield of product with m.p. 117-118°, identical to that obtained from nitration of 3-chloro-2,1-benzisothiazole (**12**). The two products were judged to be identical on the basis of mixture m.p., infrared and pmr spectra.

Nitration of 3-Chloro-2,1-benzisothiazole.

A stirred solution of 3-chloro-2,1-benzisothiazole (**12**, 0.5 g.) in concentrated sulfuric acid (5 ml.) at room temperature was treated dropwise with 70% nitric acid (0.5 ml.). After the exothermic reaction subsided, the mixture was allowed to stand for an additional 15 minutes then cautiously poured onto ice. The resulting yellow solid was collected, washed with water, and dried. This product, obtained in quantitative yield, displayed a wide melting range (96-111°) and exhibited 2 spots on tlc (silica gel/benzene). Separation of the two components was readily effected on a column of silica gel (40 g.) with toluene. Subsequent sublimation of the products thus obtained produce analytical samples.

The major component (m.p. 117-118.5°) was shown to be 3-chloro-5-nitro-2,1-benzisothiazole (**14**) by pmr and by comparison with an authentic sample prepared from 3-hydroxy-5-nitro-2,1-benzisothiazole and phosphorus oxychloride; ir (potassium bromide): 1615, 1505, 1345, 787, 815 cm^{-1}; pmr (deuteriochloroform): δ 7.88 (d, 1, J = 9.5 Hz), 8.28 (dd, 1, J = 9.5, 2.5 Hz), 8.73 ppm (d, 1, J = 2.5 Hz); uv (ethanol): λ max (ϵ) 213 (shoulder), 270 (2.44 x 10^{-4}), 297 (shoulder), 308 (6.74 x 10^{-3}), 332 (7.02 x 10^{-3}), 351 mμ (4.45 x 10^{-3}).

Anal. Calcd. for $C_7H_3ClN_2O_2S$: C, 39.18; H, 1.41; N, 13.05. Found: C, 39.09; H, 1.38; N, 13.09.

The minor component (m.p. 142-144°) was shown by pmr to be 3-chloro-7-nitro-2,1-benzisothiazole (**13**); ir (potassium bromide): 1622, 1518, 1335, 885, 815 cm^{-1}; pmr (deuteriochloroform): δ 7.47 (dd, 1, J = 8.5, 7.5 Hz), 8.09 (dd, 1, J = 8.5, 1 Hz), 8.45 ppm (dd, 1, J = 7.5, 1 Hz); uv (ethanol): λ max (ϵ) 207 (1.98 x 10^{-4}), 304 (5.13 x 10^{-3}), 315 (shoulder, 359 mμ (6.09 x 10^{-3}).

Anal. Calcd. for $C_7H_3ClN_2O_2S$: C, 39.18; H, 1.41; N, 13.05. Found: C, 39.17; H, 1.36; N, 13.03.

3-Ethylthio-2,1-benzisothiazole (**10**).

To a stirred solution of sodium methoxide (1.5 g., 22 mmoles) in methanol (30 ml.) was added ethanethiol (1.7 ml., 23 mmoles). After stirring for 15 minutes, 3-chloro-2,1-benzisothiazole (**12**, 3.4 g., 20 mmoles) was added and the solution heated under reflux for 1 hour. The reaction mixture was then poured into water and extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* leaving a quantitative yield of yellow liquid, which boiled at 108-111° (0.4 mm); ir (neat) 1615, 745 cm^{-1}; pmr (deuteriochloroform): 1.40 (t, 3, J = 7), 3.10 (q, 2, J = 7), 7.05-7.95 ppm (m, 4); uv (ethanol): λ max (ϵ), 210 (shoulder), 228 (2.12 x 10^{-4}), 2.96 (6.41 x 10^{-3}), 305 (6.96 x 10^{-3}), 353 mμ (5.89 x 10^{-3}).

Anal. Calcd. for $C_9H_9NS_2$: C, 55.35; H, 4.64; N, 7.17. Found: C, 55.55; H, 4.89; N, 7.16.

3-Pyrrolindino-2,1-benzisothiazole (**9**).

A solution of 3-chloro-2,1-benzisothiazole (**12**, 1.0 g.) in pyrrolidine (3.0 g.) was stirred at room temperature for *ca.* 15 hours

then poured into water. The resulting product was collected, washed with water, and dried, yielding 1.1 g. (91%) of yellow solid melting at 133-135°. Crystallization from aqueous-ethanol produced a sample melting at 133.5-135° (lit. (11) m.p. 144-145°).

The product was shown to be identical (tlc, ir, and pmr) to an authentic sample prepared by the published procedure (11).

3-Methoxy-2,1-benzisothiazole (**11**).

A solution of 3-chloro-2,1-benzisothiazole (**12**, 2 g., 11.8 mmoles) and sodium methoxide (1 g., 18.5 mmoles) in methanol (20 ml.) was heated under reflux for 2.5 hours, poured into water, and extracted with ether. After drying the organic layer over anhydrous magnesium sulfate, the solvent was removed *in vacuo* leaving 1.8 g. (92%) of a yellow solid, m.p. 44-57°. Vacuum distillation (93-94°/0.2 mm) produced an analytical sample as yellow solid, m.p. 56-59.5° (sinters from *ca.* 50°); ir: 1613, 1270, 1022, 755 cm^{-1}; pmr (deuteriochloroform): δ 4.22 (s, 3), 6.82-7.80 ppm (m, 4); uv (ethanol): λ max (ε) 212 (shoulder), 222 (1.50 x 10^{-4}), 285 (shoulder), 294 (3.46 x 10^{-3}), 342 mμ (3.80 x 10^{-3}).

Anal. Calcd. For C_8H_7NOS: C, 58.16; H, 4.27; N, 8.50. Found: C, 58.37; H, 4.51; N, 8.67.

1-Methyl-2,1-benzisothiazolin-3-thione (**15**).

A mixture of 1-methyl-2,1-benzisothiazolin-3-one (**2i**, 3.3 g., 20 mmoles) and phosphorus pentasulfide (4.4 g., 20 mmoles) in pyridine (50 ml.) was heated at reflux for 30 minutes. After removing the solvent *in vacuo*, the residual dark solid was suspended in water. The resulting brick-red solid was collected, washed well with water, and crystallized from aqueous-ethanol (charcoal) yielding 1.0 g. (28%) of an orange solid melting at 130-134.5°. An additional recrystallization from ethanol raised the melting point to 137° (lit. (5) 139°); ir (potassium bromide): 1605, 742 cm^{-1}; pmr (deuteriochloroform): δ 3.60 (s, 3), 7.00-8.10 ppm (m, 4); ms: m/e 181 (M^+).

1-Methyl-3-methylthio-2,1-benzisothiazolinium Iodide (**16**).

A solution of 200 mg. of **15** and methyl iodide (10 ml.) in benzene (15 ml.) was stirred at room temperature for *ca.* 24 hours. The resulting yellow precipitate was collected and dried, yielding 330 mg. (93%) of a product which melted at 139-143°. Reprecipitation of this product from methylene chloride with ether produced (after drying at 90° under high vacuum) an analytical sample, m.p., turns red *ca.* 130° and melts *ca.* 137-139°; ir: 1315, 760 cm^{-1}; pmr (DMSO-d_6): δ 319 (s, 3), 4.38 (s, 3), 7.30-8.25 ppm (m, 4); uv (ethanol); λ max (ε) 222 (2.66 x 10^{-4}), 304 (8.66 x 10^{-3}), 1.15 mμ (1.15 x 10^{-4}).

Anal. Calcd. for $C_9H_{10}INS_2$: C, 33.44; H, 3.12; N, 4.33. Found: C, 33.47; H, 3.40; N, 4.32.

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