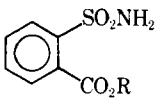
Novel Synthesis of Some 1,2-Benzisothiazoline Derivatives: Cyclization of *ortho*-Sulfamoylcinnamates by the Michael Reaction

B. K. RAO* and GLENN H. HAMOR

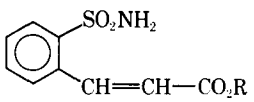
Abstract □ A new synthetic route for the preparation of the alkyl esters of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (III) is described in this paper. In attempts to prepare the alkyl esters of *ortho*-sulfamoylcinnamic acid (II) by the procedure of Leov and Kormendy, the authors observed that the compounds obtained were not the expected cinnamic acid derivatives (II), but the derivatives of 1,2-benzisothiazoline (III). The 1,2-benzisothiazoline derivatives (III) are believed to have formed as a result of an intramolecular rearrangement of the cinnamates (II) by a mechanism similar to the Michael reaction. Proof of the chemical structures is provided by UV, IR, NMR, and X-ray crystallographic studies. Six compounds were synthesized and tested for antielectroshock activity in addition to a general pharmacological screening. One compound showed a slight antielectroshock activity in mice, but in general, the compounds did not possess any significant pharmacological activity.

Keyphrases □ 1,2-Benzisothiazoline-3-acetic acid 1,1-dioxide alkyl esters—synthesis □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure □ X-Ray crystallography—structure

Alkyl esters of *ortho*-sulfamyolbenzoic acid (I) and ring-substituted *ortho*-sulfamoylbenzoic acid were reported to have antielectroshock activity in mice (1–5). In a previous paper the authors explained the purpose of synthesizing the alkyl esters of *ortho*-sulfamoylcinnamic acid (II), the vinylogs of the esters of *ortho*-sulfamoylbenzoic acid (I) (6). Attempts to prepare II by the procedure of Loev and Kormendy were unsuccessful as evidenced by the absence of the vinylene (—CH=CH—) group in the IR[1] and NMR[2] spectra of the compounds obtained, as reported earlier (4, 6). The compounds obtained were subsequently identified as the alkyl esters of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (III).



I

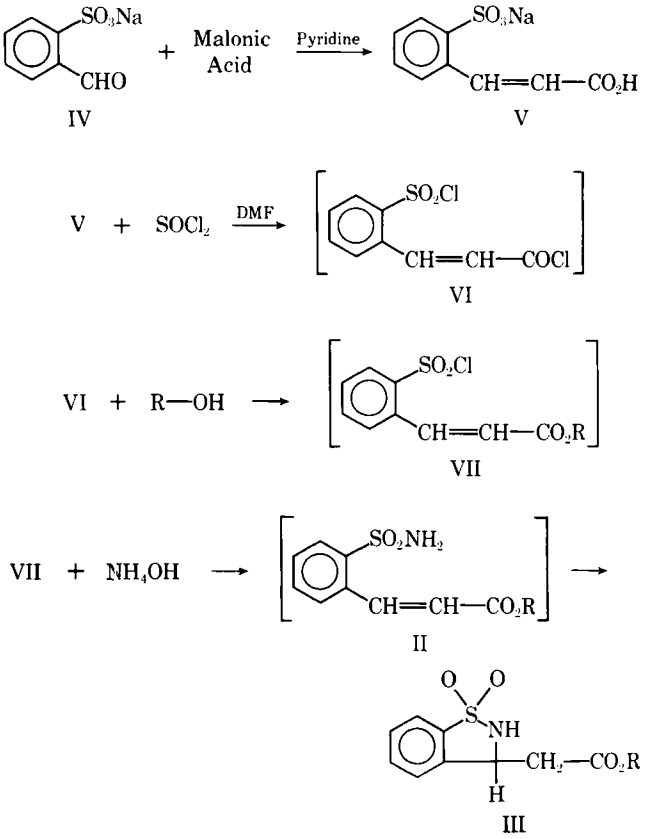


II

DISCUSSION

Alkyl esters of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (III) are synthesized according to the reactions shown in Scheme I.

ortho-Sulfocinnamic acid (V) was prepared as its sodium salt by the Knoevenagel reaction between *ortho*-benzaldehydesulfonic acid, sodium salt (IV), and malonic acid, in the presence of pyridine and piperidine (7). *ortho*-Sulfocinnamic acid (V), on treatment with thionyl chloride in the presence of catalytic amounts of DMF (dimethylformamide), forms the diacid chloride (VI), which was not isolated. After removing excess thionyl chloride from the reaction mixture, the residue was treated with the appropriate alcohol to produce the corresponding esters (VIII). The excess alcohol was removed and the residue was added to ammonium hydroxide solution (28% NH_3). The 1,2-benzisothiazoline derivatives (III) precipitated out of the mixture on allowing the reaction mixture to stand overnight. Table I shows the melting points, percent yields, and elemental analysis of the compounds synthesized.



Scheme I

Figures 1–3 show the typical IR, NMR, and UV spectra of the esters of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (III), as compared with spectra of II. Examination of the IR and NMR spectra indicated the absence of the vinylene (—CH=CH—) group in these compounds (III). It was concluded that they (III) were formed as a result of an intramolecular rearrangement of II in the presence of excess ammonium hydroxide solution. The mechanism of rearrangement appears to be similar to the Michael reaction (8). The Michael reaction is, generally, the base-catalyzed addition of a pseudo-acidic ketone, ester, nitrile, nitro-compound, or a sulfone to the α, β-double bond of a conjugated and unsaturated ketone, ester, or nitrile. The Michael reaction can occur intermolecularly, as originally described by Michael, or intramolecularly (9–11). It is understood that the carbanion formed from the donor in alkaline solution attacks the more positive end of the polarized system of the acceptor yielding an anion which, after treatment with water, yields the ultimate adduct

[1] IR spectra were taken on a Perkin-Elmer Infracord. The samples were prepared as mulls with mineral oil.

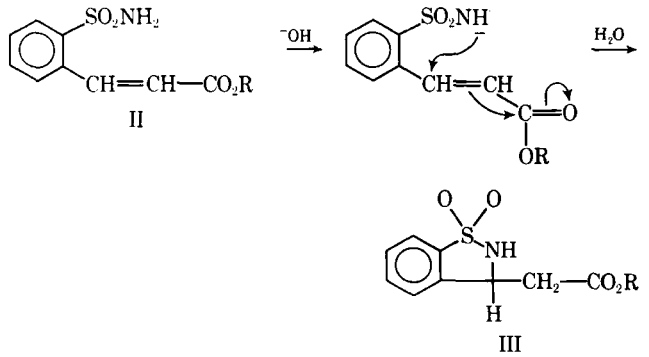
[2] NMR spectra were taken on a Varian A-60 high resolution NMR spectrophotometer, courtesy of Riker Laboratories, Northridge, Calif.

Table I—Alkyl Esters of 1,2-Benzisothiazoline-3-acetic acid 1,1-Dioxide[a]

Compd.	R	Formula	M.p.,[b] °C.	Recrystn. Solvent	Yield, %	Anal., % Calcd.	Found
1	CH_3	$C_{10}H_{11}NO_4S$	138–141	MeOH	45.5	C, 49.78 H, 4.60	C, 49.77 H, 4.61
2	C_2H_5	$C_{11}H_{13}NO_4S$	111–112.5	EtOH	40.0	C, 51.75 H, 5.13	C, 51.72 H, 5.23
3	n-C_3H_7	$C_{12}H_{15}NO_4S$	89–90	EtOH	14	C, 53.51 H, 5.61	C, 53.64 H, 5.74
4	i-C_3H_7	$C_{12}H_{15}NO_4S$	111–112.5	2-PrOH	24.0	C, 53.51 H, 5.61 N, 5.20	C, 53.50 H, 5.71 N, 5.10
5	n-C_4H_9	$C_{13}H_{17}NO_4S$	75.5–76.5	EtOH	32.0	C, 55.11 H, 6.05	C, 54.92 H, 6.06
6	s-C_4H_9	$C_{13}H_{17}NO_4S$	107–108	EtOH	32	C, 55.11 H, 6.05	C, 55.08 H, 5.99

[a] Analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. [b] Melting points were taken on Fisher-Johns melting point apparatus and are uncorrected.

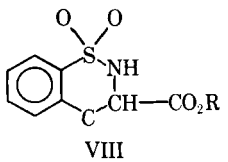
(12). The following mechanism is proposed for the rearrangement of II to yield III. In the presence of excess ammonium hydroxide, the $—SO_2^-NH$ anion acts as a donor component and the α,β-unsaturated ester group acts as an acceptor thus facilitating rearrangement Scheme II.



Scheme II

This rearrangement is significant because of the ease with which substituted 1,2-benzisothiazoline derivatives could be prepared by this method. To the authors' knowledge, there are no known examples cited in the literature involving the Michael reaction where a sulfamoyl ($—SO_2NH_2$) group acts as a donor component.

The possibility of forming a 6-membered heterocyclic compound (VIII) on rearrangement was not ruled out, although the 5-membered heterocyclic compound (III) would be favored from the standpoint of chemical reactivity of the groups concerned.



VIII

Since an α,β-unsaturated ester group is a good electron-acceptor, the 5-membered heterocyclic compound was predicted to form in preference to the 6-membered compound. X-ray crystallographic[3] studies confirmed this prediction and the compounds obtained were in fact the 5-membered heterocyclic (III) compounds (Fig. 4).

[3] The authors thank Dr. Okaya, International Business Machines, New York, for kindly providing the X-ray crystallographic data.

PHARMACOLOGICAL PROPERTIES

The alkyl esters of the 1,2-benzisothiazoline-3-acetic acid 1,1-dioxide (III) were tested for antielectroshock activity, in addition to a primary screening procedure.[4] Results of these tests were discussed in an earlier report (6). In general, the compounds did not possess any appreciable activity.

EXPERIMENTAL

The following is a typical procedure for the synthesis of the 1,2-benzisothiazoline derivatives (III). *ortho*-Sulfocinnamic acid (V) was prepared as its sodium salt, by reacting *ortho*-benzaldehydesulfonic acid, sodium salt (IV), with malonic acid in the presence of pyridine and piperidine by the Knoevenagel

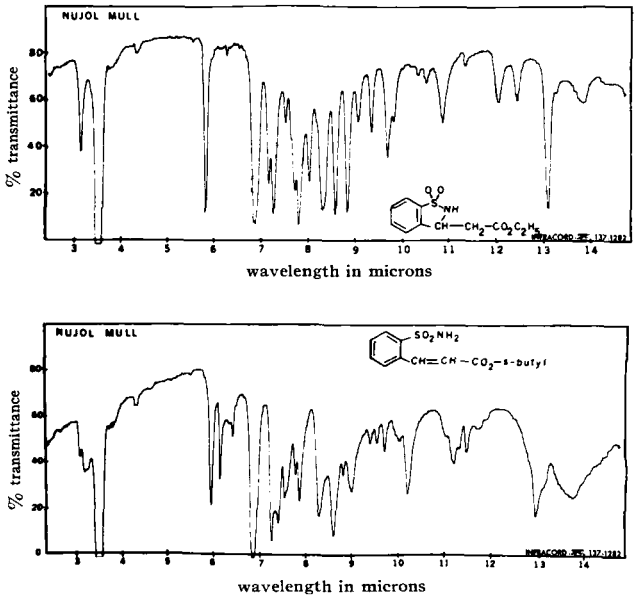


Figure 1—*IR spectra. Key: upper spectrum, Compd. III; lower spectrum, Compd. II.*

[4] The authors thank Riker Laboratories, Northridge, Calif. for screening the compounds for pharmacological activity, and also the Walter Reed Army Medical Center for testing these compounds for antimalarial activity.

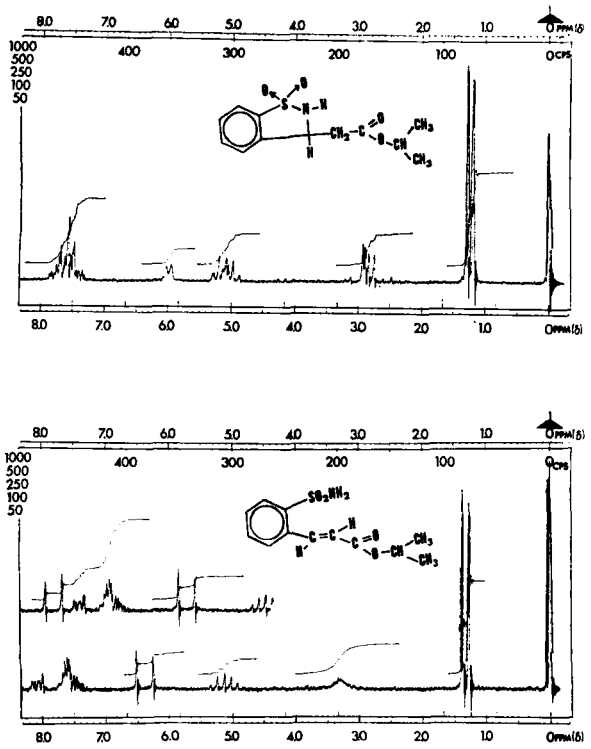


Figure 2—*NMR spectra. Key: upper spectrum, Compd. III; lower spectrum, Compd. II.*

reaction as reported earlier (6, 7). *ortho*-Sulfocinnamic acid (V) (25 g., 0.1 mole) was dispersed in ether (about 100 ml.) in a 250-ml. round-bottom flask, equipped with a reflux condenser and a drying tube containing anydrous calcium chloride. The reaction was carried out in ether to minimize polymerization.

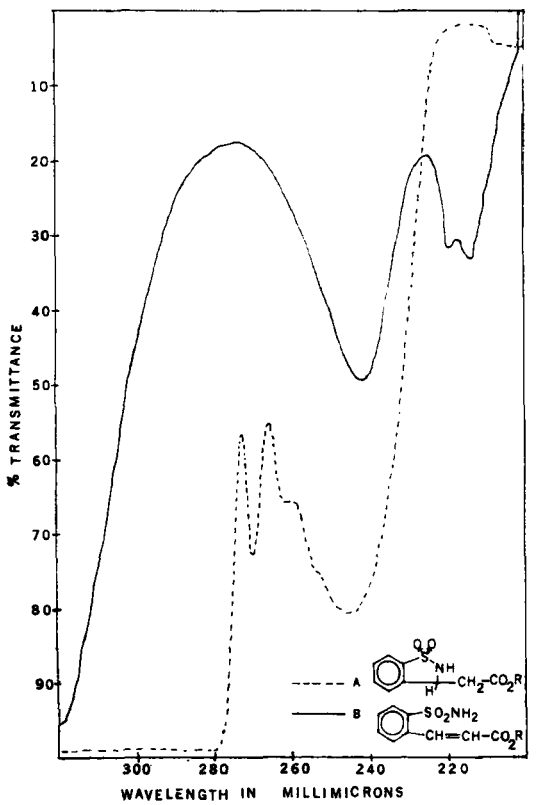


Figure 3—*UV spectra. Key: A, Compd. III; B, Compd. II.*

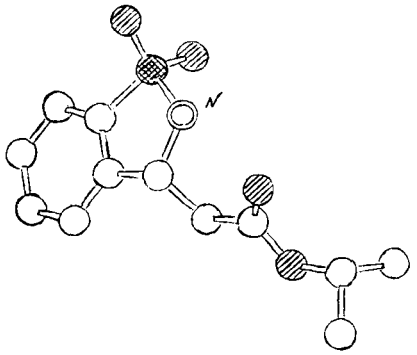


Figure 4—*X-Ray crystallographic sketch of Compd. III.*

About 1 ml. of DMF was added to this suspension and the flask was cooled in an ice bath. Thionyl chloride (30 ml.) was added in small portions at a time. There was a spontaneous reaction and the ether layer slowly turned greenish yellow. The flask was heated gently under reflux for about 24 hr. in a hot-water bath (about 35°). The contents of the flask were mixed frequently. The clear ether layer was decanted and the residue was extracted twice with two portions of ether (2 × 25 ml.). From the combined ether extracts, the excess thionyl chloride and ether were removed under reduced pressure. A deep red residue was obtained. The flask was cooled in ice and the residue was treated slowly with the appropriate alcohol (about 70 ml.). After the initial reaction subsided, the flask was heated gently under reflux for about 30 min. in a hot-water bath maintained at about 50–55°. The excess alcohol was removed under reduced pressure at about the same temperature. A dark viscous residue was obtained. The residue was added in small portions to well-cooled ammonium hydroxide (28% NH_3) solution. The residue reacted vigorously with ammonia. Sufficient ammonia was used to ensure the basicity of the reaction mixture. The reaction mixture was heated on a steam bath for about 5 min. to complete the reaction, and it was allowed to stand overnight. A yellow residue was obtained, which was collected on a filter and washed thoroughly with cold water to remove the accompanying ammonium chloride. The crude substance was recrystallized from the appropriate alcohol. A colorless crystalline substance was obtained (Table I).

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* Present address: College of Pharmacy, South Dakota State University, Brookings, SD 57006