2-position and removing the dihydric phenolic substituent abolishes activity (homoeriodictyol *versus* esculin and esculetin). However, the addition of a methyl group in this position restores part of the activity (homoeriodictyol *versus* 4-methylesculetin).

Antagonism of the spasmogenic activity of bradykinin by flavonoid compounds also appears to involve the phenolic hydroxyl groups in Positions 5 and 7 because methoxylation in Position 7 decreases activity ten times (quercetin *versus* rhamnetin). However, the dihydric phenolic substituent in Position 2 of the γ-benzopyrone nucleus must also contribute to activity because shifting one hydroxy from the 3′- to the 2′-position decreases activity (quercetin *versus* morin). In the coumarin derivatives, the glycoside linkage seems to be necessary for activity (esculin *versus* esculetin and 4-methylesculetin). In general, the aglucones have greater activity than the glycosides (quercetin *versus* quercitrin and rhamnetin *versus* xanthorhamnin).

Antagonism of the spasmogenic activity of eledoisin by the flavonoid compounds again demonstrated the requirement of free phenolic hydroxyls in the 5,7-positions of the γ-benzopyrone nucleus. Methoxylation of the 7-position resulted in a large decrease in activity (quercitrin and morin *versus* rhamnetin). In general, all compounds, except the coumarin derivatives, showed some degree of activity against eledoisin but structure-activity relationships are somewhat obscure.

REFERENCES

(1) A. L. Gascon and E. J. Walaszek, *J. Pharm. Pharmacol.*, **18**, 479(1966).

(2) J. G. Leme and E. J. Walaszek, *Pharmacologist*, **9**, 242(1967).

(3) J. T. Litchfield, Jr. and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99(1949).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 25, 1968, from the *Department of Pharmacology, School of Medicine, University of Hawaii, Honolulu, HI 96816*

Accepted for publication January 9, 1969.

The authors thank Ciba Pharmaceutical Company and Sandoz Pharmaceuticals for the angiotensin, bradykinin, and eledoisin. The esculin, 4-methylesculetin, and esculetin were obtained from National Drug Co. and the balance were extracted from natural products by the junior author.

* East-West Center Grantee.

Sulfones of Potential Medicinal Value I: Diazonium Coupling Products of Ethyl *p*-Toluenesulfonylacetate

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Abstract □ A coupling of various aryldiazonium salt solutions with ethyl *p*-toluenesulfonylacetate has been effected at pH 7.5–8.5. Experimental details and physical properties of the products of this reaction are given. In order to establish whether the coupled product exists as an azo or as the isomeric hydrazo, NMR and IR spectroscopic data were obtained. Both sets of data confirm that the azo form is the proper structural assignment.

Keyphrases □ Ethyl *p*-toluenesulfonylacetate diazonium derivatives—synthesis □ TLC—separation □ IR spectrophotometry—identity, structure □ NMR spectroscopy—identity, structure

The present project was begun in order to determine what spectrum of pharmacological activity one might expect from compounds containing the sulfone group, either as an active or ancillary moiety. The sulfone group, which in some ways resembles the ketone moiety, has received very little consideration in prior pharmacological studies.

DISCUSSION

For preparation of the anhydrous sodium *p*-toluenesulfinate from the commercial hydrous form,[1] the drying procedure recommended by Panizzi and Nicolaus (1) was used. A modification of the procedure of Ashley and Shriner (2) was employed for preparation of ethyl *p*-toluenesulfonylacetate.

Early in the present studies an attempt to couple diazonium salts with α-arylsulfonyl-substituted propionic acids was made. Rather than affording the expected Japp-Klingemann reaction product the process gave only tarry products from which the isolation of pure compounds was not feasible. In an attempt to simplify the product mixture the corresponding ester, *i.e.*, ethyl α-*p*-toluenesulfonylpropionate, was used based on an hypothesis that the decarboxylation which results from Japp-Klingemann condensations could be a major complicating factor in the present example. While considerable qualitative improvement appeared to result, TLC on silica gel revealed the presence of at least eight compounds among the products.

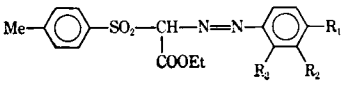
At this point, it became obvious that additional studies were required in order to determine the conditions which were optimum for such coupling reactions and to determine the precise structure and chemical properties of the coupling products. This report is the first in a series which deals with this phase of the overall objective.

An attempt to couple benzenediazonium chloride with ethyl *p*-toluenesulfonylacetate in alcoholic solution at 5–10° according to the procedure of Bülow and Neber (3) gave unsatisfactory results. In this procedure buffers such as sodium acetate are not employed and the initially formed mixture is therefore strongly acidic (about pH 2.0). Cautious addition of 5% potassium hydroxide solution led to formation of a sticky product in poor yield. A crystalline product could not be obtained by this procedure.

In a subsequent trial run, the pH of the diazonium salt solution was adjusted to pH 5.0 before addition and then immediately adjusted to pH 8.0 after addition to the sulfone solution. Im-

[1] Aldrich Chemical Co.

Table I—Ethyl α-Arylazo-α-*p*-Toluenesulfonylacetate



No.	R_1	R_2	R_3	Formula	M.p., °C.[a]	Color[b]	Yield, %	Microanalysis, %[c] Calcd.	Found
1	H	H	H	$C_{17}H_{18}N_2O_4S$	132–134[d]	Y-Or	52.1	C, 58.95 H, 5.23 N, 8.08	C, 58.78 H, 5.21 N, 7.86
2	Br	H	H	$C_{17}H_{17}BrN_2O_4S$	153–154	Br	47.0	C, 48.00 H, 4.03 N, 6.58	C, 48.26 H, 4.11 N, 6.53
3	Cl	H	H	$C_{17}H_{17}ClN_2O_4S$	158–159	Y-Or	37.7	C, 53.64 H, 4.50 N, 7.36	C, 53.51 H, 4.42 N, 7.16
4	CN	H	H	$C_{18}H_{17}N_3O_4S$	202–204	Y	56.7	C, 58.20 H, 4.61 N, 11.31	C, 58.19 H, 4.84 N, 11.18
5	COOEt	H	H	$C_{20}H_{22}N_2O_6S$	148–150	Y-G	30.2	C, 57.40 H, 5.30 N, 6.69	C, 57.62 H, 5.35 N, 6.62
6	F	H	H	$C_{17}H_{17}FN_2O_4S$	173–174	Y-Or	38 0	C, 56.05 H, 4.67 N, 7.69	C, 56.07 H, 4.40 N, 7.38
7	NO_2	H	H	$C_{17}H_{17}N_3O_6S$	161–163	Y-Br	9.4	C, 52.17 H, 4.37 N, 10.73	C, 52.21 H, 4.31 N, 10.52
8	SO_2NH_2	H	H	$C_{17}H_{19}N_3O_6S_2$	174–176	Y	47.0	C, 47.99 H, 4.50 N, 9.87	C, 47.87 H, 4.79 N, 9.58
9	CF_3	H	H	$C_{18}H_{17}F_3N_2O_4S$	132–134	Y	38.7	C, 52.70 H, 4.13 N, 6.76	C, 52.86 H, 4.12 N, 6.76
10	H	Cl	H	$C_{17}H_{17}ClN_2O_4S$	188–189	Y	35.1	C, 53.64 H, 4.50 N, 7.36	C, 53.40 H, 4.59 N, 7.21
11	Cl	H	NO_2	$C_{17}H_{16}ClN_3O_6S$	190–192	Or-Br	31.4	C, 47.94 H, 3.79 N, 9.87	C, 47.99 H, 3.89 N, 9.78
12	OMe	H	NO_2	$C_{18}H_{19}N_3O_7S$	162–164	C-Br	46.0	C, 51.30 H, 4.54 N, 9.96	C, 51.34 H, 4.64 N, 9.92

[a] Melting points were taken in a Thomas-Hoover melting point apparatus and are uncorrected. [b] Color codes: Y = yellow, Br = brown, Or = orange, C-Br = chocolate-brown, G = green. [c] Microanalyses by Galbraith Laboratories, Inc., Knoxville, TN 37921. [d] Literature m.p. = 134° (4).

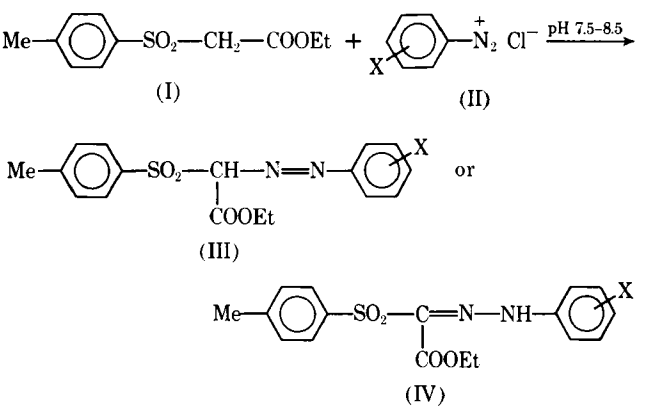
proved yields and higher purity resulted from this latter modification.

Tröger and Berndt (4) found that if sodium hydroxide was added in a manner such that an alkaline pH was maintained throughout the addition of the aryldiazonium chloride solution coupling reactions with arylsulfonylacetates could result. Condensations in the presence of sodium acetate, however, were reported to be unsuccessful. These observations were further supported by the work of Hünig and Boes (5) who found that coupling of diazonium salts with ethyl methanesulfonylacetate occurs only above pH 8.0.

Application of modifications of procedure suggested by the works of Tröger and Berndt (4) and of Hünig and Boes (5) afforded derivatives of various aryldiazonium chlorides and ethyl *p*-toluenesulfonylacetate in from 30 to 90% crude yields. In most cases, TLC revealed only trace contamination of the crude product with by-product. A typical preparative procedure is given in the *Experimental* section. The compounds prepared by this procedure are given in Table I along with pertinent physical data.

The preparative reaction for this series (Scheme I) reveals that the product could have either Structure III (azo) or Structure IV (hydrazo). Although Tröger and Berndt (4) favored Structure III, proof was not offered. Parmerter (6), in a review on diazonium coupling reactions at aliphatic carbon atoms, asserted that while it is difficult to establish with certainty the structures in cases involving tautomers, "it is generally assumed that the hydrazone is the stable form whenever coupling occurs at a methyl or methylene carbon. Wiley and Jarboe (7) have presented ultraviolet and infrared absorption data which corroborate this view."

In the course of these investigations the authors were able to obtain NMR and IR spectroscopic evidence that the azo form (III) appears to be favored and seemingly quite stable in the present series. In Structure III the tautomeric proton is of the methine



Scheme I

type and should be sufficiently removed from the X-substituent's sphere of influence so that no chemical shift should be observed on variations in X. In Structure IV, however, the tautomeric proton resides on an anilinic nitrogen and should exhibit a measurable chemical shift in response to variations in X.

The NMR spectra were obtained on a spectrometer[2] using deuterochloroform as a solvent. In compounds where X = H, F, Cl, Br, and NO_2 (all in *para* position), the position of the tautomeric proton (singlet) was found to be 12.42, 12.44, 12.39, 12.38, and 12.44 p.p.m., respectively. No perceptible exchange was ob-

[2] Varian HA-100.

served on use of deuterium oxide as solvent with or without deuterotrifluoroacetic acid as catatyst. That the position of the absorption band was in an extreme downfield position and unresponsive to either the presence of variations in X or to labile deuterium ions in the media suggests that Structure III is most representative of the correct assignment. These data are not, however, incontrovertible.

The presence of a single strong absorption band between 1650 and 1800 cm.$^{-1}$ was of particular interest since both C=O and C=N produce strong, sharp absorption bands in this range. The single band is consistent, therefore, with Structure III but not with Structure IV. The band assigned to the carboethoxy carbonyl group fell in the 1674 to 1684 cm.$^{-1}$ range for ten of the twelve compounds. The remaining two compounds exhibited strong absorption at 1668 cm.$^{-1}$ for the one and at 1663 cm.$^{-1}$ for the other. The low-frequency position for the ester carbonyl, which ordinarily falls near 1735 cm.$^{-1}$, might be expected in view of the presence of both arylazo and arylsulfonyl substituents on the α-carbon. For example, ethyl diazoacetate in $CHCl_3$ has been reported to absorb at 1695 cm.$^{-1}$ (8) while ethyl α-chloro-α-nitroacetate exhibited absorption at 1672 cm.$^{-1}$ in KBr (9).

EXPERIMENTAL

Ethyl p-Toluenesulfonylacetate (I)—The procedure used by Ashley and Shriner (2) for the preparation of ethyl phenylsulfonylacetate in 51.8% yield was modified by use of the appropriate anhydrous sulfinate (1), ethyl bromoacetate, in place of the corresponding chloroacetate, and the continuation of reflux for 24 hr. in place of 10 hr. called for in the original procedure. There was obtained an 83.4% yield, based on unrecovered ethyl bromoacetate, of a colorless solid (b.p. 150–152°/0.25 mm., m.p. 30–32°).

Anal.—Calcd. for $C_{11}H_{14}O_4S$: C, 54.51; H, 5.82. Found: C, 54.63, H, 6.01. The IR spectrum was consistent with the proposed identity.

Ethyl p-Toluenesulfonyl-p-bromophenylazoacetate (III, X = Br)—A clear solution of *p*-bromophenyldiazonium chloride was prepared at 0° (ice-salt bath) by the slow addition of a solution of 2.07 g. (0.03 mole) of sodium nitrite in 10 ml. of water to a well-stirred solution of 5.16 g. (0.03 mole) of bromoaniline in 20 ml. of 5 *N* hydrochloric acid. The cold solution of *p*-bromophenyldiazonium chloride was then added portionwise to a solution composed of 7.26 g. (0.03 mole) of ethyl *p*-toluenesulfonylacetate and 95% alcohol. The solution was continuously stirred and maintained at 0–5° throughout the reaction by means of an ice-bath. After each portion of diazonium salt solution was added to the sulfone solution a similar portion of cold, aqueous 1 *N* potassium hydroxide was added in order to maintain pH at 7.0–8.5. In general, the higher pH value proved to be more suitable for condensation. After addition of the final portions of diazonium salt and base, the ice-cold solution was placed in the ice chest for 3 hr. after which time 8.8 g. (69%) of crude, brown-colored solid was obtained by filtration and air-drying. Recrystallization from 95% ethanol gave yellow flakes melting at 152–153° in 47% yield. Additional data for this and other compounds in the series are contained in Table I.

REFERENCES

(1) L. Panizzi and R. A. Nicolaus, *Gazz. Chim. Ital.*, **80,** 431 (1950); through *Chem. Abstr.*, **45,** 3812(1951).

(2) W. C. Ashley and R. L. Shriner, *J. Am. Chem. Soc.*, **54,** 4410 (1932).

(3) C. Bülow and P. Neber, *Ber.*, **45,** 3732(1912).

(4) J. Tröger and A. Berndt, *J. Prakt. Chem.*, **102,** 1(1921).

(5) S. Hünig and O. Boes, *Ann.*, **579,** 28(1953).

(6) S. M. Parmerter, in "Organic Reations," vol. 10, R. Adams, Ed., Wiley, New York, N. Y., **1959,** p. 1.

(7) R. H. Wiley and C. H. Jarboe, Jr., *J. Am. Chem. Soc.*, **77,** 403(1955).

(8) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *ibid.*, **79,** 5756(1957).

(9) H. Hellmann, G. Hallmann, and F. Lingens, *Chem. Ber.*, **86,** 1346(1953).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 21, 1968, from the *Department of Medicinal Chemistry, School of Pharmacy, The University of Georgia, Athens, GA 30601*

Accepted for publication January 10, 1969.

Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.

The generous financial support by the General Research Office is gratefully acknowledged.

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