β-diethylaminoethyl chloride (0.22 mole) (prepared from the hydrochloride by basification with aqueous sodium hydroxide) was added with stirring, the mixture was refluxed for 5 min. and, after cooling, basified with aqueous sodium hydroxide. The reaction product was extracted in methylene chloride, the solution dried over sodium sulfate, the solvent distilled and the residue vacuum-fractionated. The hydrochlorides were prepared with hydrogen chloride in ether solution, and recrystallized from benzene or cyclohexane. The ethers and their hydrochlorides are listed in Table II. Most of the ethers were non-crystalline viscous oils; those which were solid were recrystallized from heptane.

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Phenyl-bridged Analogs of Phenylbutazone

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The side-reactions of phenylbutazone[1] which limit its useful anti-inflammatory activity spurred a search for less toxic analogs. The suggestion by Bavin and co-workers[2] that the toxicity is associated with the hydrazobenzene portion of the molecule seemed logical. Since the character of hydrazobenzene might be sharply affected by bridging the *ortho* positions of the phenyl rings, we prepared a few such analogs as shown in Table I.

At the start of this work the closest analogs to this series were two benzo[c]cinnoline derivatives (I, X = −, R = H, Bu) reported by Kühn and Erlenmeyer.[3] Quite recently several sulfone-bridged analogs (I, X = SO_2) have been reported by Michel and Matter[4] at Haco, A. G., and two Belgian patents[5] indicate that workers at Geigy have also explored the series reported here.

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd Ed., The Macmillan Co., New York, N. Y., 1955, p. 322.

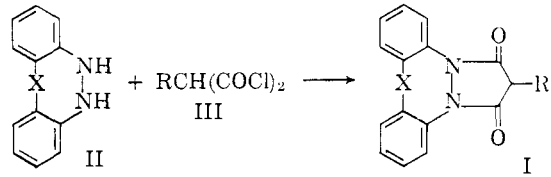
(2) E. M. Bavin, D. J. Drain, D. E. Seymour, and P. D. Waterhouse, *J. Pharm. Pharmacol.*, **7**, 1022 (1955).

(3) H. Kühn and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 531 (1955).

(4) K. Michel and M. Matter, *ibid.*, **44**, 2204 (1961).

(5) J. R. Geigy, S. A., Belgian Patents 605,985, and 607,062.

TABLE I



II I

			Analyses %					
			Calcd.			Found		
I: X	R	M.p., °C.[a]	C	H	N	C	H	N
CH_2CH_2	n-C_4H_9	122–125	75.42	6.63	8.38	75.54	6.68	8.40
CH_2CH_2	$CH_2C_6H_5$	238–241M	78.24	5.47	7.61	77.86	5.75	7.79
CH_2CH_2	C_6H_5	185–190B	77.94	5.12	7.91	77.52	5.06	7.82
CH_2CH_2	C_2H_5	160–164	74.49	5.92	9.15	74.35	5.72	8.90
S	n-C_4H_9	199–200	67.43	5.36	8.28	67.06	5.45	8.22
S	s-Bu	152–153.5	67.43	5.36	8.28	67.27	5.42	8.03
S	C_2H_5	141–142	65.78	4.55	9.03	65.37	4.91	8.86
S	CH_3	238–240	64.84	4.08	9.46	64.82	4.08	9.46
S	$CH_2CH_2C_6H_5$	207–208.5M	71.48	4.69	7.25	71.07	4.65	7.39
S	n-C_5H_{11}	188–190	68.15	5.72	7.95	68.28	5.46	8.47
O	n-C_4H_9	129–130	70.79	5.63	8.69	70.56	5.74	8.73
CH_2	n-C_4H_9	176–177	74.97	6.29	8.74	74.91	6.48	8.42
NCH_3	n-C_4H_9	165–168	71.62	6.31	12.53	71.57	6.33	12.56

[a] Recrystallized from ether except for M = methanol, B = benzene.

The hydrazo intermediates II, X = CH_2CH_2 or S, were prepared by reduction of the corresponding bis(2-nitrophenyl) derivative with zinc dust and barium hydroxide[5] followed by reduction of any azo group remaining, with hydrazine and platinum oxide in ether.[7] The other hydrazo compounds were prepared by the methods of Allinger and Youngdale[7] (including purification by chromatography) except that Duval's conditions[6] were used to prepare the azo intermediates instead of lithium aluminum hydride. Preparation of the required malonyl chlorides, III, and reaction with the hydrazo intermediates followed the conditions of Budziarek and co-workers.[8]

Anti-inflammatory activity[9] was not as great as that of phenylbutazone for the series in Table I, and the most active anti-inflamma-

(6) M. H. Duval, *Bull. soc. chim. France*, [4] **7**, 727 (1910).

(7) N. L. Allinger and G. A. Youngdale, *J. Am. Chem. Soc.*, **84**, 1020 (1962).

(8) R. Budziarek, D. J. Drain, F. J. Macrae, J. McLean, G. T. Newbold, D. E. Seymour, F. S. Spring, and M. Stansfield, *J. Chem. Soc.*, 3158 (1955).

(9) We are indebted to Dr. F. J. Saunders and his staff of the Endocrine Section for these data obtained on yeast-induced, foot edema in the rat.

(10) We are indebted to Dr. W. G. Hambourger of the Biological Research Department for these data. The method is that of L. C. Miller and N. L. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 261 (1944).

tory derivative, I, X = S, R = Bu, was about six times as toxic (intraperitoneally in mice; acute) as phenylbutazone.[10]

Experimental[11]

The preparation of I, X = S, R = Bu, is typical: To a stirred solution of 4.8 ml. of pyridine in 200 ml. of methylene chloride cooled to about −70° in a Dry Ice–acetone bath was added 5.3 g. of butylmalonyl dichloride followed by portionwise addition of a solution of 5.4 g. of II, X = S, in 100 ml. of methylene chloride, while maintaining the temperature below −50°. The solution was allowed to warm slowly to room temperature and to stand for 3 days. It was washed well with dil. hydrochloric acid, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in dilute potassium carbonate, washed once with ether, stirred with activated charcoal, filtered, and acidified to pH 4 with dil. hydrochloric acid. The oil was extracted in 4 l. of ether which was dried and condensed to 300 ml. After cooling to 0°, the white needles were filtered off and dried; yield, 4.0 g. (47%), m.p. 198–200°. Recrystallization of an analytical sample from ether raised the m.p. to 199–200°; the analysis is given in Table I.

(11) All melting points are corrected. Microanalysis were performed by the Microanalytical Department under Dr. R. T. Dillon, or by Microtech Laboratories, Skokie, Ill.

Methanesulfonates of Tertiary and Quaternary Amino Alcohols[1]

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Myers and Kemp[2] showed that methanesulfonyl fluoride is a reasonably potent inhibitor of cholinesterase. They suggested that its mechanism of inhibition and also that of dimethylcarbamyl fluoride might be similar to the action of dialkyl phosphorofluoridates which were known to produce phosphorylated enzyme derivatives. It has been shown recently[3] that dimethylcarbamyl fluoride and other carbamates do produce carbamyl enzyme derivatives with acetylcholinesterase. It was of interest therefore to synthesize a group of methanesulfonates in which the fluorine atom is replaced by groupings

(1) This work was supported by the Division of Research Grants and Fellowships of the National Institutes of Health, Grant No. B-573 C13.

(2) D. K. Myers and A. Kemp, *Nature*, **173**, 33 (1954).

(3) I. B. Wilson, M. A. Hatch, and S. Ginsburg, *J. Biol. Chem.*, **235**, 2312 (1960); I. B. Wilson, M. A. Harrison, and S. Ginsburg, *ibid.*, **236**, 1498 (1961).