no effect on sodium excretion in adrenalectomized male rats. These effects are indicative of a sodium retainer.

(11) Melting points were taken in open capillary tubes and are uncorrected.

Synthesis of Sydnones and Sydnone Imines[1]

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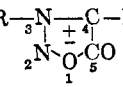
The interesting meso-ionic character[3] and the biological activity[4] exhibited by sydnones (I) have, in recent years, inspired the investigation of this type of compound by many workers. Daeniker and



I

Druey[5] reported that some polymethylene-bis-sydnones and polymethylene-bis-hydrazines showed slight tumor inhibitory activity *in vivo*. These facts, together with the information that 3-phenylsydnone (I, R = C_6H_5, R′ = H) possesses antitumor properties,[6] directed our attention to the preparation and evaluation of some 3-benzylsydnones, 3-alkylsydnones and sydnone imines for the general program of cancer chemotherapeutic studies.

The 3-substituted sydnones (IV, see Table III) have been prepared by the nitrosation of the appropriate N-substituted glycine (II, see Table I) and treatment of the N-nitroso derivative (III, see Table II) with acetic anhydride, by the procedure of Fugger, Tien, and Hunsberger.[3b] The sydnone imines (IX, see Table IV) were obtained as follows: condensation of glycolonitrile (VI) with the appropriate amine (V) yielded the corresponding N-substituted glycine nitrile

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) To whom all inquiries should be sent.

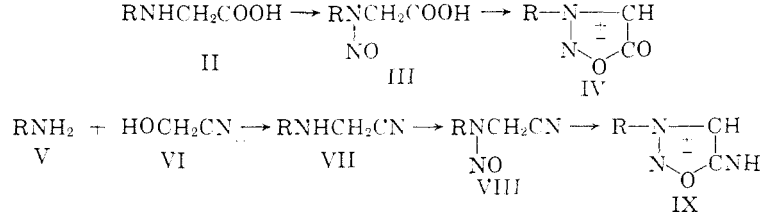
(3) For a general review of sydnones and related compounds see, for example, (a) W. Baker and W. D. Ollis, *Quart. Revs.*, **11**, 15 (1957); (b) J. Fugger, J. M. Tien, and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 1843 (1955); (c) J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955); **83**, 178 (1961); (d) A. R. Katritzky, *Chem. Ind.*, 521 (1955); (e) A. Lawson and D. H. Miles, *J. Chem. Soc.*, 2865 (1959); (f) J. Ogilvie, V. K. Miyamoto, and T. C. Bruice, *J. Am. Chem. Soc.*, **83**, 2493 (1961).

(4) (a) P. Brooks and J. Walker, *J. Chem. Soc.*, 4409 (1957); (b) R. W. Putter and G. Wolfrum, German Patent 1,057,124 (Oct. 22, 1959), German Patent 1,069,633 (Nov. 26, 1959), Brit. Patent 823,001 (Nov. 4, 1959); (c) W. H. Edgerton, U. S. Patent 2,916,495 (Dec. 8, 1959).

(5) H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **40**, 918 (1957).

(6) Dr. Ronald B. Ross, National Cancer Institute, private communication. 3-Phenylsydnone had been submitted by Dr. D. J. Brown of the Australian National University.

(VII). The latter was then nitrosated *in situ* and cyclized in methanolic hydrogen chloride to give the desired sydnone imine (IX).



Preliminary biological evaluations of this type of compound have shown that 3-(*p*-methoxybenzyl)-sydnone (IV, R = *p*-$CH_3OC_6H_4CH_2$) possesses confirmed activity in carcinoma 755 in mice. This compound is inactive in sarcoma-180 and leukemia-1210 systems.[7]

Experimental[8]

A. General Preparation of N-Alkyl and N-(Substituted-benzyl)-glycine Hydrochloride (II, see Table I).—The procedure described by Fugger, Tien, and Hunsberger[9b] was satisfactorily adopted for this preparation. Ethyl bromoacetate (1 mole) was added cautiously to a solution of 2 moles of the appropriate alkylamine or substituted benzylamine in 500 ml. of dry benzene. The mixture was then refluxed for 2–5 hr. and cooled. The amine hydrobromide was filtered and washed with a small amount of benzene. After removing benzene from the combined filtrate, the residual ethyl ester of N-substituted glycine was slowly added to a boiling solution of 200 ml. of water containing 40 g. of sodium hydroxide. After refluxing for 45 min. the alkaline solution was cooled and extracted with 4 × 100 ml. of ether and the extract discarded. The aqueous portion was acidified (ice bath) with concd. hydrochloric acid to *p*H 2. The acidic reaction mixture was evaporated to dryness and the residue treated with hot concd. hydrochloric acid. The insoluble inorganic salt was filtered while hot and the filtrate was cooled to yield the desired N-substituted glycine hydrochloride.

B. General Preparation of N-Nitroso-N-(substituted)-glycine (III, see Table II). To a suspension of 0.4 mole of N-substituted glycine hydrochloride in 200 ml. of water at 0° was added concd. sodium hydroxide solution until a clear solution resulted. To this solution was added 32 g. (0.46 mole) of sodium nitrite in 50 ml. of water. The *p*H of the resulting solution was adjusted carefully to 2 with slow addition of concd. hydrochloric acid (during which the temperature of the rapidly stirred mixture was maintained at 0–2°; this required about 1 hr.) The resulting oily mixture was chilled overnight, whereupon the oil solidified. The crude nitrosoglycine was filtered and washed with water.

C. General Preparation of 3-Substituted Sydnones (IV, see Table III).—3-Substituted sydnones were cyclized from the corresponding N-nitroso-N-(substituted) glycine with acetic anhydride, according to the procedure of Fugger,

(7) Testing work was carried out by Dr. Carl Cohen and his associates at the Battelle Memorial Institute, Columbus, Ohio, and also by other Contract Screeners of CCNSC.

(8) All melting points were taken on a Thomas–Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2.

TABLE I

$RNHCH_2COOH \cdot HCl$

R	Recryst. solvents[a]	M.p. °C.	Yield %	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_3H_7	A	195–196	32	$C_5H_{12}ClNO_2 \cdot {}^1/_2H_2O$	36.3	7.12	8.67	36.1	7.40	8.62
iso-C_3H_7	A	199–201	43	$C_5H_{12}ClNO_2$	39.1	7.86	9.14	39.5	7.42	9.30
iso-C_4H_9	A	208–210	26	$C_6H_{14}ClNO_2 \cdot H_2O$	38.8	7.55	7.55	38.6	7.80	7.65
sec-C_4H_9	A	173–174	59	$C_6H_{14}ClNO_2$	43.0	8.42	8.35	42.9	8.45	8.60
tert-C_4H_9	A	210–213	23	$C_6H_{14}ClNO_2$	43.0	8.42	8.35	42.8	8.18	8.40
n-C_5H_{11}	A	210–213	27	$C_7H_{16}ClNO_2 \cdot H_2O$	42.3	8.05	7.04	42.6	7.98	7.07
p-$CH_3C_6H_4CH_2$	B	219–220	75	$C_{10}H_{14}ClNO_2$	55.7	6.55	6.50	55.9	6.37	6.24
3,4-$(CH_3)_2C_6H_3CH_2$	C	214–215	100	$C_{11}H_{16}ClNO_2$	57.5	7.04	6.15	57.2	7.03	5.95
p-$ClC_6H_4CH_2$	B	215–217	98	$C_9H_{11}Cl_2NO_2$	45.8	4.66	5.93	46.1	4.45	5.68
o-$ClC_6H_4CH_2$	C	208–210	83	$C_9H_{11}Cl_2NO_2$	45.8	4.66	5.93	45.6	4.91	6.05
2,4-$Cl_2C_6H_3CH_2$	C	191–193	93	$C_9H_{10}Cl_3NO_2$	40.0	3.72	5.17	40.0	3.72	4.95
p-$CH_3OC_6H_4CH_2$	C	218–219	69	$C_{10}H_{14}ClNO_3$	51.9	6.10	6.08	52.0	5.73	6.14

[a] (A) Glacial acetic acid, (B) water, (C) hydrochloric acid–water (1:1).

TABLE II

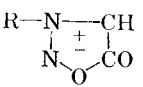
$RN(NO)CH_2COOH$

R	Recryst. Solvents[a]	M.p., °C.	Yield, %	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n-C_3H_7	A	65–66	52	$C_5H_{10}N_2O_3$	41.0	6.85	19.2	41.2	7.05	19.2
iso-C_3H_7	B	76–78	73	$C_5H_{10}N_2O_3$	41.0	6.85	19.2	41.2	7.10	19.5
iso-C_4H_9	B	54–56	50	$C_6H_{12}N_2O_3$	45.0	7.54	17.5	44.7	7.37	17.2
sec-C_4H_9	A	71–73	68	$C_6H_{12}N_2O_3$	45.0	7.54	17.5	45.2	7.85	17.9
tert-C_4H_9	B	104–105	58	$C_6H_{12}N_2O_3$	45.0	7.54	17.5	45.0	7.50	17.7
n-C_5H_{11}	A	55–56	53	$C_7H_{14}N_2O_3$	48.3	8.09	16.1	48.1	7.86	16.3

p-$CH_3C_6H_4CH_2$	C	100–101	72	$C_{10}H_{12}N_2O_3$	57.6	5.79	13.4	57.4	5.49	13.4
3,4-$(CH_3)_2C_6H_3CH_2$	D	oil	69	...	..	..	..	..	..	..
p-$ClC_6H_4CH_2$	C	121–122	74	$C_9H_9ClN_2O_3$	47.3	3.97	12.2	47.5	4.05	11.9
o-$ClC_6H_4CH_2$	B	44–46	71	$C_9H_9ClN_2O_3$	47.3	3.97	12.2	46.9	4.10	11.8
2,4-$Cl_2C_6H_3CH_2$	B	38–41	49	$C_9H_8Cl_2N_2O_3$	41.2	3.34	10.6	41.0	3.12	10.2
p-$CH_3OC_6H_4CH_2$	C	103–105	88	$C_{10}H_{12}N_2O_4$	53.6	53.9	12.5	53.8	5.35	12.5

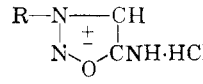
[a] (A) Ether and hexane, (B) precipitated product washed with water, unrecrystallized, (C) ethanol and water, (D) oil failed to crystallize, used without further purification.

TABLE III



	B.P.		Yield,	Ultraviolet absorption (ethanol)			Analyses, %					
							Calcd.			Found		
R	°C.	mm.	%	λ_{max} (mμ)	ϵ	Molecular formula	C	H	N	C	H	N
CH_3	130–132	0.46	49	289	5,500	$C_3H_4N_2O_2$	36.0	4.03	28.0	36.3	4.20	27.8
n-C_3H_7	112	0.10	74	289	6,800	$C_5H_8N_2O_2$	46.8	6.25	21.9	47.1	6.20	22.2
iso-C_3H_7	125	0.33	75	290	7,700	$C_5H_8N_2O_2$	46.8	6.25	21.9	46.6	6.25	22.0
sec-C_4H_9	129–130	0.30	94	289	7,700	$C_6H_{10}N_2O_3$	50.8	7.50	19.7	50.7	7.24	20.0
n-C_5H_{11}	151	0.49	68	288	6,600	$C_7H_{12}N_2O_2$	53.9	7.72	17.9	53.6	7.90	18.1
p-$CH_3C_6H_4CH_2$	M.p. 87–88		69	292	6,650	$C_{10}H_{10}N_2O_2$	63.1	5.29	14.7	63.0	5.40	14.8
3,4-$(CH_3)_2C_6H_3CH_2$	M.p. 72–73		33	293	6,350	$C_{11}H_{12}N_2O_2$	64.6	5.91	13.7	64.7	5.90	13.8
p-$ClC_6H_4CH_2$	M.p. 98–99		55	293	6,950	$C_9H_7ClN_2O_2$	51.4	3.25	13.3	51.3	3.02	13.6
o-$ClC_6H_4CH_2$	M.p. 58–59		41	293	6,300	$C_9H_7ClN_2O_2$	51.4	3.25	13.3	51.1	3.40	13.5
2,4-$Cl_2C_6H_3CH_2$	M.p. 113–114		56	294	6,600	$C_9H_6Cl_2N_2O_2$	44.2	2.47	11.5	43.9	2.66	11.6
p-$CH_3OC_6H_4CH_2$	M.p. 54–55		59	225	10,900	$C_{10}H_{10}N_2O_3$	58.2	4.85	13.6	58.0	4.74	13.3
				290	6,400							

TABLE IV



R	M.p., °C.	Yield, %	Ultraviolet absorption (ethanol) λ_{max} (mμ)	ϵ
CH_3	158 d.	15	293	6,800
C_2H_5	142–143 d.	24	292	6,150
n-C_3H_7	138–139 d.	90	293	6,500
iso-C_3H_7	146–147 d.	43	292	8,350
n-C_4H_9	148 d.	49	293	8,900

	Analyses, %					
	Calcd.			Found		
R	C	H	N	C	H	N
CH_3	26.6	4.46	31.0	26.5	4.30	30.7
C_2H_5	32.0	5.39	28.2	31.8	5.60	27.7
n-C_3H_7	36.8	6.12	25.7	36.6	6.10	26.0
iso-C_3H_7	36.8	6.12	25.7	36.7	6.25	25.8
n-C_4H_9	40.8	6.80	23.7	41.1	6.90	23.6

Tien, and Hunsberger.[3b] The alkyl-substituted sydnones were purified by vacuum distillation and the benzyl-substituted sydnones by recrystallizing from ethanol–water.

D. General Preparation of 3-Substituted Sydnone Imines (IX, see Table IV).—To 2 moles of substituted amine was added cautiously 163 g. (2 moles) of 70% glyconitrile with stirring and cooling. To the cooled solution 400 ml. of 6 *N* hydrochloric acid was added, the temperature being maintained at <20° throughout the addition. The mixture was then cooled to 0° and 138 g. (2 moles) of sodium nitrite, dissolved in a minimum amount of water, was added. After 15 hr. of refrigeration and stirring, the light green solution was extracted with 3 × 200 ml. of ether. The ether extracts were dried over sodium sulfate, filtered and evaporated *in vacuo* to a light green oil. This was added, with cooling and stirring, to 150 ml. of methanol saturated with dry hydrogen chloride. After storing the reaction mixture at room temperature for 15 hr., the excess methanol and hydrogen chloride was removed *in vacuo* to give a light green oil, which was diluted with anhydrous ether to precipitate the sydnone imine as a white crystalline powder, which was purified by recrystallization from a mixture of benzene and acetone.

Acknowledgment.—The authors wish to express their appreciation to Dr. Roland K. Robins for his encouragement and to Miss Phyllis G. Shaul and Mrs. Carol R. Tuttle for their valuable assistance in performing analytical and instrumental measurements.