Some *N*-Arylsulfonyl-*N'*-alkylureas

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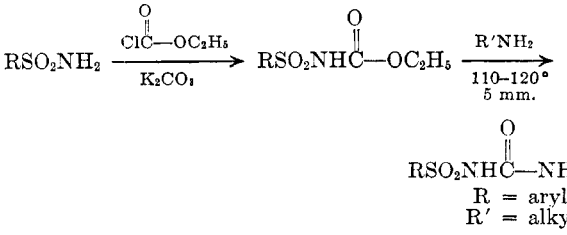
The clinical application of *N*-(*p*-aminophenylsulfonyl)-*N'*-*n*-butylurea (BZ 55, Carbutamide) as an effective oral agent for lowering blood sugar has been reported.[1] Insulin has been used very successfully for this purpose since its introduction thirty-five years ago but has the disadvantage that it must be given by injection. Although BZ 55 is effective only in selected cases of diabetes, it did seem to offer a partial answer to the problem of overcoming this disadvantage. The present study was undertaken to prepare additional compounds having hypoglycemic activity.

A number of derivatives (Table II) have been prepared according to the following reaction scheme.



The optimum temperature for the reaction between the amines and the sulfonylcarbamates (Table I) was found to be 110–120°. At higher temperatures (up to 150°) the reaction tended to produce varying amounts of the original sulfonamides.

Efforts to prepare a *p*-allyloxyphenyl derivative were unsuccessful because attempted chlorosulfonation of allyl phenyl ether did not yield the desired sulfonyl chloride.

Extensive comparative pharmacology has been carried out on several of the sulfonylureas and the detailed results of these studies will be reported elsewhere.

The most effective compound, when tested orally in dogs, was *N*-(*p*-chlorophenylsulfonyl)-*N'*-*n*-propylurea. The hypoglycemic effect of this compound is slightly more than twice that of BZ 55 tested under the same conditions. On the basis of these results, a number of derivatives were prepared in which the position or nature of the halogen was varied. Also, several dichloro and methyl chloro compounds were synthesized. None of these were as active as the original *p*-chlorophenyl derivative.

TABLE I

N-ARYLSULFONYLCARBAMATES

$RSO_2NHC(=O)—OC_2H_5$

R	Yield, %	M.P., °C.	Recryst. Solvent[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	84	108–110		$C_9H_{11}NO_4S$	[b]			
2-$CH_3C_6H_4$	57	121–123	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_4S$	49.35	5.38	49.44	5.34
3-$CH_3C_6H_4$	70	66–68	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_4S$	49.35	5.38	49.32	5.42
4-$(CH_3)_2CHC_6H_4$	75	[c]						
4-$CH_3OC_6H_4$	71	118–120	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_5S$	46.32	5.06	46.60	5.35
4-$C_2H_5OC_6H_4$	90	98–100	EtOAc–pet. ether	$C_{11}H_{15}NO_5S$	48.34	5.54	48.30	5.53
4-(*n*-C_4H_9O)C_6H_4	72	69–71	EtOAc–pet. ether	$C_{13}H_{19}NO_5S$	51.82	6.36	51.94	6.47
2,4-$(CH_3O)_2C_6H_3$	82	155–157	C_6H_6–pet. ether	$C_{11}H_{15}NO_6S$	45.68	5.23	45.87	5.41
2-CH_3-4-$CH_3OC_6H_3$	45	128–130	Dil. ethanol	$C_{11}H_{15}NO_5S$	48.34	5.54	48.56	5.58
4-$CH_3SC_6H_4$	65	139–141	$CHCl_3$–pet. ether	$C_{10}H_{13}NO_4S_2$	43.65	4.76	43.83	4.94
4-BrC_6H_4	69[d]	88–90	EtOAc–pet. ether	$C_9H_{10}BrNO_4S$	35.04	3.27	35.31	3.53
2-ClC_6H_4	90	151–153	Dil. ethanol	$C_9H_{10}ClNO_4S$	41.00	3.86	41.32	3.84
4-ClC_6H_4	80	92–93	$CHCl_3$–pet. ether	$C_9H_{10}ClNO_4S$	41.00	3.86	41.56	3.87
					N, 5.32		N, 5.34	
2,4-$Cl_2C_6H_3$	40	136–137	C_6H_6–pet. ether	$C_9H_9Cl_2NO_4S$	36.24	3.04	36.45	3.30
3,4-$Cl_2C_6H_3$	67	115–117	Dil. ethanol	$C_9H_9Cl_2NO_4S$	36.24	3.04	36.51	3.32
2,5-$Cl_2C_6H_3$	74	151–153	Dil. ethanol	$C_9H_9Cl_2NO_4S$	36.24	3.04	36.47	3.39
3-Cl-4-$CH_3C_6H_3$	84	78–80	EtOAc–pet. ether	$C_{10}H_{12}ClNO_4S$	43.25	4.36	42.83	4.66
4-Cl-3-$CH_3C_6H_3$	84	87–89	EtOAc–pet. ether	$C_{10}H_{12}ClNO_4S$	43.25	4.36	42.93	4.23
					N, 5.05		N, 5.10	
4-FC_6H_4	88	91–93	EtOAc–pet. ether	$C_9H_{10}FNO_4S$	43.72	4.04	44.11	4.18

[a] The petroleum ether used was the fraction boiling at 60–71°. [b] O. C. Billeter, *Ber.*, **37**, 690 (1904). [c] Viscous oil did not crystallize and was used as such. [d] Yield based on sulfonamide actually consumed.

(1) J. D. Achelis and K. Hardebeck, *Deutsche med. Wochschr.*, **80**, 1455 (1955); F. Bertram, E. Bendfeldt, and H. Otto, *Deutsche med. Wochschr.*, **80**, 1452 (1955); H. Franke and J. Fuchs, *Deutsche med. Wochschr.*, **80**, 1449 (1955).

TABLE II

ARYLSULFONYLUREAS

$$RSO_2NH—\overset{\overset{O}{\|}}{C}—NHR'$$

R	R′	Yield, %	M.P., °C.	Recryst. Solvent[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	n-C_3H_7	27	118–120	Dil. ethanol	$C_{10}H_{14}N_2O_3S$	49.58	5.82	49.83	5.83
C_6H_5	n-C_4H_9	62	130–132	Dil. ethanol	$C_{11}H_{16}N_2O_3S$	51.54	6.29	51.45	6.45
C_6H_5	*iso*-C_5H_{11}	63	120–122	Dil. ethanol	$C_{12}H_{18}N_2O_3S$	53.30	6.72	53.55	6.84
C_6H_5	C_6H_{11}[b]	33	185–186	Dil. ethanol	$C_{13}H_{18}N_2O_3S$	55.29	6.43	55.53	6.31
C_6H_5	3-$CH_3O(CH_2)_3$	55	110–112	Dil. ethanol	$C_{11}H_{16}N_2O_4S$	48.54	5.93	48.74	5.96
C_6H_5	3-$CH_3S(CH_2)_3$[c]	71	130–131	Dil. ethanol	$C_{11}H_{16}N_2O_3S_2$	45.81	5.59	46.07	5.24
2-$CH_3C_6H_4$	n-C_4H_9	52	159–161	Ethanol–pet. ether	$C_{12}H_{18}N_2O_3S$	53.30	6.72	53.68	6.47
3-$CH_3C_6H_4$	n-C_3H_7	18	108–110	Dil. ethanol	$C_{11}H_{16}N_2O_3S$	51.54	6.29	51.22	6.07
3-$CH_3C_6H_4$	n-C_4H_9	22	106–108	C_6H_6–pet. ether	$C_{12}H_{18}N_2O_3S$	53.30	6.72	53.68	6.90
4-$(CH_3)_2CHC_6H_4$	n-C_4H_9	62	130–132	C_6H_6–pet. ether	$C_{14}H_{22}N_2O_3S$	56.36	7.43	56.30	7.50
4-$CH_3OC_6H_4$	n-C_3H_7	22	120–122	Dil. ethanol	$C_{11}H_{16}N_2O_4S$	48.54	5.93	48.63	6.04
4-$CH_3OC_6H_4$	n-C_4H_9[d]	46	118.5–120	Dil. ethanol	$C_{12}H_{18}N_2O_4S$	50.30	6.34	50.68	6.38
4-$CH_3OC_6H_4$	*iso*-C_5H_{11}	38	125–127	Dil. ethanol	$C_{13}H_{20}N_2O_4S$	51.96	6.72	52.08	6.81
4-$CH_3OC_6H_4$	3-$CH_3O(CH_2)_3$	63	115–117	Dioxane–pet. ether	$C_{12}H_{18}N_2O_5S$	47.68	6.00	47.04	6.20
4-$C_2H_5OC_6H_4$	n-C_3H_7	53	177–178	Ethanol	$C_{12}H_{18}N_2O_4S$	50.30	6.34	50.08	6.50
4-$C_2H_5OC_6H_4$	n-C_4H_9	33	158–160	Dil. ethanol	$C_{13}H_{20}N_2O_4S$	51.96	6.72	52.09	6.91
4-(n-C_4H_9O)C_6H_4	n-C_3H_7	55	125–126	C_6H_6–pet. ether	$C_{14}H_{22}N_2O_4S$	53.48	7.05	53.76	7.09
2,4-$(CH_3O)_2C_6H_3$	n-C_3H_7	31	199–200	Dil. dioxane	$C_{12}H_{18}N_2O_5S$	47.68	6.00	47.95	6.00
2,4-$(CH_3O)_2C_6H_3$	n-C_4H_9	40	184–185	Dil. dioxane	$C_{13}H_{20}N_2O_5S$	49.33	6.37	49.57	6.35
2,4-$(CH_3O)_2C_6H_3$	*iso*-C_5H_{11}	25	172–174	Dil. dioxane	$C_{14}H_{22}N_2O_5S$	50.84	6.72	51.05	6.76
2,4-$(CH_3O)_2C_6H_3$	3-$CH_3O(CH_2)_3$	33	147–149	Dil. ethanol	$C_{13}H_{20}N_2O_6S$	46.96	6.06	47.12	5.75
2-CH_3-4-$CH_3OC_6H_3$	n-C_4H_9	45	163–165	Dil. ethanol	$C_{13}H_{20}N_2O_4S$	51.96	6.72	52.15	6.87
2-CH_3-4-$CH_3OC_6H_3$	C_6H_{11}	31	188–190	Dil. dioxane	$C_{15}H_{22}N_2O_4S$	55.20	6.78	54.95	6.85
4-$CH_3SC_6H_4$	n-C_3H_7	54	140–141	Dil. dioxane	$C_{11}H_{16}N_2O_3S_2$	45.81	5.59	45.82	5.67
4-$CH_3SC_6H_4$	n-C_4H_9	45	116–117	Dil. dioxane	$C_{12}H_{18}N_2O_3S_2$	47.66	6.00	47.94	6.50
4-$CH_3SC_6H_4$	C_6H_{11}	58	187–188	Dil. dioxane	$C_{14}H_{20}N_2O_3S_2$	51.20	6.13	51.09	6.29
4-BrC_6H_4	C_2H_5	68	147–149	Dil. ethanol	$C_9H_{11}BrN_2O_3S$	35.19	3.61	35.61	4.01
4-BrC_6H_4	n-C_3H_7	49	138–140	Dil. ethanol	$C_{10}H_{13}BrN_2O_3S$	37.38	4.08	37.40	4.11
4-BrC_6H_4	n-C_4H_9[e]	55	128–129	Dil. ethanol	$C_{11}H_{15}BrN_2O_3S$	39.45	4.52	39.64	4.64
2-ClC_6H_4	n-C_3H_7	37	176–178	Dil. ethanol C_6H_6–pet. ether	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.50	5.01

EXPERIMENTAL

Arylsulfonamides. The arylsulfonamides were all prepared by addition of the sulfonyl chloride[2] to a large excess of aqueous ammonium hydroxide. It was found to be advantageous to dissolve the solid sulfonyl chlorides in a volume of dioxane equal to their weight.

N-Arylsulfonylcarbamates.[3,4] To a mixture of 0.5 mole of the sulfonamide and 1.3 moles of anhydrous potassium carbonate in 600 ml. of reagent acetone was added, during 3 hr. with stirring, 0.66 mole of ethyl chlorocarbonate. The mixture was then stirred and refluxed for 18 hr., was allowed to cool, and was filtered. The solid residue was dissolved in about 1500 ml. of water. Any insoluble material was removed by filtration. If the amount was appreciable it was treated with more water. (Only in the case of the *p*-bromophenylsulfonylcarbamate was it impossible to dissolve almost all the material. In this one case a considerable amount of the starting sulfonamide was recovered.) The solution was acidified with concentrated hydrochloric acid. If the product did not crystallize readily, decantation of the acidic supernatant liquid and stirring the oily carbamate with water promoted crystallization. The crude product was used for reaction with the amines. Samples were purified for analysis.

N-Arylsulfonyl-N′-alkylureas.[3,5] A mixture of 0.1 mole of a *N*-sulfonylcarbamate and 0.3–0.4 mole of an alkylamine was shaken and, if necessary, warmed at about 80° until solution was complete. The excess amine was removed under reduced pressure and the residue was heated at 110–120° at a pressure of about 5 mm. for 6 hr. The product was first isolated by crystallization from dilute ethanol and was then purified from the solvents indicated in Table II.

(2) The arylsulfonyl chlorides which were not available commercially were prepared by chlorosulfonation. For general references on the sulfonyl chlorides and sulfonamides, see E. H. Huntress and F. H. Carten, *J. Am. Chem. Soc.*, **62,** 511, 603 (1940) and E. H. Huntress and J. S. Autentrieth, *J. Am. Chem. Soc.*, **63,** 3446 (1941).

(3) The method of preparation was essentially that which was kindly communicated to us by E. Haack and A. Hagedorn, C. F. Boehringer and Soehne, Mannheim-Waldhof, Germany.

(4) A similar method of preparation of a related carbamate is contained in British Patent **538,884** [*Chem. Abstr.*, **36,** 3512 (1942)].

(5) The preparation of this type compound has also been described in British Patent **604,259** [*Chem. Abstr.*, **43,** 1061 (1949)] using glycol monomethyl ether as a solvent.

TABLE II (*Continued*)

R	R′	Yield, %	M.P., °C.	Recryst. Solvent[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-ClC_6H_4	*n*-C_4H_9	64	164–166	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	45.75	5.39
3-ClC_6H_4	*n*-C_3H_7	60	133–134	Dil. ethanol C_6H_6–pet. ether	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.73	4.95
4-ClC_6H_4	C_2H_5	73	144–146	Dil. ethanol	$C_9H_{11}ClN_2O_3S$	41.16	4.22	41.17	4.25
4-ClC_6H_4	*n*-C_3H_7	47	127–129	Dil. ethanol	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.48	4.84
4-ClC_6H_4	*iso*-C_3H_7	31	155–156	Dil. ethanol	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.56	4.63
4-ClC_6H_4	*n*-C_4H_9[e]	54	115–117	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	45.70	5.23
4-ClC_6H_4	3-$CH_3O(CH_2)_3$	41	103–105	Dil. ethanol	$C_{11}H_{15}ClN_2O_4S$	43.06	4.93	43.16	5.08
4-ClC_6H_4	3-$CH_3S(CH_2)_3$	44	135–137	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S_2$	40.88	4.66	40.84	4.81
2,4-$Cl_2C_6H_3$	*n*-C_4H_9	82	171–173	Dil. ethanol	$C_{11}H_{14}Cl_2N_2O_3S$	40.62	4.34	40.84	3.99
2,5-$Cl_2C_6H_3$	*n*-C_3H_7	48	201–203	C_6H_6–pet. ether	$C_{10}H_{12}Cl_2N_2O_3S$	38.60	3.89	38.66	3.91
2,5-$Cl_2C_6H_3$	*n*-C_4H_9	73	194–195	C_6H_6	$C_{11}H_{14}Cl_2N_2O_3S$	40.62	4.34	40.76	4.46
3,4-$Cl_2C_6H_3$	*n*-C_3H_7	62	144–146	Dil. ethanol	$C_{10}H_{12}Cl_2N_2O_3S$	38.60	3.89	38.78	3.86
3-Cl-4-$CH_3C_6H_3$	*n*-C_3H_7	41	132–133	Dil. ethanol	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	45.15	5.46
3-Cl-4-$CH_3C_6H_3$	*n*-C_4H_9	41	146–148	Dil. ethanol C_6H_6–pet. ether $NaHCO_3$ reppt.	$C_{12}H_{17}ClN_2O_3S$	47.26	5.62	47.60	5.53
4-Cl-3-$CH_3C_6H_3$	*n*-C_3H_7	44	142–144	Dil. ethanol C_6H_6–pet. ether	$C_{11}H_{15}ClN_2O_3S$	45.42	5.20	46.04	5.32
4-Cl-3-$CH_3C_6H_3$	C_2H_5	30	153–155	Dil. ethanol	$C_{10}H_{13}ClN_2O_3S$	43.40	4.73	43.21	4.71
4-FC_6H_4	*n*-C_3H_7	43	131–133	Dil. ethanol	$C_{10}H_{13}FN_2O_3S$	46.11	5.03	46.02	4.98
4-FC_6H_4	*n*-C_4H_9	52	103–104	Dil. ethanol	$C_{11}H_{15}FN_2O_3S$	48.16	5.52	48.41	5.75

[a] The petroleum ether used was the fraction boiling at 60–71°. [b] Since prepared in this study, this compound has been reported in Accepted German Patent Specification **F 18339 IVb/12o** (Dec. 27, 1956). [c] The required amine has been reported by W. Schneider, *Ann.*, **375**, 245 (1910). In this present work it was prepared by lithium aluminum hydride reduction of 3-methylmercaptopropionitrile [C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, **69**, 2328 (1947)] by the method of L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951). [d] Since prepared in this present investigation, this compound has been described in Accepted German Patent Specification **F 18136 IVb/12o** (Sept. 27, 1956). [e] This compound has since been reported independently in Accepted German Patent Specification **F 18659 IVb/12o** (Dec. 27, 1956).

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Steroid Epoxides

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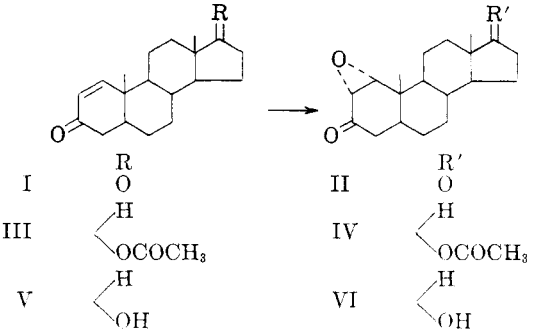
1α, 2α-Epoxyandrostane-3,17-dione (II),[1] a compound useful in the determination of the structure of ruscogenin,[2] was prepared from 1-androstene-3,17-dione (I)[3] by using alkaline hydrogen peroxide.[4] The same procedure was used in attempt to obtain the corresponding epoxide from 17β-acetoxy-1-androsten-3-one(III), but without success. Further attempts to obtain the epoxide of III were made using perbenzoic acid in chloroform solution and with peracetic acid in benzene. Modification[5] of the method used for the epoxidation of I yielded the



(1) *Cf.* P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954) for discussion of the configuration of 1,2-epoxides.

(2) W. R. Benn, F. Colton, and R. Pappo, *J. Am. Chem. Soc.*, **79**, 3920 (1957). For other references concerning the structure of ruscogenin see A. L. Nussbaum, F. E. Carlon, D. Gould, E. P. Oliveto, E. B. Hershberg, M. L. Gilmore, and W. Charney, *J. Am. Chem. Soc.*, **79**, 4814 (1957); D. Burn, B. Ellis, and V. Petrow, *Proc. Chem. Soc.*, 119 (1959); H Lapin and C. Sannie, *Bull. soc. chim.*, 1552 (1955).

(3) A. Butenandt and H. Dannenberg, *Ber.*, **69**, 1158 (1936).

(4) P. L. Julian, W. Cole, E. W. Meyer, and B. M. Regan, *J. Am. Chem. Soc.*, **77**, 4601 (1955).

(5) The author gratefully acknowledges a suggestion by R. Pappo of our laboratories for this modification.