[CONTRIBUTION FROM THE CHEMICAL LABORATORY, NORTH TEXAS STATE COLLEGE]

α-(4-Aminophenylsulfonyl)-acetophenone Derivatives[1]

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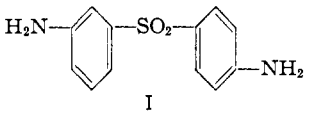
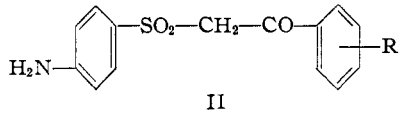
Numerous attempts have been made to decrease the toxicity of the tuberculostatic compound, 4,4′-diaminodiphenyl sulfone, I.[5-10]

Markees and Burger[11] have reported that the replacement of the sulfone linkage of Promizole with the cyclopropyl group led to a compound active against *M. tuberculosis* in Dubos' medium. Thus, it appears that the $-SO_2-$ linkage in some of the antitubercular sulfones can be replaced by other groups without destroying its activity. However, little work has been carried out to find the effect on the physiological activity that would be produced by replacing this sulfone linkage by other sulfone bearing groups. The present paper is a report of the synthesis of a group of compounds differing from the diaminodiphenyl sulfones in that the $-SO_2-$ group has been replaced by $-SO_2-CH_2-CO-$ as shown by comparing formula I with II.



I



II

Alkaline cleavage of these phenacyl phenyl sulfones has also been studied. It is noted that these keto sulfones could theoretically be hydrolyzed to yield a benzoic acid and a methyl sulfone or an acetophenone and a sulfonic acid. α-Phenylsulfonylacetophenone, gave a 97% yield of benzoic acid; however, only 75% of the methyl phenyl sulfone could be isolated. α-Phenylsulfonyl-4-chloro-acetophenone gave a 90% yield of *p*-chlorobenzoic acid; α-(4-nitrophenylsulfonyl)-acetophenone gave only a 64% yield of benzoic acid; α-phenylsulfonyl-2-acetonaphthone gave 65% yield of 2-naphthoic acid. The kinetics of these hydrolyses are now under investigation in this Laboratory.

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(5) Bauer, THIS JOURNAL, **61**, 617 (1939).

(6) Raiziss, Clemence and Freifelder, *J. Am. Pharm. Assoc.*, **33**, 43 (1944).

(7) Bambas, THIS JOURNAL, **67**, 671 (1945).

(8) Feldman and Hinshow, *Proc. Staff Meeting, Mayo Clinic*, **19**, 25 (1944).

(9) Ainstutz and Neumoyer, THIS JOURNAL, **69**, 1925 (1947).

(10) Gilman and Broadbent, *ibid.*, 2053.

(11) Markees and Burger, *ibid.*, **70**, 3329 (1948).

Five of the sulfones reported in this paper have been tested for activity against tuberculosis but none showed appreciable activity, as compared to 4,4′-diaminodiphenyl sulfone.

Experimental

4-Nitroacetophenone.—A solution of 3.6 g. (0.087 mole) of diazomethane and 5 g. (0.027 mole) of 4-nitrobenzoyl chloride in dry ether at 0°. The reaction of this diazo ketone with hydriodic acid gave 2.1 g. of product, m. p. 80°. Barkenbus and Clements[12] prepared this compound by another method and reported it to melt at 80-81°.

4-Nitrophenacyl Chloride.—This compound was prepared by the action of concentrated hydrochloric acid on 4-nitrophenyl diazomethyl ketone. The same quantities of reagents as in the previous preparation gave 1.8 g. of 4-nitrophenacyl chloride, m. p. 107°.[13]

α-(4-Nitrophenylmercapto)-acetophenone, Table I. Procedure A.[14]—A solution of 40.1 g. (0.334 mole) of acetophenone in 100 cc. of carbon tetrachloride was added to a solution of 4-nitrophenylsulfenyl chloride,[15] m. p. 94-95°, obtained from 50 g. of 4,4′-dinitrodiphenyl disulfide. After refluxing four hours, a yellow granular solid separated and was filtered. Recrystallization gave the desired mercapto compound.

Procedure B.[16]—A suspension of 0.25 mole of sodium 4-nitrothiophenolate in 300 cc. of dry benzene was cooled to 0° and 38.6 g. (0.25 mole) of phenacyl chloride in dry ether was added dropwise. The temperature was kept below 10° during the addition. After removal of the sodium chloride, concentration of the filtrate gave yellow crystals.

The remaining compounds of this type, were prepared by one of these methods and the pertinent data recorded in Table I.

α-(4-Nitrophenylsulfonyl)-acetophenone, Table II.—To a suspension of 20 g. of α-(4-nitrophenylmercapto)-acetophenone, in 200 cc. of glacial acetic acid and 50 cc. of acetic anhydride at 80° was added dropwise 50 cc. of 30% hydrogen peroxide. The light yellow solid which separated on dilution with water was filtered and recrystallized from a chloroform–hexane solution.

The oxidations of the various sulfides were carried out in the same manner and the data recorded in Table II.

α-(4-Aminophenylsulfonyl)-acetophenone, Table III.—To a suspension of 6.1 g. (0.2 mole) of α-(4-nitrophenylsulfonyl)-acetophenone, in 100 cc. of water was added 15 g. of iron powder and 0.1 cc. of glacial acetic acid and the mixture stirred at 85-90° for ten hours. The product was extracted from the insoluble filter cake by means of hot alcohol or acetone. Recrystallization from ethanol gave very light tan flakes.

The reduction of the other nitro sulfones was fashioned in the same manner, except in one instance (see note *b*, Table III) catalytic reduction was used instead of the iron reduction and the yield from this reduction with hydrogen and Raney Ni catalyst gave almost twice as good a yield and the product had a better appearance. However, the amino compound from each procedure had the same melting point.

The data for all the corresponding compounds are recorded in Table III.

Hydrolysis of α-Phenylsulfonylacetophenone.—A mixture of 2.63 g. (0.01 mole) of α-phenylsulfonylacetophe-

(12) Barkenbus and Clements, *ibid.*, **56**, 1369 (1934).

(13) Dale and Nierenstein, *Ber.*, **60**, 1027 (1927).

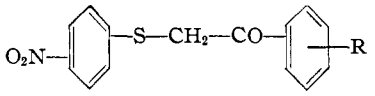
(14) Zincke, *Ann.*, **406**, 126 (1914).

(15) "Organic Syntheses," Coll. Vol. II, sec. ed., p. 455.

(16) Waldron and Reid, THIS JOURNAL, **45**, 2399 (1923).

TABLE I

α-(4-NITROPHENYLMERCAPTO)-ACETOPHENONES

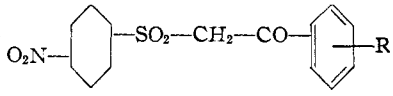


R	Method of prepn.	Yield, % A	Yield, % B	M. p.,[a] °C.	Recryst. from	Color of crystals	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Hydrogen	A, B	96	91	139	Acetone–H_2O	Yel. gr. plates	$C_{14}H_{11}NO_3S$	5.12	5.19
p-Methyl	A	85		123	Ace.–H_2O	Yel. flakes	$C_{15}H_{13}NO_3S$	4.88	4.79
p-Methoxy	A	88		158	Alcohol	Wh. ndls.	$C_{15}H_{13}NO_4S$	4.62	4.69
p-Bromo	A	90		132	Alc. ace.–H_2O	Yel. ndls.	$C_{14}H_{10}BrNO_3S$	3.87	3.83
p-Chloro	A, B	35	58	121	Alcohol	Lt. yel. ndls.	$C_{14}H_{10}ClNO_3S$	4.55	4.57
p-Nitro	A, B	80	83	160	Alc.–H_2O	Lt. cream ndls.	$C_{14}H_{10}N_2O_5S$	8.81	8.91
m-Nitro	A	92		134	Acetone	Lt. yel. matted nd.	$C_{14}H_{10}N_2O_5S$	8.81	8.82
[b]	A	70		153	Alcohol	Yel. flakes	$C_{18}H_{13}NO_3S$	4.33	4.45

[a] All melting points with the Fisher–Johns melting point apparatus. [b] The phenyl radical to which the R group is attached is replaced by the 2-naphthyl radical.

TABLE II

α-(4-NITROPHENYLSULFONYL)-ACETOPHENONES

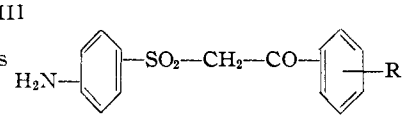


R	Yield, %	M. p., °C.	Recryst. from	Color of crystals	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Hydrogen	90	129	$CHCl_3C_6H_{14}$	Lt. cream rods	$C_{14}H_{11}NO_5S$	4.59	4.67
p-Methyl	95	155	Alc. H_2O	Wh. ndls.	$C_{15}H_{13}NO_5S$	4.39	4.57
p-Methoxy	93	258	Alcohol	Wh. ndls.	$C_{15}H_{13}NO_6S$	4.17	4.19
p-Bromo	80	161	Alc. H_2O	Lt. yel. ndls.	$C_{14}H_{10}BrNO_5S$	3.65	4.14
p-Chloro	94	146	Acetone	Lt. yel. ndls.	$C_{14}H_{10}ClNO_5S$	4.12	4.15
p-Nitro	92	257	Alcohol	V. long yel. ndls.	$C_{14}H_{10}N_2O_7S$	8.00	8.22
m-Nitro	87	145	Acetone	Wh. rods	$C_{14}H_{10}N_2O_7S$	8.00	8.17
[a]	99	171	Ace.–H_2O	Cream[b] ndls.	$C_{18}H_{13}NO_5S$	3.94	4.06

[a] 2-Naphthyl group replaces the phenyl group to which R is attached and R is hydrogen. [b] Light burnt-orange color from alcohol.

TABLE III

α-(4-AMINOPHENYLSULFONYL)-ACETOPHENONES



R	Yield, %	M. p., °C.	Recryst. from	Color of crystals	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Hydrogen	60	165	Ace. H_2O	Lt. tan flakes	$C_{14}H_{13}NO_3S$	5.09	5.09	11.64	11.34
p-Methyl	55	157	Alcohol	White flakes	$C_{15}H_{15}NO_3S$	4.84	4.78	11.09	11.24
p-Methoxy	45	123	Acetone	Gray flakes	$C_{15}H_{15}NO_4S$	4.59	4.50		
p-Bromo	50	197	*i*-Pr. alc.	White flakes	$C_{14}H_{12}BrNO_3S$	3.95	3.98	9.03	8.63
p-Chloro	27	179	Acetone	Cream flakes	$C_{14}H_{12}ClNO_3S$	4.52	4.70	10.33	10.09
p-Amino[a]	44	230	Alcohol	Lt. cream ndls.	$C_{14}H_{14}N_2O_3S$	9.66	9.89	11.03	10.92
m-Amino	35	240	Alcohol	Yel. ndls.	$C_{14}H_{14}N_2O_3S$	9.66	9.85	11.03	10.87
[b]	84[c]	158	Alcohol	Gray cream plates	$C_{18}H_{15}NO_3S$	4.31	4.28	9.84	9.67

[a] The preparation of this compound was described in a recent patent by F. Bergel, A. Morrison, A. R. Moss and H. Rinderknecht, British Patent 601,329, May 4, 1948. These workers prepared this compound by the method described by Troeger and Beck, *J. prakt. Chem.*, [2] **87**, 299 (1913). The reaction involves the interaction of substituted phenacyl chlorides with substituted sodium benzenesulfenates. This patent states that the above compound melted at 227°. We found that this substance melted at 230° [b] The phenyl ring with the R group is replaced by 2-naphthyl and R is hydrogen. [c] Catalytic reduction with Raney nickel and hydrogen at 40 pounds pressure. Iron reduction gave only 44% yield and the product was slightly reddish and this color could not be removed.

none and 11.51 cc. of 0.877 molar potassium hydroxide (0.01 mole) was refluxed for 100 minutes. The reaction solution was diluted to 200 cc. with water, cooled and extracted four times with 50-cc. portions of ether. Evaporation of this ether extract gave 1.207 g. of ether soluble product, m. p. 85°. Recrystallization raised the melting point to 87°. Acetophenone melts at 88°. This yield represented 74% of the theoretical.

The aqueous solution obtained after ether extraction was acidified and the insoluble precipitate weighed 1.19 g. and melted at 121.5° without recrystallization. Benzoic acid melts at 122°. This represents a yield of 97% of the theoretical of benzoic acid.

Hydrolysis of α-(4-Nitrophenylsulfonyl)-acetophenone.—Hydrolysis of 3.00 g. (0.0098 mole) of α-(4-nitrophenylsulfonyl)-acetophenone gave 0.50 g. of benzoic acid, 62% of theoretical, m. p. 119°.

Hydrolysis of α-(4-Nitrophenylsulfonyl)-2-acetonaphthone.—Hydrolysis of 2.1 g. (0.006 mole) of α-(4-nitrophenylsulfonyl)-2-acetonaphthone according to the pre-

vious procedure gave 0.66 g., 65%, of 2-naphthoic acid, m. p. 183°. 2-Naphthoic acid is recorded as melting at 185°.

Hydrolysis of α-(4-Nitrophenylsulfonyl)-4-chloro-acetophenone.—Hydrolysis of 2.34 g. (0.007 mole) of this compound gave 0.97% g., 90% of 4-chlorobenzoic acid, m. p. 238. The literature gives the melting point of this compound as 243°.

Summary

The synthesis of eight α-(4-nitrophenylmercapto)-acetophenones has been accomplished by one of two procedures and in some instances by both procedures. Each of the mercapto compounds was subsequently oxidized to the sulfone, then followed by reduction to the corresponding α-(4-aminophenylsulfonyl)-acetophenone.

None of the compounds tested were found to be active against tuberculosis.

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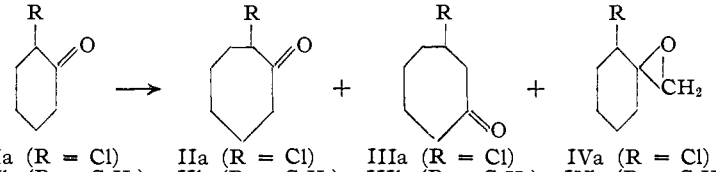
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Ring Enlargements. I. The Ring Enlargement of 2-Chlorocyclohexanone and 2-Phenylcyclohexanone

BY C. DAVID GUTSCHE

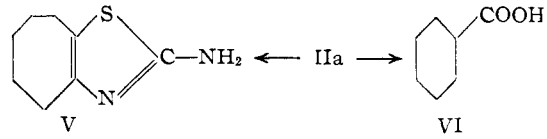
The ring enlargement of carbocyclic ketones by means of diazomethane has received occasional attention in the two decades since Mosettig and Burger[1] found that cyclohexanone could be smoothly converted to cycloheptanone through the action of this reagent. The synthetic value of these reactions, however, has been largely confined to the ring enlargement of symmetrical ketones, for unsymmetrically substituted ketones often yield mixtures of products.[2] The ratio of isomers present in such mixtures has in no case been accurately ascertained, as a consequence of which considerable confusion exists concerning the course of certain ring enlargements. The present communication discusses the ring enlargement of two 2-substituted cyclohexanones, (Ia) and (Ib), for which the ratio of isomers produced has been determined with fair accuracy.



Ia (R = Cl) IIa (R = Cl) IIIa (R = Cl) IVa (R = Cl)
Ib (R = C_6H_5) IIb (R = C_6H_5) IIIb (R = C_6H_5) IVb (R = C_6H_5)

Ring Enlargement of 2-Chlorocyclohexanone (Ia).—The reaction of Ia with ethereal diazomethane was reported by Giraitis and Bullock[3] in a Communication to the Editor which has not been followed by a fuller exposition of their work. These experimenters claimed that the product from this reaction was pure 2-chlorocycloheptanone (IIa) and that it was obtained in practically quantitative yield. Steadman,[4] using Meerwein's[5] procedure for conducting diazomethane ring enlargements, later showed that chlorocycloheptanone was produced in only 50–60% yield and that the isomeric oxide (IVa) accounted for at least 16% of the product. Steadman sought to prove the structure of the former by the base-catalyzed conversion to cyclohexanecarboxylic acid (VI), a reaction characteristic of cyclic 2-chloroketones.[6] From the chlorocycloheptanone fraction he obtained, upon treatment with alcoholic sodium hydroxide, a 36% yield of "somewhat impure" VI which was identified by conversion to the known amide. The relatively low yield of VI was not rationalized and, as will be shown below, was actually due to the fact that the chlorocycloheptanone fraction consisted of a mixture of the 2- and 3-chloro compounds.

2-Chlorocyclohexanone was treated with nitrosomethylurethan according to the directions of Steadman[4] and his reported yields were duplicated. Two reactions characteristic of the 2-chloroketo grouping were carried out with the chlorocycloheptanone fraction, and the results were compared with the same reactions in which authentic IIa was used as the starting material. In both reactions the material from the ring enlargement resembled the authentic 2-chloroketone qualitatively but not quantitatively. Authentic IIa could be converted by treatment with thiourea to 2-amino-4,5,6,7-tetrahydro-4-cycloheptathiazole, V, in 72% yield whereas the product of ring enlargement produced V in only 17.5% yield. Thus, on the basis of these data, the product of ring enlargement is indicated to consist of 24% of IIa and 76% of IIIa. This ratio of isomers was closely substantiated in the base-catalyzed conversion of the chloroketone to cyclohex-



V VI

(1) Mosettig and Burger, THIS JOURNAL, **52**, 3456 (1930).
(2) Adamson and Kenner, *J. Chem. Soc.*, 181 (1939).
(3) Giraitis and Bullock, THIS JOURNAL, **59**, 951 (1937).
(4) Steadman, *ibid.*, **62**, 1606 (1940).
(5) Meerwein, German Patent 579,309 [*C. A.*, **27**, 4546 (1933)].
(6) Favorskii and Boshowski, *J. Russ. Phys.-Chem. Soc.*, **50**, 582 (1917) [*C. A.*, **18**, 1476 (1924)].