ing at room temperature for one hour, approximately 30 g. of crushed ice was added; the precipitate was filtered off and crystallized from toluene or 50% acetic acid.

Phenylmercaptodiphenylacetic acid: prepared from thiophenol and benzilic acid, 99.3% yield, m.p. 127–129° (lit. 126–128°). *Anal.* Calcd. for $C_{20}H_{16}O_2S$: neut equiv., 320.4. Found: neut. equiv., 324.3.

***n*-Butylmercaptodiphenylacetic acid**: prepared from *n*-butylmercaptan and benzilic acid; crystallized from 50% acetic acid, 48.8% yield, m.p. 106–107.5°. *Anal.* Calcd. for $C_{18}H_{20}O_2S$: S, 10.67; neut. equiv., 300.4. Found: S, 10.71; neut. equiv., 300.0.

Benzylmercaptodiphenylacetic acid: prepared from benzylmercaptan and benzilic acid, 90.8% yield; crystallized from toluene, m.p. 180.5–182°. *Anal.* Calcd. for $C_{21}H_{18}O_2S$: S, 9.59; neut. equiv., 334.4. Found: S, 9.47; neut. equiv., 338.8.

The Decomposition of Tetraphenylthiodiacetic Acid in Anhydrous Pyridine at Room Temperature.—A solution of 0.5194 g. (0.0011 mole) of tetraphenylthiodiacetic acid in 50 ml. of anhydrous pyridine was allowed to stand for 6 hours at room temperature with occasional shaking. A deep blue color slowly developed during the first 1–2 hours. The pyridine was distilled off at approximately 30° (1 mm.), and the oily, blue, solid residue was dissolved in benzene. The benzene solution was extracted with 5% sodium bicarbonate. The aqueous extract, when acidified with dilute hydrochloric acid, yielded 0.2203 g. of a white solid which melted at 144.5–146°. This material, which was thought to be diphenylacetic acid, melted, after one recrystallization from water, at 146.5–147.5° (lit. 148°). The anilide of the acid was prepared in the usual manner, m.p. 181–182° (lit. 180°). The yield of diphenylacetic acid was 90.8%.

The blue benzene solution was evaporated to dryness at room temperature in a stream of air. The residue was converted to the 2,4-nitrophenylhydrazone of thiobenzophenone in the usual manner. The quantity of pure derivative isolated weighed 0.1690 g. (40.8%) and melted at 237–239° (lit. 239°).

The liberation of carbon dioxide in this reaction was proven by dissolving a second 0.5-g. sample of tetraphenylthiodiglycolic acid in 50 ml. of pyridine in a 3-necked flask which had previously been swept out with nitrogen. After standing several hours a nitrogen stream was swept over the surface of the pyridine solution and into a solution of saturated barium hydroxide. A heavy white precipitate of barium carbonate was rapidly formed.

LEXINGTON, KENTUCKY

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Thionocarbanilates with Anthelmintic Activity

BY ROBERT P. MULL

RECEIVED AUGUST 4, 1954

A variety of thionocarbanilates were prepared and characterized. Butyl *p*-allyloxythionocarbanilate manifests exceptional anthelmintic activity in mice against the oxyurid worms, *Aspiculuris tetraptera* and *Syphacia obvelata*.

The use of thionocarbanilates as local anesthetics has been investigated previously[1,2] as has their fungistatic,[3] insecticidal[4] and other biological properties.[5] On the whole, however, these compounds either have failed to manifest sufficient activity or exhibited certain deleterious effects which have precluded their use as effective chemotherapeutics.

The present work describes the synthesis of several new thionocarbanilates which are relatively non-toxic and evince anthelmintic activity. Most of these thionocarbanilates were prepared by condensation of an appropriately substituted phenyl isothiocyanate and sodium alcoholate (method A) in the manner reported by Bost and Andrews.[1] The attempted preparation of butyl *o*-hydroxythionocarbanilate according to this procedure, however, resulted in the formation of 2-benzoxazolethiol.[6] In this and a few other necessary cases, therefore, the synthesis was accomplished by reaction of butyl or phenyl chlorothionoformate with the respective aromatic amine (method B). Both methods avoided excessive heat and prolonged reflux, thus minimizing the likelihood of side product formation; the yields were good. Almost all of the compounds were low melting crystalline solids that could be purified by recrystallization. High vacuum sublimation or distillation in all cases resulted in the decomposition of the product.

Except for the two hydrochlorides, all the thionocarbanilates listed in Table I were moderately soluble in ethanol and difficultly soluble in water. This latter quality is advantageous since the anthelmintic must reach the habitat of the parasite and therefore resist rapid absorption and destruction in the host's organism. Of the numerous compounds investigated, butyl *p*-allyloxythionocarbanilate was found to possess exceptional activity as an anthelmintic when tested in mice against the oxyurid worms, *Aspiculuris tetraptera* and *Syphacia obvelata*, occurring either singly or simultaneously.[7]

Of the three isomeric ethers, it was found that the butyl *m*-allyloxythionocarbanilate was intermediate in activity between the more active butyl *p*-allyloxy and the moderately active butyl *o*-allyloxythionocarbanilates. Maximum enhancement of the anthelmintic properties of this class of compounds was observed in the case of the butyl esters.

Experimental

Substituted Phenyl Isothiocyanates.—These compounds were prepared from the appropriate aromatic amine by the use of thiophosgene[8] according to the general method of Dy-

(1) R. W. Bost and E. R. Andrews, THIS JOURNAL, **65**, 900 (1943).

(2) T. F. Wood and J. H. Gardner, *ibid.*, **63**, 2741 (1941); Y.-T. Huang, Y.-W. Yieh and I. Chang, *Brit. J. Pharmacol.*, **3**, 297 (1948).

(3) W. H. Davies and W. A. Sexton, *Biochem. J.*, **40**, 331 (1946).

(4) W. H. Davies and W. A. Sexton, *ibid.*, **43**, 461 (1948).

(5) W. G. Templeman and W. A. Sexton, *Proc. Roy. Soc.* (*London*), **B133**, 480 (1946); C. Mentzer and D. Molho, *Compt. rend.*, **230**, 406 (1950); H. Nagai, *J. Pharm. Chem.*, **24**, 35 (1952); M. Araki, Y. Yokota, M. Kuga, S. Chin, F. Fujikawa, K. Nakajima, H. Fujii, A. Tokuoka and Y. Hirota, *J. Pharm. Soc. Japan*, **72**, 979 (1952).

(6) G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

(7) Thanks are due to Dr. G. Rawson and his associates of the Microbiology Division of Ciba for the testing of these compounds, the details of which will be published elsewhere.

(8) Rapter Laboratories, Argo, Illinois.

TABLE I

THIONOCARBANILATES R—C₆H₄—NH—C(=S)—OR'

R	R'	Yield, %[a]	Crystallized from	M.p., °C.[b]	Molecular formula	Analyses, % Calcd. N	Calcd. S	Found N	Found S
.....	CH_3	89	Benzene–hexane	93–95[c]	C_8H_9NOS	8.38	19.17	8.45	19.21
.....	C_2H_5	91	Hexane	69–71[d]	$C_9H_{11}NOS$	7.73	17.69	7.81	17.69
.....	$(CH_2)_3CH_3$	86	Benzene–pet. eth.	52–55[e]	$C_{11}H_{15}NOS$	6.69	15.32	6.79	15.10
p-CH_3	$(CH_2)_3CH_3$	80	Hexane	64–66[f]	$C_{12}H_{17}NOS$	6.27	14.36	6.30	14.42
p-$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	85	Methanol–hexane	47–49	$C_{15}H_{23}NOS$	5.28	12.08	5.47	11.96
o-OH	$(CH_2)_3CH_3$[g]	33	Hexane	73–76	$C_{11}H_{15}NO_2S$	6.22	14.23	6.36	14.28
m-OH	$(CH_2)_3CH_3$	80	Ether–hexane	109–110	$C_{11}H_{15}NO_2S$	6.22	14.23	6.20	14.11
p-OH	$(CH_2)_3CH_3$	96	Ether	79–81	$C_{11}H_{15}NO_2S$	6.22	14.23	6.28	13.83
p-CH_3O	$(CH_2)_3CH_3$	80	Methanol	37–39	$C_{12}H_{17}NO_2S$	5.85	13.40	6.06	13.44
p-C_2H_5O	C_2H_5	88	Ethanol	92–96[h]	$C_{11}H_{15}NO_2S$	6.22	14.23	6.27	14.32
p-C_2H_5O	$(CH_2)_3CH_3$	88	Hexane	69–71	$C_{13}H_{19}NO_2S$	5.53	12.65	5.44	12.58
p-C_2H_5O	$(CH_2)_4CH_3$	82	Hexane	62–64	$C_{14}H_{21}NO_2S$	5.24	11.99	5.33	11.91
p-C_2H_5O	$(CH_2)_7CH_3$	83	Petr. ether	36–38	$C_{17}H_{27}NO_2S$	4.53	10.36	4.37	9.86
p-C_2H_5O	$(CH_2)_2N(C_2H_5)_2.HCl$	69	Methanol–ether	145–146	$C_{15}H_{25}ClN_2O_2S$	8.42	[i]	8.45	...
p-$CH_3(CH_2)_3O$	C_2H_5	89	Hexane	64–66	$C_{13}H_{19}NOS$	5.53	12.65	5.71	13.02
p-$CH_3(CH_2)_3O$	$(CH_2)_3CH_3$	91	Hexane	49–52	$C_{15}H_{23}NO_2S$	4.98	11.39	5.18	11.25
p-$CH_3(CH_2)_4O$	$(CH_2)_3CH_3$	82	Hexane	43–45	$C_{15}H_{25}NO_2S$	4.74	10.85	4.79	10.95
o-CH_2=$CHCH_2O$	$(CH_2)_3CH_3$	73	....	[j]	$C_{14}H_{19}NO_2S$	5.28	12.08	5.42	11.70
m-CH_2=$CHCH_2O$	$(CH_2)_3CH_3$	85	Hexane	45–47	$C_{14}H_{19}NO_2S$	5.28	12.08	5.32	12.21
p-CH_2=$CHCH_2O$	CH_3	71	Hexane	69–70	$C_{11}H_{13}NO_2S$	6.28	14.34	6.23	14.48
p-CH_2=$CHCH_2O$	C_2H_5	90	Petr. ether	63–64	$C_{12}H_{15}NO_2S$	5.90	13.51	5.85	13.24
p-CH_2=$CHCH_2O$	$(CH_2)_2CH_3$	85	Petr. ether	57–58	$C_{13}H_{17}NO_2S$	5.57	12.76	5.53	12.56
p-CH_2=$CHCH_2O$	$(CH_2)_3CH_3$	85	Petr. ether	46–48	$C_{14}H_{19}NO_2S$	5.28	12.08	5.44	12.18
p-CH_2=$CHCH_2O$	$(CH_2)_4CH_3$[k]	45	Petr. ether	54–56	$C_{15}H_{21}NO_2S$	5.01	11.48	5.29	11.70
p-CH_2=$CHCH_2O$	$(CH_2)_5CH_3$	53	Petr. ether	[l]	$C_{16}H_{23}NO_2S$	4.77	10.93	4.87	11.03
p-CH_2=$CHCH_2O$	$CH(CH_3)_2$	72	Petr. ether	62–64	$C_{13}H_{17}NO_2S$	5.57	12.76	5.50	12.64
p-CH_2=$CHCH_2O$	$CH_2CH(CH_3)_2$	71	Petr. ether	65–66	$C_{14}H_{19}NO_2S$	5.28	12.08	5.21	12.04
p-CH_2=$CHCH_2O$	CH_2CH=CH_2	50	Petr. ether	64–65	$C_{13}H_{15}NO_2S$	5.60	12.86	5.81	12.21
p-CH_2=$CHCH_2O$	$(CH_2)_2N(C_2H_5)_2.HCl$	74	Methanol–ether	145–147	$C_{16}H_{25}ClN_2O_2S$	8.12	[m]	8.16	...
p-Cl	C_2H_5	83	Hexane	104–106[n]	$C_9H_{10}ClNOS$	6.49	14.86	6.66	15.06
p-C_6H_5O	$(CH_2)_3CH_3$	87	Methanol–hexane	70–72	$C_{17}H_{19}NO_2S$	4.65	10.64	4.88	10.80
.....	C_6H_5[g]	60	Chloroform	135–138[o]	$C_{13}H_{11}NOS$	6.12	13.98[o]	6.17	13.94
p-CN	C_2H_5	65	Benzene	126–129[p]	$C_{10}H_{10}N_2OS$	13.58	15.54	13.71	15.78
p-CN	CH_2CH_2CN	66	Chloroform	144–145	$C_{11}H_9N_3OS$	18.19	13.88	17.92	13.72
p-CN	C_6H_5[g]	62	Benzene–pet. eth.	112–122	$C_{14}H_{10}N_2OS$	11.02	12.61	11.06	12.59

[a] Yields are for material melting within five degrees of the analytical sample. [b] The melting points and boiling points are corrected [c] Ref. 1 reported m.p. 92–93°. [d] Ref. 1, reported m.p. 70–72°. [e] Ref. 1, reported m.p. 51–53° [f] F. D. Chattaway, R. K. Hardy and H. G. Watts, *J. Chem. Soc.*, **125**, 1552 (1924), reported m.p. 65°. [g] Method B. [h] D. W. Browne and G. M. Dyson, *J. Chem. Soc.*, 3285 (1931), reported m.p. 95°. [i] *Anal.* Calcd.: Cl, 10.65. Found: Cl, 10.92. [j] Colorless oil, b.p. 188–191° dec. (761 mm.); $n^{23}D$ 1.5760; see Experimental part for details. [k] Prepared without heating by standing at room temperature for 48 hours. [l] Recrystallized in cold room, m.p *ca.* 20°, b.p. 197–199° dec (758 mm.), $n^{23}D$ 1.5708. [m] *Anal.* Calcd.: Cl, 10.28. Found: Cl, 10.25 [n] Ref. *h* reported m.p. 105°. [o] *Anal.* Calcd.: C, 68.12; H, 4.80. Found: C, 67.93; H, 4.86. The melting point varied appreciably with the rate of heating, *e.g.*, with a rapid rise it melted at 153–155°. Ref. 15 reported the melting point to be indefinite; W. Schneider and F. Wrede, *Ber.*, **47**, 2038 (1914), isolated the compound *via* the silver salt and reported m.p. 142°. [p] Ref. *h* reported m.p. 110°, no analysis given; ref. 10 reported m.p. 122°.

son, *et al.*[6,9] *p*-Tolyl isothiocyanate,[6] *p*-chlorophenyl isothiocyanate,[6] *p*-cyanophenyl isothiocyanate,[10] *m*-hydroxyphenyl isothiocyanate,[6] *p*-hydroxyphenyl isothiocyanate,[6] *p*-methoxyphenyl isothiocyanate,[9b] *p*-phenetyl isothiocyanate,[9b] *m*-allyloxyphenyl isothiocyanate[11] and *p*-phenoxyphenyl isothiocyanate[12] have been described in the literature. *p*-Butylphenyl isothiocyanate, b.p. 154–157° (14 mm.), $n^{23}D$ 1.5942; *p*-butoxyphenyl isothiocyanate, b.p. 110–117° (0.25 mm.), $n^{23}D$ 1.5596; *p*-pentyloxyphenyl isothiocyanate, b.p. 147–150° (0.8 mm.), $n^{23}D$ 1.5901; *o*-allyloxyphenyl isothiocyanate, b.p. 110–118° (0.8 mm.), $n^{23}D$ 1.6242; and *p*-allyloxyphenyl isothiocyanate, b.p. 131–133° (0.9 mm.), m.p. 23.5°, $n^{32}D$ 1.6266, have not been characterized previously.

Method A.—The following examples serve to illustrate the procedure employed, although in the first instance the mild reaction conditions and method of purification are not typical; ordinarily a five-minute heating period on the steam-bath was sufficient to complete the reaction.

Butyl *o*-**Allyloxythionocarbanilate.**—*o*-Allyloxyphenyl isothiocyanate (9.5 g., 0.05 mole) in butyl alcohol (10 ml.) was added to cool sodium butoxide (4.8 g., 0.05 mole). The reaction mixture was let stand at room temperature overnight and then poured into ice-water and acidified with dilute hydrochloric acid. This solution was extracted with petroleum ether, dried over sodium sulfate and chromatographed over alumina previously activated with hydrochloric acid. The product was readily eluted from the column with fresh petroleum ether to give 9.7 g. (73%) of a colorless oil, b.p. 188–191° dec. (761 mm.), $n^{23}D$ 1.5760.

Anal. Calcd. for $C_{14}H_{19}NO_2S$: N, 5.28; S, 12.10. Found: N, 5.42; S, 11.70.

Cyanoethyl *p*-**Cyanothionocarbanilate.**—*p*-Cyanophenyl isothiocyanate (16 g., 0.1 mole) and 8.53 g. (0.12 mole) of hydracrylonitrile were dissolved in 15 ml. of benzene and heated at 80° for 72 hours. The solid which separated after cooling was recrystallized from chloroform to give 15.2 g. (66%) of pale yellow crystals, m.p. 144–145°.

Anal. Calcd. for $C_{11}H_9N_3OS$: N, 18.19; S, 13.88. Found: N, 17.92; S, 13.72.

Method B.—Butyl chlorothionoformate was prepared in a manner similar to that employed for the ethyl ester.[13] The former, which decomposed on distillation, was utilized without purification.

Butyl *o*-**Hydroxythionocarbanilate.**—Butyl chlorothionoformate (10 g., 0.1 mole) in 15 ml. of ether was added dropwise with stirring to a cooled solution of 10.9 g. (0.1 mole)

(9) (a) G. M. Dyson, H. J. George and R. F. Hunter, *J. Chem. Soc.*, 3041 (1926); (b) G. M. Dyson, H. J. George and R. F. Hunter, *ibid.*, 436 (1927).

(10) M. O. Farooq and R. F. Hunter, *Rec. trav. chim.*, **54**, 122 (1935).

(11) H. Spiegelberg and G. Rey-Bellet, U. S. Patent 2,595,723 (1952).

(12) M. E. Roberts and F. B. Dains, *Univ. Kansas Sci. Bull.*, **25**, 213 (1938).

(13) H. Rivier and P Richard, *Helv. Chim. Acta*, **8**, 490 (1925).

of *o*-aminophenol in 2 l. of ether. After standing for 10 minutes, the reaction mixture was filtered and concentrated; 200 ml. of petroleum ether was added to the residue and the solution again filtered to remove amorphous material. The residue obtained after concentration was crystallized from hexane to give 3.74 g. (33%) of light brown needles,[14] m.p. 73–76°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: N, 6.22; S, 14.23. Found: N, 6.33; S, 14.28.

Phenyl *p*-Cyanothionocarbanilate.—Phenyl chlorothionoformate[15] (10.4 g., 0.06 mole) in 35 ml. of chloroform was added slowly with cooling to 14.2 g. (0.12 mole) of *p*-aminobenzonitrile dissolved in 75 ml. of chloroform. After standing overnight at room temperature and subsequent filtration, the filtrate was concentrated to an oil which was purified by recrystallization from benzene–petroleum ether to give 9.39 g. (62%) of colorless needles, m.p. 112–122°.

Anal. Calcd. for $C_{14}H_{10}N_2OS$: N, 11.02; S, 12.61. Found: N, 11.06; S, 12.59.

Acknowledgment.—The author wishes to express his appreciation to Miss Mary Dapero and Mrs. Lois Polansky for their technical assistance and to Mr. Louis Dorfman and his associates for the microanalyses.

SUMMIT, NEW JERSEY

(14) The surmise, ref. 6, that the inhibitory effect of a hydroxyl group in the *o*-position to the amino group is slight, is confirmed by the ability to prepare the desired thionocarbanilate by method B.

(15) H. Rivier, *Bull. soc. chim. France*, [3] **35**, 837 (1906).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

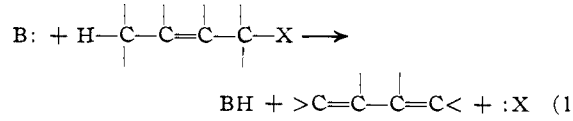
Mechanisms of Elimination Reactions. XIII. 1,4-Conjugate Eliminations. I. Some *meso*-Dihydroanthracene Derivatives[2]

BY STANLEY J. CRISTOL, WERNER BARASCH AND CHARLES H. TIEMAN

RECEIVED JUNE 28, 1954

The dibenzoates and diacetates of *cis*- and *trans*-1,5-dichloro-9,10-dihydro-9,10-anthradiol and the *trans*-monobenzoate have been prepared and characterized. The products of alkaline treatment of these compounds have been determined and the rates of their reactions with sodium hydroxide in ethanol–dioxane have been measured at various temperatures. Both thermal and base-promoted 1,4-conjugate elimination of acetic acid or benzoic acid from the diacetates or dibenzoates are considerably faster with the *trans* isomers than with the *cis* compounds, as is base-promoted loss of water from the two diols. Thus *cis* 1,4-conjugate elimination appears to be superior to the corresponding *trans* process. *trans*-1,8-Dichloroanthracene 9,10-dichloride was readily dehydrochlorinated (*cis* elimination) by alkali to give 1,8,10-trichloroanthracene. The ultraviolet absorption spectra of 1,5-dichloro-9-anthryl acetate and benzoate, of 1,5-dichloro-9-anthrone, of 1,5-dichloro-9-anthroxide ion and of 1,5-dichloro-9,10-anthraquinone are tabulated.

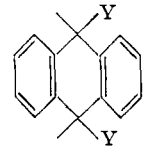
Elimination of groups from vicinal carbon atoms (1,2- or β-elimination) has been subjected to considerable investigation recently. In particular, we have been concerned with the establishment and understanding of the steric requirements of bimolecular 1,2-elimination. Reaction-rate data and quantities of activation have been used as evidence in support of mechanisms for *cis* and *trans* elimination.[2] It seemed worthwhile to extend our studies to include 1,4-conjugate elimination of the type



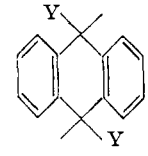
$$B: + H-C-C=C-C-X \longrightarrow BH + >C=C-C=C< + :X \quad (1)$$

to determine how important steric factors are in such systems.[3]

9,10-Dihydroanthracene derivatives may lose substituents from the *meso* (9 and 10) positions and thus represent examples in which the stereochemistry of 1,4-conjugate elimination may be studied without the possibility of 1,2-elimination interference. Thus *cis* isomers of type I and *trans* isomers of type II can be studied in elimination (aromatization) reactions to determine what advantage *cis* or *trans* elimination may have over the other type.



I



II

Several examples of 1,4-conjugate elimination from such systems have been described previously.[4-7] Barnett and his co-workers[6] have suggested that both thermal and base-promoted elimination of *cis* groups from the *meso* positions occur exclusively. However, this rule appears to be intuitive, the evidence for it appears to be incomplete or faulty, and it has been criticized by Bergmann and Weizmann.[7] In view of the confused picture available from previous work and the fact that no studies had been conducted with *cis–trans* pairs, we attempted, without success thus far, the preparation of a pair of isomeric 9,10-dihalides. Such dihalides of anthracene and substituted anthracenes have received considerable

(1) Previous paper in series: S. J. Cristol, W. P. Norris, A. Begoon and P. S. Ramey, THIS JOURNAL, **76**, 4558 (1954). A portion of this work was described at the Conference on Organic Reaction Mechanisms at Bryn Mawr, Penna., September 10, 1952.

(2) See, for example: (a) S. J. Cristol, N. L. Hause and J. S. Meek, THIS JOURNAL, **73**, 674 (1951); (b) S. J. Cristol and A. Begoon, *ibid.*, **74**, 5025 (1952).

(3) We have chosen to denote the process described in equation (1) as "1,4-conjugate elimination" in view of its obvious relationship to its opposite, 1,4-conjugate addition. The shorter term, "1,4-elimination," is subject to confusion with closure to a four-membered ring with elimination of groups in 1,4-position and is therefore not as precise a term.

(4) O. Dimroth, *Ber.*, **34**, 219 (1901).

(5) C. Liebermann and M. Beudet, *ibid.*, **47**, 1011 (1914).

(6) E. d. B. Barnett, M. A. Mathews and J. W. Cook, *Rec. trav. chim.*, (a) **43**, 530 (1924); **44**, (b) 217; (c) 728; (d) 818; (e) 894 (1925); **45**, (f) 68, (g) 558 (1926).

(7) E. Bergmann and A. Weizmann, THIS JOURNAL, **60**, 1801 (1938).