The experiment was repeated as above with the following modification. Instead of separating the phenylhydrazine derivative on the basis of its solubility in alcohol into fractions A and B, the product was recrystallized from boiling distilled water. The material obtained was dried first on porous tile and second under reduced pressure, 3 mm., at room temperature; Formula XIV—H_2O.

Anal. Calcd. for $C_{45}H_{52}O_8N_{10}\cdot 2H_2O$: C, 60.26; H, 6.25; N, 15.60. Found: C, 60.04; H, 5.98; N, 15.77.

The reaction of diethyl acetonedicarboxylate with D-*xylose in concentrated hydrochloric acid at 0°.* To a solution of 3 g. of xylose in concd. hydrochloric acid at 0°, 2 ml. of diethyl acetonedicarboxylate was added with stirring. The mixture was placed in a refrigerator and allowed to stand for 3 days, then the calculated amount of sodium acetate was added to neutralize the hydrochloric acid. The mixture was shaken with ether and petroleum ether to remove any unchanged ester. The product in the water layer was converted to a phenylhydrazine derivative in the usual way. The precipitate was dissolved in alcohol and reprecipitated with distilled water. The precipitate was filtered and dried in a desiccator, m.p. 176°; Formula (XV).

Anal. Calcd. for $C_{45}H_{50}O_8N_{10}\cdot 2H_2O$: C, 60.26; H, 6.29; N, 15.60. Found: C, 60.14; H, 5.95; N, 15.91.

Further work is in progress with other reagents having active *alpha* carbon hydrogen adjacent to a carbonyl or other appropriate group, with the aldoses, ketoses, and dialdehyde monoses.

Acknowledgment. The author wishes to express his appreciation to his student, Marshall Jacks, for his cooperation.

OMAHA, NEB.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Hydrolysis of 5,5-Disubstituted Barbituric Acids

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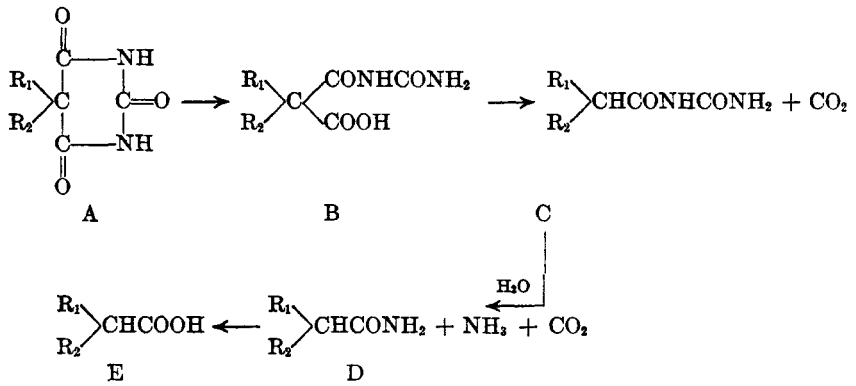
A rapid and simple method of hydrolysis of 5,5-disubstituted barbituric acids to the corresponding amides is reported. High yields are obtained when the reactions are carried out in dilute aqueous ammonia at 200° for five to ten minutes. In only one case was acylated urea obtained. Twenty-three of the compounds reported are new.

Amides of the type $R_1R_2CHCONH_2$ (where R_1 and R_2 are one or both of alkyl, unsaturated alkyl, and cycloalkyl groups) are widely reported. They normally are prepared from disubstituted acetic acids $-R_1R_2CHCOOH-$ by classical methods. The substituted acetic acids generally are obtained by hydrolysis and decarboxylation of dialkylated malonic or cyanoacetic esters.

The conversion of these esters to the corresponding acetic acids is time consuming and often troublesome.[1a,b] However, it is well known that the condensation of such esters with urea in the presence of sodium ethoxide[2] gives 5,5-disubstituted barbituric acids in good yield. Therefore it appeared advantageous to investigate their hydrolysis as a method of preparing disubstituted acetamides.

The hydrolysis of barbituric acids proceeds first by opening of the pyrimidine ring and decarboxylation to form an acylurea (C), followed by decomposition to the corresponding amide (D), carbon dioxide, and ammonia. More vigorous hydrolysis leads to E.



The alkaline hydrolysis of A at atmospheric conditions and at 100° in a bomb[1b] has been reported to give ureas (C). In a study of the hydrolysis of 5-substituted barbituric acids at 5–10 atmospheres pressure under various *p*H conditions Ruhkopf[3] obtained both ureas and amides. He

(1) (a) F. F. Blicke and P. Centolella, *J. Am. Chem. Soc.*, **60**, 2923 (1938), (b) E. H. Volwiler and D. L. Tabern, *J. Am. Chem. Soc.*, **58**, 1352 (1936) report on the difficulty of hydrolyzing certain higher substituted malonic esters.

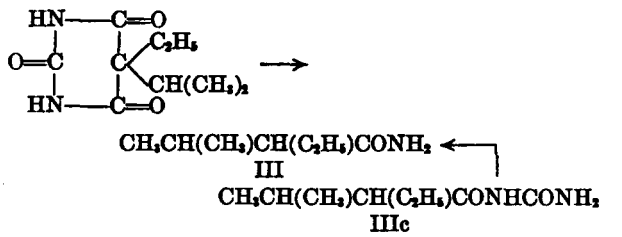
(2) W. J. Doran, *Medicinal Chemistry*, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 5.

(3) H. Ruhkopf, *Ber.*, **73**, 938 (1940). The author also cites references describing the path of hydrolysis.

suggests that formation of either is dependent on pressure and the buffer.

The formation of two gaseous products of hydrolysis, ammonia and carbon dioxide, the volume of reactants, and the void of the reaction vessel will all have an effect on the pressure temperature relationship. As the size of the autoclave is not mentioned in Ruhkopf's experimental data, placing dependence on pressure could lead to erroneous conclusions.

We therefore thought more reliable results would follow if the course of the reaction were observed and the temperature and pressure noted. We found that at about 200° a significant surge of pressure took place. This rise, up to 25 atmospheres and above, suggested that this temperature was the point of optimum hydrolysis to the amide. This observation led us to conclude that most intermediate ureas would not be stable under such conditions. The absence of any urea (IIIc) in the hydrolysis of 5-ethyl-5-isopropylbarbituric acid and a comparison of this hydrolysis with that of α-ethyl-β-methylbutyrylurea in excess dilute aqueous ammonia for five to ten minutes reaction time at 200° seems to support this conclusion. From each reaction III was obtained in 91.8 and 93.5% yields, respectively.

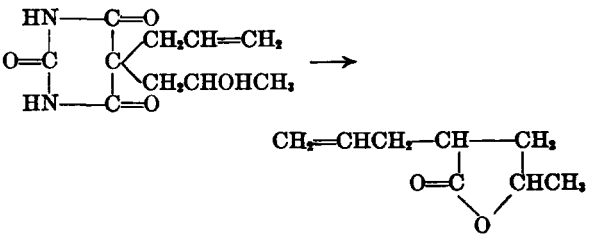


In order to determine the best reaction medium we hydrolyzed 5-ethyl-5-(1-methylpropyl)barbituric acid in water or with an equivalent of aqueous sodium hydroxide, and in excess dilute aqueous ammonia for the five to ten minute period at 200°. When Ruhkopf's conditions[3] were used with this same barbituric acid, the yield obtained compared well with the other procedures. However, its purity was questionable, as it melted over a wide range. When the reaction temperature was raised to 200° for six hours, a good product resulted.

Hydrolysis in water proved satisfactory only if the reaction were carried out at higher temperature and for a longer heating period (one hour). At 200° 95% of the starting barbituric acid was recovered. Lower yield was obtained with sodium hydroxide. The use of excess sodium hydroxide in hydrolysis is known to give malonamides.[4] When the best yield of X (90%) was obtained by hydrolysis of 5-ethyl-5-(1-methylpropyl)barbituric acid in dilute aqueous ammonia, we used this medium as the one of choice in most of the experiments.

With a few exceptions, hydrolysis at 200° with aqueous ammonia gave good yields (75–97.5%). In only one experiment was any acrylurea obtained. When 5-(1-methylbutyl)-5-propargylbarbituric acid was hydrolyzed we were able to isolate and identify 2-propargyl-3-methylhexanoylurea in addition to compound XXX. It should be noted that, while we were able to obtain an amide (XXIII) from the corresponding thiobarbituric acid, in general hydrolysis of this group of compounds gave materials difficult to purify.

Of particular interest was the hydrolysis of 5-allyl-5-(β-hydroxypropyl) barbituric acid. Even under the mildest conditions (at 120°) the lactone was formed and in no instance were we able to isolate either amide or urea.



EXPERIMENTAL

The barbituric acids used in this work were prepared by literature methods or were commercially available.

The following is an example of the preferred method of hydrolysis. *2-Ethyl-3-methylpentamide* (X). Twenty grams (0.0945 mole) of 5-ethyl-5-(1-methylbutyl)barbituric acid was dissolved in 50 cc. of water and 50 cc. of concd. aqueous ammonia (29%). The solution was placed in a 183-cc. stainless steel rocker type bomb and heated for 5–10 min. at 200°. The vessel was removed from the source of heat and cooled to at least 70° before opening. The contents were cooled thoroughly, filtered, and washed with cold water. The product melted at 112° and weighed 13.3 g. (almost quantitative). After recrystallization from dilute alcohol the melting point rose to 113.5–114° and the yield was 90%. In general, the saturated amides were recrystallized from dilute alcohol or water. The unsaturated amides were recrystallized from petroleum ether (b.p. 63–68°).

Hydrolysis in water. Fifty grams (0.236 mole) of 5-ethyl-5-(1-methylpropyl)barbituric acid was placed in a 1 l. stainless steel rocker type bomb along with 500 cc. of water. The mixture was heated for 1 hr. at 225°. The reaction vessel was removed from the source of heat immediately and cooled. After opening, the contents were cooled thoroughly and filtered. The amide melting at 112° was obtained in 82% yield. Recrystallization from dilute alcohol raised the melting point to 113–115°. When this reaction was run at 200° for 10 min., 95% of the barbituric acid was recovered.

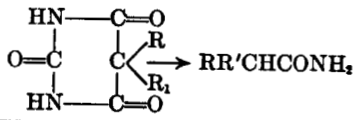
Method of Ruhkopf.[3] The same experiment was carried out at 180°[5] for 6 hr. After thoroughly cooling the contents of the reactor, the precipitate was filtered and washed with cold water and dried. An 85.8% yield of product melting from 90–105° was obtained. It was suspended in dilute sodium hydroxide, stirred, filtered, and washed with cold

(4) H. Aspelund, *Acta Acad. Aboensis, Math. et Phys.*, 20, 16 pp. (1955) or *Chem. Abstr.*, 50, 11351 (1956) reports that hydrolysis at 100° with two or more equivalents of sodium hydroxide leads to malonamides. With 5,5-diethylbarbituric acid at 200° we obtained diethylmalonic acid.

(5) The pressure resulting from heating water in a closed system at 180° is about 10 atm.

TABLE I

HYDROLYSIS TO AMIDES



	Amides R	Amides R_1	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	C_2H_5	C_2H_5	74.5	112[a]	$C_6H_{13}NO$						
II	C_2H_5	CH_2=$CHCH_2$	63	75–77	$C_7H_{13}NO$	66.10	66.03	10.30	10.06	11.01	11.00
III	C_2H_5	$(CH_3)_2CH$	91.8	137.5[b]	$C_7H_{15}NO$						
IV	$CH_3CH_2CH(CH_3)$	CH_3	80.2	90–91	$C_7H_{15}NO$	65.17	65.43	11.72	11.96	10.86	10.57
V	CH_2=$CHCH_2$	CH_2=$CHCH_2$	75	84–85[c]	$C_8H_{13}NO$	69.03	69.07	9.41	9.56	10.06	10.10
VI	CH_2=$CHCH_2$	$(CH_3)_2CH$	82	108–110[d]	$C_8H_{15}NO$	68.04	67.81	10.71	10.72	9.92	9.73
VII	CH_2=$C(CH_3)CH_2$	C_2H_5	70	67–68	$C_8H_{15}NO$	68.04	67.91	10.71	10.88	9.92	9.76
VIII	CH_2=$CHCH_2$	C_3H_7	87	95–96	$C_8H_{15}NO$	68.04	67.99	10.71	10.71	9.92	10.11
IX	C_4H_9	C_2H_5	86	101.5[e]	$C_8H_{17}NO$	67.09	67.39	11.96	11.88		
X	$CH_3CH_2CH(CH_3)$	C_2H_5	90	113.5–114[f]	$C_8H_{17}NO$						
XI	CH_2=$C(CH_3)CH_2$	CH_2=$CHCH_2$	81	69–70	$C_9H_{15}NO$	70.55	70.85	9.87	10.11	9.14	9.35
XII	$CH_3CH_2CH(CH_3)$	CH_2=$CHCH_2$	84	92	$C_9H_{17}NO$	69.63	69.83	11.04	11.16	9.02	9.16
XIII	C_4H_9	CH_2=$CHCH_2$	78.5	92–92.5	$C_9H_{17}NO$	69.63	69.50	11.04	11.03	9.02	9.22
XIV	$(CH_3)_2CHCH_2$	CH_2=$CHCH_2$	97.5	78–79	$C_9H_{17}NO$	69.63	69.73	11.04	11.23	9.02	9.17
XV	$(CH_3)_2CHCH_2CH_2$	C_2H_5	88	110–111[g]	$C_9H_{19}NO$	68.74	68.87	12.18	11.94	8.91	9.02
XVI	$CH_3CH_2CH(CH_3)CH_2$	CH_2=$CHCH_2$	74	68–69	$C_{10}H_{15}NO$	70.96	70.92	11.32	11.56	8.28	8.38
XVII	C_5H_{11}	CH_2=$CHCH_2$	90	70–71	$C_{10}H_{15}NO$	70.96	71.11	11.32	11.50	8.28	8.30
XVIII	$C_3H_7CH(CH_3)$	CH_2=$CHCH_2$	91.8	79.5–80[h]	$C_{10}H_{15}NO$[i]	70.96	71.11	11.32	10.89	8.28	8.42
XIX	$C_2H_5CH(C_2H_5)CH_2$	C_2H_5	81.8	50–52	$C_{10}H_{21}NO$	70.11	69.80	12.36	12.60	8.18	8.00
XX	C_6H_{13}	C_2H_5	93.3	103.5–104	$C_{10}H_{21}NO$	70.11	70.36	12.36	12.52	8.18	8.42
XXI	$C_3H_7CH(CH_3)$	C_3H_7	81.5	108.5–110[j]	$C_{10}H_{21}NO$	70.11	70.16	12.36	12.45	8.18	8.35
XXII	$C_6H_{11}CH_2$	C_2H_5	78.5	99	$C_{11}H_{21}NO$	72.07	71.86	11.55	11.68	7.64	7.74
XXIII	C_6H_{13}	CH_2=$CHCH_2$	58[k]	79–81	$C_{11}H_{21}NO$	72.07	72.10	11.55	11.55	7.64	7.49
XXIV	C_4H_9	$C_3H_7CH(CH_3)$	89.8	95–96[l]	$C_{11}H_{23}NO$	71.29	71.16	12.51	12.71	7.56	7.84
XXV	C_5H_{11}	$(CH_3)_2CHCH_2$	95.2	69–71	$C_{11}H_{23}NO$	71.29	71.39	12.51	12.71	7.56	7.49
XXVI	$(CH_3)_2CHCH_2CH_2$	$(CH_3)_2CHCH_2$	87.6	82–83	$C_{11}H_{23}NO$	71.29	70.98	12.51	12.71	7.56	7.54
XXVII	C_5H_{11}	C_4H_9	94.8	117–118	$C_{11}H_{23}NO$[m]	71.29	71.01	12.51	12.71	7.56	7.68
XXVIII	$CH_3CH(CH_3)CH_2CH(CH_3)CH_2$	C_2H_5	85	50–52[n]	$C_{11}H_{23}NO$	71.29	71.38	12.51	12.71	7.56	7.63
XXIX	$C_4H_9CH(C_2H_5)CH_2$	C_2H_5	96.9	58–59.5	$C_{12}H_{25}NO$	72.31	71.96	12.64	12.64	7.03	7.12
XXX	$C_3H_7CH(CH_3)$	CH≡CCH_2	50.2	Oil[o]	$C_{10}H_{17}NO$						

[a] M. Freund and P. Hermann, *Ber.*, **23**, 190 (1890) gives m.p. of 105°, 107° recorded by E. Fischer and A. Dilthey, *Ber.*, **35**, 844 (1902). [b] Described m.p. 134–134.5°, A. W. Crossley and H. R. Le Sueur, *J. Chem. Soc.*, **77**, 83 (1900). [c] Described 82.5°, E. Oberreit, *Ber.*, **29**, 2005 (1896). [d] Reported as 107° by J. D. Riedel, German Patent **461,814** (1930). [e] H. S. Raper, *J. Chem. Soc.*, 91, 1831 (1907) gives 101.5°; F. F. Blicke and A. P. Centolella, *J. Am. Chem. Soc.*, **60**, 2924 (1938) report 106–107° (from water). [f] N. M. Katznelson and M. S. Kondakova, Russ. Pat. *40350* (1934) report 114–115°. [g] Ref. 1b gives 106–108°. [h] Ref. 1b gives 90–91°. [i] Also analyzed for oxygen. Calcd., 9.44. Found, 9.72. [j] First distilled at 195° (2 mm.), then recrystallized from dil. alcohol. [k] This amide was prepared from the corresponding thiobarbituric acid. [l] See ref. 1b, m.p. 97–98°. [m] Also analyzed for oxygen. Calcd., 8.69. Found, 8.61. [n] Distilled at 127–129° (1.5–1.7 mm.). The product solidified and melted at 48°. The distilled product appeared to pick up moisture and equilibrate at about 0.25 H_2O. Calcd. for hydrate: C, 69.61; H, 12.47; O, 10.54. Found: C, 70.11; H, 12.42; O, 10.65. After 48 hours drying m.p. rose to 50–52° and analysis was satisfactory for dried compound. [o] Liquid boiling at 140° (2.8 mm.). The distilled product seems to be hygroscopic and equilibrates at about 0.25 H_2O. Calcd. for hydrate: C, 69.90; H, 10.27; N, 8.15; O, 11.54. Found: C, 69.92; H, 10.27; N, 8.31; O, 10.99.

water. The yield dropped to 70.5% and the product still melted poorly (103–110°). However, after recrystallization from dilute alcohol the melting point was satisfactory. When this same experiment was carried out at 200° for 6 hr. an 83.5% yield of X was obtained. It melted at 110–113° before recrystallization.

Hydrolysis with sodium hydroxide. When the sodium salt of the barbituric acid in water (*p*H 9.0) was heated at 200° for 5–10 min. a 78% yield of X melting at 110–112° was obtained. However, when the free acid was hydrolyzed in the presence of an equivalent of sodium hydroxide under the same conditions, the yield dropped unless the *p*H of the solution had been adjusted with acetic acid to about *p*H 9.0 before reaction.

2-Allyloctanamide (XXIII). *Hydrolysis of 5-allyl-5-hexylthiobarbituric acid.* 5-Allyl-5-hexylthiobarbituric acid (8.05 g., 0.03 mole) in 25 cc. of water and 25 cc. of concd. aqueous ammonia were placed in a glass lined Hastelloy bomb and heated for 5–10 min. at 200°. After cooling, the vessel was vented. A strong odor of hydrogen sulfide was noted. The white crystalline solid was filtered and washed with cold water. It did not give satisfactory analysis after recrystallization from petroleum ether (b.p. 63–68°). It was then dissolved in anhydrous ether, filtered from insoluble material, and dried in a rotary drier with slight warming while under reduced pressure. After thorough drying, the product gave a satisfactory analysis (see Table I).

Several other thiobarbituric acids were subjected to the same conditions, but isolation difficulties caused us to abandon any further work with them.

2-Propargyl-3-methylhexanoylurea. A solution of 9.0 g. (0.038 mole) of 5-propargyl-5-(1-methylbutyl) barbituric acid in 40 cc. of water and 40 cc. of concd. aqueous ammonia was heated for 5–10 min. at 200°. After removal from the source of heat and cooling as in the other examples a crystalline solid plus some oily material was obtained. The mixture was treated with anhydrous ether and filtered. The solid was ether insoluble. The filtrate was further extracted for work up and distillation and isolation of compound XXX.

The ether insoluble product weighing 2.0 g. was recrystallized from dilute alcohol. It melted at 200°.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.82; H, 8.62; N, 13.32. Found: C, 62.92; H, 8.85; N, 13.32.

α-Allyl-γ-methylbutyrolactone. Thirty-three grams (0.146 mole) of 5-allyl-5-(2-hydroxypropyl)barbituric acid was hydrolyzed in 75 cc. of water and 75 cc. of concd. aqueous ammonia for 5–10 min. at 200°. The resulting product was an oil which was extracted from the reaction mixture with ether. The ether extract was dried over anhydrous magnesium sulfate and then the ether was removed. The residue was distilled and the fraction boiling at 77–80°; 1 mm., n^{25}_D 1.4519 was collected. The yield amounted to 60%.

Anal. Calcd. for $C_6H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.87; H, 8.77.

Similar runs at 150° and even at 120° yielded the same product. All were shown to be identical by infrared analysis.

α-Ethyl-β-methylbutyramide (III). A mixture of 17.2 g. (0.1 mole) of α-ethyl-β-methylbutyrylurea and 75 cc. of water was heated in a 183 cc. stainless steel bomb for 5–10 min. at 200°. After cooling the bomb and contents, 12.0 g. (93.5% yield) of III melting at 137° was obtained.

In a similar experiment with 5-ethyl-5-isopropylbarbituric acid in diluted aqueous ammonia 91.8% yield of III melting at 137.5° was obtained. The melting point did not change after recrystallization from water.

Acknowledgment. The authors are indebted to Mr. E. F. Shelberg and Mr. O. F. Kolsto and staff for the microanalyses. They also wish to thank Mr. W. Washburn and his group for infrared analysis.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE ANIMAL RESEARCH INSTITUTE, RESEARCH BRANCH, CANADA DEPARTMENT OF AGRICULTURE]

Syntheses of N^{ϵ}-Tosyl-L-lysine Peptides[1a]

JOHN D. CIPERA

Received March 18, 1960

A novel approach to the incorporation of N^{ϵ}-tosyl-L-lysine into the peptide chains is outlined. The syntheses of several sequences appearing in the ACTH and MSH molecules are described in detail.

Lysine figures prominently in the active portions of the adrenocorticotropic hormones,[1b] melanotropic hormones,[2] and other biologically active peptides.[3] Thus, efficient methods for linking lysine into peptide chains are of considerable interest. Such methods must, however, take into account the difficulties inherent in the condensation reactions involving the carboxyl group of lysine.[4] These difficulties are compounded when two lysine moieties are to be coupled together.

Best results with this general type of reaction have been reported when both α- and ε-amino groups of lysine were protected by a carbobenzyloxy radical.[4,5] However, such products cannot be used effectively for selective reactions involving only one of the two amino groups, since both amino groups are protected by the same

(1) (a) Supported by a grant from the American Cancer Society, this investigation was carried on in the Biochemistry Department of the School of Medicine, University of Pittsburgh. It was presented in part at the 136th Meeting of the American Chemical Society in Atlantic City, N. J., September 1959.

(1) (b) P. H. Bell, *J. Am. Chem. Soc.*, **76**, 5565 (1954).

(2) I. I. Geschwind, C. H. Li, and L. Barnafi, *J. Am. Chem. Soc.*, **79**, 620 (1957).

(3) F. Sorm, B. Keil, V. Holeysovsky, V. Knesslova, V. Koska, P. Masiar, B. Meloun, O. Mikes, V. Tomasek, and J. Yanecek, *Collection Czech. Chem. Commun.*, **22**, 1310 (1957).

(4) J. S. Fruton, *Advances in Protein Chem.*, **5**, 58 (1949); M. Goodman, and G. W. Kenner, *Advances in Protein Chem.*, **12**, 507 (1957).

(5) B. F. Erlanger and E. Brand, *J. Am. Chem. Soc.*, **73**, 4025 (1951); S. G. Waley and J. Watson, *J. Chem. Soc.*, 475 (1953).