Purine Studies. Part VIII.[1] Formation of Alkylthiopurines from 4,5-Diaminopyrimidine- or Purine-thiones by Means of Orthoester–Anhydride Mixtures

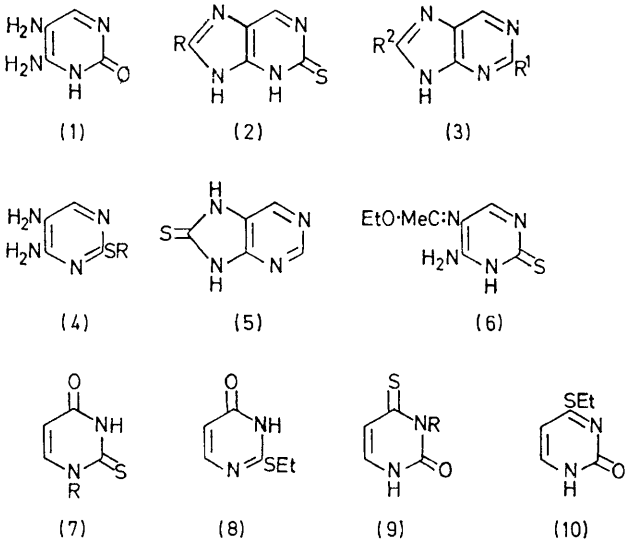
By **Rodney J. Badger, Desmond J. Brown,* and John H. Lister,** John Curtin School of Medical Research, P.O. Box 334, Canberra City, Australia 2601

Treatment of 4,5-diaminopyrimidine-2-thione (1) with freshly prepared triethyl orthopropionate–propionic anhydride gives not only the expected 8-ethylpurine-2-thione (2; R = Et) but also 8-ethyl-2-ethylthiopurine (3; R^1 = SEt, R^2 = Et). In the latter, the *S*- and 8-substituents are derived respectively from the alcoholic and acyl portions of the orthoester. The ratio of products depends on conditions. The same mixed reagents also cause *S*-ethylation of preformed purine-2(or 8)-thiones. Similar treatment of 2-thiouracil gives a separable mixture of its *S*- and *N*(1)-ethyl derivatives; 4-thiouracil yields the *S*- and *N*(3)-ethyl isomers.

APPROPRIATE mixtures of orthoesters and carboxylic acid anhydrides are commonly used to convert 4,5-diaminopyrimidines into purines.[2] We now report examples of the hitherto unsuspected [2,3] ability of such orthoester–anhydride mixtures to *S*-alkylate purinethiones, either preformed or made *in situ* from 4,5-diaminopyrimidine-thiones. The mixed reagents can also alkylate unrelated pyrimidines, *e.g.* the thiouracils, from which both *S*- and *N*-alkyl derivatives are isolated. The alkyl group is derived from the alcoholic portion of the orthoester: it seems likely that the alkylating agent is one of the labile products [4] formed on warming orthoesters with anhydrides.

The use of orthoformates with acetic anhydride seldom induced alkylation. Thus 4,5-diaminopyrimidine-2-thione [5] (1) gave only purine-2-thione [6,7] (2; R = H) on heating with acetic anhydride plus triethyl, tributyl, or triallyl orthoformate; however, trimethyl orthoformate did produce a minor product which proved to be 2-methylthiopurine [7] (3; R^1 = SMe, R^2 = H). The ethylthio-homologue (3; R^1 = SEt, R^2 = H) was made by conventional ethylation of the thione (1) and subsequent treatment of the thioether (4; R = Et) with orthoformate–anhydride.

In contrast, triethyl orthoacetate or orthopropionate plus acetic or propionic anhydride usually caused *S*-alkylation of purinethiones whether these were preformed or formed *in situ* from a diaminopyrimidine-



(1) (2) (3)

(4) (5) (6)

(7) (8) (9) (10)

thione. Thus the purine-2-thiones (2; R = H or Me) and purine-8-thione [8] (5) gave the corresponding ethyl-

[1] Part VII, D. J. Brown, R. L. Jones, A. M. Angyal, and G. W. Grigg, *J.C.S. Perkin I*, 1972, 1819.

[2] J. H. Lister, 'Purines,' Wiley-Interscience, New York, 1971, p. 50.

[3] R. H. DeWolfe, 'Carboxylic Ortho Acid Derivatives,' Academic Press, New York, 1970.

[4] H. W. Post and E. R. Erickson, *J. Org. Chem.*, 1937, **2**, 260; J. A. Montgomery and C. Temple, *ibid.*, 1960, **25**, 395; J. W. Scheeren and W. Stevens, *Rec. Trav. chim.*, 1966, **85**, 793.

[5] D. J. Brown, *J. Appl. Chem.*, 1952, **2**, 239.

[6] R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.

[7] A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060.

[8] G. B. Barlin, *J. Chem. Soc.*, 1965, 3017.

thiopurines (3; R^1 = SEt, R^2 = H or Me) and (3; R^1 = H, R^2 = SEt), whose structures were confirmed by unambiguous syntheses using conventional ethylation procedures. Likewise, 4,5-diaminopyrimidine-2-thione (1) gave the 2-ethylthiopurines (3; R^1 = SEt, R^2 = Me, Et, or Ph), according to whether the orthoacetate, orthopropionate, or orthobenzoate was used; the pre-ethylated pyrimidine (4; R = Et) gave the same ethylethylthiopurine (3; R^1 = SEt, R^2 = Et) by similar means or (less effectively) by treatment with *NN*-dimethylpropionamide plus phosphoryl chloride.

Although an excess of orthoester–anhydride was needed in all the foregoing reactions, the best molar ratio of the reagents was *ca.* 2 : 1. For example, the pyrimidinethione (1) with triethyl orthoacetate plus an excessive amount of acetic anhydride, or the purinethione (2; R = Me) with acetic anhydride alone, gave the same stable diacetyl derivative of unknown constitution; it was converted into the purinethione (2; R = Me) by simply boiling with water. On the other hand, a too high ratio of orthoester to anhydride resulted in the formation of high proportions of uncyclized intermediates, *e.g.*, 4-amino-5-α-ethoxyethylideneaminopyrimidine-2-thione [1] (6) from the thione (1) with an excess of triethyl orthoacetate and a little acetic anhydride. When a mixture (in the correct ratio) of the orthoester and anhydride was preheated for 2 h prior to addition of the thione (1), the main product was the intermediate (6). It was accompanied by a little of the purinethione (2; R = Me) but no trace of the ethylthiopurine (3; R^1 = SEt, R^2 = Me): this confirmed the transient nature [4] of the alkylating agent present in orthoester–anhydride mixtures.

The alkylating ability of such mixtures was not confined to purinethiones. On treatment with triethyl orthopropionate plus propionic anhydride, 2-thiouracil (7; R = H) gave a mixture of the *N*- and *S*-methyl-2-thiouracils (7; R = Et) and (8). Similar treatment of 4-thiouracil (9; R = H) gave the corresponding alkyl derivatives (9; R = Et) and (10).

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 33° on a Perkin-Elmer R10 60 MHz instrument (tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulphonate as standard); *J* values are in Hz. The orthoesters (Fluka, *purum* or *pract.*) were used without purification (two typical reactions were unaffected by preliminary careful fractionation).

Purine-2(3H)-thione (2; R = H).—(*a*) 4,5-Diaminopyrimidine-2-thione [5] (0·2 g), triethyl (or tributyl) orthoformate (1·5 ml), and acetic anhydride (0·5 ml) were boiled under reflux for 4—11 h. The mixture was cooled and filtered. The solid was washed with ether and crystallized from water to give the anhydrous purinethione (90%; *cf.* ref. 6: 65%), decomp. >280° (Found: C, 39·5; H, 2·8; N, 36·8. Calc. for $C_5H_4N_4S$: C, 39·5; H, 2·7; N, 36·8%). Unlike this material, the quarter-hydrate previously described [7] showed carbonyl absorption at 1690 cm^{-1}, probably indicating persistent contamination by a formamidopyrimidine intermediate. The use of triallyl orthoformate produced a dark mixture from which only the thione (30%) could be isolated.

(*b*) Repetition of (*a*) using trimethyl orthoformate (1·5 ml) and an 11 h heating period gave a crude product from which chloroform extracted 2-methylthiopurine (25%), identified with authentic material [7] by i.r. and mixed m.p. comparison. The residue was purine-2-thione (51%) as above.

4,5-Diamino-2-ethylthiopyrimidine (4; R = Et).—4,5-Diaminopyrimidine-2-thione [5] (2·0 g), ethanolic 0·1M-sodium ethoxide (20 ml), and ethyl iodide (2·3 g) were stirred at 25° until the solid had dissolved (*ca.* 5 h). Evaporation gave the *ethylthiopyrimidine* (85%), m.p. 155—157° (from water) (Found: C, 42·6; H, 5·8; N, 33·0. $C_6H_{10}N_4S$ requires C, 42·3; H, 5·9; N, 32·9%).

2-Ethylthiopurine (3; R^1 = SEt, R^2 = H).—(*a*) The above diamine (0·5 g), triethyl orthoformate (2·1 ml), and acetic anhydride (0·7 ml) were boiled under reflux for 4 h. Evaporation of the suspension gave the *ethylthiopurine* (78%), m.p. 141—143° (from water containing 10% ethanol) (Found: C, 46·6; H, 4·5; N, 31·05. $C_7H_8N_4S$ requires C, 46·6; H, 4·5; N, 31·1%).

(*b*) Purine-2-thione (0·3 g), triethyl orthopropionate (5 ml), and acetic anhydride (1·5 ml) were boiled under reflux for 4 h. The residue from evaporation was triturated with ether to give a solid which on dissolution in warm M-sodium hydroxide and reprecipitation with acetic acid gave the same ethylthiopurine (30%) as above (mixed m.p., i.r. spectra).

2-Ethylthio-8-methylpurine (3; R^1 = SEt, R^2 = Me).—(*a*) 8-Methylpurine-2-thione [1] (0·1 g), triethyl orthopropionate (2 ml), and propionic anhydride (1 ml) were boiled under reflux for 4 h. After cooling, the solid was filtered off, washed with ether, and then dissolved in chloroform. Evaporation of the filtered extract gave the *ethylthio-8-methylpurine* (78%), m.p. 218—220° (from water) (Found: C, 49·4; H, 5·0; N, 28·8. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·8%), δ [$(CD_3)_2SO$] 1·36 (t, *J* 7·7, Me of SEt), 2·52 (s, 8-Me), 3·18 (q, *J* 7·7, CH_2), and 8·8 (s, 6-H). When the anhydride was omitted, the methylpurinethione was recovered.

(*b*) The same thione (0·15 g), ethanolic 0·5M-sodium ethoxide, and ethyl iodide (0·2 g) were stirred for 30 min. The solution was acidified to pH *ca.* 4 and then evaporated. Chloroform extraction of the residue and subsequent evaporation gave the same product (40%) as in (*a*).

(*c*) 4,5-Diaminopyrimidine-2-thione [5] (0·2 g), triethyl orthoacetate (1·5 ml), and acetic anhydride (0·5 ml) were boiled under reflux for 4 h. Evaporation gave a solid consisting of three products (t.l.c. in ethanol). Extraction with chloroform and evaporation of the extract gave the ethylthio-8-methylpurine (20%). Dissolution of the chloroform-insoluble residue in M-sodium hydroxide and subsequent adjustment to pH 4 gave immediately 4-amino-5-α-ethoxyethylideneaminopyrimidine-2-thione (40%), identified by n.m.r. spectral comparison with authentic material,[1] δ [$(CD_3)_2SO$–DCl] 1·21 (t, *J* 7·7, Me of OEt), 2·02 (s, Me of ethylidene), 4·05 (q, *J* 7·7, CH_2 of OEt), and 7·77 (s, 6-H) (Found: N, 26·6. Calc. for $C_8H_{12}N_4OS$: N, 26·4%). Refrigeration of the filtrate gave 8-methylpurine-2-thione (10%), identical with authentic material.[1]

When the orthoester–anhydride mixture was boiled under reflux for 2 h before addition of the pyrimidinethione, the purinethione (35%) and the ethoxyethylidenepyrimidine (60%) were the only products: no *S*-alkylation occurred.

8-Ethylpurine-2(3H)-thione (2; R = Et).—(*a*) 4,5-Diaminopyrimidine-2-thione [5] (0·3 g), triethyl orthopropionate (1·5 ml), and propionic anhydride (0·5 ml) were boiled under

reflux for 15 min. After cooling, the solid was removed and washed with ether followed by chloroform [the chloroform extract contained a small amount of 8-ethyl-2-ethylthiopurine, identical with authentic material (see later)]. The residue was recrystallized from glacial acetic acid to give the *ethylpurinethione* (58%), m.p. 282—285° (decomp.) (Found: C, 46·8; H, 4·8; N, 30·7. $C_7H_8N_4S$ requires C, 46·7; H, 4·5; N, 31·1%).

(*b*) The same pyrimidinethione (0·5 g), triethyl orthopropionate (2·3 g), and acetic anhydride (2·8 g) were boiled under reflux for 2·5 h. Evaporation gave a crude acylated product (*cf.* analogue later) which, on boiling in a little water, gave the ethylpurinethione (50%), identical with that in (*a*).

8-Ethyl-2-ethylthiopurine (3; R^1 = SEt, R^2 = Et).—(*a*) 4,5-Diamino-2-ethylthiopyrimidine (0·5 g), triethyl orthopropionate (3 ml), and propionic anhydride (1 ml) were boiled under reflux for 4 h. Refrigeration gave the *ethylethylthiopurine* (80%), m.p. 208—210° (from water) (Found: C, 52·2; H, 5·7; N, 26·8. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9%), δ [$(CD_3)_2SO$] 1·35 (t, both Me), 3·05 (m, both CH_2), and 8·83 (s, 6-H). Similar treatment of purine-2-thione as substrate gave the same product (60%).

(*b*) 4,5-Diaminopyrimidine-2-thione [5] (0·72 g), triethyl orthopropionate (12 ml), and propionic anhydride (3 ml) were heated as in (*a*). Partial evaporation and filtration gave the same ethyl-ethylthiopurine (55%) (m.p. and spectra).

(*c*) To 4,5-diamino-2-ethylthiopyrimidine (0·5 g) dissolved in *NN*-dimethylpropionamide (3·5 ml) was added phosphoryl chloride (0·5 ml) in drops. After 30 min, the mixture was poured into ice–water with stirring. After adjustment to pH 5, the aqueous mixture was extracted with chloroform. Evaporation of the dried extract gave the same ethyl-ethylthiopurine (15%) as in (*a*).

Diacetyl Derivative of 8-methylpurine-2-thione.—(*a*) 8-Methylpurine-2-thione [1] (0·1 g) or 4-amino-5-α-ethoxyethylideneaminopyrimidine-2-thione [1] was boiled under reflux with acetic anhydride (1 ml) for 90 min. Evaporation gave a single diacetyl derivative (70%), m.p. 150—552° [from benzene–hexane (1 : 3)] of unknown orientation, δ ($CDCl_3$) 2·5 (s, 8-Me), 2·88 (s, Ac), 3·03 (s, Ac), and 9·08 (s, 6-H), $\nu_{max.}$ 1758 and 1720 cm^{-1} (C=O) (Found: C, 48·3; H, 4·35; N, 22·1. $C_{10}H_{10}N_4O_2S$ requires C, 48·0; H, 4·0; N, 22·4%).

(*b*) 4,5-Diaminopyrimidine-2-thione [5] (0·2 g), triethyl orthoacetate (1·6 g), and acetic anhydride (2 g) were boiled under reflux for 4 h. Evaporation followed by trituration of the residue with ether gave the same diacetyl derivative (65%) as in (*a*).

This derivative was converted into 8-methylpurine-2-thione (>95%) either by boiling in water for a few minutes or by dissolution in M-sodium hydroxide and reprecipitation with acetic acid.

8-Ethyl-2-methylthiopurine (3; R^1 = SMe, R^2 = Et).—4,5-Diamino-2-methylthiopyrimidine [7] (0·5 g), triethyl orthopropionate (1·5 ml), and propionic anhydride (5 ml) were boiled under reflux for 4 h. After refrigeration, the *ethylmethylthiopurine* (80%) was filtered off. It had m.p. 208—210° (from 30% ethanolic water), δ [$(CD_3)_2SO$] 1·32 (t, *J* 7·5, Me of Et), 2·55 (s, SMe), 2·9 (q, *J* 7·5, CH_2), and 8·85 (s, C–H) (Found: C, 49·3; H, 5·2; N, 28·7. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·8%).

8-Ethyl-6-methyl-2-methylthiopurine.—Similar treatment of 4,5-diamino-6-methyl-2-methylthiopyrimidine [9] gave the *6-methylated purine* (50%), m.p. 200—202° (from 10% ethanolic water), δ [$(CD_3)_2SO$] 1·34 (t, Me of Et), 2·52 and 2·60 (s, SMe and 6-Me), and 2·85 (q, CH_2) (Found: C, 51·8; H, 5·6; N, 26·7. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9%).

8-Phenylpurine-2(3H)-thione (2; R = Ph) *and 2-Ethylthio-8-phenylpurine* (3; R^1 = SEt, R^2 = Ph).—4,5-Diaminopyrimidine-2-thione [5] (0·4 g), triethyl orthobenzoate (2·5 ml), and acetic anhydride (0·5 ml) were heated under reflux for 4 h. After partial evaporation *in vacuo*, the solid was dissolved in 2M-sodium hydroxide. Acidification gave a solid which was washed with a little ether and then triturated with chloroform. Evaporation of the extract gave the *ethylthiopurine* (51%), m.p. 232—234° (from aqueous ethanol), δ [$(CD_3)_2SO$] 2·2 (t, *J* 8, Me), 3·22 (q, *J* 8, CH_2); 7·62 (m, 3′,4′,5′-H_3), 8·3 (m, 2′,6′-H_2), and 8·98 (s, 6-H) (Found: C, 61·2; H, 4·8; N, 21·7. $C_{13}H_{12}N_4S$ requires C, 60·9; H, 4·7; N, 21·8%). The chloroform-insoluble residue proved to be the *phenylpurinethione* (5%), m.p. >300° (decomp.) (Found: C, 58·0; H, 3·8; N, 24·1. $C_{11}H_8N_4S$ requires C, 57·9; H, 3·5; N, 24·5%).

8-Ethylthiopurine (5).—(*a*) Purine-8-thione [8] (1·86 g), ethanolic 0·5M-sodium ethoxide (45 ml), and ethyl iodide (2·2 g) were stirred for 40 min. After acidification to pH *ca.* 5, the mixture was evaporated. Chloroform extraction and subsequent evaporation gave the *ethylthiopurine* (85%), m.p. 197° (from water), δ [$(CD_3)_2SO$] 1·43 (t, *J* 7, Me), 3·39 (q, *J* 7, CH_2), 8·81 (s, 2-H), and 8·91 (s, 6-H) (Found: C, 46·4; H, 4·5; N, 31·2. $C_7H_8N_4S$ requires C, 46·6; H, 4·5; N, 31·1%).

(*b*) Purine-8-thione (0·15 g), triethyl orthopropionate (1·5 ml), and propionic anhydride (0·8 ml) were heated for 1 h. Evaporation and trituration of the oily residue with ether gave a solid acylated product (i.r.) which was converted by crystallization from boiling water into the ethylthiopurine (70%) identical with that from (*a*).

Alkylation of 2-Thiouracil (7; R = H) *by Orthoester–Anhydride.*—2-Thiouracil (1 g) was boiled under reflux with triethyl orthopropionate (32 ml) and propionic anhydride (15 ml) for 4 h. The solution was concentrated on a rotary evaporator (90°; 40 mmHg; 1 h) to *ca.* 2 ml. After refrigeration for 12 h, the solid was filtered off and washed with light petroleum. The filtrate and washings were set aside. The solid (a mixture of two compounds: t.l.c. on silica in ether) was extracted with boiling ether (40 ml). The residue was recrystallized from water to give 1-ethyl-2-thiouracil (40 mg), m.p. 239—241° (lit.,[10] 240—241°) (Found: C, 46·5; H, 5·4. Calc. for $C_6H_8N_2OS$: C, 46·2; H, 5·2%), u.v. spectrum identical with that published,[11] δ ($CDCl_3$) 1·4 (t, Me), 4·28 (q, CH_2), 6·00 (d, 5-H), and 7·35 (d, 6-H). The residue from evaporation of the ether extract was submitted to t.l.c. (silica in ether) to give more 1-ethyl-2-thiouracil (30 mg) and 2-ethylthiopyrimidin-4(3*H*)-one (80 mg), m.p. 152—154° (lit.,[12] 151°), n.m.r. identical with that published [13] (Found: C, 46·0; H, 5·2. Calc. for $C_6H_8N_2OS$: C, 46·2; H, 5·2%). The original filtrate and washings were evaporated: prolonged refrigeration gave 1-ethyl-2-thiouracil (130 mg).

[9] R. N. Prasad, C. W. Noell, and R. K. Robins, *J. Amer. Chem. Soc.*, 1959, **81**, 193.
[10] W. C. Schneider and I. F. Halverstadt, *J. Amer. Chem. Soc.*, 1948, **70**, 2626.
[11] D. Shugar and J. J. Fox, *Bull. Soc. chim. belges*, 1952, **61**, 293.
[12] H. L. Wheeler and H. F. Mirriam, *Amer. Chem. J.*, 1903, **29**, 478.
[13] F. Nishiwaki, *Tetrahedron*, 1967, **23**, 2657.

Alkylation of 4-Thiouracil (9; R = H) *by Orthoester–Anhydride.*—4-Thiouracil [14] (0·45 g), triethyl orthopropionate (10 ml), and propionic anhydride (5·5 ml) were boiled under reflux for 1 h. Refrigeration gave *4-ethylthiopyrimidin-2(1H)-one* (0·15 g), m.p. 176—178° (from water) (Found: C, 46·3; H, 5·2; N, 18·0. $C_6H_8N_2OS$ requires C, 46·2; H, 5·2; N, 18·0%), δ [$(CD_3)_2SO$] 1·25 (t, *J* 8, Me), 3·08 (q, *J*, 8, CH_2), 6·25 (d, *J* 6, 5-H), 7·65 (d, *J* 6, 6-H), and 11·5br (s, NH), $\lambda_{max.}$ (MeOH) 295 and 278infl nm (*cf.* 4-methylthiopyrimidin-2-one: [15] 295 and 275infl). The original filtrate was evaporated to *ca.* 2 ml. Refrigeration gave a solid which was separated into two components on a silica column (ether). Evaporation of the eluate gave *3-ethyl-4-thiouracil* (0·1 g), m.p. 160—162° (from water) (Found: C, 46·2; H, 5·0; N, 17·8. $C_6H_8N_2OS$ requires C, 46·2; H, 5·2; N, 18·0%), δ [$(CD_3)_2SO$] 1·18 (t, *J* 8, Me), 4·40 (q, *J* 8, CH_2), 6·43 (d, *J* 6, 5-H), and 7·32 (d, *J* 6, 6-H), $\lambda_{max.}$ (MeOH) 260 and 325 nm (*cf.* 3-methyl-4-thiouracil: [16] 260 and 322). [Treatment of a sample with chloroacetic acid gave 3-ethyluracil, m.p. 170—172° (lit.,[17] 173—174°), $\lambda_{max.}$ (pH 5) 259 nm (lit.,[18] 258·5)]. Final elution of the column with methanol gave a second crop of 4-ethylthiopyrimidin-2-one (0·1 g).

We thank Dr. G. B. Barlin for discussions and Mr. S. E. Brown for ^1H n.m.r. spectra.

[3/698 *Received*, 3*rd April*, 1973]

[14] Y. Mizuno, M. Ikehara, and K. A. Watanabe, *Chem., and Pharm. Bull.* (*Japan*), 1962, **10**, 647.
[15] T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, 1965, **30**, 2766.
[16] T. Ueda and J. J. Fox, *J. Amer. Chem. Soc.*, 1963, **85**, 4024.
[17] T. B. Johnson and P. F. W. Heyl, *Amer. Chem. J.*, 1907, **37**, 628.
[18] D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, 1952, **9**, 199.