globulins together with protein-bound carbohydrates can be specifically elevated in certain conditions of diabetes.[24,25]

The function of these α_2-glycoproteins in the human organism is unknown. However, certain properties of their activities were observed. In contrast to the α_1-acid glycoprotein[26] the α_2-glycoproteins do not seem to have the property of affecting the restoration *in vitro* of the submicroscopic structure of collagen.[27] Further work on the inhibition of the hemagglutinating effect of inactivated influenza virus showed that the α_2-glycoprotein fraction described here strongly exhibits this effect.[22] In their studies with thyroxin, Petermann and co-workers[28,29] found that this α_2-glycoprotein fraction (probably one of its components) may be the carrier of this hormone.

Acknowledgments.—The author wishes to express his thanks to Drs. John T. Edsall and John L. Oncley for their encouragement and valuable help. The technical assistance of Miss V. R. Farrell, who carried out and calculated the electrophoretic and ultracentrifugal analyses, is gratefully acknowledged.

(21) H. Roeckl and R. Jaroschka, *Arch. Derm. Syph.*, **196**, 223 (1953).

(22) D. A. Tyrell, *J. Immun.*, **72**, 494 (1954).

(23) W. F. Lever, E. L. Schultz and N. A. Hurley, *Arch. Derm. Syph.*, **63**, 702 (1951); E. M. Greenspan, *Arch. Int. Med.*, **93**, 863 (1954).

(24) H. Rifkin and M. L. Petermann, *Diabetes*, **1**, 28 (1952).

(25) J. Berkman, H. Rifkin and G. Ross, *J. Clin. Invest.*, **32**, 415 (1952).

(26) J. H. Highberger, J. Gross and F. O. Schmitt, *Proc. Natl. Acad. Sci.*, **37**, 286 (1951).

(27) These analyses were kindly carried out by Dr. J. Gross.

(28) M. L. Petermann, J. Robbins and M. G. Hamilton, *J. Biol. Chem.*, **208**, 369 (1954).

(29) J. Robbins, M. L. Petermann and J. E. Rall, *Federation Proc.*, **13**, 280 (1954).

BOSTON, MASS.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Reductive Desulfurization of Thiohydantoins and Thiobarbituric Acids with Raney Nickel

BY W. B. WHALLEY,[1] ELVIN L. ANDERSON, F. DUGAN, JAMES W. WILSON AND GLENN E. ULLYOT

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The preparation of a number of substituted 4-imidazolidones, hexahydropyrimidine-4,6-diones and 4,6-dihydroxypyrimidines by the Raney nickel desulfurization of the corresponding 2-thiohydantoins and 2-thiobarbituric acids is described. On the basis of isolated intermediate products, possible mechanisms for the desulfurization reaction are proposed.

Recent reports[2] that the replacement of the 2-carbonyl of 5,5-disubstituted barbituric acids with a methylene group resulted in 5,5-disubstituted hexahydropyrimidine-4,6-diones (VIII) having utility as anticonvulsant agents became of interest to us because a similar transformation in the hydantoin series was reported to yield an inactive compound. Thus 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione (VIIIa) has been used successfully in the treatment of epilepsy[3] and is marketed in England under the trademark Mysoline, while 5,5-diphenyl-4-imidazolidone (Va) has been reported to be ineffective in raising the convulsant threshold of cats.[4] We decided to study the preparation of the latter and to provide an authentic sample for re-evaluation as an anticonvulsant agent.

We chose to prepare 5,5-diphenyl-4-imidazolidone from 5,5-diphenyl-2-thiohydantoin (Ia) by the previously employed[5,6] sodium and amyl alcohol reductive desulfurization procedure and to attempt the desulfurization with Raney nickel catalyst in a manner analogous to the transformation[2a] of 5-ethyl-5-phenyl-2-thiobarbituric acid (VIa) into 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione (VIIIa). The latter transformation also was studied.

During the course of our work the preparation of 5,5-diphenyl-4-imidazolidone by the Raney nickel method was reported.[7] Subsequent to our work the synthesis of a series of imidazolidones[8] and the formation of 2-alkoxy-5,5-disubstituted hexahydropyrimidine-4,6-dione (VII) intermediate reduction products[9] from the Raney nickel reduction of 5,5-disubstituted-2-thiobarbituric acids was published.

While our work duplicates in part and is in substantial agreement with the results obtained by others, we obtained a number of intermediate reduction products and several other compounds not previously reported.

When a solution of 5,5-diphenyl-2-thiohydantoin (Ia) in ethanol was refluxed for 30 minutes with three-week old Raney nickel catalyst, the product was a mixture of several difficultly separable compounds. 5,5-Diphenyl-4-imidazolidone[5-8] (Va) was always produced in low yield, accompanied by the sulfide (IIIa) and 5,5-diphenyl-2-hydroxy-4-imidazolidone[5,6,8] (IIa).[10] Sublimation of IIa readily

(1) University of Liverpool, Liverpool, England.

(2) (a) W. R. Boon, H. C. Carrington and C. H. Vasey, U. S. Patents 2,578,847 (1951), 2,576,279 (1951), and British Patent 666,027 (1952); (b) W. R. Boon, N. Greenhalgh, E. London and C. H. Vasey, U. S. Patent 2,637,730 (1953).

(3) R. Handley and A. S. R. Stewart, *Lancet*, 1, 742 (1952).

(4) H. H. Merritt and T. J. Putnam, *Epilepsia*, **3**, 51 (1945); we are indebted to Dr. Louis S. Goodman for calling this to our attention.

(5) H. Biltz and K. Seydel, *Ann.*, **391**, 215 (1912).

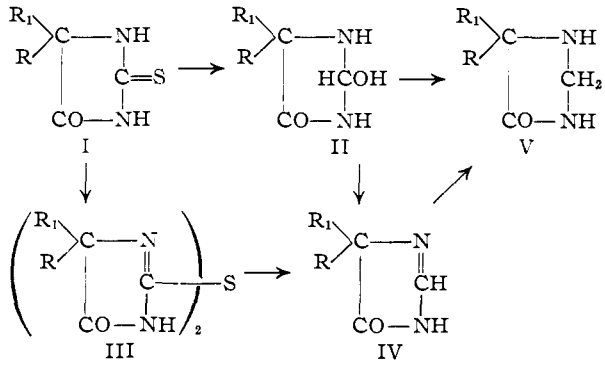
(6) H. Biltz, K. Seydel and E. Hamburger-Glasser, *ibid.*, **428**, 199 (1922).

(7) J. Stanek, *Chem. Listy.*, **45**, 459 (1951); *C. A.*, **46**, 7567 (1952).

(8) H. C. Carrington, C. H. Vasey and W. S. Waring, *J. Chem. Soc.*, 3105 (1953).

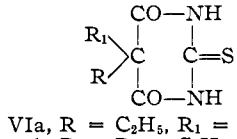
(9) W. R. Boon and C. H. Vasey, U. S. Patent 2,666,056 (1954).

(10) Carrington, Vasey and Waring (ref. 8) found a marked tendency for the 2-hydroxy compounds to be formed in the Raney nickel desulfurization of 5,5-pentamethylene-2-thiohydantoin and its 1-methyl-, 3-methyl- and 1,3-dimethyl derivatives. Interestingly, 1,3-dimethyl-5,5-diphenyl-2-thiohydantoin gave 2-ethoxy-1,3-dimethyl-5,5-diphenyl-4-imidazolidone when reduced in ethanol but gave 1,3-dimethyl-5,5-diphenyl-4-imidazolidone when reduced in methanol, propanol or cyclohexanol.

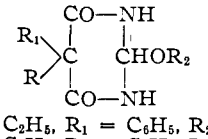


a, R = R_1 = C_6H_5
b, R = H, R_1 = C_6H_5
c, R = H, R_1 = CH_3
d, R = R_1 = CH_3
e, R = C_2H_5, R_1 = C_6H_5

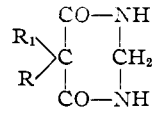
furnished 4,4-diphenyl-5-oxo-2-imidazoline[6,8,11] (IVa) which upon further reduction yielded Va. Direct reduction of IIa with additional Raney nickel gave Va almost quantitatively.



VIa, R = C_2H_5, R_1 = C_6H_5
b, R = R_1 = C_2H_5
c, R = C_2H_5, R_1 = isoamyl



VIIa, R = C_2H_5, R_1 = C_6H_5, R_2 = CH_3
b, R = C_2H_5, R_1 = C_6H_5, R_2 = C_2H_5
c, R = C_2H_5, R_1 = C_6H_5, R_2 = n-C_3H_7
d, R = C_2H_5, R_1 = C_6H_5, R_2 = n-C_4H_9



VIIIa, R = C_2H_5, R_1 = C_6H_5
b, R = R_1 = C_2H_5
c, R = C_2H_5, R_1 = isoamyl

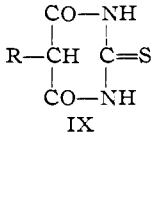
We have assigned structure IIIa to the novel sulfide intermediate on the basis of analyses, molecular weight determinations, conversion to Va by further treatment with Raney nickel, and oxidation in high yield with hydrogen peroxide to IVa. This latter reaction is essentially the same as the well known desulfurization with hydrogen peroxide of 2-mercapto-imidazoles to imidazoles,[12] and presumably occurs through acetic acid hydrolysis of the intermediate sulfone or sulfoxide.

No tangible crystalline products could be isolated when 5-phenyl- (Ib) and 5-methyl-2-thiohydantoin[13] (Ic) were treated with Raney nickel under a variety of experimental conditions. When 5,5-dimethyl-2-thiohydantoin[14] (Id) was similarly reduced, a crystalline product (m.p. 170°) was obtained. On the basis of analytical data, this product seemed to be 5,5-dimethyl-2-hydroxy-4-imidazolidone (IId). Carrington, *et al.*,[8] describe the same product and report a melting point of 169°. However, since this compound was recovered unchanged after sublimation and could not be further reduced to 5,5-dimethyl-4-imidazolidone (Vd), an alternative formulation as *a*-formylaminoisobutyramide is possible.

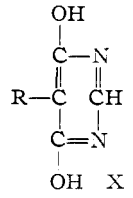
When 5-ethyl-5-phenyl-2-thiobarbituric acid (VIa) was desulfurized with Raney nickel by refluxing in boiling ethanol for four hours, 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione[2] (VIIIa) was obtained in high yield. A reflux period of 30 minutes, coupled with the use of a less active catalyst furnished appreciable quantities of a compound which must be 5-ethyl-5-phenyl-2-ethoxyhexahydropyrimidine-4,6-dione (VIIb).[9] The corresponding 2-methoxy-, 2-*n*-propoxy- and 2-*n*-butoxyhexahydropyrimidines (VIIa, VIIc, VIId) were obtained when methanol, *n*-propyl alcohol and *n*-butyl alcohol were employed as solvents instead of ethanol. All of these alkoxyhexahydropyrimidines[9] (Table I) were readily and quantitatively reduced to VIIIa by further treatment with Raney nickel. No trace of 2-hydroxyhexahydropyrimidine or of bimolecular products was detected.

5,5-Diethylhexahydropyrimidine-4,6-dione[15] (VIIIb) and 5-ethyl-5-isoamylhexahydropyrimidine-4,6-dione (VIIIc) were obtained readily by the Raney nickel desulfurization technique from the corresponding thiobarbituric acids[16] (VI), but attempts to isolate intermediate reduction products failed.

Since the production of hexahydropyrimidines from thiobarbituric acids by the use of Raney nickel has been described only for 5,5-disubstituted thiobarbituric acids it seemed of interest to investigate the behavior of 5-monosubstituted thiobarbituric acids in this reaction. Consequently, 5-phenyl- (IXa), 5-benzyl-[17] (IXb), 5-ethyl-[18] (IXc) and 5-isoamyl- (IXd) 2-thiobarbituric acids were prepared and reduced with Raney nickel. No conclusive results were obtained with 5-phenyl-2-thiobarbituric acid because of the extreme insolubility of this compound. The other three thiobarbituric acids were converted readily, however, into the corresponding 5-benzyl- (Xb), 5-ethyl-[19] (Xc) and 5-isoamyl- (Xd) 4,6-dihydroxypyrimidines (Table II). As far as we are aware, this constitutes a new synthetic approach to 5-substituted-4,6-dihydroxy-



IX



X

a, R = C_6H_5
b, R = $C_6H_5CH_2$
c, R = C_2H_5
d, R = isoamyl

(11) H. Biltz and K. Seydel (ref. 5) originally formulated this imidazoline derivative as 5,5-diphenyl-4-oxo-2-imidazoline and later proposed the isomeric structure, 4,4-diphenyl-5-oxo-2-imidazoline (IVa). Carrington, *et al.*,[8] definitely established that alkylation of the imidazoline derivative with dimethyl sulfate yielded 4,4-diphenyl-1-methyl-5-oxo-2-imidazoline and on this basis assign structure IVa to the original dihydro compound. More recently Edward and Martlew [J. T. Edward and E. F. Martlew, *Chemistry & Industry*, No. 7, 193 (1954)], on the basis of absorption data express a preference for Biltz' original formulation and suggest that the double bond shifts in the alkylation reaction.

(12) I. E. Balaban and H. King, *J. Chem. Soc.*, 1858 (1927).

(13) M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar and S. Archer, THIS JOURNAL, **70**, 2884 (1948).

(14) H. C. Carrington, *J. Chem. Soc.*, 684 (1947).

(15) J. Tafel and H. B. Thompson, *Ber.*, **40**, 4491 (1907).

(16) (a) E. Fischer and A. Dilthey, *Ann.*, **335**, 350 (1904); (b) E. H. Volwiler and D. L. Tabern, U. S. Patent 2,153,179 (1939).

(17) E. H. Volwiler and D. L. Tabern, U. S. Patent 2,153,730 (1939).

(18) J. Lee, THIS JOURNAL, **60**, 993 (1938).

(19) R. Hull, *J. Chem. Soc.*, 2214 (1951).

TABLE I

2-ALKOXY-5-ETHYL-5-PHENYLHEXAHYDROPYRIMIDINE-4,6-DIONES (VII)

R_2	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	184[a]	4	$C_{13}H_{16}N_2O_3$	62.89	62.61	6.50	6.35	11.28	11.63
C_2H_5	182[b]	48	$C_{14}H_{18}N_2O_3$	64.10	64.22	6.92	7.04	10.68	11.09
$C_3H_7(n)$	158[c]	41	$C_{15}H_{20}N_2O_3$	65.19	65.16	7.30	7.45	10.14	9.98
$C_4H_9(n)$	152.5–154[d]	30	$C_{16}H_{22}N_2O_3$	66.18	66.13	7.64	7.55	9.65	9.42

The melting points reported in reference 9 are [a]185°, [b]186°, [c]159–160°, [d]151–152°.

TABLE II

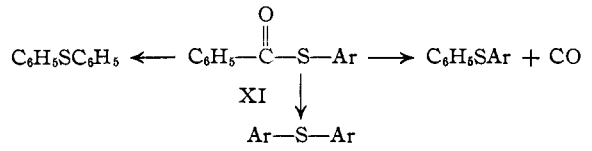
5-SUBSTITUTED-4,6-DIHYDROXY-PYRIMIDINES (X)

R	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
C_2H_5[a]	330	37	$C_6H_8N_2O_2$	51.43	51.51	5.71	5.72	20.00	19.87
$C_6H_5CH_2$	354	69	$C_{11}H_{10}N_2O_2$	65.34	65.40	5.00	5.22	13.85	13.88
iso-C_5H_{11}	289	58	$C_9H_{14}N_2O_2$	59.34	59.34	7.69	7.92	15.38	15.25

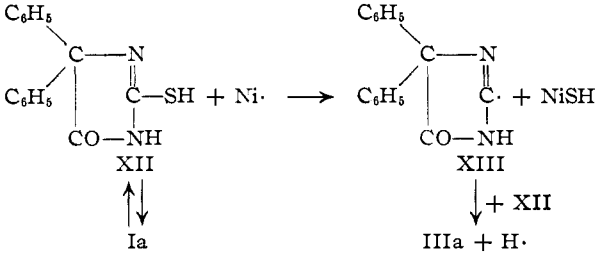
[a] R. Hull reported that this compound did not melt below 300° (see reference 19).

pyrimidines, although the removal of an alkylated mercapto group and its replacement by hydrogen using Raney nickel is a well established procedure in the pyrimidine series.[20] The production of a pyrimidine rather than a hexahydropyrimidine is attributable presumably to the 5-substituted 2-thiobarbituric acids reacting, if not actually existing, as the tautomeric 5-substituted 2-mercaptopyrimidines.

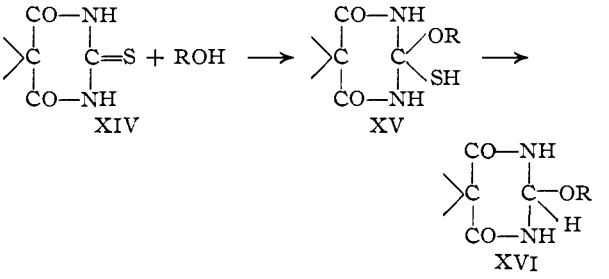
The reactions observed during the desulfurization of the 2-thiohydantoins and 2-thiobarbituric acids with Raney nickel are rather novel, and as far as we are aware no sulfur-containing intermediates have previously been isolated during the conversion of the >C=S group into $>CH_2$. Using specially prepared "hydrogen-poor" Raney nickel, Hauptmann and Wladislaw[21] were able to effect the following transformations of thio esters



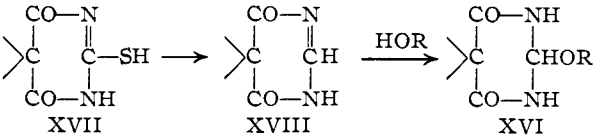
a reaction which approximates closely to that observed by us in the thiohydantoin series. The suggestion of these authors that their reactions followed a free radical mechanism is also compatible with our results in general. The production of the sulfide IIIa indicates that the reduction proceeds by ways of the mercapto form XII of the thiohydantoin.



On the other hand, the production of 2-alkoxyhexahydropyrimidines during the reduction of 2-thiobarbituric acids appears more compatible with the formation of an intermediate of the type XV followed by reductive desulfurization.[22]



However, Boon, *et al.*, have shown that such 2-hydroxy and 2-alkoxy compounds can be formed by addition of water or alcohol to 5,5-disubstituted tetrahydropyrimidine-4,6-diones[9]; thus the pathway XVII–XVIII–XVI cannot be excluded.



Experimental[23]

Reduction of 5,5-Diphenyl-2-thiohydantoin (Ia) with Raney Nickel.—A solution of 5 g. of 5,5-diphenyl-2-thiohydantoin in 125 ml. of ethanol containing 25 g. of suspended Raney nickel catalyst[24] was heated at reflux temperature for 30 minutes and filtered. The filtrate was concentrated to 25 ml., diluted with water to turbidity and allowed to stand. A crystalline product separated during 24 hours. The mother liquors were allowed to evaporate slowly at room temperature and successive crops of crystals were collected. Purification of the first crops by repeated crystallization from methanol, ethanol and ethyl acetate gave rise to a small, variable yield (0.5–1.0 g.) of **5,5-diphenyl-4-imidazolidone (Va)**,[5–8] m.p. 183°, identical with an authentic specimen.[5,6] Purification of the latter fractions from methanol, ethanol and finally from ethyl acetate–hexane gave rise to **di-2-(4,4-diphenyl-5-oxo-2-imidazolinyl) sulfide (IIIa)** in stout, colorless prisms, m.p. 195°, in yields of 0.5–1.0 g.

Anal. Calcd. for $C_{30}H_{26}N_4O_2S$: C, 71.12; H, 5.17; N,

(20) G. A. Howard, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 556 (1945).

(21) H. Hauptmann and B. Wladislaw, THIS JOURNAL, **72**, 707, 710 (1950).

(22) This mechanism is supported by the formation of 1,3-dimethyl-2-hydroxy-5,5-pentamethylene-4-imidazolidone, 1,3-dimethyl-2-ethoxy-5,5-diphenyl-4-imidazolidone and possibly by the formation of the other 2-hydroxy compounds mentioned in footnote 10.

(23) All melting points are uncorrected.

(24) H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 695 (1948).

11.06; S, 6.23; mol. wt., 506.61. Found: C, 71.56; H, 5.00; N, 11.09; S, 6.41; mol. wt., 506.05.

When a solution of 1.0 g. of the sulfide IIIa in 10 ml. of ethanol containing 4 g. of Raney nickel catalyst was refluxed for one hour and the product was isolated in the usual way, a quantitative yield of 5,5-diphenyl-4-imidazolidone was obtained, identical with an authentic specimen.[5,6]

When 2 cc. of 30% aqueous hydrogen peroxide was added to a solution of 1.0 g. of IIIa in 10 ml. of glacial acetic acid heat was evolved. After one hour the reaction mixture was diluted with 40 ml. of water. **4,4-Diphenyl-5-oxo-2-imidazoline (IVa)** separated and was crystallized from aqueous methanol or benzene–hexane to give stout, colorless prisms, m.p. 166–167°. Biltz, *et al.*,[5,6] reported a melting point of 166–167° and Carrington, *et al.*, reported 169–170°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.08; N, 11.86. Found: C, 75.88; H, 5.13; N, 11.69.

The mother liquors remaining after the separation of the sulfide and 5,5-diphenyl-4-imidazolidone slowly deposited a third product in rosettes of colorless prisms. Separation by hand picking and purification from ethyl acetate or alcohol gave **5,5-diphenyl-2-hydroxy-4-imidazolidone (IIa)** (*ca.* 100 mg.) in stout, colorless prisms, m.p. 182° dec. Upon admixture with 5,5-diphenyl-4-imidazolidone the mixture melting point was *ca.* 150°. Biltz and Seydel[5] record the melting point as 165° dec.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.86; H, 5.51; N, 11.02; S, 0.0. Found: C, 70.84; H, 5.64; N, 11.21; S, 0.0.

When a solution of 0.2 g. of II (R,R_1 = C_6H_5) in 10 ml. of alcohol containing 2 g. of Raney nickel was refluxed for two hours and the product isolated in the usual way, a quantitative yield of 5,5-diphenyl-4-imidazolidone was obtained, identified by melting point and a mixed melting point determination with an authentic sample.

When 5,5-diphenyl-2-hydroxy-4-imidazolidone (IIa) was sublimed at 160° (0.1 mm.), dehydration occurred and 4,4-diphenyl-5-oxo-2-imidazoline (IVa) was obtained in almost quantitative yield, m.p. 160–162°, undepressed upon admixture with a sample (m.p. 166–167°) prepared by permanganate oxidation[5,6] of 5,5-diphenyl-4-imidazolidone.

5-Ethyl-5-phenyl-2-thiohydantoin (Ie).—An intimate mixture of 25 g. (0.14 mole) of α-amino-α-phenylbutyric acid and 21.2 g. (0.28 mole) of thiourea was heated at 165–185° (internal temperature) for 3.2 hours. The sticky product was washed repeatedly by decantation with water and dilute hydrochloric acid. Crystallization from dilute alcohol gave 11 g. of white crystalline product, m.p. 160–165°. Further recrystallization raised the melting point to 170–172°; reported m.p. 171°.[3]

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; S, 14.56. Found: C, 60.11; H, 5.61; S, 14.45.

A small sample of the thio compound was oxidized with alkaline potassium permanganate to yield **5-ethyl-5-phenylhydantoin**, m.p. 199–202°, identical with an authentic sample of this compound.[25]

Reduction of 5-Ethyl-5-phenyl-2-thiohydantoin.—Eleven grams (0.05 mole) of this compound was reduced with sodium and isoamyl alcohol employing the procedure described by Biltz[5] for the reduction of 5,5-diphenyl-2-thiohydantoin. The product, **5-ethyl-5-phenyl-4-imidazolidone (Ve)**, after crystallization from alcohol weighed 6.1 g. (64%); m.p. 140–142°, reported m.p. 142–143°.[3]

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.54; H, 7.52; N, 14.78.

Reduction of 5,5-Dimethyl-2-thiohydantoin (Id) with Raney Nickel.—A solution of 5 g. of 5,5-dimethyl-2-thiohydantoin[14] in 125 ml. of ethanol containing a suspension of 25 g. of Raney nickel catalyst was refluxed for periods ranging from 15 minutes to four hours. Only one product was isolated in quantities from 3 to 4 g. This compound crystallized from ethyl acetate–methanol as colorless, silky needles, m.p. 170°. It was recovered unchanged after sublimation at 200° (0.5 mm.).

Anal. Calcd. for $C_5H_{10}N_2O_2$: C, 46.15; H, 7.70; N, 21.53; S, 0.0. Found: C, 46.46; H, 7.88; N, 21.47; S, 0.0.

5-Phenyl-2-thiohydantoin (Ib).—A solution of 20 g. (0.15 mole) of *dl*-α-aminophenylacetic acid and 20 g. (0.26 mole) of ammonium thiocyanate in a mixture of 10 ml. of acetic acid and 100 ml. of acetic anhydride was refluxed for 45 minutes and then poured into 1000 ml. of water. The solid monoacetyl derivative was crystallized from methanol; 17 g. (50%), m.p. 208°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.62; H, 4.53; N, 10.83.

Hydrolysis of the acetyl derivative (17 g.) by refluxing for four hours with 250 ml. of 2 *N* hydrochloric acid gave, after crystallization from methanol, 12 g. of 5-phenyl-2-thiohydantoin, m.p. 227°.

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.50; H, 4.56; N, 14.56; S, 16.60.

Attempted Reduction of 5-Phenyl- (Ib) and 5-methyl-2-thiohydantoin (Ic).—When solutions of 5 g. of either 5-phenyl-2-thiohydantoin or 5-methyl-2-thiohydantoin[13] in 125 ml. of ethanol containing a suspension of 25 g. of Raney nickel catalyst were refluxed for periods of time varying from one to four hours, the only products obtained were viscous brown oils which could not be crystallized. The material obtained from attempted reductions of 5-methyl-2-thiohydantoin had the odor of acetamide.

5-Phenyl-2-thiobarbituric Acid (IXa).—To a solution of 12 g. (0.52 mole) of sodium in 250 ml. of ethanol was added 24 g. (0.32 mole) of thiourea and 50 g. (0.21 mole) of phenylmalonic ester. After refluxing for eight hours the reaction mixture was cooled, diluted with 500 ml. of water and extracted with two 150-ml. portions of ether. The aqueous layer was acidified with concentrated hydrochloric acid. The colorless, crystalline product was recrystallized from a large volume of methanol; 40 g. (87%), m.p. 257°. It was very sparingly soluble in the usual organic solvents.

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72; S, 14.56. Found: C, 54.30; H, 4.06; N, 12.72; S, 14.24.

5-Isoamyl-2-thiobarbituric Acid (IXd).—This compound was similarly prepared in 46% yield from isoamyl malonic ester and thiourea. It melted at 162° after crystallization from methanol.

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.44; H, 6.59; N, 13.07. Found: C, 50.27; H, 6.84; N, 13.23.

Reduction of 5-Monosubstituted-2-thiobarbituric Acids (IX) with Raney Nickel Catalyst. General Procedure.—A solution of 5 g. of the thiobarbituric acid in 100 ml. of ethanol containing 25 g. of Raney nickel catalyst was refluxed for four hours. The Raney nickel was removed by filtration and the filtrate was evaporated to a small volume on the hot-plate. The **5-substituted-4,6-dihydroxypyrimidines** (X, Table II) were crystallized from methanol. In the case of the highly insoluble 5-phenyl-2-thiobarbituric acid this procedure did not yield the desired product.

5-Ethyl-5-isoamylhexahydropyrimidine-4,6-dione (VIIIc).—This compound was prepared by refluxing a solution of 5 g. of the thiobarbituric acid[16] in 120 ml. of ethanol containing 25 g. of Raney nickel catalyst for five hours. The catalyst was removed by filtration and the product was isolated by evaporation of the solvent and crystallization from methanol; 3 g. (71%), m.p. 271°.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50, N, 13.20. Found: C, 62.11, H, 9.50; N, 13.00.

5,5-Diethylhexahydropyrimidine-4,6-dione (VIIIb).—This compound was prepared from 5,5-diethyl-2-thiobarbituric acid[16] in 70% yield using the procedure described above. After crystallization from methanol it melted at 300° and sublimed unchanged at 150° (0.1 mm.). Tafel and Thompson[15] prepared this compound by electrolytic reduction and reported a melting point of 292°.

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.47; H, 8.52; N, 16.41.

5-Ethyl-5-phenyl-2-alkoxyhexahydropyrimidine-4,6-diones (VII). General Procedure.—A solution of 5 g. of 5-ethyl-5-phenyl-2-thiobarbituric acid in 100 ml. of the appropriate alcohol (methanol, ethanol, *n*-propyl alcohol, *n*-butyl alcohol) containing 25 g. of Raney nickel catalyst was refluxed for 30 minutes. The catalyst was removed by filtration and added immediately to a second solution of 5 g. of the 5-ethyl-5-phenyl-2-thiobarbituric acid in 100 ml. of the same alcohol and this mixture was again refluxed for 30 minutes. The Raney nickel was again removed and dis-

(25) H. Biltz, *Ber.*, **42**, 1796 (1909).

carded. The second filtrate was evaporated to a small volume (20–40 ml.) and allowed to stand overnight at room temperature. The 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione[2] (VIIIa), which crystallized, was removed. On further standing with slow evaporation of solvent, the crude 5-ethyl-5-phenyl-2-alkoxyhexahydropyrimidine-4,6-dione (VII, Table I) separated and was purified by repeated fractional crystallization from acetone, ethyl acetate or alcohol. In some instances where older and less active Raney nickel was used at the outset, appreciable quantities of the alkoxy compounds were obtained by concentration of the initial filtrate and repeated fractional crystallization of the crude product.

Further treatment of the 5-ethyl-5-phenyl-2-alkoxyhexahydropyrimidine-4,6-diones with fresh Raney nickel furnished nearly a quantitative yield of 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione.

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NOTES

Structure of the "Adduct" of Benzoquinone and Quinaldine

BY AKSEL A. BOTHNER-BY

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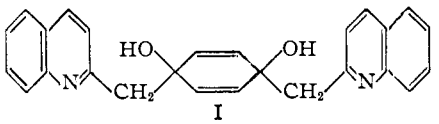
Bell[1] has reported the preparation of a crystalline material, m.p. 154°, by the reaction of benzoquinone and quinaldine in refluxing xylene. The compound gave hydroquinone diacetate on treatment with acetic anhydride, and analytical figures agreeing roughly with its formulation as an adduct of one mole of benzoquinone with two moles of quinaldine. On the basis of this evidence, he suggested the structure I for the product.



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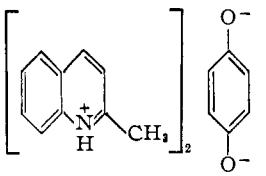

II

Since the aldol condensation leading to such a formulation did not seem very likely, nor did the manner of formation of hydroquinone diacetate seem clear, a further investigation into the structure was undertaken. The preparation of the material by the method given by Bell succeeded perfectly, but purification by crystallization was rendered difficult by tar formed during the reaction. It was found that pure white crystals could be obtained by sublimation at 160° at atmospheric pressure, and by recrystallization from ethyl acetate. An elementary analysis of the material gave figures agreeing better with an empirical formula $C_{26}H_{24}O_2N_2$ than with the empirical formula of an adduct ($C_{26}H_{22}O_2N_2$). The preparation of hydroquinone diacetate was repeated as described by Bell, and from the mother liquors it was possible to isolate in good yield quinaldine, identified as its picrate. Treatment of the "adduct" with cold dilute alkali also liberated quinaldine. All these facts point directly to the conclusion that the compound is actually an adduct of hydroquinone and quinaldine, rather than of benzoquinone and quinaldine. Such was easily demonstrated to be the case by the synthesis of the compound from these reactants. Solution of the two components in ethyl acetate resulted in quantitative formation of the compound m.p. 153–155°, identical in every respect with that obtained by Bell's procedure.

The compound in the solid state displays a diffuse infrared absorption band in the region 3.5–4.0 μ, and consequently is formulated as a salt, although it is probably completely dissociated in solution. Its formation from quinone and quinaldine is explained readily on the assumption that a part of the quinaldine is oxidized by the quinone, which is thereby reduced to hydroquinone. The salt then precipitates from the very non-polar solvent. The formation of a salt from a weak base and a weak acid, not ordinarily observed, may be promoted in this case by complexing in the crystal. That other factors than simple stoichiometry are involved is apparent from other examples of salt formation of this kind: hydroquinone and quinoline react to give a compound of the empirical formulas (quinoline)$_2$(hydroquinone),[2,3] while hydroquinone and pyridine react in a 1:1 relationship.[2]

Structure II is suggested for the compound.

Experimental

Preparation from Quinone and Quinaldine.—Quinone was freshly sublimed, and quinaldine and xylene were freshly distilled. The directions of Bell were followed. An analytical sample was prepared by sublimation, recrystallization from ethyl acetate, and resublimation, m.p. 154–155°.

Anal.[4] Calcd. for $C_{26}H_{22}O_2N_2$: C, 79.16; H, 5.62; N, 7.10. For $C_{26}H_{24}O_2N_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.64; H, 6.35; N, 7.00.

Reaction with Acetic Anhydride.—Purified "adduct" (0.666 g.) was heated on the steam-bath for two minutes with acetic anhydride (2.00 ml.), then allowed to stand overnight. Water (8.0 ml.) was added, and the suspension was then shaken for 15 minutes, and filtered. Colorless platelets of hydroquinone diacetate, m.p.[5] and mixed m.p. 122–123° were obtained in 71% yield. The filtrate was

(1) F. Bell, *J. Chem. Soc.*, 348 (1953).

(2) A. Baeyer and V. Villiger, *Ber.*, **35**, 1208 (1902).

(3) A. Bolland, *Monatsh.*, **31**, 419 (1910).

(4) Microanalysis by S. M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology.

(5) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948.