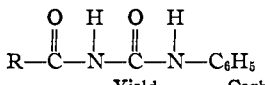
TABLE I



R-	M. p., °C.	Solvent	Color	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Furyl	186–188	EtOH	White	50	62.60	62.75	4.38	4.55	12.27	12.18
5-Bromo-2-furyl-	198–200	HOAc	White	98	46.59	46.91	2.93	2.95	9.06	9.35
5-Methyl-2-furyl-	162–163	EtOH	White	45	63.91	63.98	4.95	4.99	11.47	11.58
5-*t*-Butyl-2-furyl	186–188	EtOH	White	64	67.49	67.66	6.34	6.32	9.79	9.96
5-Nitro-2-furyl-	249–251	HOAc	Yellow	79	52.37	52.57	3.30	3.53	15.27	15.27
β-(2-Furyl)-vinyl-	198–201	EtOH	Tan	73	65.61	65.64	4.77	4.99	10.94	11.03

N-substituted furamides did not add normally to phenyl isocyanate and no characterizable product could be isolated from the reaction mixture.

Experimental

Starting Materials.—Details of the preparation of the substituted 2-furamides will appear in a later paper in this series.

Addition of Amides to Phenyl Isocyanate.—A mixture of the amide with a slight excess of phenyl isocyanate was heated under gentle reflux until entirely liquid (5–10 minutes). Ten milliliters of absolute ethanol was added cautiously to react with excess phenyl isocyanate and the solution was chilled. The solid which separated was isolated on a filter, washed with cold ethanol and recrystallized to constant melting point. The properties of the resulting 1-acyl-3-phenylureas are given in Table I.

Acylation of Phenylurea.—A solution of 6.75 g. (0.05 mole) of phenylurea in 20 ml. of benzene was heated to the reflux temperature and to the hot mixture was added slowly a solution of 6.5 g. (0.05 mole) of 2-furoyl chloride in 10 ml. of dry benzene. The mixture was heated under reflux while stirring vigorously for 6 hours.

The solution was cooled to room temperature and the solid which separated was isolated and recrystallized from hot ethanol to give 0.8 g. (7%) of 1-(2-furoyl)-3-phenylurea which melted at 187–188°. Mixing with the product from addition of 2-furamide to phenyl isocyanate did not depress the melting point of this product.

1-(5-Bromo-2-furoyl)-3-phenylurea was prepared similarly in 1% yield by acylation of a toluene solution of phenylurea with 5-bromo-2-furoyl chloride.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NEBRASKA
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COMMUNICATIONS TO THE EDITOR

ENZYMATIC PHOSPHORYLATION OF *l*-ASPARTATE

Sir:

The biological incorporation of amino acids into more complex compounds is known in certain instances[1] to utilize energy from ATP.[2] However, phosphorylated intermediates have not been demonstrated in these processes, and the mechanisms of energy transfer are obscure. The enzymatic formation of an "energy-rich" amino acid-phosphate compound, β-aspartyl phosphate, is described here. Suggestive evidence that this substance is a precursor of asparagine is the presence in the enzyme preparation of a very active asparagine "transferase" similar to the enzymes found by Waelsch and co-workers[3] in certain bacteria.

The enzyme was obtained from an extract of baker's yeast and purified about 10-fold with weak acid and ammonium sulfate. It appears to catalyze the reaction

ATP + *l*-aspartate $\rightleftarrows$ ADP + β-aspartyl phosphate

Though its equilibrium is unfavorable to accumulation of the new compound, the reaction may be followed readily if hydroxylamine is used to trap the aspartyl phosphate, forming a hydroxamic acid, as has been done with acetyl phosphate.[4] In Table I are shown the essential components of the system and the effect on hydroxamate formation of omitting each. Substitution of *d*-aspartate or *l*-glutamate reduced hydroxamic acid formation to 2 and 6%, respectively, of the value with *l*-aspartate.

TABLE I

All tubes contained 0.4 μM. hydroxylamine hydrochloride brought to *p*H 8.0 with tris. The incubation was at 30° for 30 minutes in a total volume of 1.0 ml.

Component omitted	Hydroxamic acid formed, μM.
None	3.2
25 μM. *l*-aspartate (potassium salt)	0.09
10 μM. ATP (sodium salt)	0.00
10 μM. $MgCl_2$	0.14
Enzyme, 0.1 ml.	0.00

High concentrations of aspartate and ATP favor synthesis of aspartyl phosphate, as shown in Table II. In this experiment hydroxylamine at *p*H 4.0 was added to stop the enzymatic activity after samples had been taken for phosphate analyses. Acyl phosphate was determined as hydroxamic acid,[5] and as the difference between inorganic

(1) P. P. Cohen in W. D. McElroy and B. Glass, "Phosphorus Metabolism," The Johns Hopkins Press, Baltimore, Md., 1951, Vol. I, p. 630.

(2) Abbreviations used are ATP (adenosine triphosphate), ADP (adenosine diphosphate), AMP (adenosine-5-phosphate), and tris-[tris-(hydroxymethyl)-methylamine].

(3) H. Waelsch, *Advances in Enzymol.*, **13**, 237 (1952).

(4) F. Lipmann, *ibid.*, **6**, 231 (1946).

(5) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

phosphate values obtained with the Fiske–SubbaRow[6] and Lowry–Lopez[7] methods.

TABLE II

The complete system contained in 1.0 ml. 10 μM. $MgCl_2$, 40 μM. ATP, 650 μM. *l*-aspartate, and 0.1 ml. enzyme. Both substrates were adjusted to *p*H 8.0 with tris. The incubation was at 30° for 45 minutes. Shown in parentheses are the inorganic phosphate values from which acyl phosphate was calculated.

	Acyl phosphate	
	Hydroxamic acid method, μM.	Fiske–SubbaRow P minus Lowry-Lopez P, μM.
Omit aspartate	0.02	0.1 (0.6–0.5)
Complete system	2.6	2.7 (5.6–2.9)

ADP appears to be the other reaction product, though side reactions prevent its stoichiometric demonstration. Using low initial substrate concentrations, and hydroxylamine as a trapping agent, disappearance of 1 μM. of ATP was accompanied by formation of 1.3 μM. of inorganic phosphate, 1.04 of hydroxamate, 0.64 of ADP, and 0.13 μM. of AMP. This result was not significantly changed by the presence of 0.05 molar potassium fluoride. ATP was determined by the method of Kornberg,[8] ADP and AMP according to Kalckar.[9]

Asparthydroxamic acid derived from the reaction product was characterized as the beta isomer by chromatographic comparison with beta and alpha asparthydroxamic acids. These were prepared by heating the corresponding amides, asparagine and isoasparagine, with hydroxylamine. When mixed with the substance obtained from the enzymatic reaction, only the mixture with alpha isomer could be separated into two hydroxamate fractions.

We wish to express our appreciation to Dr. J. P. Greenstein for a generous gift of isoasparagine.

(6) C. H. Fiske and Y. SubbaRow, *J. Biol. Chem.*, **66**, 375 (1925).
(7) O. H. Lowry and J. A. Lopez, *ibid.*, **162**, 421 (1946).
(8) A. Kornberg, *ibid.*, **182**, 779 (1950).
(9) H. M. Kalckar, *ibid.*, **167**, 445 (1947).

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
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SIMON BLACK
NANCY M. GRAY

RECEIVED MARCH 17, 1953

THE PREPARATION OF SAMARIUM AND YTTERBIUM METALS[1]

Sir:

After many attempts, we have succeeded in preparing massive samarium metal. Previous workers have reported the preparation of this metal by reducing samarium chloride with potassium[2] and by electrolyzing a molten salt-bath containing samarium chloride[3], but neither of these preparations gave a product which permitted characterization of this metal. Attempts to prepare samarium in our laboratory by these methods, while not exhaustive, were not fruitful, and indicated that a better method of preparing samarium was very desirable. Numerous attempts were made to reduce samarium halides by active metals including lithium, sodium, potassium, barium, calcium and magnesium,[4-7] but in each case the divalent halide of samarium was the product, indicating a high position in the electromotive series for the $Sm-Sm^{++}$ couple.

In preparing some of the heavy rare earth metals,[8] several of them were found to be distinctly more volatile than lanthanum. Vapor pressure measurements have been made on lanthanum[5] and dysprosium which indicate that dysprosium has a vapor pressure about 300 times that of lanthanum at the same temperature. Preliminary chemical and metallurgical studies on samarium indicated that it too might be more volatile than lanthanum. This low vapor pressure of lanthanum compared to other rare earth metals, its low melting point and the high heat of formation of its oxide, along with the possible high vapor pressure of samarium, suggested the preparation of samarium by distilling it from a heated mixture of samarium oxide and lanthanum metal.

Using a welded tantalum crucible[9] eight inches long and one inch in diameter with walls 2.5 mils thick, 20 g. of freshly ignited samarium oxide (98% pure, the balance consisting of other rare earths) and 20 g. of freshly prepared lanthanum turnings were heated under a vacuum of less than 1 micron to 1450° and held at this temperature for 30 minutes. The upper half of the crucible extended out of the furnace and had a perforated tantalum lid. On opening, a silvery crystalline metallic deposit was found on the upper walls of the crucible and on the bottom of the cap. Analysis of the deposit showed it to be samarium metal of greater than 98% purity with no lanthanum detectable. In a subsequent preparation, 25 g. of metal was obtained representing a yield of over 80% from the original oxide.

Thirty grams of metal prepared in this manner was melted in a tantalum crucible under a pressure of one atmosphere of purified argon. The melting point as determined with an optical pyrometer was between 1025 and 1050°, which is considerably below the figure of 1300 to 1350° given for previous preparations.[3,10] The bulk density of this fused specimen was found to be 7.53 g./cc., which would represent an atomic volume of 20 cc./mole. This would place samarium in line with the "regular" rare earths on this basis, instead of with europium and ytterbium with which it is chemically associated. Preliminary X-ray diffraction studies on single crystals separated from the condensate indicate that samarium is

(1) Contribution No. 220 from the Institute for Atomic Research and Department of Chemistry, Iowa State College. Work was performed in the Ames Laboratory of the Atomic Energy Commission.
(2) W. Klemm and H. Bommer, *Z. anorg. allgem. Chem.*, **231**, 138 (1937).
(3) W. Muthmann and L. Weiss, *Ann.*, **331**, 1–46 (1904).
(4) D. H. Ahmann, U. S. Atomic Energy Commission, AECD-3205 1950.
(5) A. H. Daane, U. S. Atomic Energy Commission, AECD-3209, 1950.
(6) F. H. Spedding, H. A. Wilhelm, W. H. Keller, D. H. Ahmann, A. H. Daane, C. C. Hach and R. P. Ericson, *Ind. Eng. Chem.*, **44**, 553 (1952).
(7) F. H. Spedding and A. H. Daane, THIS JOURNAL, **74**, 2783 (1952).
(8) A. H. Daane and F. H. Spedding, accepted for publication in *J. Electrochem. Soc.*
(9) A. H. Daane, *Rev. Sci. Instr.*, **23**, 245 (1952).
(10) W. Guertler and M. Pirani, *Z. Metallkunde*, **11**, 1 (1919).

rhombohedral with $a \cong 8$ Å. and $\alpha \cong 23.5$ Å. The metal is very soft, has the luster of silver and does not tarnish in air after a month of exposure.

Ytterbium has been prepared by this same method and appears to be more volatile than samarium. X-Ray diffraction studies on this metal indicate that it is face-centered cubic with $a = 5.460$ Å.; Klemm and Bommer reported $a = 5.468$ Å. for this metal.

A more complete description of this work will appear in the future.

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A. H. DAANE
D. H. DENNISON
F. H. SPEDDING

RECEIVED APRIL 8, 1953

SYNTHESIS OF 17α-HYDROXYCORTICOSTERONE AND ITS 9α-HALO DERIVATIVES FROM 11-EPI-17α-HYDROXYCORTICOSTERONE

Sir:

The ready availability of 11-epi-17α-hydroxycorticosterone (I) by microbiological hydroxylation[1,2,3] of Reichstein's Compound S suggests as an attractive possibility the utilization of I as an intermediate in the synthesis of 17α-hydroxycorticosterone. We wish to report such a synthesis, a distinguishing feature of which is that it dispenses with the protective derivatization of the 3- and 20-keto groups required in previous syntheses[4,5,6] during operations in ring C. Key intermediates in this synthesis are the 9α-haloderivatives of 17α-hydroxycorticosterone, which we have found to be highly active in the rat liver glycogen assay for 11-oxygenated corticoids.[7] Their activities as well as those of the corresponding cortisone derivatives are listed in Table I.

TABLE I

	Activity in rat liver glycogen test, cortisone acetate = 1
9α-Chloro-17α-hydroxycorticosterone acetate	~4.0 ± 0.6
9α-Chlorocortisone acetate	3.5 ± 0.4
9α-Bromo-17α-hydroxycorticosterone acetate	0.28 ± 0.04
9α-Bromocortisone acetate	0.54 ± 0.08
9α-Iodo-17α-hydroxycorticosterone acetate	~0.1

Acetylation of (I) with one mole of acetic anhydride followed by tosylation gave Δ^4-pregnene-11α,17α,21-triol-3,20-dione 21-acetate 11α-tosylate (II), m.p. 165–166° (dec.); $[\alpha]^{23}D$ +106° (*c*, 1.0 in $CHCl_3$); (*Anal.* Calcd. for $C_{30}H_{38}O_8S$: C, 64.51; H, 6.81; S, 5.73. Found: C, 64.55; H, 6.84; S, 5.77), which on treatment with sodium acetate in boiling glacial acetic acid yielded $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (III) m.p. 236–237°; $[\alpha]D$ +117° (*c*, 1.0 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 238 mμ (ε = 15,500); (*Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.31; H, 7.80). Reaction of (III) with N-bromoacetamide[8] in aqueous dioxane in the presence of perchloric acid[9] afforded Δ^4-9α-bromopregnene-11β,17α,21-triol-3,20-dione 21-acetate (9α-bromo-17α-hydroxycorticosterone acetate) (IV), m.p. 130–131° (dec.); $[\alpha]D$ +133° (*c*, 0.75 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 243 mμ (ε = 14,500); (*Anal.* Calcd. for $C_{23}H_{31}O_6Br$: C, 57.17; H, 6.42; Br, 16.52. Found: C, 57.40; H, 6.56; Br, 16.11). Oxidation of (IV) with chromic acid yielded 9α-bromocortisone acetate, m.p. 219° (dec.); $[\alpha]^{23}D$ +235° (*c*, 0.61 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 237 mμ (ε = 16,100); (*Anal.* Calcd. for $C_{23}H_{29}O_6Br$: C, 57.41; H, 6.03; Br, 16.61. Found: C, 57.30; H, 6.16; Br, 16.15), which on reduction with zinc in acetic acid yielded cortisone acetate identified by comparison with an authentic sample of the latter. IV on treatment with potassium acetate in boiling alcohol gave Δ^4-pregnene-9β,11β-oxido-17α,21-diol-3,20-dione acetate (V),[10] m.p. 210–12°; $[\alpha]^{23}D$ +41° (*c*, 0.69 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 243 mμ (ε = 15,500); (*Anal.* Calcd. for $C_{23}H_{30}O_6$: C. 68.63; H, 7.51. Found: C, 69.02; H, 7.42), which with HBr in acetic acid–carbon tetrachloride reverted to IV. Reaction of V with hydrochloric acid in chloroform at 0° yielded 9α-chloro-17α-hydroxycorticosterone acetate, m.p. 200–201° (dec.); $[\alpha]^{23}D$ +139° (*c*, 0.86 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 241 mμ (ε = 15,800); (*Anal.* Calcd. for $C_{23}H_{31}O_6Cl$: C, 62.93; H, 7.12; Cl, 8.07. Found: C, 63.23; H, 7.41; Cl, 7.70), which on oxidation with chromic acid yielded 9α-chlorocortisone acetate, m.p. 257–58° (dec.); $[\alpha]^{23}D$ +252° (*c*, 1.1 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 236 mμ (ε = 16,600); (*Anal.* Calcd. for $C_{23}H_{29}O_6Cl$: C, 63.22; H, 6.54; Cl, 8.11. Found: C, 62.97; H, 6.61; Cl, 8.13). Reaction of V with hydriodic acid[11] at −20° for 20 minutes gave 9α-iodo-17α-hydroxycorticosterone acetate (VI), m.p. 100–110° (dec.); $[\alpha]^{22}D$ +145° (*c*, 1.05 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 243 mμ (ε = 11,000); (*Anal.* Calcd. for $C_{23}H_{31}O_6I$: C, 52.08; H, 5.89; I, 23.93. Found: C, 52.54; H, 6.44; I, 22.60). Both IV and VI with

(1) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769, July 8, 1952.

(2) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

(3) D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub and L. M. Reineke, *ibid.*, **75**, 412 (1953).

(4) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951).

(5) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(6) R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, D. M. Searcy, M. A. Scheri and E. S. Gutsell, THIS JOURNAL, **75**, 502 (1953).

(7) M. L. Pabst, R. Sheppard and M. H. Kuizenga, *Endocrinology*, **41**, 55 (1947). We are indebted to Drs. A. Borman and F. Singer for the liver glycogen assays. The activity ratios are computed on a weight basis.

(8) The reaction of N-bromoacetamide with a $\Delta^{9(11)}$-steroid has been reported by Hicks and Wallis (*J. Biol. Chem.*, **162**, 641 (1946)) and by Stavely (*Fed. Proc.*, **9** (Part 1), 233 (1950)). These authors converted methyl 3α-acetoxy-$\Delta^{9(11)}$-cholenate into methyl 8α-acetoxy-11-ketocholanate without isolating any of the intermediates.

(9) Using sulfuric acid in this reaction as suggested by Sarett (*J. Biol. Chem.*, **162**, 601 (1946)) gave yields in the vicinity of 45%, the remainder of III having been transformed into a water-soluble substance, presumably the 11β-sulfuric acid ester of IV. The use of perchloric acid in place of sulfuric acid increased the yield to over 90%.

(10) The corresponding 9α,11α-oxide, m.p. 248–249°; $[\alpha]^{23}o$ +99° (*c*, 1.09 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 238 mμ (ε = 16,000); (Found: C, 68.74; H, 7.38) was prepared from III with perbenzoic acid.

(11) D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951). The longer reaction time recommended by these authors for the opening of a 5β,6β-oxide led in our case mainly to III;

zinc dust in dilute alcohol[12] at room temperature furnished a mixture of III and 17α-hydroxycorticosterone acetate, m.p. 217–20°; $[\alpha]^{23}D$ +156° (*c*, 0.36 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 241 mμ (ϵ = 16,700); (*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.47; H, 8.14), identified further by infrared comparison with an authentic sample.

Similarly, 11-epicorticosterone[1,2,13] on monoacetylation, followed by tosylation and elimination of toluenesulfonic acid with sodium acetate in acetic acid yielded the known $\Delta^{4,9(11)}$-pregnadiene-21-ol-3,20-dione 21-acetate,[14] m.p. 160–160.5°; $[\alpha]^{23}D$ +128° (*c*, 0.76 in acetone), +150° (*c*, 0.80 in $CHCl_3$); which on treatment with N-bromoacetamide afforded 9α-bromocorticosterone acetate, m.p. 152–53° (dec.); $[\alpha]^{23}D$ +178° (*c*, 0.94 in $CHCl_3$); (*Anal.* Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.68; Br, 17.10. Found: C, 59.15; H, 6.70; Br, 17.03).

An attractive feature of this synthetic route is that it permits the introduction of radioactive halogen or tritium into the stable 9-position in the final step.

(12) The use of other reagents commonly employed for reductive dehalogenations such as Raney nickel with or without hydrogen, chromous chloride, zinc in acetic acid and others, led to III, V and/or their 4,5-dihydro products. Of particular interest is the reaction of IV with potassium iodide in acetone, which at the boiling point yielded III and V, while at room temperature it afforded in almost quantitative yield $\Delta^{4,6,8(9)}$-pregnatriene-17α,21-diol-3,20-dione acetate, m.p. 188–191°; $[\alpha]^{23}D$ +531° (*c*, 1.02 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 244 mμ (ϵ = 14,300), 285–300 mμ (ϵ = 3,100), 385 mμ (ϵ = 6,700), *cf.* R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 4654 (1951).

(13) S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh, D. A. Lyttle, L. M. Reineke and A. Weintraub, *ibid.*, **75**, 408 (1953).

(14) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
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JOSEF FRIED
EMILY F. SABO

RECEIVED APRIL 2, 1953

DECATETRAENEDIOIC ACID, A FUMAGILLIN DEGRADATION PRODUCT

Sir:

The antibiotic fumagillin[1,2,3] has been shown to be an acid with an empirical formula of $C_{26-27}H_{34-36}O_7$. We have found that fumagillin can be hydrolyzed under mild alkaline conditions liberating a highly unsaturated acid $C_{10}H_{10}O_4$ with the properties of 2,4,6,8-decatetraenedioic acid.[4]

This appears to be the first isolation of this acid from a natural source. The ultraviolet absorption spectrum shows peaks at 336 mμ and 351 mμ similar to fumagillin. On hydrogenation, fumagillin absorbs about 5 moles of hydrogen. Hydrolysis of hydrogenated fumagillin yields sebacic acid. These facts lead us to the conclusion that fumagillin is a mono-ester of decatetraenedioic acid: $[C_{16-17}H_{25-27}O_3]$—O—CO—$(CH{=}CH)_4$COOH.

Isolation of Decatetraenedioic Acid from Fumagillin.—One gram of fumagillin was suspended in 50 ml. of alcohol, and 12 ml. of *N* NaOH added. The fumagillin dissolved, and the solution became red. The solution was boiled under reflux for 15 minutes, diluted with 35 ml. of water to redissolve a precipitate, boiled for ten minutes more, filtered, cooled and acidified. The precipitate (305 mg.) was dissolved in 3.5 ml. of *N* NaOH, treated with Darco G-60, filtered and acidified: yield, 288 mg. of a yellow powder, insoluble in chloroform, alcohol, or water, m. p. 295–297° dec.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.68; H, 5.27.

The infrared spectrum showed bands at 3.65, 3.76 and 3.90 (carboxylic OH), 5.93 (carbonyl), and 6.13 and 6.32 microns (C=C) in Nujol mulls.

The methyl ester[4] was prepared through the acid chloride, m. p. 214–217°; $E_{1\ cm.}^{1\%}$ 3180 at 335 mμ and $E_{1\ cm.}^{1\%}$ 2950 at 351 mμ in alcohol containing 2% chloroform.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.10, 64.88; H, 6.60, 6.43.

This ester was compared directly with a synthetic sample kindly supplied by Prof. R. Kuhn. The two were shown to be identical by mixed melting point, infrared (Nujol mull) and ultraviolet spectra.

Isolation of Sebacic Acid from Hydrogenated Fumagillin.—Fumagillin (10.1 g.) was hydrogenated with Adams catalyst in alcohol at room temperature and three atmospheres pressure. After 15 minutes over 5 molar equivalents of hydrogen had been consumed. The solution was filtered and concentrated with addition of water to remove alcohol. A solution of 1.67 g. (2 molar equivalents) of sodium hydroxide in 250 ml. was added and the solution heated for one hour on a steam-bath. The cooled solution was extracted with ether, evaporated to 50 ml. and acidified. A white solid (3.32 g.) precipitated, m. p. 132–133°, showing no depression with authentic sebacic acid.

The authors wish to thank E. F. Shelberg and associates for microanalyses, and W. H. Washburn for infrared spectra.

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RECEIVED APRIL 2, 1953

(5) Abbott Laboratories Fellow for 1952–1953.

A NEW CLASS OF ANTITUBERCULAR COMPOUNDS

Sir:

During the screening of a large number of substances chosen from a wide range of chemical types, the discovery was made by Dr. R. L. Mayer and co-workers of the Division of Microbiology that 4,4′-diethoxythiocarbanilide (2) had high antituberculous activity in mice infected with the H37RV strain.[1] The synthesis and testing of over 300 thiocarbanilides and related substances revealed the rather specific structural features necessary for activity.

Shortening the 4-substituent to methoxy (1) (see

(1) T. E. Eble and F. R. Hanson, *Antibiotics & Chemotherapy*, **1**, 54 (1951).

(2) I. N. Asheshov, F. Strelitz and E. A. Hall, *ibid.*, **2**, 361 (1952).

(3) Our titration and elementary analyses agree best for $C_{26}H_{34}O_7$, as do the data of Eble and Hanson; Asheshov, *et al.*, however, prefer $C_{30}H_{40}O_8$.

(4) R. Kuhn and C. Grundmann, *Ber.*, **69**, 1757 (1936).

(1) R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exp. Biol.*, in press.

TABLE I

No.	R	R'	Extension of T50 value[a]	Concn. (%) in diet	M.p., °C.	Formula	N, % Calcd.	N, % Found
1	CH_3O	CH_3O	0.5	0.5	188–189[3]			
2	C_2H_5O	C_2H_5O	>15	.1	170–171[3]			
			11	.05				
3	C_4H_9O	C_4H_9O	>15	.025	166–167	$C_{21}H_{28}N_2O_2S$	7.52	7.74
4	C_2H_5O	$C_6H_{13}O$	>15	.5	153–154	$C_{21}H_{28}N_2O_2S$	7.52	7.62
5	$C_8H_{17}O$	$C_8H_{17}O$	+1.0	.5	154–156	$C_{29}H_{44}N_2O_2S$	5.78	6.04
6	C_4H_9	C_4H_9	>15	.025	149–150	$C_{21}H_{28}N_2S$	8.23	8.41
7	$(CH_3)_3C$	$(CH_3)_3C$	0.0	.5	192–193[4]			
8	C_4H_9O	Cl	>15	.5	166–168	$C_{16}H_{19}ClN_2OS$	8.37	8.19
9	C_4H_9O	$(CH_3)_2N$	>15	.025	119–121	$C_{19}H_{25}N_3OS$	12.24	12.20
10	Cl	Cl	+0.7	.1	166–168[5]			
11	$(CH_3)_2N$	$(CH_3)_2N$	−0.5	.1	185–186[5]			
12	C_4H_9O	H	0.0	.5	136–137	$C_{17}H_{20}N_2OS$	9.33	9.50
13	2,4'-Diethoxythiocarbanilide		+2.0	.5	143–145	$C_{17}H_{20}N_2O_2S$	8.86	8.94
14	3,4'-Diethoxythiocarbanilide		−2.5	.1	110–112	$C_{17}H_{20}N_2O_2S$	8.86	8.90
15	4,4'-Diethoxy-3,3'-dimethyl-thiocarbanilide		−1.0	.5	161–162	$C_{19}H_{24}N_2O_2S$	8.13	8.15
16	4,4'-Diethoxy-N-methyl-thiocarbanilide		−2.7	.3	58–59	$C_{18}H_{22}N_2O_2S$	8.48	8.60
17	4,4'-Diethoxycarbanilide		+0.5	.3	225–226[6]			
18	1,3-Bis-(*p*-phenetyl)-guanidine		−1.3	.05	121–122[6]			
19	1-(4-Ethoxycyclohexyl)-3-(*p*-phenetyl)-2-thiourea		+1.3	.5	109–119[b]	$C_{17}H_{26}N_2O_2S$	8.69	8.69

[a] This value represents the extension of life in days of treated animals over that of controls. 50% of the control animals are dead by the 20th day. An extension of life of greater than five days is considered to indicate significant antitubercular activity. The test is carried out as described by Donovick, *et al.*[2] [b] Mixture of stereoisomers.

Table I) destroys activity, while lengthening the chain results in a fourfold increase to a maximum of activity in the neighborhood of three to four carbon atoms (3). Increase beyond this causes activity to decline (4) and disappear (5). Replacement of alkoxy by an alkyl of equivalent length (6) results in similar activity. Branching of the alkyl chain at the carbon adjoining the ring (7) causes complete loss of activity. One of the 4-alkoxy groups may be replaced by halogen (8) or dialkyl amino (9) and still retain some activity. Replacement of both of them (10) (11) causes total loss of activity. Removal of one of the 4-alkoxyl groups (12) also results in loss of activity.

That 4-substitution on both benzene rings is necessary for activity is shown by the inertness of the 2- (13) and 3- (14) position isomers. A second substituent (methyl (15), halogen, amino) in the ring destroys activity as does substitution of methyl on the ureido nitrogen (16). The thiocarbanilide moiety is shown to be essential by the inactivity of the corresponding carbanilide (17), guanidine (18), guanylthiourea, dithiobiuret, and the cyclohexyl substituted thiourea (19).

The favorable results obtained by our associates of the Division of Microbiology[1] with the more active thiocarbanilides in delayed and limited therapeutic trials in both mice and guinea pigs together with their low toxicity (M.T.D. 5% in diet) and absence of development of resistant strains suggest that they be given serious consideration in the treatment of tuberculosis.

Synthesis of the thiocarbanilides involved reaction of an amine with carbon disulfide using potassium ethyl xanthate as catalyst,[7] with thiophosgene or with an isothiocyanate.[8]

(2) R. Donovick, C. McKee, W. P. Jambor and G. Rake, *Am. Rev. Tuber.*, **60**, 90 (1949).
(3) J. v. Braun and E. Beschke, *Ber.*, **39**, 4377 (1906).
(4) A. Pahl, *ibid.*, **17**, 1235 (1884).
(5) A. Baur, *ibid.*, **12**, 534 (1879).
(6) J. Riedel, German Patent 66, 550, *Frdl.* **3**, 914.
(7) L. Guglianelli, A. Novelli, C. Ring and C. Anaslosi, *Anal. Asoc. Quim. Argent.*, **15**, 337 (1927).
(8) G. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

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RECEIVED MARCH 25, 1953

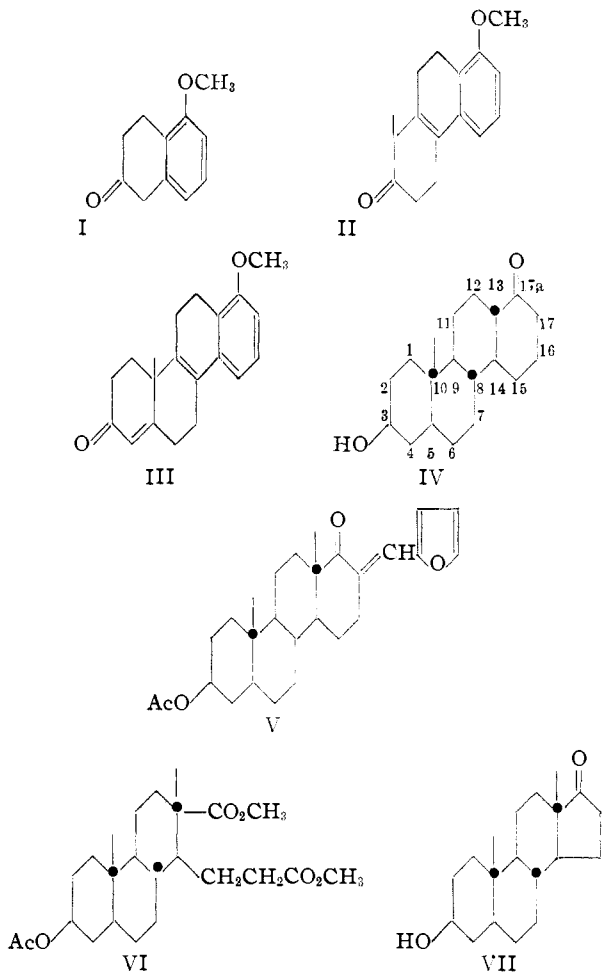
TOTAL SYNTHESIS OF EPIANDROSTERONE

Sir:

The brilliant researches of Sir Robert Robinson and collaborators on steroid synthesis have recently culminated in a "formal" total synthesis of epiandrosterone, VII, involving "relays" through intermediates which were supplied (for the further steps) by degradation of the natural steroids.[1] We are reporting herein a different approach which has been completed without relays, thus yielding totally synthetic epiandrosterone.

5-Methoxy-2-tetralone, readily produced from the sodium–alcohol reduction of 2,5-dimethoxy-

(1) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).



naphthalene,[2] was treated in the presence of sodium methoxide with 1-diethylamino-3-pentanone methiodide[3] followed—without isolation of the intermediary tricyclic compound II (m.p. 96.5–97°; C, 78.94; H, 7.55)—by methyl vinyl ketone[4] to produce the methoxyketomethyloctahydrochrysene III (m.p. 174.2–175°; C, 81.48; H, 7.61), which is thus very readily available in quantity. Reduction of 20 g. of III with lithium and alcohol in ammonia[5] followed by acid hydrolysis gave upon chromatography 5 g. of unsaturated ketonic material consisting of *dl*-D-homo-18-nor-13,14-dehydroepiandrosterone (IV with C=C at 13, 14) (m.p. 163.5–164°; λ_{max}^{EtOH} 248.5 mμ, log ε 4.12; C, 78.75; H, 9.78), and the 16,17-dehydroisomer (IV with C=C at 16,17) (m.p. 138–139°; λ_{max}^{EtOH} 226 mμ, log ε 3.89; C, 79.33; H, 10.27). Hydrogenation of the former, the preponderant isomer, over palladium catalyst gave, after isomerization with alkali, exclusively *dl*-D-homo-18-nor-epiandrosterone, IV (m.p. 159–161°; C, 78.50; H, 10.43). This same substance was produced directly on hydrogenation of the 16,17-dehydro ketone; hence the mixture of unsaturated ketones could be employed for production of pure IV. Only traces of other ketonic materials were formed in the lithium treatment; thus the two combined reduction steps, during which no less than six new asymmetric centers are introduced, nevertheless constitute stereospecific production of IV from III.

Condensation of IV with furfural, methylation,[6] and acetylation yielded an easily separable mixture of *dl*-17-furfurylidene-D-homoepiandrosterone acetate V (m.p. 192–192.5°; C, 76.19; H, 8.53), and the preponderant oily 13-iso ("lumi") compound (3-hydroxy compound, m.p. 88–90°; C, 78.26; H, 9.16). The infrared spectrum of the former was identical with that of V prepared from authentic D-homoepiandrosterone.[7]

Ozonolysis of *dl*-V followed by esterification with diazomethane afforded *dl*-dimethyl 3-β-acetoxyetioallohomobilianate VI (m.p. 136–137°; C, 68.12; H, 9.29) having an infrared spectrum identical with that of VI prepared by degradation of authentic epiandrosterone. Dieckmann cyclization of *dl*-VI with potassium *t*-butoxide, followed by acid hydrolysis, gave *dl*-epiandrosterone (m.p., 161–162°; C, 78.42; H, 10.49) having an infrared spectrum indistinguishable from that of authentic *d*-epiandrosterone. Resolution studies are in progress.

Similarly *dl*-13-iso-V yielded *dl*-13-iso-VI (m.p. 116.5–117.5°; C, 68.36; H, 9.29), which was converted to *dl*-lumiepiandrosterone (m.p. 157–158°; C, 78.32; H, 10.09), having an infrared spectrum identical with that of authentic lumiepiandrosterone.[8]

Studies to be reported in detail later have shown that intermediates can be obtained readily with the 11-oxygen function, and we are currently studying the application of our general scheme to the synthesis of the 11-oxygenated adrenal hormones as well as to other 11-desoxy hormones.

(2) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

(3) *Cf.* J. W. Cornforth and R. Robinson, ref. 2.

(4) *Cf.* The Wilds method—A. L. Wilds, J. W. Ralls, W. C. Wildman and K. E. McCaleb, THIS JOURNAL, **72**, 5794 (1950)—for directing the orientation of ring addition in the Robinson-Mannich base type of reaction through the agency of a vinylogously active methyne hydrogen.

(5) These conditions differ from those generally preferred by A. J. Birch, *Quart. Rev.*, **4**, 69 (1950), in that lithium was employed according to A. L. Wilds and N. A. Nelson (in press) and a large excess of alcohol was used.

(6) The procedure of W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943), was used, the 3-hydroxyl being protected from methylation as the tetrahydropyranyl ether; see C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(7) Obtained from epiandrosterone by the procedure of D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(8) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **34**, 2053 (1951).

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RECEIVED APRIL 6, 1953

"THERMODYNAMIC PROPERTIES OF GASEOUS DIFLUORODICHLOROMETHANE (FREON-12)[1]": A CORRECTION

Sir:

It has been called to my attention that Fig. 3 in the paper of this title[1] gives a misleading impression of the accuracy of the data of Buffington and

(1) J. F. Masi, THIS JOURNAL, **74**, 4738 (1952).

Fleischer[2] on the gaseous heat capacity of CF_2Cl_2. While the graph in question was not intended as a direct comparison of experimental data, it seems to imply a consistent disagreement of about +1% between the Buffington and Fleischer experiments and the more recent precise values being reported. The actual comparison of experimental C_p at one atmosphere gives the deviation of the older work from that of this paper as −0.16, −0.05 and +0.78%, respectively, at 0, 25.8 and 49.9°, the temperatures of Buffington and Fleischer's measurements.

(2) R. M. Buffington and J. Fleischer, *Ind. Eng. Chem.*, **23**, 254 (1931).

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RECEIVED APRIL 1, 1953

ON A PROBABLE ENZYMATIC CONVERSION OF HYDROXYCHALCONE GLYCOSIDE INTO HYDROXYBENZALCOUMARANONE GLYCOSIDE

Sir:

The co-existence of glycosides[1] of hydroxychalcones and hydroxybenzalcoumaranones in species of *Cosmos* and *Coreopsis* suggested that there may be enzymatic interconversion. Some preliminary evidence for a "Chalconase" was obtained by macerating fresh rays of *Cosmos sulphureus* or *Coreopsis lanceolata* in a glass mortar with an equal quantity of water, $^2/_5$ of McIlvaine's buffer solutions of various *p*H, and $^1/_{10}$ to $^1/_{25}$ of *M*/20 potassium cyanide. The latter was used in order to inhibit the activity of polyphenoloxidase. A hydroxybenzalcoumaranone gives a purple coloration and a hydroxychalcone gives a red one with 1 *N* sodium hydroxide solution, but the former color is apt to be obscured by the red color produced by the chalcones present. When left at *p*H 3–4 the color of the solution hardly changed; it only changed to red on the addition of sodium hydroxide solution. At *p*H 7–8 the color changed eventually to brown, owing to autoxidation in alkaline medium. The conversion of chalcone into benzalcoumaranone did not take place to any extent in these cases. However, after the mixtures were allowed to stand at *p*H 5–6, the color given by the addition of sodium hydroxide solution was strongly purple accompanied by no reddish tint, showing the complete disappearance of chalcone compound. In good accord with these observations, the brown spot of the chalcone, which was clearly visible on paper chromatograms under ultraviolet light, completely disappeared after standing at *p*H 5–6, and the golden yellow spot of the corresponding benzalcoumaranone made its appearance quite strongly. The chromatograms usually were run with *n*-butanol–acetic acid–water (4:1:1) as solvents. The time required for complete reaction was 10–15 minutes under the optimum *p*H of 5–6. This comparatively rapid conversion was effectively prevented by heating at 100° for about ten minutes.

These observations may be effected by an enzyme in the tissue of the rays. This enzyme unfortunately has not yet been extracted from the rays, owing to its insolubility in water. It is, however, at least evident that this enzyme has little to do with the usual metal-bearing oxidases which suffer severe inhibition by cyanide, although the enzyme concerned effects dehydration in the presence of oxygen.

The powder, prepared from rays after extracting several times with cold alcohol at room temperature until the anthochlor pigments were completely removed, proved to be effective in bringing about this reaction. It is very interesting to note that, when the powder thus prepared from the rays of one species was added to any chalcone glycoside isolated from other plant species, the enzymatic conversion occurred readily and apparently at the same rate and to the same degree. For example, the ray powder of *Cosmos sulphureus* proved to be active in forming benzalcoumaranone when added to the extract of the rays of *Coreopsis lanceolata*, *C. tinctoria*, *Bidens laevis* and *Dahlia variabilis*.

Acknowledgment.—Part of the cost for this study was defrayed with a Grant from the Ministry of Education in Aid for the Miscellaneous Scientific Researches (1952), to which we express our gratitude.

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RECEIVED FEBRUARY 2, 1953

ENZYMATIC REACTION OF CROTONYL COENZYME A[1]

Sir:

Evidence from various sources indicates that reactions (1),[2,3] (2)[2,4,5,6] and (3)[7] are catalyzed by soluble enzyme preparations from liver and heart.

(1) β-Hydroxybutyral-S-CoA + DPN^+ ⇌ acetoacetyl-S-CoA + DPNH + H^+

(2) Acetoacetyl-S-CoA + CoA-SH ⇌ 2 acetyl-S-CoA

(3) 2 Acetyl-S-CoA + 2 oxalacetate ⇌ 2 citrate + 2 CoA-SH

Recent results strongly suggest the occurrence in liver and heart of an enzyme catalyzing reaction (4). The name crotonase is suggested for this enzyme.

(4) Crotonyl-S-CoA + H_2O ⇌ β-hydroxybutyryl-S-CoA

(1) Supported by grants from the U. S. Public Health Service, the American Cancer Society (recommended by the Committee on Growth, National Research Council), the Williams-Waterman Fund of Research Corporation, and by a contract (N6onr279, T.0.6) between the Office of Naval Research and New York University College of Medicine. The following abbreviations are used: Coenzyme A (reduced), CoA-SH; acyl coenzyme A derivatives, acyl-S-CoA; oxidized and reduced diphosphopyridine nucleotide, DPN^+ and DPNH; adenosine triphosphate, ATP; μM, micromoles; TRIS, *tris*-(hydroxymethyl)-aminomethane.

(2) F. Lynen, L. Wessely, O. Wieland and L. Rueff, *Angew. Chem.*, **64**, 687 (1952).

(3) J. R. Stern, M. J. Coon and A. del Campillo, THIS JOURNAL, **75**, 1517 (1953).

(4) E. R. Stadtman, M. Doudoroff, and F. Lipmann, *J. Biol. Chem.*, **191**, 377 (1951).

(5) J. R. Stern, M. J. Coon and A. del Campillo, *Nature*, **171**, 28 (1953).

(6) D. Goldman, *Federation Proc.*, **12**, 209 (1953).

(7) S. Ochoa, J. R. Stern and M. C. Schneider, *J. Biol. Chem.*, **193**, 691 (1951).

(1) M. Shimokoriyama, and S. Hattori, THIS JOURNAL, **75**, 1900 (1953).

Enzyme fractions from liver and heart, which contain the enzymes catalyzing reactions (1) and (2), form citrate from crotonyl-S-CoA when supplemented with DPN^+, CoA-SH, oxalacetate, and crystalline citrate condensing enzyme. In a typical experiment with an ox liver fraction (0.49 mg. protein) and about 0.45 μM., crotonyl-S-CoA, 0.55 μM. citrate were formed in 40 minutes at 25° by the complete system. No citrate was formed in the absence of DPN^+ or crotonyl-S-CoA, or when crotonate replaced crotonyl-S-CoA. Crotonyl-S-CoA was synthesized by reaction of crotonic anhydride and CoA-SH after the procedure of Simon and Shemin[8] for the synthesis of succinyl-S-CoA.

Pigeon liver extracts also contain an enzyme(s) capable of forming β-hydroxybutyryl-S-CoA (or crotonyl-S-CoA) from *d,l*-β-hydroxybutyrate (or crotonate), ATP, and CoA-SH[9] and, with the above conditions, form citrate when the acetyl donor is either crotonyl-S-CoA or a mixture of *d,l*,β-hydroxy butyrate (or crotonate), ATP, and CoA-SH.

The coupling of reaction (4) with reaction (1) to give reaction (5) can be followed spectrophotometrically at *p*H 8.1 (Fig. 1) either by the increase

(5) Crotonyl-S-CoA + H_2O + DPN^+ $\rightleftharpoons$ acetoacetyl-S-CoA + DPNH + H^+

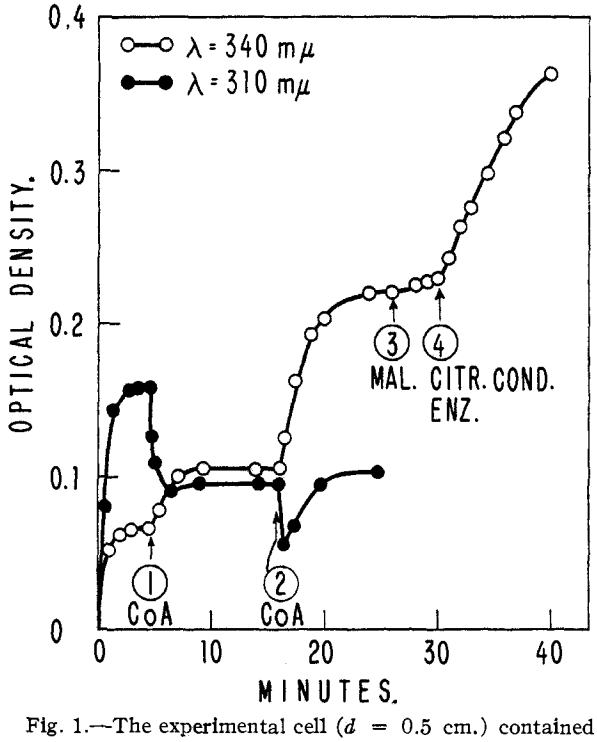

Fig. 1.—The experimental cell (d = 0.5 cm.) contained initially 100 μM. TRIS–HCl buffer, *p*H 8.1, 8 μM. $MgCl_2$, about 0.24 μM. crotonyl-S-CoA, and 0.27 μM. DPN^+. Crotonyl-S-CoA and DPN^+ were omitted from the control cell. The reaction was started by adding ox liver fraction (0.49 mg. protein). This was followed by CoA-SH (0.03 and 0.08 μM.), potassium L-malate (5 μM.) and crystalline citrate condensing enzyme (30 μg.) as indicated. Volume was 1.5 ml.; temp., 25°. The increase in light absorption at 310 mμ after the second addition of CoA–SH is due to the formation of DPNH, which absorbs also at this wave length.

(8) E. J. Simon and D. Shemin, THIS JOURNAL, in press.

(9) J. R. Stern, I. Raw and A. del Campillo, unpublished.

in light absorption at λ = 310 mμ, due to the formation of acetoacetyl-S-CoA,[2] or by the increase in absorption at λ = 340 mμ, due to the formation of DPNH. On addition of CoA-SH (arrows 1 and 2), the absorption at 310 mμ decreases while that at 340 mμ increases due to the additional occurrence of reaction (2) which shifts the equilibrium of the system to the right. On addition of L-malate and citrate condensing enzyme (arrows 3 and 4) there is further reduction of DPN^+ because of the occurrence of reaction (6) catalyzed by malic dehydrogenase together with the citrate condensing

(6) Acetyl-S-CoA + L-malate + DPN^+ $\rightleftharpoons$ citrate + CoA-SH + DPNH + H^+

enzyme.[10] Sufficient malic dehydrogenase is present in the ox liver fraction. The equilibrium of reaction (6) favors citrate formation so that the equilibrium of the system as a whole is shifted farther to the right.

When crotonyl-S-CoA (but not crotonate) is incubated with ox liver fractions (free of crotonyl-S-CoA deacylase) there occurs a decrease in light absorption at λ = 240 mμ due to the hydration of the —C=C— bond.[11] Crotonyl glutathione and crotonyl thioglycolate are not hydrated when so tested.

(10) J. R. Stern, S. Ochoa and F. Lynen, *J. Biol. Chem.*, **198**, 313 (1952).

(11) E. Racker, *Biochim. Biophys. Acta*, **4**, 211 (1950).

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RECEIVED MARCH 19, 1953

COPOLYMERIZATION OF BENZENE WITH VINYL ACETATE

Sir:

Polymerization of vinyl acetate is retarded in all aromatic solvents, including those without alkyl side-groups such as chlorobenzene[1], ethyl benzoate[2] and benzene itself.[1–4] In view of the known high reactivity of phenyl radicals,[5] an explanation based on the conventional type of transfer reaction

$$R\cdot + C_6H_6 \longrightarrow RH + C_6H_5\cdot \qquad (1)$$

is unattractive, but a hydrogen-atom transfer in the reverse direction

$$RCH_2CH(OAc)\cdot + C_6H_6 \longrightarrow RCH{=}CHOAc + C_6H_7\cdot \qquad (2)$$

would yield a cyclohexadienyl radical considerably less reactive than a vinyl acetate radical.

However, even reaction (2) fails to account for the observations, since inconsistencies are encountered in the kinetic analysis. Briefly, the difficulty is that the apparent transfer constant, as obtained from molecular-weight measurements, is far too low to account for the observed retardation and at the same time to keep the order of the

(1) G. M. Burnett and H. W. Melville, *Disc. Faraday Soc.*, **2**, 322 (1947).

(2) J. T. Clarke, unpublished measurements in this laboratory.

(3) A. C. Cuthbertson, G. Gee and E. K. Rideal, *Proc. Roy. Soc. (London)*, **A170**, 300 (1939).

(4) S. Kamenskaya and S. Medvedev, *Acta Physicochimica U.R.S.S.*, **13**, 565 (1940).

(5) D. H. Hey and W. A. Waters, *Chem. Revs.*, **21**, 169 (1937).

reaction with respect to initiator at its observed value, which is[1,4] scarcely greater than 0.5.

Using great care in purification of materials, we have again measured rates of vinyl acetate polymerization in benzene at 60° and the molecular weights of the polymers produced, with the same anomalous results. To fit the observed rates, we require the transfer constant to benzene to have a value $C = 2.5\ (\pm 0.5) \times 10^{-3}$, while the molecular weights lead to $C = 1.2 \times 10^{-4}$. It would of course still be formally possible to attribute the effect to an unusual type of impurity, but this would merely shift rather than relieve the burden of explanation.

These results require the existence of a reaction which can retard the polymerization without decreasing the molecular weight, namely, the *addition* of a radical to the aromatic nucleus

$$R(CH_2CHOAc)_x\cdot + C_6H_6 \longrightarrow R(CH_2CHOAc)_x{-}CH\begin{matrix}CH{=}CH\\ \diagup\\ \diagdown\\ CH{=}CH\end{matrix}CH\cdot \quad (3)$$

This reaction accounts for the retardation as well as does reaction (2), and if the resulting radical can add to monomer

$$R(CH_2CHOAc)_xC_6H_6\cdot + CH_2{=}CHOAc \longrightarrow R(CH_2CHOAc)_xC_6H_6CH_2CHOAc\cdot \quad (4)$$

a self-consistent explanation of all our results can be achieved.

We have shown that reaction (3) actually takes place with about the required frequency, by preparing a sample of low-conversion polyvinyl acetate at 60° in the presence of C^{14}-labelled benzene,[6] using a mole ratio 10.9 of benzene to vinyl acetate. This polymer contained radioactive carbon which could not be removed by repeated precipitations, nor by dilutions with ordinary benzene followed by evaporation; the mole ratio of benzene to vinyl acetate in the polymer remained at 0.029 ± 0.005. This figure gives a ratio of $2.7\ (\pm 0.5) \times 10^{-3}$ for the specific rate of reaction (3) to that of normal propagation, in remarkable agreement with the kinetic value. The polymerization degree $\bar{P}_n$ of the radioactive polymer sample (estimated viscometrically) was about 700, so that there were about 20 benzene residues per average molecule. The reactions above postulated would require these residues first to enter the chains as disubstituted ortho- or para-cyclohexadiene units, but we have been unable to detect any significant unsaturation in our benzene-containing samples. Presumably the cyclohexadiene units are rapidly oxidized to aromatic form, possibly by atmospheric oxygen during dissolution and precipitation of the polymer.

Addition of a free radical to an aromatic nucleus is scarcely a novel reaction.[5] Within the field of polymerization mechanism, it has been postulated as a possible step in retardation by aromatic nitrocompounds,[7] in the polymerization of styrene in aromatic solvents,[8] and indeed in the polymerization of vinyl benzoate,[9] in order to account for the ready gelation of the latter. We believe, however, that ours is the first direct proof of its occurrence in a polymerizing system. From a general comparison of transfer activity in styrene and vinyl acetate systems,[2] we estimate the reactivity-ratio (to normal propagation) of reaction (3) for a styrene radical with benzene or with styrene monomer to be not less than 10^{-5} at 60°.

We thank the American Chicle Company for a grant in aid of this investigation, and Clare M. Regan for the radioactive assay.

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RECEIVED MARCH 19, 1953

(6) Obtained from Tracerlab, Inc., on allocation from the United States Atomic Energy Commission.

(7) C. C. Price and D. A. Durham, THIS JOURNAL, **65**, 757 (1943).

(8) F. R. Mayo, *ibid.*, **65**, 2324 (1943).

(9) G. E. Ham and E. L. Ringwald, *J. Polymer Sci.*, **8**, 91 (1952).

THE RELATIONSHIP BETWEEN METALLIC RADII IN BODY-CENTERED CUBIC AND CLOSE-PACKED STRUCTURES

Sir:

In the first of two recent papers dealing with the resonance-bond theory of metals Pauling[1] develops an empirical correction for the conversion of the atomic radius corresponding to the shorter of the two bond lengths in the body-centered cubic structure to that appropriate to coördination number 12. This correction is derived from a comparison of the body-centered cubic radii with the face-centered cubic or hexagonal close-packed radii of iron, titanium, zirconium and thallium, respectively.

In every instance except that of iron, however, Pauling has compared two radii the values of which are measured at different temperatures and has not allowed for the differences which arise on account of thermal expansion. In the case of iron he appears to have used an unreliable extrapolated room temperature value for γ-Fe obtained by Jette and Foote[2] from a series of Ni-Fe alloys. This value has, therefore, been rejected by the present author and the high temperature values of the cell dimensions have been used in all cases. When allowance is made for thermal expansion, it becomes apparent that the correction, ΔR, given by Pauling's equation

$$R(1) - R(n) = 0.300 \log n$$

needs little or no modification. There is, in each instance, a small difference between the calculated and observed values of ΔR but the differences are not systematic and in any case may well arise from the uncertainties associated with the temperature corrections involved.

The cell dimensions on which the calculations are based, the values of the thermal expansion coefficients used and the resulting values of the radii for C.N. 12 at 20° are given in Table I. The cell dimensions are those given by Barrett[3] but are quoted in kX. units to conform with Pauling's usage.[4] The calculated and observed values of the

(1) L. Pauling, THIS JOURNAL, **69**, 542 (1947).

(2) E. R. Jette and F. Foote, *Metals Technology*, **3**, 1 (1936).

(3) C. S. Barrett, "Structure of Metals," 2nd Edition, McGraw-Hill Book Co., New York, N. Y., 1953.

(4) In the case of iron there is yet another reported value available for the cell dimension of γ-Fe; Wyckoff, "Crystal Structures," Vol. I, Interscience Publishers, New York, N. Y., (1948) gives $a_0 = 3.63$ kX. at 1100°. This makes iron an unfortunate choice for the present purpose.

correction, ΔR, are given in Table II. The results are, of course, quite independent of any assumptions that may be made concerning the valencies of the elements concerned.

TABLE I

DATA USED

Element	Form	a_0, kX.	c_0, kX.	Temp., °C.	Coefficient of thermal expansion $\times 10^{-6}$	R(C.N.12) at 20°, kX.
Fe	α	2.861	..	20		1.273
	γ	3.649	..	950	12[5]	1.276
Ti	α	2.945	4.674	25		1.459
	β	3.32	..	900	9[6]	1.463
Zr	α	3.223	5.123	room		1.597
	β	3.61	..	867	7.5[7]	1.594
Tl	α	3.449	5.520	room		1.713
	β	3.874		262	30[8]	1.708

Room temperature taken as 20°.

TABLE II

VALUES OF ΔR

Element	Value of ΔR Calcd.	Value of ΔR Obs.	Difference in ΔR
Fe	0.033	0.036	+0.003
Ti	0.036	0.032	−0.004
Zr	0.039	0.042	+0.003
Tl	0.041	0.046	+0.005

(5) E. A. Owen and E. L. Yates, *Phil. Mag.*, **15**, 472 (1933); A. Kochanovska, *Physica*, **15**, 191 (1949).

(6) G. L. Miller, *Ind. Chemist*, **27**, 483 (1951).

(7) R. B. Russell, M.I.T. report No. 1073, October 1951.

(8) Fizeau (1869) quoted in "Handbook of Chemistry and Physics," 33rd Edition, Chem. Rubber Publishing Co. (1951–1952), p. 1852.

ATOMIC ENERGY RESEARCH ESTABLISHMENT, HARWELL, BERKSHIRE, ENGLAND J. THEWLIS

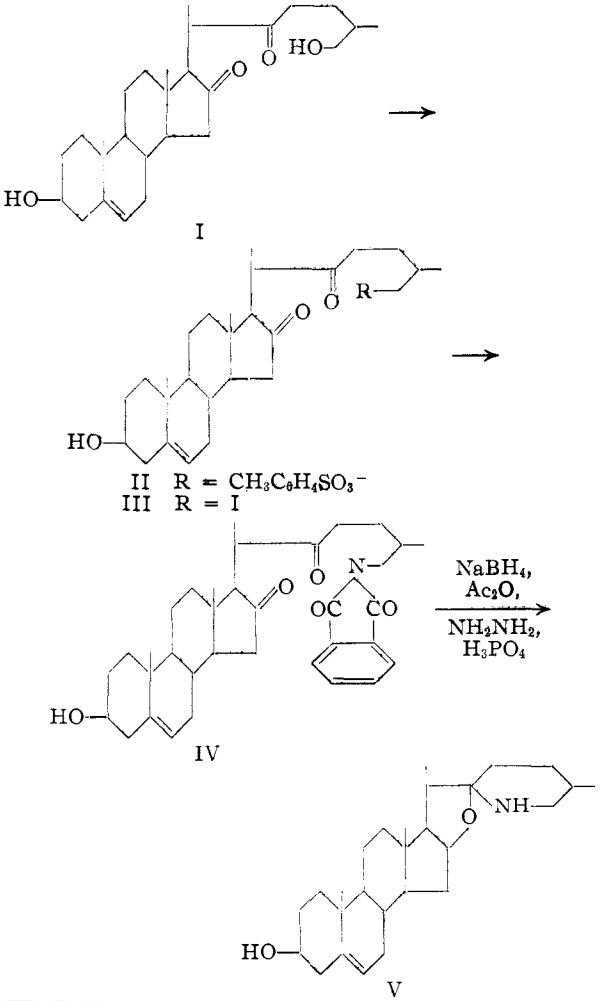
RECEIVED MARCH 12, 1953

THE TRANSFORMATION OF KRYPTOGENIN TO SOLASODINE

Sir:

Inasmuch as the secondary veratrum and solanum alkaloids yield nitrogenous degradation products identical with those derived from their tertiary congeners, the secondary alkamines may be presupposed not remotely allied in skeletal structure to the octahydropyrrocoline nucleus characteristic of solanidine,[1] rubijervine, isorubijervine, and, presumably, of cevine, germine, protoverine and zygadenine. While jervine and veratramine have been categorized as complex 2-substituted-5-methylpiperidine derivatives[2] and steroid C_{20} piperidine derivatives of this type have become available by partial synthesis,[3] a further skeletal variation consonant with the chemical behavior of other members of these series finds expression as a hexacyclic aminoketal formulation related to that which characterizes the well known spiroketal sapogenins. This representation was first considered as a theoretical possibility in earlier studies on the chemistry of jervine[4] and has more recently been incorporated into the structural postulates advanced for solasodine,[5] tomatidine,[6] and solanocapsine.[7] Solasodine has now been obtained by partial synthesis from non-nitrogenous, naturally occurring steroids.

Kryptogenin, I, has been converted to the mono-*p*-toluenesulfonate II, m.p. 165–166°, $[\alpha]^{25}D$ −144° ($CHCl_3$), *Anal.* Calcd. for $C_{34}H_{48}SO_6$: C, 69.82; H, 8.27; S, 5.48. Found: C, 69.82; H, 8.20; S, 5.28, which, in turn, has been transformed through the iodide III, m.p. 141–142°, $[\alpha]^{25}D$ −161° ($CHCl_3$), *Anal.* Calcd. for $C_{27}H_{41}O_3I$: C, 59.99; H, 7.65; I, 23.48. Found: C, 60.20; H, 7.76; I, 23.20, to the corresponding phthalimido-derivative IV, m.p. 213–214°, *Anal.* Calcd. for $C_{35}H_{45}NO_5$: C, 75.10; H, 8.10; N, 2.50. Found: C, 74.91; H, 8.01; N, 2.60. Reduction of IV with sodium borohydride, followed by treatment with acetic anhydride and subsequent cleavage with hydrazine and phosphoric acid, has afforded solasodine, V, m.p. 200–201°, $[\alpha]^{24.8}D$ −102°



(1) F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

(2) J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, THIS JOURNAL, **73**, 2970 (1951); O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

(3) F. C. Uhle, *ibid.*, **73**, 883 (1951).

(4) W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, **170**, 635 (1947).

(5) L. H. Briggs, W. E. Harvey, R. H. Locker, W. A. McGillivray and R. N. Seeyle, *J. Chem. Soc.*, 3013 (1950).

(6) T. D. Fontaine, J. S. Ard and R. M. Ma, THIS JOURNAL, **73**, 878 (1951); R. Kuhn, I. Löw and H. Trischmann, *Chem. Ber.*, **85**, 416 (1952).

(7) E. Schlittler and H. Uehlinger, *Helv. Chim. Acta*, **35**, 2034 (1952).

(methanol, c = 0.33), *Anal.* Calcd. for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 76.41; H, 10.45; N, 3.42, mixed melting point and infrared spectrum identical with that given by an authentic specimen of solasodine; picrate, m.p. 141–142°, *Anal.* Calcd. for $C_{33}H_{46}N_4O_9$: C, 61.66; H, 7.21; N, 8.72. Found: C, 62.00; H, 7.30; N, 8.95.

The partial synthesis of spiroaminoketal steroid alkaloids by transformation from the sapogenins tigogenin, sarsasapogenin and diosgenin, will be reported shortly.

The author is indebted to Mr. Louis S. Harris and Miss V. Cecile Politis for preparative assistance, to Dr. James A. Moore and Dr. E. L. Wittle, Parke, Davis and Company, for a quantity of kryptogenin diacetate, to Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology for the analytical and spectroscopic determinations, to Prof. L. H. Briggs, Auckland University College, Auckland, New Zealand, for an authentic specimen of solasodine, and to the United States Public Health Service, the Eugene Higgins Trust, and Parke, Davis and Company, of Detroit, Michigan, for financial support.

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BOOK REVIEWS

Colloid Science. Volume I. Irreversible Systems. By H. R. KRUYT, Formerly Professor of Physical Chemistry, Utrecht University, President of the National Council for Applied Scientific Research in the Netherlands, T.N.O., The Hague; English translation by Dr. L. C. Jackson (Bristol). Elsevier Publishing Company, 402 Lovett Blvd., Houston, Texas, 1952. xx + 389 pp. 16.5 × 25 cm. Price, $11.00.

This treatise on colloid science was "for practical reasons" divided into two volumes. Volume I deals with *irreversible systems*, hydrophobic colloids, and Volume II with *reversible systems*, macromolecular and association colloids. Work was started on these volumes prior to World War II but as pointed out by the editor "through accidental circumstances" Volume II was completed and published in 1949 three years before the appearance of Volume I. The volumes were written by the Editor and Dutch collaborators so that the work as a whole is largely representative of the interests and researches of the highly regarded and the highly productive Dutch School of Colloid Science.

Volume I is divided into nine sections. Section I, written by Kruyt, consists of 57 pages, 15 of general introduction discussing the scope and history of colloid systems according to the "material of the particles," followed by 42 pages of discussion of general properties of colloid systems. Many of the topics of this introduction are further developed in later sections. Section II, 51 pages written by J. Th. G. Overbeek and entitled Phenomenology of Lyophobic Systems, is general in nature and relates to methods of preparation of lyophobic sols, to purification of sols, and to properties and stability of sols with theoretical considerations on stability and flocculation. The content of this section is material one might hope to find in a portion of any well organized college text book on colloids. Section III, 25 pages written by G. H. Jonker, deals with a condensed treatment of optical properties of colloidal solutions. Sections IV to IX inclusive, all by Overbeek deal with (IV) Electrochemistry of the double layer, (V) Electrokinetic phenomena, (VI) Interaction between colloidal particles, (VII) Kinetics of flocculation, (VIII) Stability of hydrophobic colloids and emulsions, and (IX) Rheology of lyophobic systems. These sections include material from the fundamental and more generally accepted researches which have been made in the fields represented. Each of these sections is well organized, interestingly presented and ably treated by the author whose own research interests happen to be closely related to these fields.

A minor criticism of the English language edition of Volume I is that, though the translation is adequate for understanding, one is often conscious of reading a translation from a foreign language. The main criticism which will be made of this volume is that many important areas of colloid science are not represented here nor in Volume II. The authors are fully aware of this shortcoming and state in the preface "The present work has no pretention of being a complete thesis. It is only meant to be a guide to the domain of colloid science with the (object) of providing a stimulus in the branch of research with which it deals." The editor and his collaborators have succeeded in their objective. This volume, and its companion volume, will serve to stimulate interest in this continuously expanding field of science. These volumes will probably prove to be of special value as reference books and should be available to all teachers and research workers whose interests carry them into the realm of colloid science.

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Neutron Cross Sections. A Compilation of the AEC Neutron Cross Section Advisory Group. By D. J. HUGHES, Chairman, Advisory Group. Office of Technical Services Department of Commerce, Washington, D. C. 1952. xiv + 186 pp. 42 × 28 cm. Price, $1.00.

This book contains a table giving thermal neutron cross sections and, in addition, a set of experimental curves showing the variation of nuclear cross section (usually σ total) as a function of energy for isotopes scattered throughout the periodic table. In the Introduction the compilers state that they have not included all known data but have assembled what in their judgment is a set of "best values." Since the experimental information now available in this field is far from complete, the curves necessarily cover only a portion of the neutron energy spectrum, generally in the region under 10 Kev., although some extend to 100 Mev.

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Annual Review of Physical Chemistry. Volume 3. By G. K. ROLLEFSON, Editor, University of California and R. E. POWELL, Associate Editor, University of California. Annual Reviews, Inc., Stanford, California. 1952. x + 416 pp. 16 × 23 cm. Price, $6.00.

About a half century ago, it became evident that a scientist could not keep informed about all the published work of