crystallized from hot water with aid of norite; m. p. 222–223°; yield 2.5 g.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.35.

Tropic Acid.—The procedure adopted for conversion of VI to tropic acid was essentially that described by McKenzie and Strathern.[6] A concentrated aqueous solution of potassium nitrite (3 g.) was added gradually to 3 g. of β-amino-α-phenylpropionic acid dissolved in 55 cc. of normal hydrochloric acid. The reaction mixture was warmed on the water-bath for fifteen minutes; the oil which settled was separated. The aqueous solution was extracted with ether; the solvent was removed, and the residue was twice recrystallized from benzene; m. p. 116–117°; yield 0.2 g.

Anal. Calcd. for $C_9H_{10}O$: C, 65.06; H, 6.02. Found: C, 65.9; H, 6.1.

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Derivatives of Taurine and β-Alanine[1]

BY M. M. RAPPORT, J. F. MEAD, J. T. MAYNARD, A. E. SENEAR AND J. B. KOEPFLI

During an investigation of derivatives of pantoyltaurine as potential antimalarials,[2] a number of somewhat related compounds, derivatives of either taurine or β-alanine, were prepared and tested for antimalarial activity.[3]

Experimental[4]

Sodium γ-Hydroxybutyryltaurate[5] (I).—The sodium salt of taurine was heated with an excess of γ-butyrolactone for five hours at 115°. The product was extracted with boiling ethanol and treated with Norite and the solvent removed *in vacuo*. The residue after washing with acetone to remove unreacted lactone was crystallized from ethanol from which it separated as deliquescent plates, m. p. 204–210°.

Anal. Calcd. for $C_6H_{12}O_5NSNa$: N, 6.0; Na, 9.8. Found: N, 5.8; Na, 9.8.

γ-Hydroxybutyryltaurinamide (II).—The taurinamide obtained from 25 g. of taurinamide hydrochloride[2] was heated with 14 g. of γ-butyrolactone for twelve hours at 120°. The resulting oil crystallized after standing at 4° under acetone–ether solution and was recrystallized from absolute ethanol to give colorless rosets of prisms, m. p. 66–69°.

Anal. Calcd. for $C_6H_{14}O_4N_2S$: C, 34.3; H, 6.7. Found: C, 34.2; H, 6.7.

Analytical results, etc., when not given for a compound in the running text, are recorded in Table I.

p-Nitrobenzoyltaurinamide (III).—To 10 g. of taurinamide hydrochloride dissolved in 150 ml. of water containing 78 g. of sodium carbonate was added 11 g. of *p*-nitrobenzoyl chloride. The mixture was shaken and warmed on the steam-bath for two hours and then filtered. The product was washed with dilute sodium carbonate solution and water and dried *in vacuo* to give 10.5 g.

p-Aminobenzoyltaurinamide (IV).—Twelve grams of III was reduced with hydrogen at 2000 pounds pressure in dioxane over Raney nickel catalyst at 80°. After removal of the catalyst and evaporation of the solvent 8 g. of a light colored oil was obtained which crystallized on standing.

p-Nitrobenzenesulfonyltaurinamide (V).—Treatment of 4.1 g. of taurinamide hydrochloride with 6.8 g. of *p*-nitrobenzenesulfonyl chloride in a similar manner to that described for the preparation of III, yielded 8 g. of V.

p-Aminobenzenesulfonyltaurinamide (VI).—Eleven and one-half grams of V, reduced under the conditions employed to obtain IV, yielded 8.6 g. of VI.

O-Acetylmandeloyltaurinamide (VII).—To a solution of 10 g. of taurinamide hydrochloride and 13 g. of sodium bicarbonate in 100 ml. of water there was added 14.5 g. of acetylmandeloyl chloride.[6] The mixture was stirred for one hour after the evolution of gas had ceased and the precipitate filtered off, washed with sodium bicarbonate solution and water and dried *in vacuo*. The 18 g. of material thus obtained was pure enough for the next reaction, but was crystallized for analysis.

Mandeloyltaurinamide (VIII).—To 10.7 g. of VII dissolved in the minimum amount of methanol at 4° there was added 10 ml. of 2.2 *N* barium methylate[7] and the solution allowed to stand at 4° for two days. The solution was then treated with the required amount of 2 *N* sulfuric acid and centrifuged to remove the barium sulfate. The resulting solution was taken to dryness, dissolved in a little ethanol and poured into mixture of equal parts of ether and petroleum ether (30–60°). A crystalline solid was thus obtained which was recrystallized in the same way to give 8 g. of product.

N-Carbobenzoxy-β-amino-β-phenylpropionyl Chloride (IX).—To 5 g. of N-carbobenzoxy-β-phenyl-β-alanine[8] suspended in 50 ml. of dry ether there was added 3.9 g. of phosphorus pentachloride and the mixture shaken with cooling for twenty minutes. The reactants went into solution and the acid chloride began to crystallize out in long colorless needles. Two hundred milliliters of petroleum ether (30–60°) was added to complete the separation, and the mixture allowed to stand at 4° for one-half hour. The product was filtered off and washed with petroleum ether to give 4.9 g. of colorless needles, m. p. 89–91°.

Anal. Calcd. for $C_{17}H_{16}O_3NCl$: Cl, 11.2. Found: Cl, 11.8.

N-Carbobenzoxy-β-amino-β-phenylpropionyltaurinamide (X).—To 22.9 g. of IX there was added a solution of 13 g. of taurinamide hydrochloride and 18 g. of sodium bicarbonate dissolved in one liter of water. The mixture was stirred for one hour and then allowed to stand at 4° overnight. The precipitate was collected and washed with water to give 25.6 g. of product.

β-Amino-β-phenylpropionyltaurinamide (XI).—A suspension of 12 g. of X in anhydrous methanol was reduced over palladium black catalyst with hydrogen at 2500 pounds pressure for twenty-three hours. Filtration and evaporation yielded 4.5 g. of a colorless oil which crystallized on scratching.

N-Carbobenzoxy-β-amino-β-(4-nitrophenyl)-propionic Acid (XII).—A solution of β-amino-β-(4-nitrophenyl)-propionic acid[9] (14 g.) and sodium hydroxide (2.7 g.) in 400 ml. of water was chilled in an ice–salt-bath and 17.5 ml. of carbobenzoxy chloride (sp. gr. 1.16) added with continuous shaking over a period of one hour. During the reaction the solution was kept alkaline to phenol-

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

(2) Mead, Rapport, Senear and Koepfli, *J. Biol. Chem.*, **163**, 465 (1946).

(3) The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity is tabulated in a monograph entitled "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor, J. W. Edwards, Ann Arbor, Michigan, 1946.

(4) All melting points have been corrected for exposed stem. The microanalyses reported have been carried out by Dr. Gertrud Oppenheimer and Mr. G. A. Swinehart.

(5) Compare Winterbottom, Clapp, Miller, English and Roblin, THIS JOURNAL, **69**, 1393 (1947).

(6) Thayer, "Organic Syntheses," Coll. Vol. I, p. 12.

(7) Weltzien and Singer, *Ann.*, **443**, 104 (1925).

(8) Dyer, THIS JOURNAL, **63**, 265 (1941).

(9) Posner, *Ann.*, **389**, 40 (1912).

TABLE I

Compound[a]	SN	Formula	Solvent	M. p., °C.	Percentage composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
II	3274	$C_8H_{14}O_4N_2S$	Absolute E[b]	66–69	34.3	34.2	6.7	6.7
III	3284	$C_9H_{11}O_5N_3S$	Cellosolve	197–198	39.6	39.8	4.1	4.2
IV	3283	$C_9H_{13}O_3N_3S$	75% E	152–153	44.4	44.5	5.4	5.3
V	3291	$C_8H_{11}O_6N_3S_2$	I[c]	139–141	31.1	31.4	3.6	3.5
VI	3285	$C_8H_{13}O_4N_3S_2$	I	121–123	34.4	34.4	4.7	4.8
VII	3290	$C_{12}H_{16}O_5N_2S$	I	145–147	48.0	47.8	5.4	5.3
VIII	3286	$C_{10}H_{14}O_4N_2S$	...	100–102	46.5	46.3	5.5	5.5
X	..	$C_{19}H_{23}O_5N_2S$	80% E	183–186	57.5	57.4	5.9	6.2
XI	3289	$C_{11}H_{17}O_3N_2S$	E	152–154	48.8	48.8	6.3	6.0
XII	..	$C_{17}H_{16}O_6N_2$	60% E	150–151	59.3	59.3	4.7	4.4
XIII	..	$C_{19}H_{24}O_7N_4S$	80% E	200–202	50.7	51.0	4.9	4.7
XIV	..	$C_{19}H_{22}O_5N_4S$	E	177–179	54.3	54.5	5.7	5.5
XVA	..	$C_{13}H_{22}O_5N_4S$	Absolute E	150–151	45.1	45.3	6.4	6.5
XV	3632	$C_{11}H_{18}O_3N_4S$	Absolute E	135–136	46.2	46.3	6.3	6.1
XVIII	4469	$C_9H_{12}O_2N_2$	60% E	210–211[d]	60.0	60.3	6.7	6.6

[a] All compounds were crystalline and colorless. [b] E, ethanol. [c] I, Isopropyl alcohol. [d] Decomposes.

phthalein by the addition of 6 *N* sodium hydroxide when necessary. The solution was shaken an additional twenty minutes at room temperature and then extracted with three 200-ml. portions of ether, filtered and made acid to congo red with concentrated hydrochloric acid. After standing in the cold room the precipitate was filtered off and taken up in boiling ethanol, from which 13.5 g. crystallized out on addition of water.

N-Carbobenzoxy-β-amino-β-(4-nitrophenyl)-propionyltaurinamide (XIII).—A solution of 12 g. of XII and 8 g. of phosphorus pentachloride in 150 ml. of dry ether was shaken with cooling for one-half hour. The product which had precipitated was filtered off and washed with petroleum ether. The yield of acid chloride was 12.2 g., m. p. 89–91°, which was added to a solution of 5.6 g. of taurinamide hydrochloride and 7 g. of sodium bicarbonate in 300 ml. of water. After stirring for two hours, the product (13 g.) was filtered off.

N-Carbobenzoxy-β-amino-β-(4-aminophenyl)-propionyltaurinamide (XIV).—Five grams of XIII was suspended in 200 ml. of absolute methanol and reduced over palladium black with hydrogen at 3000 pounds pressure for sixteen hours. The product (3 g.) crystallized from the filtered solution after concentration. The reason that hydrogenolysis of the carbobenzo-oxy group did not occur to an appreciable extent in this single experiment has not been investigated.

β-Amino-β-(4-aminophenyl)-propionyltaurinamide (XV).—To a suspension of 22.7 g. of XIII in 150 ml. of 80% methanol containing 6 ml. of glacial acetic acid was added 0.5 g. of palladium black catalyst. The mixture was shaken under 40 pounds pressure of hydrogen until the pressure had dropped the amount calculated for the reduction of the nitro group. The stopper of the reduction bottle was then replaced with a two-hole stopper having an inlet tube for hydrogen leading almost to the bottom of the bottle and an outlet tube leading to a bubbler for determination of carbon dioxide. Hydrogen was passed into the solution slowly with vigorous shaking for three hours, at which time the formation of carbon dioxide had ceased. The solution was filtered and concentrated under reduced pressure to dryness. The residue was taken up in a small quantity of absolute ethanol and after one hour at 4° a crystalline precipitate (14.5 g.) was collected and dried at room temperature which proved to be the *acetate* (XVA).

The acetate, after long drying *in vacuo* and recrystallization from absolute ethanol, gave XV.

N-Carbobenzoxy-β-alanylamide (XVI) (SN 3272).—A suspension of 15 g. of N-carbobenzoxy-β-alanine[10] (SN 3278) and 15 g. of phosphorus pentachloride in 150 ml. of dry ether was shaken for one-half hour. After filtration and concentration under diminished pressure, the residual oil was dissolved in 200 ml. of dry ether and ammonia passed into the solution for one-half hour. The precipitated amide was collected, washed with hot dilute sodium bicarbonate and then ice-water and then crystallized from ethyl acetate to give 13 g. of colorless crystals, m. p. 163–164°.

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: N, 12.6. Found: N, 12.4.

(+)-Pantoyldiethylaspartate[11] (XVII) (SN 3292).—Fifteen grams of *l*-pantolactone was dissolved in 21.8 g. of diethyl *l*-aspartate[12] and the solution heated for three days at 55–65°. The reaction mixture was distilled and 26.9 g. of a fraction, b. p. 118° (9 mm.), was collected; $[\alpha]^{23}D$ +9.5° (6.2% in absolute ethanol).

Anal. Calcd. for $C_{14}H_{25}O_7N$: C, 52.7; H, 7.9; N, 4.4. Found: C, 53.2; H, 8.1; N, 4.3.

β-Amino-β-(4-aminophenyl)-propionic Acid (XVIII).—Prepared in almost quantitative yield by the reduction of β-amino-β-(4-nitrophenyl)-propionic acid[9] in glacial acetic acid with platinum oxide catalyst and hydrogen at 40 pounds pressure; m. p. 210–211° (dec.), from aqueous ethanol.

Anal. Calcd. for $C_9H_{12}O_2N_2$: C, 60.0; H, 6.7. Found: C, 60.3; H, 6.6.

(+)-Sodium β-Pantoylamido-β-(4-nitrophenyl)-propionate XIX.—Fifteen grams of the finely powdered and carefully dried sodium salt of β-amino-β-(4-nitrophenyl)-propionic acid[9] was heated with 10 g. of *l*-pantolactone and a few drops of absolute ethanol at 105° for two hours. After adding 60 ml. of absolute ethanol, the mixture was refluxed for four hours, cooled, filtered from 3.5 g. of unreacted sodium salt and poured into 700 ml. of isopropyl ether to precipitate the product. A sample was twice reprecipitated for analysis.

Anal. Calcd. for $C_{15}H_{19}O_7N_2Na$: N, 7.7; Na, 6.35. Found: N, 8.1; Na, 6.89.

(+)-Sodium β-Pantoylamido-β-(4-aminophenyl)-propionate (SN 3633).—Ten grams of XIX in 250 ml. of 80% ethanol was reduced with hydrogen at 40 pounds pressure over 0.38 g. of platinum oxide catalyst. When the calculated amount of hydrogen had been absorbed, the solution was filtered, evaporated to dryness *in vacuo* and the residual oil crystallized by treatment with 10 volumes of ethyl acetate and one volume of absolute ethanol. The white powder (9 g.) was further purified by precipitation from absolute ethanol with isopropyl ether; $[\alpha]^{23}D$ +8.5° (1.41% in water).

(10) Sifferd and du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

(11) Compare Weinstock, *et al.*, *J. Biol. Chem.*, **135**, 343 (1940).

(12) Fischer, *Ber.*, **37**, 4599 (1904).

Anal. Calcd. for $C_{15}H_{21}O_5N_2Na$: Na, 6.92. Found: Na, 6.99.

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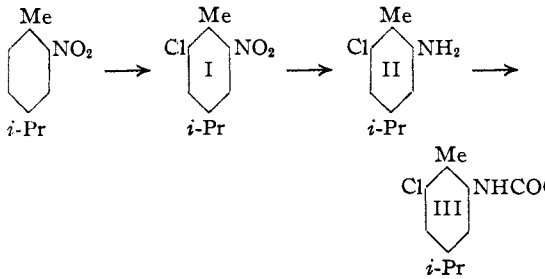
The Chlorination of 2-Nitro-*p*-cymene. I. Monosubstitution[1]

BY ALVIN S. WHEELER, J. M. EARLY AND JOSEPH N. LECONTE



The chlorination of 2-nitro-*p*-cymene yielded 2-nitro-6-chloro-*p*-cymene (I). There was evidence of the formation of 2-chloro-*p*-toluic acid, m. p. 195°, and an aldehyde fraction, b. p. 110–120°. The 2-nitro-6-chloro-*p*-cymene was reduced to 2-amino-6-chloro-*p*-cymene (II), and its acetate (III) and hydrochloride were prepared and studied. The structure of the chlorinated product was proved by reduction, diazotization to remove the amino group, and subsequent oxidation to 2-chloro-*p*-toluic acid.

Experimental

Preparation of 2-Nitro-6-chloro-*p*-cymene.—Dry chlorine gas was led into 100 g. of redistilled nitrocymene and 0.5 g. of aluminum–mercury couple until the system had gained the necessary weight for mono-substitution. The mixture was poured into water, washed first with sodium hydroxide solution, and then with sodium bisulfite solution, and finally with water. It was extracted with ether and the ethereal solution dried over calcium chloride. The ether was evaporated and the residual oil distilled under diminished pressure. That portion boiling between 152 and 153° at 26 mm. pressure was the nitrochlorocymene; yield 45.5 g. of a pale yellow, sweet aromatic odored oil.

Preparation of 2-Amino-6-chloro-*p*-cymene.—Forty-five grams of mossy tin, 39.5 g. of nitrochlorocymene, and 25 cc. of 95% ethanol were placed in a 500-cc. balloon flask, attached to a reflux condenser, and 150 cc. of concentrated hydrochloric acid was added in 10-cc. portions, precautions being taken to prevent overheating. When the initial reaction subsided, the mixture was heated on a steam-bath for four hours. The reaction mixture was then distilled with steam and the unreacted nitro compound retrieved. The mixture was now made basic with sodium hydroxide, the amine steam distilled, extracted with ether, dried over solid sodium hydroxide, the ether evaporated and the residual oil distilled under diminished pressure. The water white oil which distilled at 137–138° at 27 mm. pressure was saved; yield was 25.2 g.

Derivatives. (1) **Hydrochloride.**—Dry hydrogen chloride was passed into an ethereal solution of the amine. The precipitate was dried in a desiccator. The white solid melted 200–205° dec. It was soluble in acetone, hydrolyzed by cold water, and was insoluble in concentrated hydrochloric acid.

(2) **2-Acetamino-6-chloro-*p*-cymene.**—The compound was prepared in the usual way. Four parts of acetic anhydride, one part of the amine and pyridine (2% of the anhydride) were heated for a period of two hours, poured into water, excess anhydride destroyed by heating and the acetamino compound purified by recrystallization from ethanol; m. p. 59–60°; white needles from alcohol and from acetic acid.

TABLE I

Compound	Formula	M. p., °C.	B. p., °C.	Sp. g. 20°C.	Refractive index 26°	% Chlorine Calcd.	% Chlorine Found
2-Nitro-6-chloro-*p*-cymene (I)	$C_{10}H_{12}O_2NCl$	.....	152–153 (26 mm.)	1.1965	1.4934	16.61	16.42
2-Amino-6-chloro-*p*-cymene (II)	$C_{10}H_{14}NCl$	.....	137–138 (27 mm.)	1.0968	1.5583	19.32	19.88
Derivatives of II							
Acetate	$C_{12}H_{16}ONCl$	59–60	.....	....	....	15.74	15.66
Hydrochloride	$C_{10}H_{16}NCl_2$	206–208 dec.	.....	....	....	32.24	32.10

UNIVERSITY OF GEORGIA
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The Oxidation of Acetic Acid with Selenium Dioxide

BY R. B. THOMPSON AND J. A. CHENICEK

The oxidation of compounds that contain an activated hydrogen with selenium dioxide is now a standard preparative method.[1] The reaction is usually carried out by heating the material to be oxidized under reflux with selenium dioxide while employing a suitable inert solvent. Under these conditions acetic acid is frequently used as the inert solvent. However, it has been found that under more drastic conditions acetic acid undergoes an unexpected reaction with selenium dioxide, namely, oxidation in a small yield to succinic acid. Thus selenium dioxide (14 g.), acetic acid (75 cc.), and water (2.2 cc.), were sealed in a rotating autoclave and heated in an atmosphere of nitrogen at 200° for twelve hours. Selenium (9.7 g.) was separated by filtration. The liquid product was evaporated *in vacuo* and deposited 2 g. of solid material which was identified as succinic acid by mixed melting point with an authentic sample. Conversion to the anhydride gave a product which did not depress the melting point of an authentic sample of succinic anhydride. The only other oxidized material which could be identified was carbon di-

(1) This paper is an abstract of a thesis submitted by J. M. Early in partial fulfilment of the requirements for the degree of Master of Science at the University of North Carolina, with completion of work by J. N. LeConte now of the University of Georgia. Alvin S. Wheeler is now deceased.

(1) G. R. Waitkins and C. W. Clark, *Chem. Rev.*, **36**, 235 (1945).