[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ANTIMALARIALS.[1] AMIDES RELATED TO PHENYLPANTOTHENONE

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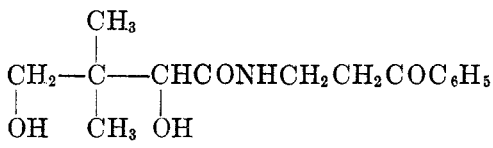
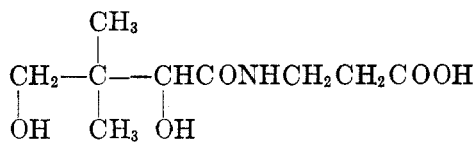
The discovery of the activity against avian malaria of (+)-phenylpantothenone (I) (1),[3] which is configurationally related to the natural pantothenic acid (II), warranted a further investigation of compounds of this type. This work was undertaken at the request of the Panel on Synthesis of Antimalarial Drugs,[1] and is concerned with the preparation of some amides which are structurally related to phenylpantothenone. Variations were designed to show the effect



I



II

on antimalarial activity of (a) inverting the stereochemical configuration; (b) substituting less complex groups for the pantoyl portion of the molecule; (c) modifying the propiophenone portion of the pantothenone molecule by removing one methylene group; (d) by removing the carbonyl group; (e) by various substitutions of possible activating groups in the phenyl nucleus; and (f) by reducing the carbonyl group to the alcohol.

The results to date, discussed in the above order, are as follows:

(a) Using a modification of the procedure of Woolley and Collyer (1b), both (−)-and (+)-pantolactones were condensed with β-aminopropiophenone in yields of 40–50%. The resulting (+)- and the new (−)-pantothenones were

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which the Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

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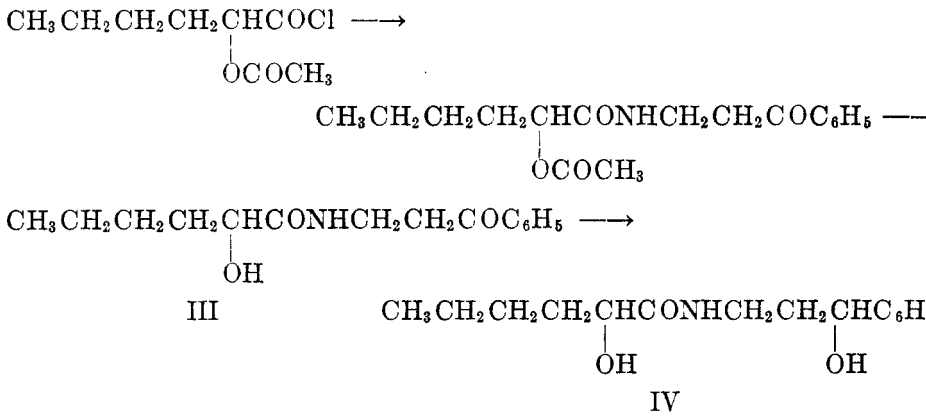
[3] Dr. K. C. Blanchard was instrumental in having this compound tested.

oils which could not be distilled even at very low pressures. Woolley and Collyer (1b) reported that (+)-phenylpantothenone was obtained as a crystalline solid (m.p. 126°) but we were unable to confirm this finding. The analytical data on these oils checked closely with the theoretical values, and the specific rotation figures for the two products were opposite in sign and of the same numerical magnitude (−35.4 and +37.1). Furthermore, the specific rotation of the (+)-tolylpantothenone (XII), which was obtained in an analytically pure, crystalline form (m.p. 88–90°), was not markedly higher (+41.1).

The (−)-phenylpantothenone (of configuration opposite to that of pantothenic acid) was inactive against avian malaria, showing the activity to be specific with respect to the natural pantothenic configuration.

(b) No difficulty was encountered in condensing caproyl chloride with β-aminopropiophenone. α-Acetoxycaproyl chloride was also condensed with the amino ketone. Preferential hydrolysis of the latter gave the hydroxy amide (III) and aluminum isopropoxide reduction yielded the dihydroxy amide (IV).

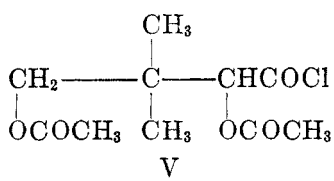


Repeated attempts to react γ-butyrolactone with β-aminopropiophenone were without success.

The lack of antimalarial activity among these compounds confirmed expectation based on the specificity of the natural pantothenic configuration.

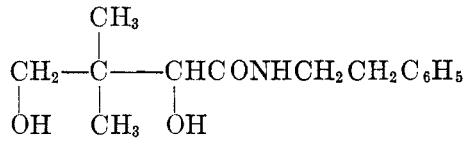
(c) Efforts to condense α-aminoacetophenone with (−)-pantolactone employing essentially the procedure used in preparing phenylpantothenone, were unsuccessful. This failure was probably due to the sensitivity of aminoacetophenone (2) in the form of the free base.

It was thought that perhaps the diacetyl derivative of pantoyl chloride (3) (V) could be condensed with α-aminoacetophenone. Removal of the acetyl



groups by preferential hydrolysis should then be possible and should give the desired amide. Judging from the ease with which caproyl chloride was condensed with aminoacetophenone, and from the successful selective hydrolysis of the acetyl derivative of N-(β-benzoylethyl)-α-hydroxycaproamide (see III), this method should be a feasible one; however, this project was not completed.

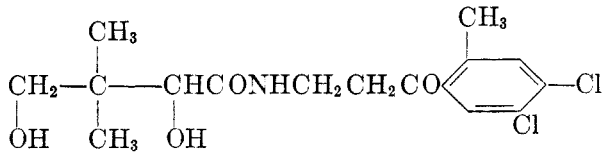
(d) β-Phenylethylamine was readily condensed with (+)-, (−)-, and (*dl*)-pantolactones to give the amides (VI).



VI

The *dl* amide (m.p. 92–93°) proved to be inactive against avian malaria [*cf.* (a)].

(e) In an effort to increase the antimalarial activity of (+)-phenylpantothenone by means of nuclear activating groups, [*cf.* (f)], 4-methyl-, 4-chloro-, and 2-methyl-4,5-dichloro-β-aminopropiophenones were prepared and condensed with (−)-pantolactone. All of the products thus obtained (*cf.* VII)



VII

were active against avian malaria, but only the *p*-chloro compound showed significant increase in activity as compared with (+)-phenylpantothenone itself.

In several of the condensations of the pantolactone with the β-aminopropiophenones, crystalline by-products were formed from the aminopropiophenones, evidently by autocondensation, since the aminopropiophenones alone when subjected to the condensation conditions gave the same materials. Three of these autocondensation products were purified. Analyses indicated that they were tertiary amines of the general formula $(RCOCH_2\underset{\sim}{C}H_2)_3N$. Substantiation of these structures is offered by the work of Blicke and Burckhalter (4) on methyl-(β-benzoylethyl)amine, which in the presence of alkali loses methylamine and forms the vinyl ketone. Reaction of a second molecule of methyl-(β-benzoylethyl)amine with the vinyl ketone then gives methyl-di-(β-benzoylethyl) amine.

In a similar way the autocondensation of aminopropiophenone can be represented as follows:

$$C_6H_5COCH_2CH_2NH_2 \rightarrow C_6H_5COCH{=}CH_2 \xrightarrow{+\ VIII}$$

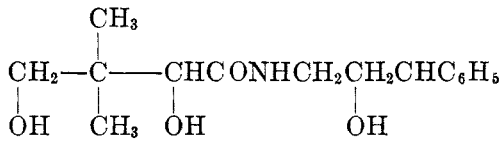
VIII IX

$$(C_6H_5COCH_2CH_2)_2NH \xrightarrow{+\ IX} (C_6H_5COCH_2CH_2)_3N$$

X

The tri-(β-benzoylethyl)amine (X) was tested and found to be inactive against avian malaria.

(f) Several attempts were made to prepare phenylpantothenol (XI) in order to determine the effect of converting the ketone into a secondary alcohol. In

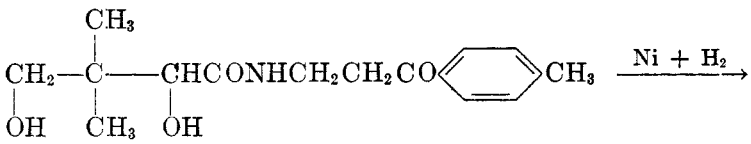


XI

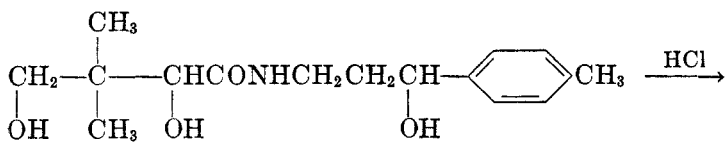
an effort to synthesize this compound directly we planned to condense γ-hydroxy-γ-phenylpropylamine with the lactone. The γ-hydroxy-γ-phenylpropylamine (5) was readily prepared by catalytic reduction of β-aminopropiophenone. However, repeated attempts to condense this amino alcohol with the lactone failed.

Phenylpantothenone, itself, with both Raney nickel and platinum catalysts showed a consistently anomalous behavior in attempted reductions (see experimental section). The results with aluminum isopropoxide were equally unsatisfactory.

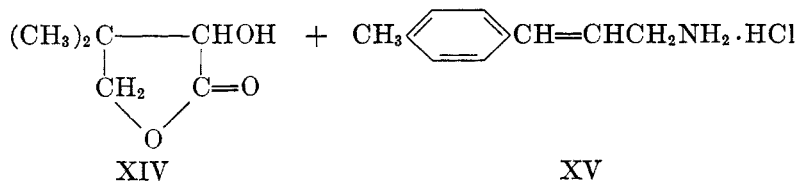
Tolylpantothenone (XII) was used in subsequent reduction experiments because it was obtained as a pure crystalline solid and was as active as the phenyl analog. Using Raney nickel catalyst and alcohol as solvent, the required volume of hydrogen was readily absorbed. The colorless viscous oil obtained was shown to be the desired tolylpantothenol (XIII) as follows: A Zerewitinoff deter-



XII



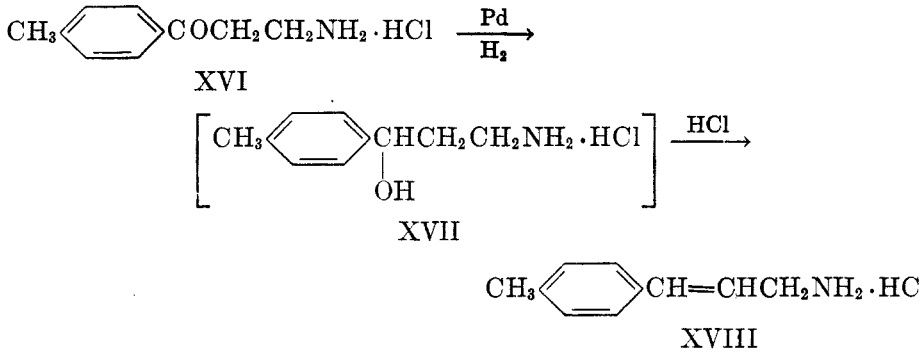
XIII



XIV XV

mination showed the expected four active hydrogens, whereas the unreduced tolylpantothenone showed only three. Hydrolysis of the tolylpantothenol according to the method of Woolley and Collyer (1b) gave the (−)-pantolactone (XIV) and a hydrochloride which melted at 239–240°, and which from the analysis appeared to be γ-(4-methylphenyl)allylamine (XV). In contrast with this result, hydrolysis of the unreduced compound gave β-amino-4-methylpropiophenone hydrochloride (m.p. 183°) and XIV.

In order to prove that the hydrochloride (m.p. 239–240°) consisted of some degradation product of the alcohol, namely γ-hydroxy-γ-(4-methylphenyl)propylamine (XVII), a sample of β-amino-4-methylpropiophenone hydrochloride itself (XVI) was catalytically reduced, using the method of Davies and Powell (5). The resulting alcohol (XVII) was not isolated, but was subjected to the same hydrolytic conditions used for preparing the pantothenol (XIII). In this way a hydrochloride (XVIII) was obtained (m.p. 240–241°) which proved to be identical with the hydrochloride obtained upon hydrolysis of the pantothenol (XIII).



The structure of this hydrochloride, namely, γ-(4-methylphenyl)allylamine (XVIII), was substantiated by analogy to the behavior of the phenyl compound. γ-Hydroxy-γ-phenylpropylamine under the same hydrolytic conditions employed with tolylpantothenol, gave the known γ-phenylallylamine hydrochloride (6) (m.p. 235°; picrate, m.p. 179–180°).

Tolylpantothenol (XIII) proved to be only very slightly active against avian malaria.

Samples of all the new compounds tested against malaria were also submitted to Dr. D. W. Woolley of The Rockefeller Institute for Medical Research and were tested for bacteriostatic activity on *Lactobacillus casei;* the results are shown in Table I, in which the activities are expressed as fractions of the activity of (+)-phenylpantothenone.

The three compounds containing the pantoyl moiety, of configurations corresponding to that of pantothenic acid, and only these, were found to possess antimalarial activity and action also against *Lactobacillus casei;* however, the relative bacteriostatic activities of these compounds did not parallel the relative antimalarial activities.

Acknowledgment. A great deal of assistance in the above described work was rendered by the following: Gilbert Ashburn, Philip S. Bailey, Marion T. Clark, Norman H. Leake, Russell J. Rowlett, Jr., Jason M. Salsbury and Newton H. Shearer, Jr. Most of the microanalyses were performed by Miss Joyce Blume and Curtis J. Floyd.

TABLE I

BACTERIOSTATIC ACTIVITY

COMPOUND	ACTIVITY
(−)-Phenylpantothenone	less than 0.03
(+)-*p*-Chlorophenylpantothenone	2.7
(+)-*p*-Tolylpantothenone	7
(+)-*p*-Tolylpantothenol	0.7
N-(β-Benzoylethyl)-α-hydroxycaproamide	less than 0.05
N-(β-Benzoylethyl)caproamide	less than 0.05
dl-N-pantoyl-β-phenylethylamide	less than 0.05
Methyldi(benzoylethyl)-amine[4]	0.07

EXPERIMENTAL[5]

β-Chloropropiophenone (m.p. 49–50°) was prepared in 80–90% yield using the procedure of Allen and Barker (7).

β-Phthalimidopropiophenone. The method of Hale and Britton (8) was modified for large scale preparation. An intimate mixture of 53 g. of the chloro ketone and 59.5 g. of potassium phthalimide (9) was heated at 130° in an oil thermostat for one hour with efficient stirring. The melt was poured from the flask while still hot. After solidification it was ground to a powder, triturated with water, and crystallized from ethanol; m.p. 129–130°; yield 81%. The crude product, however, gave satisfactory results in the next step.

β-Aminopropiophenone hydrochloride (SN-14,253). The procedure used was essentially that of Davies and Powell (5); yields of 80–85% were realized.

(−)-*Phenylpantothenone (SN-13,767).* This compound was prepared by the following method, which is a modification of that used by Woolley and Collyer (1) to obtain the compound corresponding to the natural pantothenic acid (of opposite stereochemical configuration). Twenty grams of β-aminopropiophenone hydrochloride was dissolved in 120 ml. of cold 5% sodium hydroxide. The free base was extracted from this with six 150-ml. portions of ether. The ether solution was shaken with 50 ml. of saturated sodium chloride solution and dried for one hour over sodium sulfate. The ether and traces of water were removed by evaporation under reduced pressure (0–25°) employing first a water and than a "hyvac" pump. The pale yellow oil (14.2 g.) which remained was heated with 12.4 g. of (+)-pantolactone at 82° for three hours. The resulting red oil was dissolved in 100 ml. of methanol and sufficient hydrochloric acid (1.06 *N*) was added to bring the *p*H to 3. This solution was diluted with water until slightly cloudy, cooled to 0°, and filtered to remove a small quantity of white by-product (see below). The filtrate was extracted with five 200-ml. portions of ether. The combined ether solution was shaken with two 35-ml. portions of 1 *N* sodium hydroxide solution and then with 50 ml. of saturated sodium chloride solution which contained sufficient hydrochloric acid to give this wash solution a *p*H of 6 after separation. After drying for one hour over sodium sulfate the ether was removed by evaporation under

[4] *Cf.* reference (4).

[5] Melting points reported herein are corrected.

reduced pressure. Any remaining volatile solvent was removed under reduced pressure over a prolonged period (20 hours) at room temperature with frequent agitation. Repeated attempts to crystallize this extremely viscous oil were unsuccessful. It weighed 10 g. (40%); $[\alpha]_D^{26}$ −33.4° (c = 2.73) in absolute ethanol.

Anal. Calc'd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02.
Found (different samples): C, 64.22, 64.79, 63.41; H, 7.18, 7.07, 7.62; N, 4.52, 4.53, 4.46.

Tri-(β-benzoylethyl)amine (*SN-14,219*) from the preceding condensation melted at 144–145° after several crystallizations from ethanol.

Anal. Calc'd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.36.
Found: C, 77.44; H, 6.47; N, 3.36, 3.25, 3.31.

(+)-*Phenylpantothenone* (*SN-12,610*). This compound was first prepared by Woolley and Collyer (1) and was prepared by us from (−)-pantolactone and β-aminopropiophenone using the modified procedure described for the (−)-phenylpantothenone. The by-product (m.p. 144–145°) that was obtained in the preceding condensation was also obtained here. Attempts in this laboratory to crystallize this compound were unsuccessful. It was obtained in yields of 40–50%; $[\alpha]_D^{20}$ +37.1° (c = 0.998) in absolute ethanol.

Anal. Calc'd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58.
Found (different samples): C, 64.79, 65.29, 65.49; H, 7.11, 7.45, 7.49.

N-(2-Benzoylethyl)caproamide (*SN-13,771*). To a solution of 15 g. of β-aminopropiophenone hydrochloride in 150 ml. of cold water was added with stirring 15 g. of *n*-caproyl chloride and then 65 ml. of 15% sodium hydroxide solution. After stirring for thirty minutes the amorphous white solid was filtered and recrystallized from benzene-ligroin; 15 g. (75%); m.p. 63–65°. Two additional recrystallizations raised the melting point to 65–66°.

Anal. Calc'd for $C_{15}H_{21}NO$: C, 72.84; H, 8.56; N, 5.66.
Found: C, 73.46; H, 8.89; N, 5.78.

dl-α-Hydroxycaproic acid. A preparative method for this compound has been described in the literature (10). The following method, however, eliminates the necessity of isolating the product through its copper salt.

A solution of 170 g. of α-bromocaproic acid (11) in 2 l. of 10% sodium carbonate was refluxed for six hours. The resulting straw colored solution was cooled in an ice-bath and carefully neutralized with concentrated sulfuric acid. Continuous extraction (24 hours) with ether and removal of the ether by evaporation under reduced pressure gave 115 g. of a mobile oil. Cooling in an ice-chest for twelve hours gave 29 g. of white plates. Prolonged cooling gave an additional 15 g. of product; total yield 44 g. (42%); m.p. 59–61°.

dl-N-(2-Benzoyethyl)-α-hydroxycaproamide (*SN-13,773*). A mixture of 20 g. of α-hydroxycaproic acid and 35 g. of acetyl chloride was refluxed for five minutes. The excess acetyl chloride was removed by distillation and the residual straw colored syrup was refluxed for three hours with 64 g. of thionyl chloride. The excess thionyl chloride was removed by distillation under reduced pressure. The residual crude acid chloride was added at once with stirring to a cold (0°) solution of 24.6 g. of β-aminopropiophenone hydrochloride in 200 ml. of water. After stirring for fifteen seconds a cold solution of sodium hydroxide (11.9 g. in 80 ml. of water) was added. A viscous oil soon separated and quickly solidified. After stirring for ten minutes the solid was filtered and washed well with water; yield 31.5 g. (66%); m.p. 58–64°. Eighteen grams of this crude acetyl derivative was hydrolyzed by dissolving in 170 ml. of ethanol containing 2.5 g. of sodium hydroxide and allowing the resulting solution to stand at room temperature for five hours. Dilution with 50 ml. of water and cooling gave 13 g. (82%) of a white crystalline precipitate; m.p. 118–119°. Recrystallization from benzene gave 11 g. melting at 118–119°.

Anal. Calc'd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32.
Found: C, 68.48; H, 8.34; N, 4.90.

The *semicarbazone* after crystallization from an ethanol-water solution melted at 159–160°.

Anal. Calc'd for $C_{16}H_{24}N_4O_3$: N, 17.49. Found: N, 17.35.

dl-N-1-[(3-Hydroxy-3-phenyl)propyl]-α-hydroxycaproamide. A solution of 6.5 g. of N-(β-benzoylethyl)-α-hydroxycaproamide and 20 g. of aluminum isopropoxide in 50 ml. of dry toluene was heated at reflux temperature for nineteen hours. The straw colored solution was cooled in an ice-bath and extracted with an excess of conc'd hydrochloric acid. The aqueous layer was separated and extracted with a small volume of toluene. The combined toluene solution was washed with water and dried over sodium sulfate. Sufficient ligroin was added to cause a slight cloudiness. Cooling overnight in an ice-chest gave 5 g. of a crude product melting at 65–80°. Three recrystallizations from ethanol-water gave a white crystalline product; m.p. 98–99°.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28.
Found: C, 67.81; H, 8.76; N, 5.06.

Attempts to prepare N-(β-benzoylethyl)-γ-hydroxybutyramide by condensing γ-butyrolactone (12) and β-aminopropiophenone, failed, using both the procedure of Woolley and Collyer and the modified procedure developed here. Consistently high yields of tri-(β-benzoylethyl)amine (m.p. 144–145°) were obtained. The oil which remained after the removal of this by-product could not be crystallized, and analytical data indicated that it was not the desired product.

Attempted preparation of (+)-phenylpantothenol. (a) γ-Phenyl-γ-hydroxypropylamine was prepared from β-aminopropiophenone hydrochloride by the method of Davies and Powell (5). On long heating (at 75° and 95°) with (−)-pantolactone the amino alcohol failed to condense, and none of the desired product could be obtained. In an earlier attempt to prepare γ-phenyl-γ-hydroxypropylamine, β-phthalimidopropiophenone was reduced to the corresponding alcohol with aluminum isopropoxide but all attempts to hydrolyze this compound to the amino alcohol were unsuccessful.

(b) In an attempt to reduce (+)-phenylpantothenone at room temperature and atmospheric pressure using Raney nickel catalyst and ethanol as solvent, the required volume of hydrogen was absorbed in a period of five hours. Using platinum catalyst the required volume of hydrogen was absorbed in four hours. The oily products, however, did not exhibit the expected properties. Zerewitinoff determinations showed that phenylpantothenone had three active hydrogens. Phenylpantothenol, then, should show four active hydrogens. The products in each case, however, possessed only three active hydrogens, indicating that no reduction had occurred. Furthermore, both of the oily products on hydrolysis with hydrochloric acid according to the method of Woolley and Collyer (1) gave only the (−)-lactone and β-aminopropiophenone hydrochloride, the products obtained when (+)-phenylpantothenone is hydrolyzed.

(c) (+)-Phenylpantothenone, when refluxed with an excess of aluminum isopropoxide in isopropanol for three hours, also gave a product which showed only three active hydrogens, and which gave only β-aminopropiophenone hydrochloride and the (−)-lactone on hydrolysis.

β-Phthalimidoethylbenzyl alcohol. Twenty-four grams of β-phthalimidopropiophenone was added to 200 cc. of dry isopropanol and 100 cc. of aluminum isopropoxide. Reduction by the Pondorff method was carried out for 2½ hours, after which the excess isopropanol was evaporated under reduced pressure. The resulting material was carefully hydrolyzed by adding 200 cc. of water and slowly dropping in dilute hydrochloric acid until *p*H 5 was reached. A thick brown oil resulted which was extracted into ether and dried over sodium sulfate. After evaporation of the ether an oil was left which crystallized upon slowly cooling a hot concentrated ether solution; 12.1 g. (50%); m.p. 75–76°; white needles.

Anal. Calc'd for $C_{17}H_{15}NO_3$: N, 4.98. Found: N, 4.81.

γ-Phenylallylamine hydrochloride. Both Posner (6a) and Emde (6b) have prepared this compound from cinnamyl chloride and ammonia. Posner reports the melting point 210° and Emde gives the melting point as 236°. The picrate according to Posner melts at 173°. The hydrochloride was prepared in this laboratory in approximately 60% yield by subjecting γ-hydroxy-γ-phenylpropylamine hydrochloride to the same conditions which

Woolley and Collyer (1b) used to hydrolyze (+)-phenylpantothenone. It melted at 235°. The picrate melted at 179–180°.

β-Chloro-p-methylpropiophenone, made by the method of Kenner and Statham (13) and crystallized from hexane, melted at 77–80°; yield 56%.

p-Methyl-β-phthalimidopropiophenone. This compound was obtained in 87% yield using the same procedure employed in preparing β-phthalimidopropiophenone itself. The crude product was used without further purification. An analytical sample, prepared by crystallization from ethanol, melted at 132–135°.

Anal. Calc'd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15.
Found: C, 73.80; H, 5.32.

β-Amino-p-methylpropiophenone hydrochloride. The method which Davies and Powell (5) used in preparing β-aminopropiophenone hydrochloride was modified slightly in preparing the compound. The period of reflux was increased to twenty hours and additional hydrochloric acid was introduced during the course of the hydrolysis. The tolyl compound was less soluble in water than the phenyl analog and as a consequence a larger volume of water was required in separating it from the phthalic acid. The product (rectangular plates) was crystallized from ethanol-acetone in 71% yield; m.p. 182–186°.

Anal. Calc'd for $C_{10}H_{13}NO \cdot HCl$: C, 60.15; H, 7.07.
Found: C, 60.23; H, 7.29.

Tri-[(p-methylbenzoyl)ethyl]amine by autocondensation of β-amino-p-methylpropiophenone. Five grams of the amino ketone (free base) was heated at 70–80° for sixteen hours. When cold, the thick waxy oil was shaken with a small volume of ether. The small amount of white solid which separated was removed by filtration; m.p. 126–128°. Recrystallization from ethanol did not raise the melting point.

Anal. Calc'd for $C_{30}H_{33}NO_3$: C, 79.09; H, 7.30.
Found: C, 79.18; H, 7.36.

(+)-p-Tolylpantothenone (SN-14,688). The procedure used to prepare (−)-phenylpantothenone was modified slightly. The (−)-lactone and the free base were heated at 70–80° for sixteen hours. After the same purification procedure, the extremely viscous product was dissolved in a very small volume of benzene, and the solution stirred at 8° for fifty hours. Crystallization of the tolylpantothenone produced an almost solid mass. After dilution with ether the product was separated by filtration. Two recrystallizations from benzene gave a 36% yield; m.p. 88–90°; $[\alpha]_D^{22}$ +41.1° (c = 2.190) in absolute ethanol.

Anal. Calc'd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90.
Found: C, 65.24; H, 7.96.

Hydrolysis of (+)-tolylpantothenone by the procedure of Woolley and Collyer (1) for hydrolyzing (+)-phenylpantothenone gave two products which were isolated and identified by mixture melting points with authentic samples; namely, β-amino-*p*-methylpropiophenone hydrochloride (m.p. 182–186°) and (−)-pantolactone (m.p. 88–91°).

(+)-p-Tolylpantothenol (SN-15,032). A solution of 15 g. of (+)-tolylpantothenone in 400 ml. of ethanol, containing 10 g. of Raney nickel, was hydrogenated at room temperature and atmospheric pressure. After fourteen hours the required volume of hydrogen was absorbed. Removal of the catalyst, and of the solvent by evaporation under reduced pressure at 45°, gave a viscous oil. This product, supposedly a mixture of epimers, was purified using the same procedure as was employed in purifiying (−)-phenylpantothenone. The clear oil thus obtained weighed 4 g. (27%); $[\alpha]_D^{19}$ +32.6° (c = 1.133) in absolute ethanol. A Zerewitinoff determination showed four active hydrogens (the unreduced compound showed only three).

Anal. Calc'd for $C_{16}H_{25}NO_4$: C, 65.10; H, 8.52; N, 4.75; active hydrogens, 4.
Found: C, 64,18; H, 8.47; N, 4.68; active hydrogens, 4.12.

γ-(p-Tolyl)allylamine hydrochloride. Hydrolysis of (+)-*p*-tolylpantothenol by the procedure of Woolley and Collyer gave two products. One was shown to be (−)-pantolactone by a mixture melting point with an authentic sample. The other product, a hydrochloride, melted at 236–239° after crystallization from absolute ethanol.

Anal. Calc'd for $C_{10}H_{13}N \cdot HCl$: C, 65.50; H, 7.68; N, 7.63; Cl^-, 19.30.
Found: C, 65.10; H, 7.52; N, 7.30; Cl^-, 20.48.

In order to obtain additional evidence for the structure, 1 g. of β-amino-*p*-methylpropiophenone hydrochloride was catalytically reduced to the alcohol according to the procedure of Davies and Powell (5) for preparing γ-phenyl-γ-hydroxypropylamine. The alcohol was not isolated but it was subjected to the same conditions used in the hydrolysis of the (+)-*p*-tolylpantothenol. This procedure gave a white hydrochloride which melted at 240–241° after two recrystallizations from absolute ethanol. A mixture melting point with the hydrolysis product above (m.p. 236–239°) showed no depression.

β,p-Dichloropropiophenone. Allen, Cressman, and Bell (14), employing the method of Hale and Britton (8) as modified by Allen and Barker (7) for the preparation of *p*-phenyl-β-chloropropiophenone, prepared this compound in a 38% yield. A much improved yield was realized here by refluxing the Friedel-Crafts reaction mixture for three hours and then allowing it to stand overnight at room temperature. After hydrolysis and filtration the carbon disulfide phase was separated, shaken with dilute potassium carbonate solution, and with water. The carbon disulfide was removed by distillation under reduced pressure and the residual oil was dissolved in the minimum volume of hot ethanol. Treatment with decolorizing carbon followed by cooling gave a 63% yield of white crystalline product; m.p. 49–50° (A., C., and B., 48°).

p-Chloro-β-phthalimidopropiophenone. The same procedure was used here as was employed in preparing β-phthalimidopropiophenone. Recrystallization from absolute ethanol gave a 79% yield; m.p. 152°.

Anal. Calc'd for $C_{17}H_{12}ClNO_3$: N, 4.67. Found: N, 4.39.

p-Chloro-β-aminopropiophenone hydrochloride (SN-14,036.). The hydrolysis of the phthalimido compound was carried out as previously described for the *p*-tolyl analog. The time of reflux was shortened to twelve hours. The product was crystallized from absolute ethanol; yield 61%; m.p. 219°.

Anal. Calc'd for $C_9H_{10}ClNO \cdot HCl$: Cl^-, 16.11. Found: Cl^-, 16.13.

Tri-[β-(p-chlorobenzoyl)ethyl]amine by autocondensation of β-amino-p-chloropropiophenone. One gram of the free base was heated at 80–82° for three hours. Crystallization of the resulting pale yellow solid from methanol gave 0.5 g. of a white crystalline solid; m.p. 148–149°. A mixture melting point with the by-product (m.p. 147–149°) from the condensation below showed no depression. Further recrystallization from ethanol gave a product melting at 154–155°.

Anal. Calc'd for $C_{27}H_{24}Cl_3NO_3$: C, 62.74; H, 4.68; N, 2.71.
Found: C, 62.55; H, 4.70; N, 2.70.

(+)-p-Chlorophenylpantothenone (SN-13,776). The condensation of 6.2 g. of β-amino-*p*-chloropropiophenone and 3.8 g. of the (−)-lactone was carried out as previously described in the preparation of (−)-phenylpantothenone. The usual purification procedure gave 8 g. of a viscous oil which contained small amounts of a waxy solid. This solid by-product (m.p. 147–149°, approx. 1.5 g.) was separated by dissolving the mixture in hot methanol, cooling, and filtering. Removal of the methanol by evaporation under reduced pressure gave 6 g. (43%) of a viscous orange oil; $[\alpha]_D^{29}+25.7°$ (c = 2.456) in absolute ethanol.

Anal. Calc'd for $C_{15}H_{20}ClNO_4$: C, 57.23; H, 6.37; N, 4.45.
Found: C, 58.76; H, 6.19; N, 3.98.

2-Methyl-β-4,5-trichloropropiophenone. Seventy-five grams of β-chloropropionyl chloride was added dropwise to a mechanically stirred mixture of 87 g. of 3,4-dichlorotoluene and 70 g. of powdered anhydrous aluminum chloride. The temperature of the reaction mixture was maintained at 80–90° during the addition and for two hours afterwards. Upon hydrolysis with an ice-hydrochloric acid mixture, the crude product was extracted into 800 ml. of ether. This solution was washed with water and dried over sodium sulfate. Removal of the ether gave 106 g. (78%) of an oil which was used without further purification (the assumed orientation here is based on analogy to the acetylation reaction, where rigorous structural proof has been obtained (15)).

The *2,4-dinitrophenylhydrazone*, made in the usual way, melted at 285° after crystallization from dioxane.

Anal. Calc'd for $C_{16}H_{13}Cl_3N_4O_4$: N, 12.97. Found: 12.92.

4,5-Dichloro-2-methyl-β-phthalimidopropiophenone. An intimate mixture of 106 g. of crude 2-methyl-β-4,5-trichloropropiophenone and 65 g. of potassium phthalimide was heated at 145° for one hour. A mixture of 600 ml. of acetone and 1000 ml. of benzene was added to the resulting melt. The potassium chloride was removed by three extractions with water. After drying over sodium sulfate, the solution was concentrated to a volume of 200 ml. The phthalimide which separated was removed and sufficient ethanol was added to give a slightly turbid solution. After standing for three hours the product was separated; a second crop was obtained by concentrating the filtrate; total yield after crystallization from ethanol, 22 g. (14%); m.p. 123–124°.

Anal. Calc'd for $C_{18}H_{13}Cl_2NO_3$: N, 3.87. Found: N, 3.88.

β-Amino-4,5-dichloro-2-methylpropiophenone hydrochloride. The above phthalimido compound was hydrolyzed, using essentially the procedure of Davies and Powell (5). The time of reflux was increased to 35 hours; yield 62%; m.p. 184–185° after crystallization from absolute ethanol.

Anal. Calc'd for $C_{10}H_{11}Cl_2NO \cdot HCl$: C, 44.76; H, 4.48; Cl^-, 13.18.
Found: C, 44.64; H, 4.58; Cl^-, 13.32.

(+)-4,5-Dichloro-2-methylphenylpantothenone (SN-9973). The procedure used in preparing (−)-phenylpantothenone was again modified slightly. The initial condensation time was increased to seventeen hours. The final product (an oil) was dissolved in a small volume of ethanol and filtered from a small amount of insoluble amorphous solid. Removal of the ethanol by evaporation under reduced pressure and subsequent evacuation using a "hyvac" pump for sixty hours gave a very viscous oil; yield 40%; $[\alpha]_D^{23}+17°$ (c = 1.745) in absolute ethanol.

Anal. Calc'd for $C_{16}H_{21}Cl_2NO_4$: C, 53.01; H, 5.83; N, 3.87.
Found: C, 53.77; H, 5.02; N, 3.51.

dl-N-Pantoyl-β-phenylethylamide (SN-14,254). A mixture of 9.3 g. of β-phenylethylamine and 10 g. of *dl*-pantolactone was heated at 82° for three hours. The straw colored product crystallized slowly on standing at room temperature for two days. Two recrystallizations from butanone-ligroin gave 13 g. (68%) of a white crystalline product; m.p. 92–93°.

Anal. Calc'd for $C_{14}H_{21}NO_3$: C, 66.89; H, 8.42. Found: C, 66.49; H, 8.07.

(+)-N-Pantoyl-β-phenylethylamide. A mixture of 9.6 g. of (−)-pantolactone and 9 g. of β-phenylethylamine was heated at 82° for three hours. The viscous oily product was dissolved in 80 ml. of butanone and 100 ml. of ligroin was added. This solution was cooled to 0° and crystallization was induced by scratching the walls of the beaker. Several crystallizations in this fashion gave 8 g. (42%) melting at 72–74°; $[\alpha]_D^{27}+44.8°$ (c = 2.052) in absolute ethanol.

Anal. Calc'd for $C_{14}H_{21}NO_3$: N, 5.58. Found: N, 5.54.

(−)-N-Pantoyl-β-phenylethylamide. This compound was prepared from the (+)-lactone using the same procedure employed in the preceding experiments; m.p. 72–74°; yield 60%; $[\alpha]_D^{27}$ −45.9° (c = 2.047) in absolute ethanol.

Anal. Calc'd for $C_{14}H_{21}NO_3$: N, 5.58. Found: N, 5.59.

A mixture of 0.50 g. of the (−)-butyramide (above) and 0.50 g. of the (+)-butyramide was dissolved in 15 ml. of butanone. This solution was diluted with 35 ml. of ligroin and cooled to 0°. The white crystalline precipitate was removed by filtration. It melted at 92–93° and was identical with the previously prepared *dl*-compound as shown by a mixture melting point.

β-Aminopropiophenone hydrobromide. This compound (m.p. 216–218°) was prepared from phenacyl bromide in 85% yield through the hexamethylenetetramine addition compound in the manner of Mannich and Hahn (16). This procedure gave a much better yield than either of two alternate methods, namely, the treatment of phenacyl bromide with excess ammonia in alcohol (17), or the Gabriel synthesis using potassium phthalimide (2).

N-(Benzoylmethyl)caproamide. To a solution of 6.3 g. of α-aminopropiophenone hydrobromide in 50 ml. of water was added with efficient stirring 6.8 g. of caproyl chloride and then 20 ml. of 30% potassium hydroxide. A red oil separated and solidified after an additional hour of stirring. Crystallization from ethanol gave 2 g. (29%) of a white solid; m.p. 75–77°. An additional crystallization from hexane-ether gave long white rods; m.p. 76–77°.

Anal. Calc'd for $C_{14}H_{19}NO_2$: N, 6.01. Found: N, 5.82.

SUMMARY

The following variations from the phenylpantothenone structure were made to test the effect on antimalarial activity:

(a) The (−)-phenylpantothenone was made of configuration opposite to that of natural pantothenic acid.

(b) The caproyl and α-hydroxycaproyl analogs were synthesized and the latter, N-(2-benzoylethyl)caproamide, was reduced to the corresponding alcohol.

(c) An attempt was made to condense the pantolactone with α-aminoacetophenone.

(d) The pantoyl amide of β-phenylethylamine was made in *d*, *l*, and *dl* forms.

(e) The 4-methyl-, 4-chloro-, and 4,5-dichloro-2-methyl analogs of phenylpantothenone were prepared, only the former being obtained in crystalline form. By-products were shown to be autocondensation products of the β-aminopropiophenones used.

(f) *p*-Tolylpantothenone was reduced to the alcohol *p*-tolylpantothenol. Hydrolysis of this gave pantolactone and γ-(4-methylphenyl)allylamine, the structure of which was demonstrated by synthesis through reduction of β-amino-*p*-methylpropiophenone, followed by dehydration.

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