The mixture was heated on an oil-bath until water started to collect in the water separator. The reaction then was cooled to 50–60° and 16.1 g. of O,O-diethyl chlorothiophosphate was added from a dropping-funnel. The dropping-funnel was rinsed with 10 ml. of dry benzene and refluxing was resumed. After 15 hours of refluxing, the reaction was cooled and 100 ml. of cold water was used to transfer the reaction mixture to a 250 ml. separatory-funnel. The benzene layer was separated and washed with 30 ml. of 10% NaOH and then with 30-ml. portions of water until the water was neutral to litmus. The benzene extract was dried over calcium chloride for 15 minutes, then was transferred to a 100-ml. separatory-funnel and dried over fresh calcium chloride for 1$^1/_2$ hours.

Aliquots of the benzene extract then were filtered into a 50-ml. round-bottom flask attached to a distilling head and the benzene was stripped off with a stream of dry air under reduced pressure. After most of the benzene had been removed in this manner, the system was placed under a vacuum of 0.25 mm. and heat was applied. The unreacted O,O-diethyl chlorothiophosphate and other low-boiling materials were distilled off (42–45°). The oil-bath temperature then was raised to a temperature of 120° for $^1/_2$ hour. The residue in the flask contained crude Diazinon. The yield on the final step was 62%.

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(8) Contribution No. 646.

2-Pyrones. XX. Carboxydehydroacetic Acid and Its Derivatives

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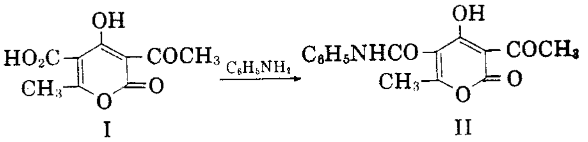
In re-examining some details of the structure and reactions of dehydroacetic acid in terms of its 4-hydroxy-2-pyrone structure,[1] our attention was directed to the compound 5-carboxydehydroacetic acid[2] (I) which was first described in 1893[3] by von Pechman and Neger. This compound shows infrared absorption characteristics similar to those of dehydroacetic acid itself and of triacetic lactone which has been established[4] as having a 4-hydroxy-2-pyrone structure. Some important points for comparison are summarized in Table II. There is a narrow absorption band in the O—H stretching range at 3.30 μ, similar to that observed with dehydroacetic acid, rather than the broad absorption indicative of extensive hydrogen-bonding observed with triacetic lactone. There is another absorption band not observed with dehydroacetic acid. This is at 5.66 μ and, even though not at the customary carboxyl carbonyl position, is attributed to the carbonyl of the carboxyl group since this is the only difference in the two structures.



I II

The most unusual feature of the chemical behavior of this acid is the ease with which it has been reported[3] to form its anilide (5-phenylcarbamyldehydroacetic acid, II). This reaction is said to take place on heating the acid with aniline in acetic acid for 10 minutes on the water-bath. This is the only example known to the authors in which amide formation takes place under such conditions. Since previous studies[5] have shown that there are many possible reactions which might take place between 2-pyrones and aniline, it seemed desirable to provide additional information about this reaction and additional data establishing the structure of this product. We have observed that the anilide is also formed on refluxing the reactants in benzene or toluene. The anilinium salt, which first precipitates and can be isolated and identified as such, is converted under these conditions to the anilide. To substantiate the hypothesis that the product of this reaction is in fact the anilide we have prepared the acid chloride from thionyl chloride and the carboxydehydroacetic acid and observed that on reaction with aniline it gives the same product. The infrared absorption spectra shows a general similarity to the spectra of related compounds. The disappearance of the absorption band at 5.66 μ on converting the carboxylic acid to the amide is significant evidence for the phenylcarbamyl structure. Furthermore, both of the bands in the range commonly associated with the two amide carbonyl bands (at 6.0 and 6.45) are much more strong in the anilide than they are in the acid. The synthetic data and infrared absorption characteristics appear

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[1] R. H. Wiley, C. H. Jarboe, and H. G. Ellert, *J. Am. Chem. Soc.*, **77**, 5102 (1955).

[2] The Chemical Abstracts systematic name for this structure is 3-acetyl-5-carboxy-6-methyl-2H-pyran-2,4(3H)-dione. Since dehydroacetic acid is indexed as dehydroacetic acid the carboxy derivative may be indexed as a pyrandione or as a derivative of the acid.

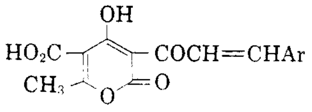
[3] H. von Pechman and F. Neger, *Ann.*, **273**, 186 (1893).

[4] R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.*, **77**, 624 (1956).

[5] R. H. Wiley, L. H. Knabeschuh, A. L. Duckwall, and N. R. Smith, *J. Am. Chem. Soc.*, **76**, 625 (1954).

to establish the anilide structure satisfactorily. We have used this reaction to prepare a variety of anilides of therapeutic interest whose properties are listed in Table I. It is interesting that even with ethyleneimine under conditions where one would expect salt formation the amide forms readily and in good yield.

Carboxydehydroacetic acid condenses readily with some, but not all, aromatic aldehydes. The products from *p*-dimethylamino- and 2,3-dimethoxy-benzaldehyde were prepared by the technique described previously[1] or a modification thereof. These products apparently have the same cinnamoyl structure (III) assigned to similar products obtained from dehydroacetic acid.[1] Other aldehydes gave solid products for which analytical data were not in good agreement with the cinnamoyl structure or any other obvious structure. Also the analytical data for condensation products obtained from several of the amides and a variety of aldehydes were not in close agreement with the cinnamoyl structure. This type of condensation is much more readily completed and the products are much more readily characterized when the reaction is run with dehydroacetic acid.



III

Acknowledgment. The authors wish to acknowledge with appreciation support of various portions of this research by grants from the U. S. Public Health Service, the National Science Foundation, and the Damon Runyon Foundation.

EXPERIMENTAL[6]

The acetonedicarboxylic acid used in the preparation of carboxydehydroacetic acid was prepared by a modification of a procedure previously described.[7] Our observation that 90% yields were obtained by conducting the citric acid-fuming sulfuric acid reaction at 60–70° are at variance with the observations of others.[8] The product was precipitated by the addition of ice to the reaction mixture.

5-Carboxydehydroacetic acid. Acetonedicarboxylic acid (73 g.) is added slowly to 250 g. of acetic anhydride at 5–20°. The resulting solution is heated on a boiling water-bath with stirring. After 10–15 minutes at about 90° crystals of the product will form on the stirring rod when it is removed from the reaction mixture. At this time the mixture is poured into 500 ml. of ice-water to precipitate the crude product, m.p. 154°, which is sufficiently pure for many purposes. Recrystallization from benzene gives 74 g. (70%) of white plates, m.p. 155°. The product gives a red ferric chloride test. This reaction is catalyzed by traces of sulfuric acid usually carried along from the preparation of acetonedicarboxylic acid. If the acid is obtained from other sources and is free from sulfuric acid, three drops of sulfuric acid are added to the reaction mixture.

Anal. Calc'd for $C_9H_8O_4$: C, 50.95; H, 3.80. Found: C, 50.97; H, 3.84.

Anilinium 5-carboxydehydroacetate. To a warm solution of 2.1 g. of carboxydehydroacetic acid in 50 ml. of toluene is added 0.9 g. of aniline in 10 ml. of hot toluene. After one hour in a boiling water bath, the reaction mixture is cooled to precipitate the crude product. Recrystallization from benzene gives 2.8 g. (91.7%) of the anilinium salt, m.p. 145°.

Anal. Calc'd for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95. Found: C, 58.65; H, 5.23.

5-Phenylcarbamyldehydroacetic acid. (*a*). *By heating anilinium carboxydehydroacetic acid.* The anilinium salt (2 g.) is heated in boiling bromomesitylene for 15 minutes. On cooling 1.4 g. (85%) of the anilide separates. Recrystallization from toluene gives white needles, m.p. 189°. Reported[3] m.p. 185°. The product gives a red ferric chloride test.

Anal. Calc'd for $C_{15}H_{13}NO_5$: C, 63.78; H, 5.02. Found: C, 64.16; H, 5.48.

(*b*). *From carboxydehydroacetic acid chloride.* A solution of 6.0 g. of carboxydehydroacetic acid in a slight excess of thionyl chloride was refluxed for 45 minutes. The excess thionyl chloride was removed under a vacuum. Aniline (2.8 g.) was added to the residue to give a crude solid which was recrystallized from benzene to give 5.2 g. (86%) of the anilide, m.p. 189–190°.

(*c*). *From carboxydehydroacetic acid.* Carboxydehydroacetic acid (6 g.) was dissolved in boiling benzene. To this solution was added 2.8 g. of aniline. The reaction mixture was refluxed for several hours during which time a solid separated from the reaction mixture. The solid product was recrystallized from benzene to give 5.7 g. (95%) of the anilide, m.p. 189–190°.

(*d*). *From carboxydehydroacetic acid and aniline in acetic acid.*[3] On heating the reactants for 10 minutes at 90°, the anilide, m.p. 186°, separated. The melting points of samples prepared by these different methods were not depressed on mixture with an analytically pure sample of the anilide.

5-(4′-Biphenylylcarbamyl)dehydroacetic acid. Carboxydehydroacetic acid (6 g., 0.028 mole) and 5.08 g. of 4-aminobiphenyl were refluxed for one hour with excess bromomesitylene. The water formed during the reaction was removed using a Barrett adapter. The crude product (5.0 g.), which separated on cooling, was recrystallized from ethyl acetate-toluene to give 3.5 g. (58%) of the anilide, m.p. 235–236°.

5-(p-Dimethylaminophenylcarbamyl)dehydroacetic acid. A solution of 2.1 g. (0.01 mole) of 5-carboxydehydroacetic acid and 1.4 g. (0.01^+ mole) of *p*-dimethylaminoaniline in 100 ml. of benzene was refluxed for six hours. Then 50 ml. of benzene was removed by distillation. On cooling there was obtained 3.45 g. of crude anilide, m.p. 193–198°. Recrystallization from benzene gave 1.4 g. (42%) of product, yellow needles, m.p. 198–199°. By using excess amine the yield can be raised to 62%. The anilides listed in Table I, except as noted, were prepared by this procedure. When applied to 3-aminoquinoline a product was obtained which did not analyze in accord with the N-quinolinylcarboxamide structure.

3-(p-Dimethylaminocinnamoyl)-4-hydroxy-6-methyl-2-pyrone-5-carboxylic acid. A solution of 0.004 mole (0.848 g.) of carboxydehydroacetic acid and 0.004 mole (0.60 g.) of *p*-dimethylaminobenzaldehyde in 50 ml. of methanol was stirred for 18 hours at room temperature. The precipitated product then was filtered, washed with 25 ml. of hot methanol, and recrystallized from ethyl acetate to give 0.38 g. (27.7% of theory) of black crystals, m.p. 200–201°.

Anal. Calc'd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 63.06; H, 5.17; N, 4.11.

3-(2,3-Dimethoxycinnamoyl)-4-hydroxy-6-methyl-2-pyrone-5-carboxylic acid. This compound was prepared by the same

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(6) Analyses by Micro Tech Laboratories, Skokie, Illinois.

(7) C. K. Ingold and L. C. Nickolls, *J. Chem. Soc.*, 121, 1642 (1922).

(8) R. Adams, H. M. Chiles, and C. F. Rasswiler, *Org. Syntheses*, Coll. Vol. 1, 10 (1941).

TABLE I

N-Substituted Amides of 5-Carboxydehydroacetic Acid

Substituent	Yield, %	Recryst'd[a] from	M.P., °C.	Analysis Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
C_6H_5		B or T	189						
p-$C_6H_5C_6H_4$[b]	58	EA-T	235	69.41	4.72		69.36	4.66	
p-$O_2NC_6H_4$[b]	55	T	203–204	54.22	3.64		54.78	3.55	
p-$CH_3OC_6H_4$	90	B	210	60.56	4.77		60.63	4.89	
o-$CH_3OC_6H_4$			178	60.56	4.77		60.77	5.02	
p-$(CH_3)_2NC_6H_4$	62	B	198	61.81	5.49	8.48	62.22	5.52	8.52
p-$(C_2H_5)_2NC_6H_4$	60	B	176			7.82			7.90
2,5-$(CH_3O)_2C_6H_3$	90	M	161	68.79	4.93		59.17	5.07	
—CH_2CH_2—[c]	90	[d]	132			5.91			5.83

[a] B, benzene; T, toluene; EA, ethyl acetate; M, methanol. [b] Prepared in bromomesitylene. [c] From ethyleneimine. [d] Analyzed after washing with benzene. Not recrystallized.

TABLE II

Infrared Absorption Characteristics of Dehydroacetic Acid Derivatives[a]

DHA[b]	TAL[c]	CDHA[d]	PCDHA[e]
3.40 n	3.40 br	3.30 n	3.30 br
		5.66	
5.80	5.85	5.78	5.77
	6.05	6.00 w	6.05 s
6.18	6.18	6.26	6.27
6.25	6.30	6.47 w	6.48 s
6.50	6.52		
6.92	6.95	6.81	6.82
7.45	7.45	7.35	7.36

[a] n, narrow; br, broad; w, weak; s, strong. [b] Dehydroacetic acid. [c] Triacetic lactone. [d] 5-Carboxydehydroacetic acid (I). [e] 5-Phenylcarbamyldehydroacetic acid (II).

procedure previously described[5] for the preparation of the 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones. The crude product was obtained in 45% yield. Recrystallization from chloroform gave the pure product characterized as golden needles, m.p. 175°.

Anal. Calc'd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.8; H, 4.62.

The anilides listed in Table I were prepared by heating the appropriate aniline with the acid in benzene following the procedure outlined above for the dimethylaminophenylcarbamyl derivative. The ethylene imine reaction mixture was not heated. After filtration and evaporation the imide precipitated.

The infrared data were obtained using potassium bromide pellets and a Baird double beam recording infrared spectrophotometer.

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11-Oxygenated Steroids. XVII. 1,4-Pregnadien-21-al-17α-ol-3,11,20-trione Hydrate

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Received January 25, 1956

It has been observed that 4-pregnene-21-al-17α-ol-3,11,20-trione, the 21-aldehyde derived from cortisone, is an active cortical substance.[1,2] With this in mind we have converted 1,4-pregnadiene-17α,21-diol-3,11,20-trione (I),[3,4] a recently discovered, potent, anti-inflammatory agent, to 1,4-pregnadien-21-al-17α-ol-3,11,20-trione hydrate (IV) by the procedure of Leanza and coworkers.[2] Reaction of I with p-toluenesulfonyl chloride in pyridine afforded 1,4-pregnadien-17α-ol-3,11,20-trione-21-pyridinium chloride (II) in good yield. Displacement of the pyridine moiety in II with p-nitrosodimethylaniline yielded 1,4-pregnadien-17α-ol-3,11,20-trione-21-(p-dimethylaminophenyl)nitrone (III) smoothly. The nitrone III was hydrolyzed with aqueous hydrochloric acid to the desired aldehyde hydrate, IV.

The adrenocortical activities of III and IV were assessed by the eosinophile test[5] and these compounds were found to be at least as active as cortisone. The biological results will be reported in greater detail elsewhere. We are indebted to Drs. Sibylle Tolksdorf, P. L. Perlman, and their associates for the results of the biological tests.

EXPERIMENTAL

All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of these laboratories and by the Galbraith Laboratories, Knoxville, Tenn.

1,4-Pregnadien-17α-ol-3,11,20-trione-21-pyridinium chloride (II). The procedure of Leanza and coworkers[2] was followed. From 6 g. of I there resulted 5.45 g. of II, m.p. 304–305° (dec.). Reprecipitation from methanol with ether did

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(1) J. J. Schneider, *J. Am. Chem. Soc.*, **75**, 2024 (1953).

(2) W. J. Leanza, J. P. Conbere, E. F. Rogers and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **76**, 1691 (1954).

(3) Meticorten (brand of prednisone, formerly metacortandracin).

(4) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman, and M. M. Pechet, *Science*, **121**, 176 (1955); A. Nobile, *et al.*, *J. Am. Chem. Soc.*, **77**, 1484 (1955).

(5) R. S. Speirs and R. K. Meyer, *Endocrinology*, **48**, 316 (1951); E. Rosemberg, *et al.*, *Endocrinology*, **54**, 363 (1954).