Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.5; H, 4.59; N, 12.8. Found: C, 60.3; H, 4.45; N, 12.9.

The spectral data agree with that reported for the corresponding methyl ester (VIIIb).[13] If the above fusion is above 190°, the yields are poor. Knape[15] has reported that the intermediate ethoxalyl anthranilamide (IV) is obtained by fusing the above components at 170°.

4-Quinazolone-2-carboxylic Acid (IX).—A mixture of 500 mg. (2.3 mmoles) of the corresponding ester (VIIIa) and 10 ml. of 5% aqueous sodium hydroxide was stirred at room temperature for 2 hr. The filtered solution was cooled in an ice bath and acidified with 3 *N* hydrochloric acid to about pH 3. The product was collected on a filter, washed with water, and dried over phosphorus pentoxide in a vacuum dessicator at room temperature; yield, 400 mg. (92%), m.p. 212–215° dec. For analysis the compound was dissolved in 20 ml. of 2% aqueous sodium bicarbonate, the solution was filtered, then acidified with 3 *N* hydrochloric acid with ice-cooling; the product was collected and washed with filtered water. This reprecipitation was repeated once more to give white crystals, m.p. 215–216° dec.; $\nu_{\max}^{\mathrm{KBr}}$ 2100–3100 (broad acidic OH); 1670 (amide C=O); 1640 (carboxyl C=O); 1600 (amide II and C=N); 1980, 1550 cm.$^{-1}$ (weak zwitterion); $\lambda_{\max}^{\mathrm{Me.\ Cell.}}$ 229 (ϵ 20,500); 285 (ϵ 9,950); 305 (ϵ 7,350, inflection); 318 mμ (ϵ 4720).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.9; H, 3.16; N, 14.7. Found: C, 56.7; H, 3.34; N, 14.4.

Recrystallization from ethanol lead to partial decarboxylation to 4-quinazolone as shown by ultraviolet and combustion analyses. Knape[15] has recorded a m.p. of 201–202°, prepared by a different route. This compound readily dissolved in concentrated ammonium hydroxide and did not precipitate on insoluble ammonium salt; an attempt to isolate the soluble ammonium salt by evaporation *in vacuo* and recrystallization from aqueous methanol appeared to lead partially to decarboxylation to 4-quinazolone.

4-Quinazolone-2-carboxamide (VII).—To a stirred and ice-cooled saturated solution of ammonia in 95% alcohol was added 500 mg. (2.2 mmoles) of the ester (VIIIa). Solution took place immediately and within 10 min. the product began to separate. After 30 min., the product was collected on a filter; yield, 100 mg. After standing overnight, the solution deposited an additional 200 mg. (total, 80%) of product as white leaflets, m.p. 230°, that was identical with the first crop. This second crop was analyzed and had $\nu_{\max}^{\mathrm{KBr}}$ 3400, 3270 (NH); 1670, 1650 (amide C=O); 1600 cm.$^{-1}$ (amide II and C=N); $\lambda_{\max}^{\mathrm{Me.\ Cell.}}$ 229 (ϵ 20,400); 297 (ϵ 9,600); 318 mμ (ϵ 5200, inflection).

Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.2; H, 3.70; N, 22.2. Found: C, 57.1; H, 3.84; N, 22.2.

N-Acetylanthranilamide.—Strenuous conditions for acetylation of anthranilamide could be expected to give 2-methyl-4-quinazolone. Although no attempt was made to ascertain optimum conditions, the ring closure could be avoided as follows: To a solution of 1.00 g. (7.5 mmoles) of anthranilamide in 10 ml. of 50% acetic acid was added 0.62 ml. (15 mmoles) of acetic anhydride. Within 15 min., the product began to separate. Crystallization was complete after standing overnight; yield, 250 mg. (21%), m.p. 180°. Recrystallization from methanol gave white crystals of unchanged m.p.; $\nu_{\max}^{\mathrm{KBr}}$ 3400, 3200 (NH); 1670 (amide C=O); 1630, 1600 (amide II); 1580, 1520 cm.$^{-1}$ (C=C); $\lambda_{\max}^{\mathrm{Me.\ Cell.}}$ 219 (ϵ 25,200); 255 (ϵ 15,600); 302 mμ (ϵ 5,100).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.6; H, 5.61; N, 15.7. Found: C, 60.5; H, 5.46; N, 15.6.

Ethoxalylanthranilic Acid (III).—Fusion of 20 g. (0.146 mole) of anthranilic acid with 44 g. (0.30 mole) of ethyl oxalate at 140–150° for 1 hr. as described by Bogert[10] gave 20 g. (58%) of product, m.p. 180°; $\nu_{\max}^{\mathrm{KBr}}$ 3300 (NH); 1730 (ester C=O); 1720 (carboxyl C=O); 1670 (amide C=O); 1600 (amide II); 1580, 1520 cm.$^{-1}$ (C=C); $\lambda_{\max}^{\mathrm{alc}}$ 235 (ϵ 13,500); 275 (ϵ 8,800); 287 (ϵ 8,300, inflection); 305 mμ (ϵ 8,500).

Bogert and Gortner[10] recorded a m.p. of 184°. Acetone is much more efficient than boiling water for separation of the product from the insoluble by-product of disubstituted oxamide.

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[15] E. Knape, *J. prakt. Chem.* [2], **43**, 209 (1891).

Reaction of *meso*- and *dl*-Dimethylsuccinic Acids with Acetyl Chloride[1]

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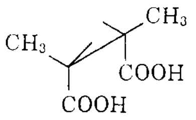
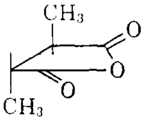
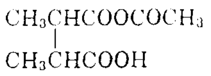
The observation was made by Bone and Sprankling[3] that *dl*-dimethylsuccinic acid (*dl*-I) undergoes ring closure to the *trans* anhydride (*trans*-II) when dissolved in cold acetyl chloride solution under reaction conditions which fail to convert the *meso* isomer (*meso*-I) to the *cis* anhydride (*cis*-II), but give recovered *meso* acid. These results suggested the possible explanation that the *cis* effect of the two methyl groups is responsible for the reluctance of the *meso* isomer to cyclize.[4] Further investigation of this reaction, however, has shown that such is not the case. In fact, the over-all rate of the reaction is not the rate of ring-closure at all but appears to depend on the rate of formation of an intermediate, probably the mixed anhydride III.



dl-I



trans-II



$$\begin{array}{l}CH_3CHCOOCOCH_3\\ \quad\;\;|\\ CH_3CHCOOH\end{array}$$

III

The difference in the rates of reaction in acetyl chloride medium apparently is due primarily to the difference in the rates of solution of *dl*- and *meso*-I.

Evidence for this point of view was obtained from two sources. First, when dilatometric rates were measured in dioxane solution, the order of reactivities was reversed, the *meso* isomer being somewhat faster than the *dl*. Second, when succinic acid was treated with ketene in dioxane solution, it was converted to the cyclic anhydride in a reaction with an estimated one-half time of not more than two minutes, very much faster than when acetyl chloride is employed. The formation of the initial linear

[1] Taken from the Ph.D. thesis submitted by Richard Charles Thamm to the University of Illinois, 1957, and available from Univ. Microfilms, Ann Arbor, Mich., as Publication No. 23395.

[2] Rohm & Haas Fellow, 1955–1956. We are indebted to E. I. du Pont de Nemours and Company for a Grant-in-Aid which supported a part of this work.

[3] W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **75**, 856 (1899); *ibid.*, **77**, 654, 1300 (1900).

[4] D. Y. Curtin, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.) **15**, 122 (1954).

anhydride with ketene apparently is faster and more complete than with the acid chloride. The result is acceleration of the over-all process which would not be observed if the ring-closure were rate-limiting.

Experimental[5]

Rates of Reaction of Succinic Acid, *meso*- and *dl*-Dimethylsuccinic Acid (*meso*- and *dl*-I) in Dioxane Solution with Acid Chlorides.—The dilatometer was modeled after that described by Tong and Olson.[6] Succinic acid was crystallized to a constant m.p. of 185.0–185.5°. *meso*-I, m.p. 207–208° (lit.[7] 208°), was obtained by recrystallization of the mixture of diastereoisomers obtained in the synthesis.[7] The *dl*-isomer *dl*-I, m.p. 124–125° (lit. m.p. 129°,[7] 122–123°[8]) was best purified by conversion of the acid to the *trans*-anhydride, m.p. 87–88° (lit.[7] m.p. 88°), which was recrystallized from ether-petroleum ether, and then hydrolyzed in boiling water. Acetyl chloride and dioxane were purified by the methods described by Fieser.[9] Trichloroacetyl chloride,[10] b.p. 115–116.5° at 760 mm., was prepared from trichloroacetic acid and benzoyl chloride and distilled through a glass-helix packed column. The calculated amount of the succinic acid was dissolved in 50.0 ml. of dioxane and transferred to the mixing chamber of the apparatus. The appropriate amount of acid chloride in enough dioxane to bring the volume to 70.0 ml. was placed in a separate vessel and the solutions allowed to come to thermal equilibrium (8 hr.) in a constant temperature bath at 26.62° regulated to ±0.0015°. The solutions then were mixed with mechanical stirring and rapid stirring was continued for 15 min. to dissipate heat of mixing. The acid chloride was present in 20- to 80-fold excess. Rate constants and probable errors were determined from the equation $kt = \ln (V_\infty - V_0)/(V_\infty - V)$ by the method of least squares. Plots were linear for at least 50% reaction. That the reactions were first order in acid chloride as well as succinic acid was indicated by the fact that doubling the initial concentration of acid chloride doubled the apparent rate constant. The results are listed in Table I.

TABLE I
RATES OF FORMATION OF CYCLIC ANHYDRIDE FROM SUCCINIC ACID AND ACETYL CHLORIDE IN DIOXANE AT 26.6°

Initial concentrations, moles/l.				
Succinic acid	Acetyl chloride	10^5k_1, sec.$^{-1}$	10^5k_2, l. mole^{-1} sec.$^{-1}$	Range of % reaction
0.100	1.99	2.85 ± 0.01	1.43	5–48
0.0500	1.99	2.68 ± 0.02	1.34	10–50
0.0500	4.00	5.46 ± 0.03	1.36	10–45
			Av. 1.38	

An attempt was made to follow the reaction by cooling the reaction tube to −40° after a given time and then adding α-naphthylamine to convert the succinic anhydride to the anilide which was readily separated from unchanged succinic acid. These data failed to give linear first or second order plots and it seems likely that the reaction of amine with anhydride was too slow to "freeze" the reaction mixture at the composition at the time of cooling. A half-time determined by this method was 50 min. as compared with 200 min. determined with the dilatometer. The data at any rate serve to confirm that the stoichiometry of the reaction is as assumed and confirm the order of magnitude of the reaction rate.

The reactions of the dimethylsuccinic acids with acetyl chloride and with trichloroacetyl chloride failed to give linear plots over a large fraction of reaction. There was reasonable linearity over the first 50% reaction of the trichloroacetyl chloride reactions and the data summarized in Table II at least serve to establish the point that the closure to the *cis* anhydride is as fast or slightly faster than closure to the *trans*.

TABLE II
RATES OF REACTION OF SUCCINIC ACID AND THE 2,3-DIMETHYLSUCCINIC ACIDS WITH TRICHLOROACETYL CHLORIDE IN DIOXANE AT 26.6°

Acid	Initial concentrations, moles/l. acid	Acid chlorine	10^5k_2, l. mole^{-1} sec.$^{-1}$	$t_{1/2}$ min.
Succinic	0.0505	1.89	1.04	586
meso-Dimethyl	0.0750	2.60	2.20	202
dl-Dimethyl	0.0500	1.89	2.02	301

Reaction of Succinic Acid with Ketene.—Ketene[1] (a threefold excess) was passed through a solution of 0.50 g. (0.0042 mole) of succinic acid in 10 ml. of dioxane for 7.5 min. at 0°. The infrared spectrum was measured as quickly as possible (12 min. from the beginning of the ketene addition). Strong absorption at 1825 cm.$^{-1}$ and 1785 cm.$^{-1}$ attributable to the five-membered cyclic anhydride failed to increase further in intensity when the solution was allowed to stand for 47 min. more and the spectrum again measured. The assumption that the reaction is 98% complete in 12 min. leads to a calculated lower limit for the ring-closure rate of 5×10^{-3} l. mole^{-1} sec.$^{-1}$ or $t_{1/2} = 2$ min.

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[5] All melting points are corrected. Infrared spectra were measured with a Perkin-Elmer Model 21 spectrophotometer by Miss Helen Miklas, Mr. James Brader, Mrs. Louise Griffing, and Mr. Sy Portnow. Spectral and other data are available in the thesis referred to in ref. 1.

[6] L. K. Tong, and A. R. Olson, *J. Am. Chem. Soc.*, **65**, 1704 (1943).

[7] W. A. Bone and W. H. Perkin, *J. Chem. Soc.*, **69**, 253 (1896). Samples not extremely pure showed decomposition at 180–190° unless heated very rapidly. See J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *J. Am. Chem. Soc.*, **64**, 1747 (1942).

[8] R. Leukart, *Ber.*, **18**, 2344 (1885).

[9] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 380.

[10] H. C. Brown, *J. Am. Chem.*, *Soc.*, **60**, 1325 (1938).

[11] J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).

Quinazolines and 1,4-Benzodiazepines. IX. 2-Carbobenzoxyglycylamidobenzophenones and Their Conversion to 1,4-Benzodiazepinones

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The discovery by Sternbach and co-workers[1] that 2-glycylamidobenzophenones (III) can be used as intermediates in the synthesis of benzodiazepinones (IV) and also possess pharmacological activity similar to the corresponding benzodi-

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[1] Paper VI in this series, L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).