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[11] (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.

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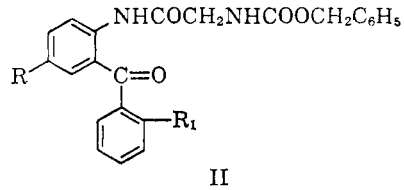
The discovery by Sternbach and co-workers[1] that 2-glycylamidobenzophenones (III) can be used as intermediates in the synthesis of benzodiazepinones (IV) and also possess pharmacological activity similar to the corresponding benzodi-

(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).

TABLE I



II

	R	R_1	Yield, %	Cryst.[a] from	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	H	H	70	b. + h.	116–117	$C_{23}H_{20}N_2O_4$	71.12	5.19		70.95	5.46	
b[2]	Cl	H	68	EtOH	116–117	$C_{23}H_{19}ClN_2O_4$	65.33	4.53	6.63	65.74	4.66	6.63
c	CF_3	H	21	b. + h.	128–130	$C_{24}H_{19}F_3N_2O_4$	63.16	4.20	6.14	63.38	4.17	6.32
d	Cl	Cl	61	b. + h.	148–149	$C_{23}H_{18}Cl_2N_2O_4$	60.41	3.97	6.13	60.47	4.25	6.15
e	H	NO_2	39	b. + h.	131–132	$C_{23}H_{19}N_3O_6$	63.73	4.42	9.70	63.82	4.23	9.73
f	CH_3O	H	43	EtOAc + h.	130–132	$C_{24}H_{22}N_2O_5$	68.89	5.30	6.70	69.23	5.32	6.63

[a] b. = benzene, h. = hexane, EtOH = ethanol, EtOAc = ethyl acetate.

azepinones prompted an investigation of methods of synthesis of these glycylamidobenzophenones. One approach studied was the synthesis of glycine amides in which the amino group of glycine was protected by a carbobenzoxy group. Removal of the protective group would then give the desired glycylamidobenzophenone. Three reagents, carbobenzoxyglycyl chloride,[2] carbobenzoxyglycine anhydride, and carbobenzoxyglycine were used. In the latter reaction, condensation was effected employing the carbodiimide method of Sheehan and Hess.[3]

Carbodiimides, particularly dicyclohexylcarbodiimide, were found by Buzas, *et al.*,[4] to give amides of aromatic amines and aliphatic and aromatic acids in high yield. In Table I are listed six carbobenzoxyglycylamidobenzophenones (II) prepared in this manner from the corresponding 2-aminobenzophenones (I) and carbobenzoxyglycine. The yields were generally good and ranged from 21–70%. In the preparation of compound IIe chromatography on alumina was necessary to obtain a pure product. As a by-product, particularly in cases where the yield of compound II was low, we were able to isolate (2,4-dicyclohexylallophanoylmethyl)carbamic acid benzyl ester.[5]

The amide IIb was also prepared in 30% yield by the reaction of 2-amino-5-chlorobenzophenone (Ib) and carbobenzoxyglycine anhydride.[6] When carbobenzoxyglycyl chloride was used, the yield was only 6%. (See reaction scheme, p. 4719.)

Two methods for removal of the carbobenzoxy group were tried. Catalytic reduction in acidic medium using palladium on charcoal removed the protective group, but there was also a simultaneous reduction of the ketone. However, cleavage of the carbobenzoxy group with hydrobromic acid in acetic acid[7] was achieved in good yield (Table II) with no further split of the amide group. One of the glycylamidobenzophenones (IIIe) was isolated as the hydrobromide while the others were obtained as the free base. In several cases (IVb,c,f) the glycylamides (III) cyclized during recrystallization to the corresponding benzodiazepinones (IV). Compound IIIb was obtained from a mixture of cold benzene and hexane while recrystallization from hot benzene gave only the cyclic compound (IVb). Cyclization of compounds of type III can be prevented by isolation of the glycylamido compounds as salts.

Experimental[8]

The following experiments are typical and illustrate the preparation of compounds in Tables I and II.

(2-Benzoyl-4-chlorophenylcarbamoylmethyl)carbamic Acid Benzyl Ester (IIb) (Carbodiimide Method).—To a solution of 2.3 g. of 2-amino-5-chlorobenzophenone and 2.1 g. of carbobenzoxyglycine in 25 cc. of tetrahydrofuran 2.2 g. of *N,N'*-dicyclohexylcarbodiimide was added. After stirring for several minutes, dicyclohexylurea began to crystallize. Stirring was continued for 2 hr. and dicyclohexylurea (1.8 g.; m.p. 219–222°) was filtered off. The filtrate was then treated with 2 cc. of acetic acid to decompose any excess *N,N'*-dicyclohexylcarbodiimide. After 15 min. an additional 250 mg. of dicyclohexylurea was removed by filtration. The filtrate was taken to dryness *in vacuo* and the residue (3.8 g.) was dissolved in benzene and washed successively with 1 *N* hydrochloric acid, water and 5% sodium bicarbonate, then dried over sodium sulfate. The benzene layer was concentrated to *ca.* 30 cc. and hexane then added to turbidity. On seeding, (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester crystallized (yield, 2.6 g.; 68%, m.p. 113–115°). Recrystallization from ethanol gave a product melting at 116–117°.

(2-Benzoyl-4-chlorophenylcarbamoylmethyl)carbamic Acid Benzyl Ester (IIb) (Anhydride Method).—A solution of 1.1 g. of 2-amino-5-chlorobenzophenone and 2.0 g. of carbobenzoxyglycine anhydride[6] in 25 cc. of dry pyridine was

(2) Following the completion of this work, S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962), reported the use of this reagent. These authors did not isolate the glycylamidobenzophenone but cyclized it by heating to the corresponding benzodiazepinone (IVb).

(3) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(4) A. Buzas, C. Egneli, and P. Freon, *Compt. rend.*, **252**, 896 (1961).

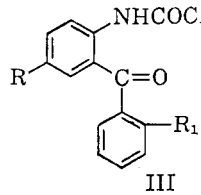
(5) H. Zahn and J. F. Diehl, *Z. Naturforsch.*, **12B**, 85 (1957).

(6) I. Muramatsu, *J. Chem. Soc. Japan*, **82**, 83 (1961).

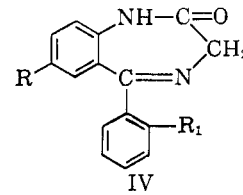
(7) D. Ben Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(8) All melting points are uncorrected. Infrared spectra of the compounds in Tables I and II are consistent with the structures shown. Compounds in Table II prepared by other workers were identified by mixed melting point determinations and comparison of the infrared spectra.

TABLE II



III



IV

			III			IV		
	R	R_1	Yield, %	M.p.	Cryst.[a] from	Yield, %	M.p.	Cryst. from
a	H	H	41	76–77[b]	b. + h.			
b	Cl	H	61	101–103[c]	Cold b. + h.	53	214–215[d]	Hot b.
c	CF_3	H				13	197–201[e]	h.
d	Cl	Cl	74	121–122[c]	b. + h.			
e	H	NO_2	78	201–203[f,g]	m. + e.			
f	CH_3O	H				60	215–218[c]	b. + h.

[a] b. = benzene, h. = hexane, m. = methanol, e. = ether. [b] *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.61; H, 5.81; N, 10.70. [c] See footnote 1. [d] L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961). [e] G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962). [f] Isolated as hydrobromide. *Anal.* Calcd. for $C_{15}H_{14}BrN_3O_4$: C, 47.38; H, 3.71; N, 11.05. Found: C, 47.93; H, 4.00; N, 11.09. [g] Free base will be described in paper X of this series.

stirred for 2 hr. at room temperature, kept overnight at room temperature and then heated for 1 hr. on a steam bath. The solvent was removed by distillation *in vacuo* and the residue then dissolved in 75 cc. of benzene, washed with dilute hydrochloric acid, water, and dilute sodium bicarbonate. After drying over sodium sulfate, the solvent was removed *in vacuo* and the residue crystallized from ethanol to give 600 mg. (30% yield) of (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester, m.p. 114–116°. A mixed melting point with material prepared above showed no depression.

(2-Benzoyl-4-chlorophenylcarbamoylmethyl)carbamic Acid Benzyl Ester (IIb) (Acid Chloride Method).—To a solution of 7.1 g. of crude carbobenzoxyglycine chloride[9] in 150 cc. of dry pyridine 7.0 g. of 2-amino-5-chlorobenzophenone was added. After warming for 1 hr. on a steam bath, the solvent was distilled *in vacuo*. The residue was dissolved in methylene chloride and washed successively with dilute hydrochloric acid, water, and dilute sodium carbonate. After drying over sodium sulfate, the solvent was removed *in vacuo* and the residue crystallized from ethanol to give 800 mg. of (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester, m.p. 109–113°. Recrystallization from ethanol raised the melting point to 114–115°. A mixed melting point with a sample prepared above showed no depression.

5-Chloro-2-glycylamidobenzophenone (IIIb).—A solution of 3.1 g. of (2-benzoyl-4-chlorophenylcarbamoylmethyl)-carbamic acid benzyl ester in 30 cc. of 20% hydrogen bromide in acetic acid[7] was stirred for 35 min. at room temperature. Then 175 cc. of anhydrous ether was added rapidly while stirring. The gummy material that separated was stirred for 10 min., the supernatant liquid decanted, and the product again stirred for 10 min. with 125 cc. of ether. The ether was decanted and the residue dissolved in 100 cc. of water to produce a turbid solution of pH 2.1. This solution was extracted twice with ether and the washings discarded. On addition of ammonia to the aqueous solution to pH 11, a white crystalline product separated. This was extracted with methylene chloride and after drying over sodium sulfate, the methylene chloride was evaporated *in vacuo* at 20° leaving a residue of 1.75 g. Crystallization from cold benzene–hexane gave 1.4 g. (61% yield) of 5-chloro-2-glycylamidobenzophenone, m.p. 101–103°.

7-Chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (IVb).—A solution of 3.1 g. of (2-benzoyl-4-chlorophenylcarbamoylmethyl)carbamic acid benzyl ester in 30 cc. of 20% hydrobromic acid in glacial acetic acid was stirred for 45 min. at room temperature. On addition of 175 cc. of anhydrous ether, a gummy solid separated. After several minutes, the ether solution was decanted. About 155 cc. of ether was added to the residue and after chilling in an ice bath, 10% sodium hydroxide was added until the mixture was alkaline. The ether layer was separated, washed twice with water, and dried over sodium sulfate. After filtration, the ether solution was concentrated to dryness *in vacuo*. The residue was crystallized from hot benzene to yield 1.05 g. (53%) of 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, m.p. 214-215°.

Acknowledgment.—We are indebted to Dr. A. Steyermark and his staff for microanalyses and Dr. A. Motchane and Mr. S. Traiman for the infrared spectra.

(9) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

16-Hydroxylated Steroids. XXIV.[1] 16α,17α-Ortho Esters and Their Transformation Products

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The synthesis of polyhydroxylated steroids has been the subject of an extensive investigation in these laboratories. In addition to their synthesis, considerable effort has been directed to effect selective protection of the various reactive hydroxyl groups in these molecules. We shall discuss in this Note some aspects connected with the use of ortho esters as protective groups and as inter-

(1) Paper XXIII, S. Bernstein, R. B. Brownfield, R. H. Lenhard, S. Mauer, and I. Ringler, *J. Org. Chem.*, **27**, 690 (1962).