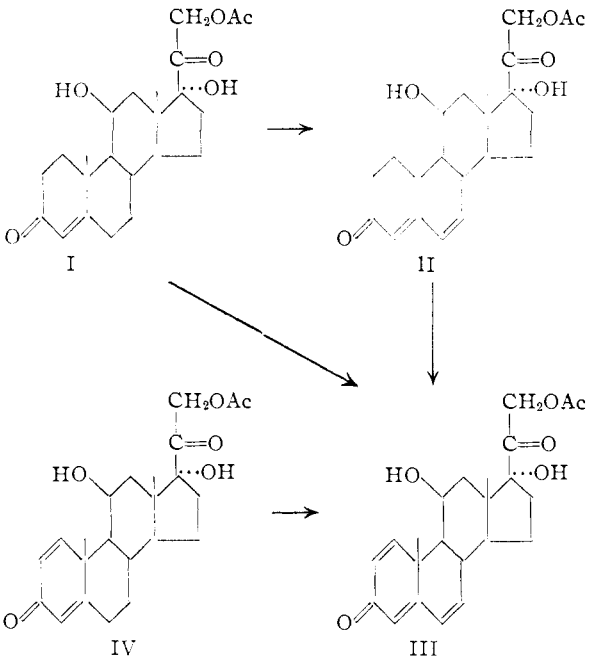
$H_{30}O_6$: C, 68.6; H, 7.51. Found: C, 68.6; H, 7.52. II was convertible to the known $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,11,20-trione acetate by chromic acid oxidation.

When I was treated with chloranil in refluxing *n*-amyl alcohol, the major product[1] was $\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione acetate (III),[2] m.p. 210.1–211.3°, $[\alpha]^{24}D$ +131° (dioxane), λ_{max}^{alc} 223 mμ (13,400), 253 mμ (10,500), 301 mμ (13,300).[3] *Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 69.0; H, 7.05. Found: C, 69.3; H, 7.12. The structure of III was confirmed by two independent syntheses: (a) from II by dehydrogenation with chloranil or selenium dioxide[4] and (b) from prednisolone acetate (IV) by dehydrogenation with chloranil. Compound III has been found in animals to be a potent glucocorticoid.[5]

Under conditions analogous to those used in the preparation of II, a number of Δ^6-dehydro steroids



(some of them not attainable by conventional methods) have been prepared, for example: $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,11,20-trione acetate[6] (45% yield), m.p. 233.3–235.8°, $[\alpha]^{25}D$ +265° (dioxane), λ_{max}^{alc} 281 mμ (25,400); $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione acetate[7] (47% yield), m.p. 221.4–223.7°, $[\alpha]^{25}D$ +112° ($CHCl_3$), λ_{max}^{alc} 283 mμ (22,500); $\Delta^{4,6}$-pregnadiene-11β,14α,-17α,21-tetrol-3,20-dione acetate (Δ^6-dehydro-14α-hydroxyhydrocortisone acetate) (50% yield), m.p. 245.3–247.1°, $[\alpha]^{24}D$ +230° (dioxane), λ_{max}^{alc} 283 mu (24,800). *Anal.* Calcd. for $C_{23}H_{30}O_7$: C, 66.0; H, 7.23. Found: C, 65.4; H, 7.20; and $\Delta^{4,6}$-pregnadiene-14α,17α,21-triol-3,11,20-trione acetate (Δ^6-dehydro-14α-hydroxycortisone acetate) (25% yield), m.p. above 260°, $[\alpha]^{20}D$ +292° (dioxane), λ_{max}^{alc} 282 mμ (24,300). *Anal.* Calcd for $C_{23}H_{28}O_7$: C, 66.3; H, 6.78. Found: C, 66.6; H, 6.89.

After this communication was submitted for publication, the synthesis of III by another route was reported by D. Gould, *et al.*, THIS JOURNAL, **79**, 502 (1957).

Details of the method and synthesis of related compounds will be reported in a subsequent communication.

(1) The reaction proceeds through the initial formation of Δ^6-dehydrohydrocortisone acetate (II), which is the major product when a lower ratio of chloranil to steroid is used.

(2) Saponification of III by conventional methods afforded $\Delta^{1,4,6}$-pregnatriene-11β,17α,21-triol-3,20-dione, m.p. 232.8–234.2°, $[\alpha]^{24}D$ +114° (dioxane), λ_{max}^{alc} 221 mμ (11,500), 255 mμ (9,300), 298 mμ (12,400). *Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.4; H, 7.31. Found: C, 70.1; H, 7.32. Oxidation of III with chromic acid yielded $\Delta^{1,4,6}$-pregnatriene-17α,21-diol-3,11,20-trione acetate, m.p. 222.5–226.2°, $[\alpha]^{20}D$ +284° (dioxane), λ_{max}^{alc} 223 mμ (10,700), 255 mμ (9800), 297 mμ (12,100). *Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.3; H, 6.58. Found: C, 69.3; H, 6.47.

(3) $\Delta^{1,4,6}$-Triene-3-ones are reported to exhibit λ_{max} 223 mμ, 256 mμ and 298 mμ; L. Dorfman, *Chem. Rev.*, **53**, 70 (1953).

(4) During the course of a broader study of dehydrogenation techniques in this laboratory it was found, as others have already described (ref. 4a, b, c, d), that selenium dioxide effects dehydrogenation of a variety of 3-ketosteroids to yield $\Delta^{1,4}$-diene-3-ketones. However, the conversion of a $\Delta^{4,6}$-3-ketosteroid to a $\Delta^{1,4,6}$-triene-3-one derivative has not been reported previously. (a) K. Florey and A. R. Restivo, Abstracts of Papers, Delaware Valley Regional Meeting, Feb. 16, 1956. (b) H. Ringold, *et al.*, *J. Org. Chem.*, **21**, 239 (1956). (c) Ch. Meystre, *et al.*, *Helv. Chim. Acta*, **39**, 734 (1956). (d) S. A. Szpilfogel, *et al.*, *Rec. Trav. Chim.*, **75**, 475 (1956).

(5) The results of the animal tests, which were performed by Dr. R. I. Dorfman of the Worcester Foundation for Experimental Biology, will be reported in another communication.

(6) V. R. Mattox, *et al.*, *J. Biol. Chem.*, **197**, 261 (1952), report m.p. 236–237°, $[\alpha]D$ +243° (acetone), λ_{max}^{alc} 280 mμ (26,000).

(7) F. Sondheimer, *et al.*, THIS JOURNAL, **75**, 5392 (1953), report m.p. 220–222°, $[\alpha]^{20}D$ +104° ($CHCl_3$), λ_{max}^{alc} 284 mμ (log ϵ 4.47).

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GENERAL ACID-BASE CATALYSIS IN THE INTRAMOLECULAR HYDROLYSIS OF PHTHALAMIC ACID[1]

Sir:

It has been shown recently that imidazole, which has been postulated to be a constituent of the active site of hydrolytic enzymes, catalyzes the hydrolysis of some substrates of α-chymotrypsin but is markedly less effective than the enzyme.[2,3] Enzymatic processes proceed through the formation of an adsorptive complex between substrate and enzyme, followed by a catalytic process during which the substrate is constrained with respect to the reactive site. Such constraint likens enzymatic action to intramolecular catalysis, and like many intramolecular reactions in organic chemistry, enzymatic catalysis should proceed at a greater rate than the corresponding intermolecular process.[4]

To test this hypothesis, the hydrolysis of phthalamic acid was investigated.[5] The infrared spec-

(1) This research was supported by Grant H-2416 of the National Institutes of Health. Paper VIII of the series, "The Mechanism of Enzymatic Hydrolysis."

(2) T. C. Bruice and G. L. Schmir, *Arch. Biochem. Biophys.*, **63**, 484 (1956); THIS JOURNAL, **79**, April (1957).

(3) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, April (1957).

(4) This statement implies that imidazole is the sole agent in enzymatic hydrolysis. While there is no question of its participation in enzymatic catalysis, it also appears that the side chain of serine is a participant. See H. Gutfreund and J. S. Sturtevant, *Biochem. J.*, **63**, 656 (1956), and G. H. Dixon and H. Neurath, *J. Biol. Chem.*, in press (1957).

(5) O. Aschan, *Ber.*, **19**, 1402 (1886); E. Chapman and H. Stephens, *J. Chem. Soc.*, **127**, 1793 (1925).

trum of phthalamic acid in deuterium oxide exhibited bands at 1694 and 1625 cm.$^{-1}$, corresponding to carboxylic acid and amide groups. The carboxylic acid band remained constant with time but the amide band was slowly replaced by a new carboxylate band at 1560 cm.$^{-1}$.[6]

The kinetics of the hydrolysis of phthalamic acid in water are shown in Table I.

TABLE I

THE KINETICS OF HYDROLYSIS OF PHTHALAMIC ACID[a,b]

	$k_{obs.} \times 10^4$ (sec.$^{-1}$)			
*p*H	47.3°	35.0°	24.8°	24.8°[d]
1.3	2.35			
1.8	2.37[c]	0.66	0.21	0.31
2.6	2.32			
3.4	1.70			
4.2	0.58			
5.0	0.11			

[a] Measurements made at 292 mμ with a Beckman DU spectrophotometer. [b] $\Delta H^{\ddagger}$ 20.7 kcal./mole; $\Delta S^{\ddagger}$ −12.4 e.u. For benzamide, $\Delta H^{\ddagger}$ 22.8 kcal./mole; $\Delta S^{\ddagger}$ −13.9 e.u. Apparently a more positive entropy is not the sole cause of the increased rate of intramolecular catalysis. [c] Variation in the ionic strength from 0.016 to 0.12 *M* produced no change in the rate constant. [d] Deuterium oxide solution.

The variation in rate with *p*H indicates kinetic dependence on the undissociated phthalamic acid and independence of external hydrogen ion. The hydrolysis of phthalamic acid is about 10^5 faster than the hydrolysis of benzamide with a comparable concentration of hydrogen ion.[7] This large rate enhancement suggests that the *ortho*-carboxylic acid group does not exert a substituent effect but rather catalyzes the amide hydrolysis by a direct intramolecular process.

A similar internal mechanism occurring in the hydrolysis of glycyl-L-asparagine and L-leucyl-L-asparagine was suggested to proceed through an internal proton transfer.[8] However, the relatively high basicity of amides precludes this as the full explanation.[9] It is suggested that this intramolecular process is a general acid–general base catalyzed reaction, and that the carboxylic acid performs a dual role, similar to a bifunctional catalyst,[10] attacking the carbonyl carbon atom of the amide, and simultaneously donating a proton to the departing ammonia molecule, with the formation of phthalic anhydride. An alternative mechanism which must be considered is a preequilibrium involving the transfer of the proton to the amide nitrogen, followed by reaction of the zwitterion to form the anhydride. These mechanisms differ in the relative position of the proton and the distribution of charge in the transition state. The effect of D_2O on the rate favors the latter path. The lack of dependence of the rate on the ionic strength of the medium suggests that the distribution of charge in the transition state is similar to that in the reactant. An anhydride intermediate is postulated to form in other general basic catalyses,[3] including some intramolecular catalyses,[11] and is known to be rapidly hydrolyzed by water.[12]

The hydrolysis of an amide, which is specific hydronium and hydroxide ion-catalyzed in intermolecular catalysis,[13] appears to be subject to general acid-base catalysis in this intramolecular process.[14]

(6) G. Ehrlich, THIS JOURNAL, **76**, 5263 (1954); G. Ehrlich and G. B. B. M. Sutherland, *ibid.*, **76**, 5268 (1954).

(7) B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **20B**, 73 (1942).

(8) S. J. Leach and H. Lindley, *Trans. Faraday Soc.*, **49**, 921 (1953). These examples do not show as pronounced rate enhancements or as favorable stereochemistry as the present case.

(9) A. R. Goldfarb, A. Mele and N. Gutstein, THIS JOURNAL, **77**, 6194 (1955).

(10) C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2538 (1952).

(11) H. Morawetz and P. E. Zimmering, *J. Phys. Chem.*, **58**, 753 (1954); J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952), and references cited therein. Only the carboxylate ion participates in these reactions.

(12) A. C. D. Rivett and N. V. Sidgwick, *J. Chem. Soc.*, **97**, 1683 (1910).

(13) M. L. Bender, unpublished results.

(14) The author acknowledges valuable discussions with Drs. E. M. Kosower, G. J. Buist and R. W. Taft, Jr.

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FORMATION OF CYCLOPROPANE FROM METHYLENE AND ETHYLENE

Sir:

Recently a suggestion was made[1] that cyclopropane is the immediate product of reaction between methylene and ethylene, even though propylene is the identified product, the explanation being that cyclopropane so formed has a very short lifetime because of large energy content and therefore isomerizes into propylene.

The only experimentally proven formation of the cyclopropane ring in the gas phase by the reaction of methylene with an olefin is that of *cis*-1,2-dimethylcyclopropane.[2] In the liquid phase other olefins have been shown to form three-membered rings when reacting with methylene.[2,3,4] In all these cases methylene has been shown also to attack the carbon–hydrogen bond.

Ketene was used as the source for photochemically produced methylene. A low pressure mercury arc and a Pyrex reaction vessel insured that the 3130 Å. lines of the mercury spectrum were mainly responsible for the reaction.[5] Ketene–ethylene mixtures in the ratio 1:7.5 were photolysed at room temperature at a series of initial pressures. About 25% of ketene was decomposed in each run. Since methylene reacts faster with ethylene than with ketene under the experimental conditions chosen,[6,7] there should be very little complication due to the latter reaction.[6,7,8] The reaction products condensable in liquid nitrogen were separated by means of vapor chromatography and the three-carbon fraction was then analyzed mass spectrometrically.

Cyclopropane was found, the relative yield increasing with pressure as shown in Fig. 1. The solid line drawn is consistent with the mechanism:

(1) G. B. Kistiakowsky and Kenneth Sauer, THIS JOURNAL, **78**, 5699 (1956).

(2) P. S. Skell and R. C. Woodworth, *ibid.*, **78**, 4496 (1956).

(3) W. von E. Doering, R. G. Buttery, R. G. Laughlin and N. Chaudhuri, *ibid.*, **78**, 3224 (1956).

(4) W. von E. Doering and P. LaFlamme, *ibid.*, **78**, 5447 (1956).

(5) A. N. Strachan and W. A. Noyes, Jr., *ibid.*, **76**, 3258 (1954).

(6) G. B. Kistiakowsky and N. W. Rosenberg, *ibid.*, **72**, 321 (1950).

(7) G. B. Kistiakowsky and W. L. Marshall, *ibid.*, **74**, 88 (1952).

(8) R. A. Holroyd and W. A. Noyes, Jr., *ibid.*, **78**, 4831 (1956).