

observed differences in the course of the alkaline degradation of chlorotetracycline and oxytetracycline.

Although tetracycline lacks both the 5-hydroxyl group of oxytetracycline and the 7-chloro group of chlorotetracycline, it possesses *in vitro* activity (Table I) against a variety of microorganisms which parallels the broad antimicrobial spectra of these two antibiotics.^{9,10}

TABLE I
ACTIVITY¹¹ IN VITRO OF TETRACYCLINE

| Species | Minimum inhibitory concentration, mcg./ml. |
|---------------------------------|--|
| <i>Aerobacter aerogenes</i> | 50.0 |
| <i>Klebsiella pneumoniae</i> | 12.5 |
| <i>Escherichia coli</i> | 1.56 |
| <i>Salmonella typhosa</i> | 0.78 |
| <i>S. paratyphi</i> | 0.78 |
| <i>Staphylococcus aureus</i> | <0.19 |
| <i>Proteus sp.</i> | 50.0 |
| <i>Pseudomonas sp.</i> | 12.5 |
| <i>Brucella bronchisepticae</i> | 0.39 |
| <i>Mycobacterium ranae</i> | <0.19 |
| <i>Streptococcus faecalis</i> | <0.19 |

(9) A. C. Finlay, G. L. Hobby, S. Y. P'an, P. P. Regna, J. B. Routien, D. B. Seeley, G. M. Shull, B. A. Sobin, I. A. Solomons, J. W. Vinson and J. H. Kane, *Science*, **111**, 85 (1950).

(10) T. F. Paine, Jr., H. S. Collins and M. Finland, *J. Bact.*, **56**, 489 (1948).

(11) A serial dilution procedure was employed to determine the minimum concentration of tetracycline at which growth was completely inhibited.

RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC.
BROOKLYN 6, N. Y.

L. H. CONOVER
W. T. MORELAND
A. R. ENGLISH
C. R. STEPHENS
F. J. PILGRIM

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LOW PRESSURE VALIDITY OF THE BET EQUATION Sir:

As a prelude to a systematic study of the adsorption of gases on solids in the micron and sub-micron pressure range, we have determined the adsorption isotherms of heptane on ferric oxide at 29.55, 23.10 and 16.55° and at pressures ranging from 0.01 to 70 microns. We failed to find the first order transition reported for this system by Jura, Loeser, Basford and Harkins¹ and our results are in qualitative agreement with those reported by Smith² and by Young and Beebe.³ Certain experimental difficulties associated with the use of mercury float valves were encountered; it is possible to attribute the apparent first order transition previously reported to an artifact of this sort as well as to the possible lack of equilibrium suggested by Young and Beebe. Equilibrium was attained only after two weeks at one micron pressure when the conventional adsorption bulb was employed; this time was shortened to approxi-

(1) G. Jura, E. H. Loeser, P. R. Basford and W. D. Harkins, *J. Chem. Phys.*, **14**, 117 (1946).

(2) L. N. Smith, *THIS JOURNAL*, **74**, 3477 (1952).

(3) D. M. Young and R. A. Beebe, private communication.

mately two days through use of the tray system described by Jura and Criddle.⁴

The specific surface area of the ferric oxide as calculated from a BET plot of the nitrogen adsorption data at liquid nitrogen temperature is 6.82 sq. meters per gram. The adsorption data for heptane at constant temperature may be fitted by the equation $p/v = k_1p + k_2$ for relative pressures ranging from 3×10^{-4} to the highest measured; a relative pressure of 3×10^{-4} corresponds to a surface coverage, θ , of approximately 0.4 monolayer. In the pressure range investigated the above equation is characteristic of the Langmuir and the Brunauer, Emmett and Teller isotherms. In the BET notation, v_m ranges from 0.367 cc. at 29.55° to 0.401 cc. at 16.55°, while "c" ranges from 2070 to 2470. If the nitrogen surface area be accepted as correct, the area per heptane molecule in the monolayer varies from 63 sq. angstrom at 16.55° to 69 sq. angstroms at 29.55°; these values may be compared with that of 65 sq. angstroms at 25° reported by Loeser and Harkins.⁵ The isosteric heat changes rapidly with θ up to approximately 0.4; for higher values of θ the isosteric heat is roughly constant at 14.5 kcal. per mole. The heat of adsorption calculated from the BET "c" is 13.5 kcal. per mole.

It is customary to state the range over which the BET equation fits the experimental data in terms of relative pressure; the low point of this range is generally given as 0.05. The fact that the low point of this range in our experiments is 0.0003 indicates that this statement is incorrect. In general the BET equation is valid for θ less than unity when the heat of adsorption is roughly independent of surface coverage. It might be expected that the relative pressures corresponding to this portion of the isotherm would become lower as the heat of adsorption increases. Thus it would seem preferable to state the region in which the BET equation fits the data in terms of surface coverage rather than relative pressure.

The data at hand permit the calculation of the full set of thermodynamic functions described by Hill, Emmett and Joyner.⁶ These functions as well as complete details of the experimental procedure will be presented in a future publication.

(4) G. Jura and D. Criddle, *J. Phys. Coll. Chem.*, **55**, 163 (1951).

(5) E. H. Loeser and W. D. Harkins, *THIS JOURNAL*, **72**, 3247 (1950).

(6) T. L. Hill, P. H. Emmett and L. G. Joyner, *ibid.*, **73**, 5102 (1951).

GENERAL ELECTRIC COMPANY
SCHENECTADY, NEW YORK

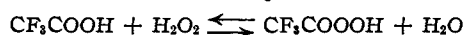
MYRON L. CORRIN

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OXIDATION REACTIONS WITH PERTRIFLUOROACETIC ACID

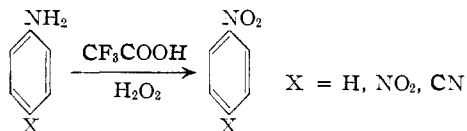
Sir:

We have recently observed that a solution of hydrogen peroxide in trifluoroacetic acid has unique properties as an oxidizing agent presumably due to the *in situ* formation of pertrifluoroacetic acid.



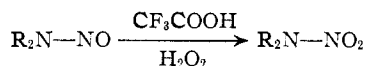
This reagent has been found to oxidize aniline and

substituted anilines to nitrobenzenes in excellent yields. Aniline, *p*-nitroaniline, and *p*-aminobenzonitrile were converted to nitrobenzene, *p*-dinitrobenzene and *p*-nitrobenzotrile in yields of 79, 86 and 98, respectively. In contrast peracetic acid oxidation of aniline yields 11% nitrobenzene and 71% azoxybenzene.¹



It has also been demonstrated that pertrifluoroacetic acid is an extremely active reagent for the hydroxylation of olefins. Thus oleic acid was rapidly hydroxylated in quantitative yield in chloroform solution. The hydroxylation of this olefin has been reported with performic acid, but the reaction with pertrifluoroacetic acid appears to be much faster.² In reactions of this type the initial product is, of course, the hydroxytrifluoroacetate of the α -glycol but this is easily hydrolyzed to the glycol.

Nitrosoamines have also been oxidized to nitramines smoothly with pertrifluoroacetic acid. Di-



ethylnitrosamine and dibutylnitrosamine were converted to the corresponding nitramines in 76 and 77% yield, respectively. The oxidation of nitrosoamines to nitramines has been reported in a few instances, but in general the reaction has been unsatisfactory as a general preparative method.^{3,4}

The experimental procedures for these oxidations have in most cases been quite simple. Excess trifluoroacetic acid was normally employed as solvent and on addition of hydrogen peroxide to this reagent no evolution of heat was observed. Hydrogen peroxide was usually used as the 90% reagent although the oxidation of oleic acid was also carried out with 30% hydrogen peroxide. The equilibrium between hydrogen peroxide and trifluoroacetic acid is apparently established very rapidly and the solution of pertrifluoroacetic acid so obtained appears to be relatively stable.

In a typical experiment 5.1 ml. (0.2 mole) of 90% hydrogen peroxide was added at 20° to 40 ml. of trifluoroacetic acid. To this solution was added 5.9 g. (0.05 mole) of *p*-aminobenzonitrile in one portion. The temperature of the resulting solution was allowed to rise to 50° and kept there by intermittent cooling for one hour. The mixture was then poured into ice water and 7.2 g. (98%) of *p*-nitrobenzotrile obtained.

ROHM AND HAAS COMPANY
JOSIAH GORGAS LABORATORY
REDSTONE ARSENAL
HUNTSVILLE, ALABAMA

WILLIAM D. EMMONS
ARTHUR F. FERRIS

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- (1) F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947).
- (2) D. Swern, G. N. Billen, T. Findley and J. T. Scanlan, *This Journal*, **67**, 1786 (1945).
- (3) F. S. Brockman, D. C. Downing and G. B. Wright, *Can. J. Research*, **27B**, 469 (1949).
- (4) R. Steurmer, *Ber.*, **91**, 2590 (1898).

THE THREE-DIMENSIONAL STRUCTURE OF COCAINE

Sir:

Ecgonine is converted by the prolonged action of 33% aqueous potassium hydroxide at 100° to pseudoecgonine.¹ On the other hand, cocaine (benzoylecgonine methyl ester) has now been found to yield pseudoecgonine methyl ester by the action of as little as a tenth of a molar proportion of sodium methoxide in hot absolute methanol. The yield of pure pseudo ester is 75%: m.p. 114–116°, $[\alpha]^{20}_D +22.8^\circ$ (*c* 1.7, H₂O).

The reaction of ecgonine methyl ester with methyl iodide has been reported to yield a number of products according to the conditions employed.² Although somewhat different results have been obtained in attempting to reproduce this work, the rather remarkable discovery of Willstätter that both ecgonine methyl ester and the pseudo isomer react with methyl iodide to give pseudoecgonine methyl ester methiodide has been confirmed (calcd. for C₁₁H₂₀INO₃: C, 38.72; H, 5.91; I, 37.2. Found: C, 38.72; H, 5.88; I, 37.4). Both derivatives melted at 216–216.5° and had $[\alpha]^{20}_D +11.3^\circ$ (*c*, 2.0, methanol). The melting point of a mixture of the two products was undepressed.

These two isomerizations indicate that the ecgonine-pseudoecgonine transformation involves epimerization at the α -carbon atom (C₂, structure I). It is well known that the α -hydrogen of carboxylate ions is less labile than that of esters thereof,³ and the lability of hydrogen in analogous quaternary ammonium compounds has also been established.^{3,4} It is difficult to account for these two reactions by means of Willstätter's opinion that this transformation involves the epimerization of the β -carbon atom (C₃, structure I),^{2,5} and it appears that he did not consider the possibility of epimerization at C₂.



- I, R = R' = H IV, R = R' = H
 II, R = CH₃, R' = H V, R = CH₃, R' = H
 III, R = CH₃, R' = COC₆H₅ VI, R = CH₃, R' = COC₆H₅

That the transformation does not affect both the α - and β -carbon atoms is evident from G. Fodor's demonstration that the carboxyl and hydroxyl groups are *cis* to one another in ecgonine but *trans* in pseudoecgonine.⁶ Fodor has found also that the ease of isomerization of N-acetylnorpseudoecgonine ethyl ester (to the O-acetyl isomer) is comparable to that of N-benzoyl- and N-acetylnorpseudotropine.^{6,7} It is therefore concluded that

- (1) A. Einhorn and A. Marquardt, *Ber.*, **23**, 468 (1890).
- (2) R. Willstätter, O. Wolfes and R. Mader, *Ann.*, **434**, 111 (1923).
- (3) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, pp. 243–244.
- (4) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 523 (1933).
- (5) (a) R. Willstätter and A. Bode, *Ann.*, **326**, 42 (1903); (b) R. Willstätter and M. Bommer, *ibid.*, **422**, 15 (1921).
- (6) G. Fodor, *Nature*, **170**, 278 (1952).
- (7) G. Fodor and K. Nádor, *ibid.*, **169**, 462 (1952); see also, A. Nickin and L. Fieser, *This Journal*, **74**, 5566 (1952).