The parallelism between E_T and Y as well as the obvious similarity between equations (1) and (2) suggests that the first intermediate in solvolysis, the "intimate ion-pair" may derive a portion of its binding energy from charge-transfer forces, and that charge-transfer may contribute to the stabilization of the transition state for its formation. Simple electrostatic attraction *cannot account* for the light absorption of the pyridinium iodide complexes; in addition, theory[8] implies that the behavior of E_T with solvent change is, in part, a reflection of a change in the degree of bonding between the pyridinium ion and the iodide ion. The empirical constant, Y, is therefore a measure of the total solvent effect, summing changes in binding as well as changes in solvation for the pyridinium iodide complexes. The expression of the first ion-pair (and of the intermediate of Streitwieser and Doering)[9] as a c-t. complex is a formulation which may permit application of the theory already available to solvolysis problems.[8] The correspondence of the equations (1) and (2) also implies that the complex *is* the intermediate in additions to the pyridinium ring,[10] and therefore, in nucleophilic aromatic substitution as well, especially of the "activated" type.[11] The study of the interaction of ethoxide ion with polynitroaromatics points in the same direction.[12]

The E_T values offer an interesting way of investigating solvent "ionizing power" with respect to structure, salt effects, and temperature, and is of special utility for those solvents which are unsuitable for the usual kinetic measurements.

(9) *Cf.* A. Streitwieser, Jr., *Chem. Rev.*, **56**, 570 (1956).
(10) E. M. Kosower, THIS JOURNAL, **78**, 3497 (1956).
(11) The results of Ross with aniline and 2,4-dinitrochlorobenzene are probably due to a complex which has the incorrect orientation for substitution; S. D. Ross, *et al.*, *ibid.*, **76**, 3000 (1954); **77**, 4916 (1955).
(12) J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 2528, 2540, 2546 (1956).

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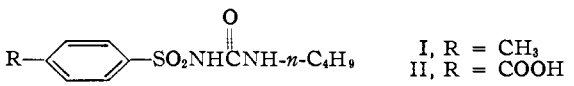
THE STRUCTURE OF A URINARY EXCRETION PRODUCT OF 1-BUTYL-3-*p*-TOLYLSULFONYLUREA (ORINASE)

Sir:

Recent investigations by Franke and Fuchs,[1] Achelis and Hardebeck,[2] Bertram, *et al.*,[3] Mirsky, *et al.*,[4] Kinsell, *et al.*,[5] Miller and Dulin,[6] Ridolfo and Kirtley,[7] and Fajans, *et al.*,[8] have shown that certain arylsulfonylureas reduce the concentration of sugar in the blood of experimental animals and in man after oral administration. An excretion product from one of these drugs, Orinase (I),[9] has been isolated from the urine of normal and diabetic humans. This metabolite does not produce hypoglycemia in dogs, rats[10] or humans.[8] It has been identified as 1-butyl-3-*p*-carboxyphenylsulfonylurea (II).



I, R = CH_3
II, R = COOH

The metabolite crystallized in crude form from urine which had been adjusted to *p*H 1 with hydrochloric acid and allowed to stand at room temperature for 1 to 2 hours. Purification was accomplished by repeated washes with water and three recrystallizations from 70% ethanol, using a Norite decolorization in the first stage.

The amount of this material isolated when 6 g. per day (1.5 g. every six hours) was given to normal men was approximately 75% of the amount of Orinase administered. When 3 to 4 g. was given orally to diabetic subjects, excretion of this metabolite ranged from 24 to 67% of the largest amount possible. These recoveries indicate that this material is very likely the principal metabolic product of Orinase.

The colorless crystalline product melted at 215–217°, and elemental analyses indicated an empirical formula of $C_{12}H_{16}N_2O_5S$. Potentiomeicti tration in water–ethanol showed an equivalent weight of 149.1 and two acidic groups of pK_a' 5.2 in 45% ethanol and 6.2 in 43% ethanol. The pK_a' of 6.2 parallels that of Orinase (pK_a' 6.5 in 44% ethanol) sufficiently so that it can be assigned to the acidic hydrogen of the sulfonyl-urea grouping. The pK_a' of 5.2 is characteristic of a carboxylic acid or a readily enolizable carbonyl.

The infrared spectrum of the excretion product showed that many of the structural characteristics of Orinase had been retained. In addition, the presence of a carboxyl group was indicated by the increased intensity of the carbonyl absorption at 1685 cm.$^{-1}$ relative to that of Orinase; carboxyl OH bands at 2670 and 2550 cm.$^{-1}$; and a band at 931 cm.$^{-1}$ which is characteristic of dimeric carboxylic acids.

This evidence indicated that the excretion product differed from Orinase ($C_{12}H_{18}N_2O_3S$) in having a carboxyl group in place of a methyl group. The ultraviolet absorption maxima (alkaline and acidic ethanol solutions) of the excretion product occurred at longer wave lengths than those of Orinase, indicating that the carboxylic function was on the aromatic ring. That the carboxylic group was indeed on the aromatic ring in the *para* position was proved by hydrolytic cleavage. A quantity of the excretion product was heated under reflux with 50% sulfuric acid for thirty minutes. On cooling, a solid separated which, after recrystallization from water, melted at 275–278°. This material was identified as *p*-carboxybenzenesulfonamide by comparison with authentic material. The comparison included infrared and ultraviolet spectra, elemental

(1) H. Franke and J. Fuchs, *Deut. med. Wochschr.*, **80**, 1449 (1955).
(2) J. D. Achelis and K. Hardebeck, *ibid.*, **80**, 1452 (1955).
(3) F. Bertram, E. Bendfelt and H. Otto, *ibid.*, **80**, 1455 (1955).
(4) I. A. Mirsky, D. Diengott and H. Dolger, *Science*, **123**, 583 (1956).
(5) L. W. Kinsell, F. R. Brown, R. W. Friskey and G. D. Michaels, *ibid.*, **123**, 585 (1956).
(6) W. Miller and W. Dulin, *ibid.*, **123**, 584 (1956).
(7) A. S. Ridolfo and W. R. Kirtley, *J. Am. Med. Assn.*, **160**, 1285 (1956).
(8) S. S. Fajans, J. W. Conn, L. H. Louis, H. S. Seltzer, R. D. Johnson, R. D. Gittler, A. R. Hennes, B. L. Wajchenberg, I. P. Ackerman, to be published.
(9) Orinase is the Upjohn trademark for its brand of 1-butyl-3-*p*-tolylsulfonyl-urea.
(10) W. Miller and W. Dulin, private communication.

analysis, titration characteristics and melting point.[11] Thus it is concluded that this primary excretion product of Orinase (I) is 1-butyl-3-*p*-carboxyphenylsulfonyl-urea (II).

ADDED IN PROOF.—After submission of this paper, T. Dorfmueller, *Deut. med. Wochschr.*, **81**, 888 (1956), appeared, indicating the same finding on the structure of the Orinase excretion product.

(11) The authors wish to thank Susan Theal for the potentiometric titrations, James E. Stafford for the ultraviolet spectral studies, and Albert Lallinger for technical assistance.

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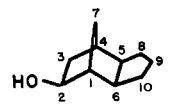
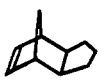
THE DEHYDRATION PRODUCT OF *exo*-TRIMETHYLENE-2-*exo*-NORBORNANOL[1]

Sir:

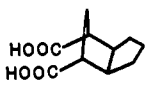
In 1948, Bruson and Riener[2] reported the phosphoric acid catalyzed dehydration of *exo*-trimethylene-2-*exo*-norbornanol (I). The olefinic product was assigned structure II, but no evidence was presented to support this assumption. Very recently, Wilder and Youngblood[3] examined the bromination of the dehydration product, again formulated as II, as well as studying several reactions of the resultant dibromide. It is significant that the permanganate oxidation of the olefin was reported to give a dicarboxylic acid of m.p. 162–163° (uncor.), a value quite different from that of the diacid, m.p. 182–184°, to which the structure III can be reliably assigned.[4,5]



I

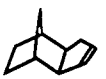


II

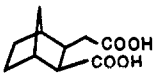


III

We wish to report evidence that the dehydration product (b.p. 760 mm.) 180.1°, $n^{25}D$ 1.4985, when purified by distillation through an efficient column) has been incorrectly formulated as II, and in fact was *exo*-trimethylene-8-norbornene (IV). The infrared spectrum of the olefin in question was identical in all respects with that of an authentic sample of IV, b.p. 760 180.1°, $n^{25}D$ 2.4985, whose structure can be considered to have been established rigorously.[5] Neither spectrum showed a band at 6.35 μ, possessed by all bicyclo[2.2.1]-2-heptene derivatives,[6] but rather absorbed at 6.18 μ, a value characteristic of the presence of a carbon–carbon double bond in an unstrained five membered ring. Permanganate oxidation of both samples of IV, produced by the two methods, gave the same diacid V, m.p.'s and mixed m.p. 165.1–165.6° (cor.). The dehydration product did not react with phenyl azide at room temperature indicating that it did not possess the norbornene structure.[7]



IV



V

Authentic *exo*-trimethylene-2-norbornene (II), b.p. (760 mm.) 176.0°, $n^{25}D$ 1.4927, could be prepared easily by sodium ethoxide dehydrohalogenation of *exo*-trimethylene-2-*exo*-norbornyl iodide.[8] The spectrum of this hydrocarbon was completely different from that of IV and possessed the expected band at 6.35 μ. The phenyl azide adduct, which formed unusually rapidly, had m.p. 144.6–145.1. *Anal.* Calcd. for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 76.09; H, 7.66; N, 16.84. Oxidation gave diacid III, m.p. 182.9–183.2°; the mixed m.p. with an authentic sample[4] of m.p. 182.8–183.2° was 183.0–183.3°.

Distillation of hydrocarbon II from phosphoric acid resulted in almost complete conversion into IV. Dehydration of other stereoisomers of alcohol I gave also the same product. Possible mechanistic interpretations of the above rearrangements as well as a discussion of some further reactions of hydrocarbons II and IV will be presented in future publications.

(1) It is suggested that the semi-trivial name "trimethylenenorbornane," numbered as in I, be utilized for the nomenclature of this series in a similar manner to that suggested for "bornane" and "norbornane," in the naming of other bicyclo[2.2.1]heptane derivatives ("Nomenclature for Terpene Hydrocarbons," No. 14, Advances in Chemistry Series, Am. Chem. Soc., Washington, D. C., 1955).

(2) H. A. Bruson and T. W. Riener, THIS JOURNAL, **70**, 2809 (1948).

(3) P. Wilder, Jr., and G. T. Youngblood, *ibid.*, **78**, 3795 (1956).

(4) H. A. Bruson and T. W. Riener, *ibid.*, **67**, 723 (1945).

(5) P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946).

(6) Unpublished observations: *cf.*, P. R. Schleyer, paper presented at the 130th ACS Meeting, Atlantic City, N. J., Sept., 1956.

(7) K. Alder, G. Stein and W. Friedrichsen, *Ann.*, **501**, 1 (1933).

(8) The method used was analogous to that employed for the preparation of *exo*-dicyclopentadiene (P. D. Bartlett, and I. S. Goldstein, THIS JOURNAL, **67**, 2553 (1947)).

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FORMIMINO-TETRAHYDROFOLIC ACID AND METHENYLTETRAHYDROFOLIC ACID AS INTERMEDIATES IN THE FORMATION OF N^{10}-FORMYLTETRAHYDROFOLIC ACID

Sir:

In a previous communication[1] evidence was presented for the formation of 10-formyl-THF[2] from FIG and THF by purified extracts of *Clostridium cylindrosporum*, as shown by reaction (1)

$$\text{FIG} + \text{THF} \longrightarrow \text{10-formyl-THF} + \text{glycine} + NH_3 \quad (1)$$

This over-all reaction has now been shown to be the sum of the three reactions, given by the equations.[3]

Enzymes I and II, acting together, are responsible for the formation of an intermediate in reaction (1) having an absorption maximum at 356 mμ and other spectral characteristics of 5,10-methenyl-THF. Evidence for the enzymatic formation of

(1) J. C. Rabinowitz and W. E. Pricer, Jr., THIS JOURNAL, **78**, 4176 (1956).

(2) Abbreviations used are: FIG, formiminoglycine; THF, tetrahydrofolic acid; 10-formyl-THF, N^{10}-formyltetrahydrofolic acid; 5-formyl-THF, N^5-formyltetrahydrofolic acid (leucovorin or citrovorum factor); 5-formimino-THF, N^5-formiminotetrahydrofolic acid; 5,10-methenyl-THF, the cyclic N^5-N^{10}-imidazolinium derivative of 5-formyl-THF, previously abbreviated as 5,10-formyl-THF[1] (anhydroleucovorin or anhydrocitrovorum factor); EDTA, ethylenediaminetetraacetic acid.

(3) R = benzoyl-L-glutamic acid.