dropwise over a 30-min. period, during which time the temperature was maintained at 70–75°. The heating was then discontinued and the solution stirred for 1 hr. at room temperature. The resulting solution was then washed once with a saturated solution of sodium carbonate, twice with water and dried over anhydrous sodium sulfate. The ethyl acetate was then removed under reduced pressure, and the residue was suspended in 200 ml. of anhydrous ethyl ether and filtered. Recrystallization of the solid from an ethyl acetate-*n*-heptane mixture gave 46 g. of colorless crystals, m.p. 139–140°.

*Anal.* Calcd. for $C_{13}H_{15}ClN_4O_3$: C, 50.2; H, 4.8; N, 18.1. Found: C, 49.9; H, 4.8; N, 18.0.

**6-(6-Chloro-9-purinyl)-tetrahydropyran-2-methanol (VI).** —Ten grams of 6-(6-chloro-9-purinyl)-tetrahydropyran-2-methanol acetate (V) was dissolved in 150 ml. of methanol which had previously been saturated with ammonia at 0°. The resulting solution was stirred vigorously at 0° for 8 hr. then placed overnight in the refrigerator. The methanol and excess ammonia were removed under reduced pressure. To the syrupy residue was added 100 ml. of petroleum ether and the product allowed to crystallize. Recrystallization from benzene–petroleum ether (b.p. 60–110°) gave 4.5 g. of white product, m.p. 139–140°.

*Anal.* Calcd. for $C_{11}H_{14}ClN_4O_2$: C, 49.2; H, 4.8; N, 20.8. Found: C, 49.4; H, 5.1; N, 20.6.

**6-(6-Thio-9-purinyl)-tetrahydropyran-2-methanol (VIII)** —Eight grams of 6-(6-chloro-9-purinyl)-tetrahydropyran-2-methanol acetate (V) was dissolved in 125 ml. of absolute methanol. To this solution was added 250 ml. of a solution of sodium hydrosulfide in methanol (prepared as in the preparation of 9-(tetrahydro-2-pyranyl)-6-purinethiol). The solution was heated on the steam-bath for 30 min. and filtered. The filtrate was carefully neutralized to pH 7 with glacial acetic acid. The solution was then cooled and the product collected by filtration. Recrystallization of the crude product from a dimethylformamide–water mixture gave 6.5 g. of pale-yellow crystals which decomposed, without melting, > 200°.

*Anal.* Calcd. for $C_{11}H_{14}N_4SO_2$: C, 49.7; H, 5.3; N, 21.0. Found: C, 49.6; H, 5.4; N, 20.9.

**6-(6-Amino-9-purinyl)-tetrahydropyran-2-methanol (VII).** —6-(6-Chloro-9-purinyl)-tetrahydropyran-2-methanol acetate (V) (25 g.) was added to 250 ml. of ethanol, which had previously been saturated with anhydrous ammonia at 0°, and the resulting solution was allowed to stand at room temperature for 48 hr. The solution was then evaporated to dryness and the residue suspended in 200 ml. of chloroform and filtered. Recrystallization of the solid from absolute ethanol gave 18.7 g. of colorless leaf-shaped crystals, m.p. 200–201°.

*Anal.* Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.1; H, 6.0; N, 28.2. Found: C, 53.1; H, 6.1; N, 28.4.

# COMMUNICATIONS TO THE EDITOR

## EVIDENCE FOR NITROGEN MIGRATION IN THE BENZILIC ACID REARRANGEMENT OF ALLOXAN AND DERIVATIVES
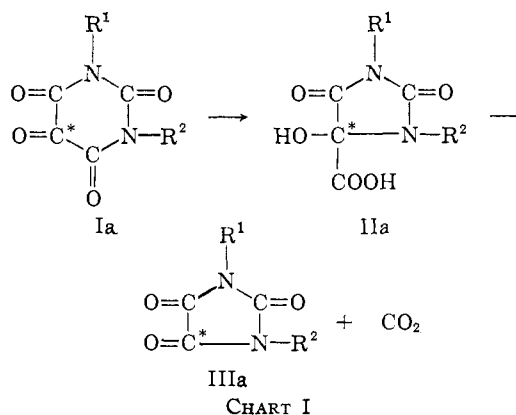
*Sir:*

The benzilic acid rearrangement of alloxan (I) to alloxanic acid[1] (II) has been the subject of a recent[2] kinetic study, on the basis of which it was suggested that three different anions could be formed, any one of which could conceivably be a rearrangement intermediate. These results led to the proposal[2] that not only a carbon–carbon shift but also a nitrogen–carbon shift was possible during the rearrangement I → II. Although both possibilities had been suggested before,[1b,3] the work of Kwart and Sarasohn[2] appears to be the first presumptive evidence that a nitrogen-carbon shift during a benzilic acid rearrangement is possible. Tracer studies with carbon-14 now have been carried out which show unambiguously that the nitrogen shift takes place to the exclusion of the carbon shift during rearrangement of alloxan and several of its derivatives under widely differing conditions of pH. Alloxan [Ia, $R^1 = R^2 = H$] labeled in the 5-position was prepared by oxidation with chromic anhydride of the barbituric acid obtained from urea and methylene-labeled malonic ester[4]; it

(1) (a) F. Wöhler and J. V. Liebig, *Ann.*, **26**, 241 (1838); A. Schlieper, *ibid.*, **263**, 55 (1845); (b) H. Biltz, M. Heyn and M. Bergius, *ibid.*, **413**, 68 (1916); (c) G. M. Richardson and R. K. Cannon, *Biochem. J.*, **23**, 68 (1928); (d) J. W. Patterson, A. Lazarow and S. Levey, *J. Biol. Chem.*, **177**, 187 (1949).

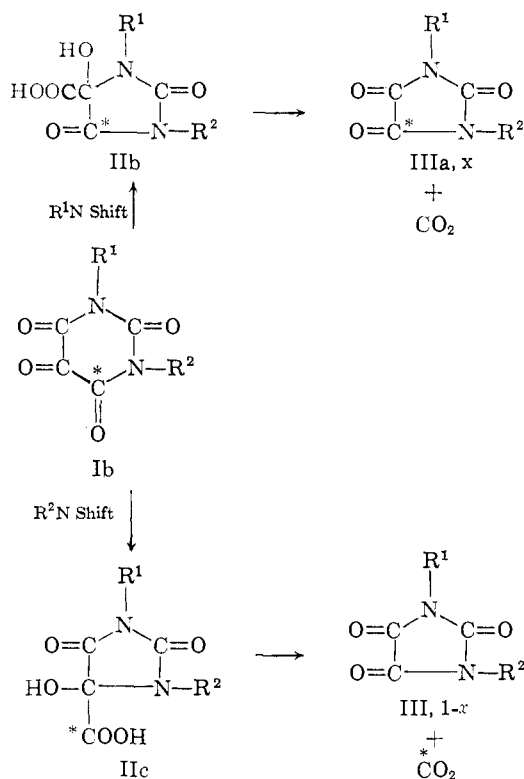(2) H. Kwart and I. Sarasohn, *J. Am. Chem. Soc.*, **83**, 909 (1961).

(3) (a) S. Selman and J. F. Eastham, *Quarterly Reviews*, **14**, 234 (1960); (b) F. R. Fisher and R. A. Day, *J. Am. Chem. Soc.*, **77**, 4895 (1955).

(4) According to the procedure of A. V. Holmgren and W. Wenner, *Organic Syntheses*, **32**, 6 (1952), John Wiley and Sons, New York, N. Y.

CHART I

was then subjected to rearrangement (a) at pH 7–10 in potassium hydroxide solution; (b) at pH 13 in sodium hydroxide solution; (c) at pH 9.4 in sodium hydroxide–sodium borate buffered solution; (d) at pH 7.2–7.5 in sodium hydroxide–sodium phosphate buffered solution and (e) at pH *ca.* 1 in nitric acid. In the experiments performed under alkaline conditions the alloxanic acid (IIa) was oxidized to parabanic acid IIIa with nitric acid solution, whereas in the acid-catalyzed rearrangement, parabanic acid [IIIa] was formed directly. Radioactivity assay of IIIa and Ia (or its barbituric acid precursor) or IIa demonstrated that the samples of IIIa possessed 98.5–102.6% of the original radioactivity (see Chart I). Several derivatives of alloxan labeled in the 4-positions[5]

(5) The synthetic route employed in the synthesis of N-methylalloxan and of N-phenylalloxan starts with the appropriate monosubstituted urea and cyanoacetic-*carboxyl*-$C^{14}$ acid to yield RNH-$CONHC^*OCH_2CN$, which undergoes ring closure in the presence of

IIb  →  IIIa, x  +  CO₂

R¹N Shift ↑

Ib

R²N Shift ↓

IIc  →  III, 1-x  +  CO₂

CHART II

next were prepared; such derivatives, designated Ib (Chart II), were subjected to most of the same conditions of rearrangement as was the isotope position isomer Ia. The values $(x)$ and $(1 - x)$ are the mole fractions of product formed through shift of R¹N- or R²N, respectively. If no isotope effect is exhibited, it would be expected, when R¹ = R², that $x = 0.500$, whereas if R¹ ≠ R², $x$ could have values of zero to unity. The results of experiments with Ib are given in Table I.

Although the data of Table I deviate somewhat from the theoretical values of $x = 0.500$ and $x = 1.00$ (excluding for the moment lines 8 and 9 concerning N-methylalloxan-4-C¹⁴), the deviations are no greater than those to be expected from the operation of normal intramolecular or intermolecular isotope effects. We therefore conclude that: (a) each rearrangement takes place with exclusive shift of nitrogen, rather than of carbon, and (b) in the rearrangements of N-phenylalloxan-4-C¹⁴ the shift of N–Ph takes place to the exclusion of unsubstituted nitrogen.[6] Turning now to the data for the rearrangement of N-methylalloxan-4-C¹⁴ (lines 8 and 9, Table I), auxiliary experiments with N-methylalloxan-5-C¹⁴ [Ia, R¹ = CH₃, R² = H] indicate that the parabanic acid [IIIa, R¹ =

alkali to produce the mono-substituted iminobarbituric acid [W. Traube, *Ber.*, **33**, 3039 (1900)]. Hydrolysis of the imine to the barbituric acid with 6 N HCl and then chromic acid oxidation[4] produced the N-methyl- or N-phenylalloxan-4-C¹⁴. Alloxan-4-C¹⁴ and N,N-dimethylalloxan-4-C¹⁴ were prepared according to the procedure of ref. 4, using carboxyl-labeled malonic ester and urea or dimethylurea as reactants.

(6) This result is to be contrasted with the observations of W. E. Doering, T. I. Taylor and E. F. Schoenewaldt, *J. Am. Chem. Soc.*, **70**, 455 (1948), and of O. K. Neville, *ibid.*, **70**, 3499 (1948), that in the rearrangement of phenylglyoxal to mandelic acid it is only the hydrogen which undergoes migration.

## TABLE I

RADIOCHEMICAL RESULTS OF THE REARRANGEMENT OF ALLOXAN-4-C¹⁴ AND DERIVATIVES [Ib]

| $pH$ ca. | Substituent in I, II and III R¹ | R² | $x^a$ | $1 - x^b$ |
|---|---|---|---|---|
| <1 | H | H | 0.533 | 0.467 |
| 7.5 | H | H | .542 | .458 |
| 9.4 | H | H | .503 | .497 |
| 7–10 | H | H | .498 | .502 |
| >13 | H | H | .550 | .450 |
| <1 | CH₃[c] | CH₃[c] | .528 | .472 |
| 7–8 | CH₃ | CH₃ | .529 | .471 |
| <1 | CH₃[d] | H[d] | .754 | .246 |
| 7–8 | CH₃ | H | .803 | .197 |
| <1 | Ph[e] | H[e] | .973 | .027 |
| 7–8 | Ph | H | .960 | .040 |
| >13 | Ph | H | .990 | .010 |

*a* Based on radioactivity assay of the appropriate parabanic acid [III].  *b* By difference.  *c* I and III, R¹ = R² = CH₃: E. Fischer, *Ber.*, **14**, 1912 (1881); A. Strecker, *Ann.*, **118**, 174 (1861).  *d* I, II and III, R¹ = CH₃, R² = H: E. Fischer, *Ber.*, **15**, 455 (1892); H. B. Hill, *ibid.*, **9**, 1092, 1093 (1876); I and III, R¹ = Ph, R² = H: N. M. Winslow, *J. Am. Chem. Soc.*, **61**, 2089 (1939); H. Kammerer, *Ber.*, **40**, 3741 (1907).

CH₃, R² = H] obtained upon rearrangement at $pH < 1$ contained 93.7% and at $pH$ 7–8 contained 96.7% of the original radioactivity of reactant N-methylalloxan-5-C¹⁴. From lines 8 and 9 (Table I) it can thus be calculated that the migration ratios, or "migratory aptitudes," of CH₃-N *versus* H–N under the two reaction conditions studied are 3:1 and 4:1, respectively.

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## AMIDO NITROGEN MIGRATION IN A BENZILIC ACID REARRANGEMENT AS PART OF THE RING CONTRACTION OF ISOQUINOLINEDIONES TO PHTHALIMIDES.

*Sir:*

Kwart and Sarasohn in a paper just appeared[1] have raised the question of whether amido-nitrogen migration may occur in the benzilic acid rearrangement of alloxan to alloxanic acid; the reaction previously has been interpreted both as occurring by migration of carbon[2] and by migration of nitrogen.[3] We wish to report a resolution of this problem for a system containing a somewhat similar heterocyclic ring, phthalonimide(III). This compound and its N-methyl derivative, like alloxan, dissolve readily in aqueous alkali, presumably because of formation of the anion of a *gem*-diol derived from the ketonic carbonyl.

Our investigations have been concerned with a

(1) H. Kwart and I. M. Sarasohn, *J. Am. Chem. Soc.*, **83**, 909 (1961).

(2) S. Selman and J. F. Eastham, *Quart. Revs.*, **14**, 221 (1960).

(3) H. Biltz, M. Heyn and M. Bergius, *Ann.*, **413**, 68 (1916).