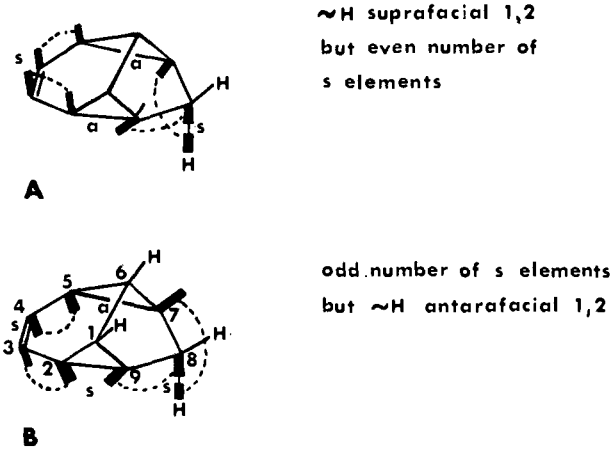
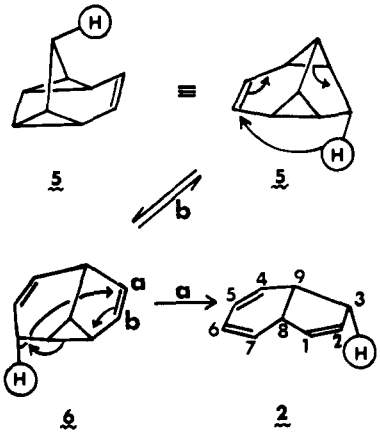
category ii. The observed value is too high to permit exclusive operation of category i and implicates the intramolecular Diels–Alder mechanism *via* tetracyclic olefin **5** as a major pathway.[8]

In the conversion of **5** to **2**, can the hydrogen transfer be concerted with the cleavage of both C–C bonds? Regardless of mechanistic details, simple geometric factors impose the condition that all the newly created double bonds of the product **2** must be cis. Only two types of concerted transition state can be constructed with orbitals that meet the cis double bond requirement. One, A, involves a suprafacial vicinal hydrogen shift but an *even* number of symmetric (s) reaction elements and therefore is "forbidden" by orbital symmetry.[9] The other, B, employs an odd number of s elements but now must use an antarafacial vicinal hydrogen shift and therefore is sterically difficult. Similar conclusions apply to processes in which the other methylene hydrogen migrates. However, it might be possible to effect the **5** → **2** rearrangement by *two successive "allowed"* 1,5-homodienyl hydrogen shifts, *viz.*, **5** → **6** → **2** (Scheme I). This hypothetical process would result again in overall shift of the circled hydrogen to a vicinal position, but only by an indirect pathway which involves initial transannular shift to give **6** followed by "rebound" of the same hydrogen to its ultimate lodgment at C-3 of **2**. We find that pyrolysis at 293° of hypothetical intermediate **6**, independently synthesized[10] in six steps from 1,4-dihydrobenzoic acid, gives **2** quantitatively at a rate at least 65 times that of the **1** → **2** reaction. Diene **6** is therefore a permissible intermediate in the **1** → **2** rearrangement.



The pyrolysis of tricyclic diene **6** does not produce appreciable quantities of bicyclic triene **1**. Since it is likely that any of the tetracyclic olefin **5** formed from **6** would revert immediately to **1**,[11] the absence of **1** suggests that if **6** is an intermediate in the **1** → **2** rearrangement (Scheme I), it must execute the second

Scheme I



hydrogen transfer to point a (reaction **6** → **2**) much faster than the reverse of the first (transfer to b, reaction **6** → **5**). The first hydrogen transfer (reaction **5** → **6**) then must be the overall rate-determining step in the **1** → **2** rearrangement by this mechanism.

Molecular models indicate that the circled hydrogen in **6** must leap about 2.8 Å to point a, but only about 2.3 Å to point b. Nevertheless, path a is preferred, presumably because of the exothermicity of the **6** → **2** reaction.

It seems likely that the "hydrogen-rebound" mechanism may provide an indirect but convenient device by which rearranging systems in the C_nH_{n+1} (n odd) series can avoid "forbidden" reactions. Such hydrogen shifts may thereby facilitate deep-seated carbon skeletal rearrangements.

(8) Starting material **1**-7,8-d_2 is recovered with no detectable deuterium position rearrangement from partial pyrolysis. This excludes a competing [1,3]-degenerate rearrangement of **1**-7,8-d_2 to **1**-2,3-d_2, which if it occurred, would lower the intensity ratio in the ultimate product **2**. Similarly, independently synthesized labeled product **2**-2,3,4,5-d_4 is recovered with an intact labeling pattern after pyrolysis. The ratio in **2** obtained from **1**-7,8-d_2 must therefore result either from a mixture of i and ii or from partial position mixing in an intermediate.

(9) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(10) R. R. Boettcher, Ph.D. Thesis, University of Wisconsin, 1970.

(11) Olefin **5** is probably an intermediate in the formation of **1** by pyrolysis of the sodium salt of cycloheptatrienylacetaldehyde *p*-toluenesulfonylhydrazone.[12] Strong support for a facile **5** → **1** reaction also comes from observations of the analogous transformations of tetracyclo[4.4.0.$0^{2,10}$.$0^{5,7}$]deca-3,8-dienes to bicyclo[4.2.2]deca-2,4,7,9-tetraenes.[13–15]

(12) H. Tsuruta, K. Kurabayashi, and T. Mukai, *J. Amer. Chem. Soc.*, **90**, 7167 (1968).

(13) M. Jones, Jr., and B. Fairless, *Tetrahedron Lett.*, 4881 (1968).

(14) S. Masamune, R. T. Seidner, H. Zenda, M. Wiesel, N. Nakatsuka, and G. Bigam, *J. Amer. Chem. Soc.*, **90**, 5287 (1968).

(15) (a) W. Grimme, H. J. Riebel, and E. Vogel, *Angew. Chem.*, **80**, 803, 823 (1968); (b) E. Babad, D. Ginsburg, and M. B. Rubin, *Tetrahedron Lett.*, 2361 (1968); (c) J. Altman, E. Babad, M. B. Rubin, and D. Ginsburg, *ibid.*, 1125 (1969); (d) J. S. McConaghy, Jr., and J. J. Bloomfield, *ibid.*, 1121 (1969).

(16) Supported by Postdoctoral Fellowship No. FO2 AM 36193-02 from the National Institute of Arthritis and Metabolic Diseases.

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Isoracemization of *N*-Carbobenzoxyamino Acid Ester Derivatives

Sir:

We wish to report that the racemization by α-hydrogen abstraction of two *N*-carbobenzoxyamino acid active esters in a nonpolar solvent proceeds *via* isoracemization in the presence of triethylamine. We recently reported that racemization of *N*-carbobenzoxy-*S*-benzyl-L-cysteine active esters does not proceed

through β elimination–readdition[1] but rather through α-hydrogen abstraction which may be considerable under conditions used for peptide synthesis in the presence of triethylamine.[2]

In order to investigate the details of the mechanism of racemization by α-hydrogen abstraction, the base-catalyzed racemization and deuterium exchange of *N*-carbobenzoxy-*S*-benzyl-L-cysteine pentachlorophenyl ester were studied in chloroform in the presence of triethylamine and monodeuteriomethanol. The ratio, k_e/k_α, of the one-point pseudo-first-order rate constants for exchange and racemization of three parallel experiments of 2 hr was found to be 0.056 ± 0.002.[3] This result suggests isoracemization,[4] a process first described by Cram[4] in which racemization occurs without exchange of the proton. Our observation is the first for an amino acid derivative or, in general, for a compound which has an asymmetric carbon α to a carboxyl group, and therefore we have studied the kinetics of this racemization in greater detail.

N-Carbobenzoxy-*S*-benzyl-L-cysteine pentachlorophenyl ester was racemized with 7 equiv of triethylamine in a chloroform solution[5] containing 53 equiv of methanol-*O*-*d*. Aliquots were removed at given intervals, the reaction was quenched with 20% deuterium sulfate in deuterium oxide, and the pentachlorophenyl ester was isolated.[6] The optical rotations were determined on each sample and are given in Table I. The deuterated active ester content of the isolated active ester[6] was determined by mass spectrometric analysis[7] using the following peaks: *m/e* 328–329 due to the acylium ions, *m/e* 300–301 which are formed by the loss of carbon monoxide from the acylium ion, and *m/e* 256–257 which arise by rearrangement of the *m/e* 300–301 ions with loss of carbon dioxide.

The concentration of the active ester continuously decreases through an ester exchange reaction which yields methyl ester. The rate constant (k_m) of the methyl ester formation was determined[6] and from this the decrease of the concentration of the active ester was calculated. These data were taken into account for the calculations of the exchange rate constant (k_e) from the mass spectral data.[8] Correction for the methylation reaction was not necessary in the racemization studies since the racemization reaction is relatively fast. Pseudo-first-order rate constants were determined; the duplicate values obtained for exchange[9] and racemization are $k_e = 5.44 \times 10^{-6}$ sec^{-1} and 4.15×10^{-6} sec^{-1} and $k_\alpha = 1.06 \times 10^{-4}$ sec^{-1} and 0.89×10^{-4} sec^{-1}. The single determination made of k_m gave a value of 5.29×10^{-6} sec^{-1}.

Table I. Kinetic Data for Triethylamine[a]-Catalyzed Racemization and Deuterium Exchange of *N*-Carbobenzoxy-*S*-benzyl-L-cysteine Pentachlorophenyl Ester[b] in the Presence of Methanol-*O*-*d*[c] in Chloroform[d]

Time, min	$[\alpha]^{22.5}D$,[e] deg	% deuterated active ester in the isolated ester[f]
30	−34.4	
60	−28.1	
90	−26.8	
120	−19.0	3.8
180	−13.8	
240	−10.3	
360	−4.1	12.9
615		21.3
780		29.2
1,140	0.0	32.6
1,470	0.0	39.1
2,040	0.0	47.8
2,880	0.0	59.9

[a] The triethylamine concentration was 0.31 *M*. [b] The active ester concentration was 0.0435 *M*. [c] The concentration of methanol-*O*-*d* was 2.3 *M*. [d] The reaction was carried out at a constant temperature of 32°. [e] *c* 2, dimethylformamide. [f] Reference 6; from *m/e* 328 and 329 ions.

The ratio of the rate constants for the exchange reaction and racemization, k_e/k_α, was found to be 0.05 ± 0.01. This ratio was not significantly changed ($k_e/k_\alpha = 0.06$) when the racemization reaction was carried out under the same conditions described above, but in the presence of 1.2×10^{-3} *M* triethylamine hydrochloride.[10] These results further support the hypothesis that the racemization of *N*-carbobenzoxy-*S*-benzylcysteine under these conditions occurs *via* isoracemization.

In order to ascertain whether isoracemization is not specific for cysteine derivatives, *N*-carbobenzoxy-L-phenylalanine pentachlorophenyl ester was racemized under identical conditions described for the cysteine derivative in Table I. The optical rotations of the isolated active ester samples after 0, 24, and 49 hr

(1) J. Kovacs, G. L. Mayers, R. H. Johnson, and U. R. Ghatak, *Chem. Commun.*, 1066 (1968).

(2) J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *ibid.*, 53 (1970); J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *J. Org. Chem.*, **35**, 1810 (1970).

(3) This was reported at the 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 22–27, 1970; G. L. Mayers and J. Kovacs, *Chem. Commun.*, 1145 (1970).

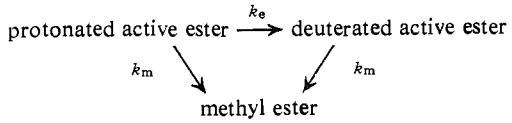
(4) J. Almy and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 4459, (1969); D. J. Cram and L. Gosser, *ibid.*, **86**, 5457 (1964); D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

(5) Reagent grade chloroform was washed with water, dried over anhydrous potassium carbonate, and distilled from phosphorus pentoxide; triethylamine (Baker) was dried over sodium. Methanol-*O*-*d* (99% D) was obtained from Stohler, Rutherford, N. J.

(6) The quenched reaction mixture was washed three times with water, dried, and evaporated. The residue was dissolved in tetrahydrofuran–methanol (1:1) and refluxed for 10 min to replace the deuterium on the amide nitrogen with hydrogen. The solvent was removed and the solid residue was triturated with pentane and/or methanol, which removes the *N*-carbobenzoxy-*S*-benzylcysteine methyl ester formed by transesterification. The amounts of methyl ester in the aliquots for 30, 120, 240, 360, 500, 1140, and 1470 min were estimated using the infrared method and were found to be 1, 1.8, 7, 14, 15, 32, and 36% of the starting material, respectively. The pentachlorophenyl ester was recovered in good yield (52–80%) for all aliquots and samples after 60, 180, 360, and 2040 min analyzed correctly for C, H, N, and Cl. Thin-layer chromatography of the isolated active ester on silica gel developed with benzene–ethyl acetate (9:1) showed a single spot alone and when it was cochromatographed with the unracemized active ester.

(7) The mass spectrometric analysis was done at the Battelle HRMS Center facilities by Dr. R. L. Foltz, and by Morgan Schaffer Corp., Montreal, Canada. The elemental compositions of *m/e* 328.0983 and 256.1173 ion were determined by Dr. Foltz and found to be $C_{18}H_{18}NO_3S$ and $C_{16}H_{18}NS$, respectively.

(8) The following reaction scheme was postulated and used in analyzing the data



(9) The pseudo-first-order rate constants given in the text were determined for exchange using the *m/e* 328–329 peaks. The rate constants obtained from *m/e* 300–301 and 256–257 peaks were within ±20% of those obtained from *m/e* 328–329 peaks.

(10) This experiment was carried out on the suggestion of Professor D. J. Cram in a private communication.

were: $[\alpha]^{22}D$ −53.1, −33.8, and −20.5° (*c* 1, dimethylformamide), respectively. The deuterated active ester contents of these samples were 0, 0, and 4% as determined by mass spectrometric analysis using *m/e* 282–283 peaks. The ratios of k_e/k_α of the one-point pseudo-first-order rate constants for two experiments of 24 and 49 hr were found to be 0.00 and 0.03, respectively, indicating isoracemization.[11]

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM 06579 and 08795). We are grateful to Dr. R. L. Foltz for the mass spectrometric analysis which was done at the Battelle HRMS Center facilities, and to Dr. I. Lengyel for the helpful discussion of the mass spectra.

(11) In these calculations the transesterification reaction was not taken into account; however, consideration of this side reaction would decrease the k_e/k_α value.

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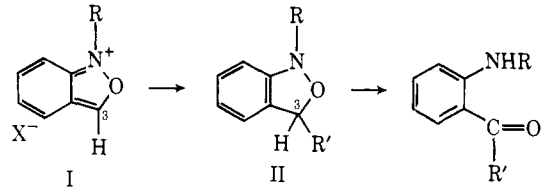
Reactions of Anthranilium Salts with Bases. Isolation of *N-tert*-Butylbenzoazetinone

Sir:

A recent report[1] that *N-tert*-butylanthranilium BF_4^- (Id) is reduced by $NaBH_4$ to the isoxazoline (IId, R′ = H) which can be thermally rearranged to 2-*tert*-butylaminobenzaldehyde (IIId, R′ = H) prompts us to communicate some of our own results on the reactions of 3-unsubstituted anthranilium cations I with nucleophiles.

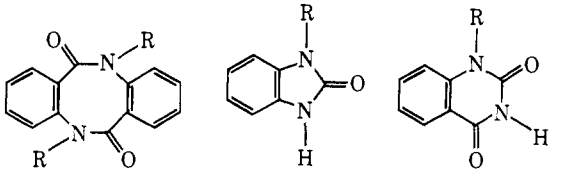


I II III

a, R = CH_3
b, R = CH_2Me
c, R = $CHMe_2$
d, R = CMe_3

The salts[2] I are all easily prepared by alkylation of anthranil with oxonium or carboxonium ions[3] or $HClO_4$–*tert*-BuOH mixtures[4] (nmr Ia–d, C_3H ~ δ 9.95, CD_3NO_2) and they react cleanly with many anions besides hydride to give the simple C_3 addition products II.[5] For example, the ethyl salt Ib yielded the acetal IIb (R′ = OMe, bp 75–76° (0.3 mm), C_3H at δ 6.42) on treatment with MeOH containing Et_3N and similarly on reaction with aqueous solutions of NaCN or NaN_3 the respective unstable adducts IIb (R′ = CN, ir 4.50 μ (w), C_3H at δ 6.23; R′ = N_3, ir 4.77 μ, C_3H at δ 6.33) rapidly oiled out.[6] Note that the experiments in water show that, as expected, attack of I by anions is much more facile than reaction with uncharged nucleophiles, a selectivity which as will be seen in later papers has valuable consequences in some new synthetic methods based on this work.

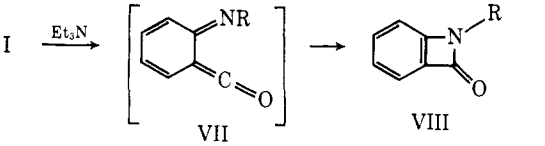
The thermal conversion of II to III also occurred in these more complex systems though often additional complications were observed. For example, IIb (R′ = OMe) rearranged to the known amino ester[7] IIIb (R′ = OMe) when refluxed in xylene, but the dimeric IVb (mp 192°) was also formed[8] (IVb was the only isolable product from the thermolysis of IIb, R′ = CN). When boiled in CCl_4 the azide IIb (R′ = N_3) was cleanly converted to the benzimidazolone Vb (compared with authentic sample[9]). This product would be anticipated



IV V VI

from a Curtius rearrangement of an initially generated acyl azide IIIb (R′ = N_3). Direct spectroscopic evidence for the intermediacy of the related IIId (R′ = N_3, ir 4.67, 6.04 μ) was secured in the analogous transformation of IId (R′ = N_3) to Vd (mp 145–146°). The entire process, I → V, could be performed as one step, and in another example the known quinazoline[10] VIb was made (60%) just by heating Ib with NaOCN in CH_3CN [Ib → IIb (R′ = NCO) → IIIb (R′ = NCO) → VIb].

The isolable but thermally unstable acyl azide IIId (R′ = N_3) and other compounds of structure III could be synthesized directly from I at room temperature by titration of I in CH_2Cl_2 with 1 equiv of Et_3N or *i*-Pr_2NEt[11] followed by addition of R′H, the conjugate acid of the nucleophile. Based on spectroscopic evidence (strong ir peak 5.5–5.6 μ) the species obtained in the first step in this latter procedure is the benzoazetinone (VIII). At 25° in solution VIIIa



I VII VIII

and VIIIb decomposed within 1 hr while VIIIc had a lifetime of a day. The more hindered *N-tert*-butylbenzoazetinone (VIIId), however, was stable (though very reactive toward nucleophiles to give IIId) and could be obtained pure in 84% yield by precipitation

(1) R. V. Coombs and G. E. Hardtmann, *J. Org. Chem.*, **35**, 2440 (1970).

(2) Satisfactory elemental analyses and corroborative spectroscopic data have been obtained for all stable new compounds.

(3) H. Meerwein, *Org. Syn.*, **46**, 113, 120 (1966); R. B. Silverman and R. A. Olofson, *Chem. Commun.*, 1313 (1968); S. Kabuss, *Angew. Chem., Int. Ed. Engl.*, **5**, 675 (1966); K. Dimroth and P. Heinrich, *ibid.*, **5**, 676 (1966); R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969): Ia, mp 64–65°; Ib, 79.5–80.5°; Ic, 78–79° (all X = BF_4).

(4) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966); D. J. Woodman, *ibid.*, **33**, 2397 (1968): Id (X = ClO_4) mp 146° dec.

(5) This also seems to be the preferred site of nucleophilic attack on the parent anthranils though simple adducts are not isolated: E. C. Taylor and J. Bartulin, *Tetrahedron Lett.*, 2337 (1967), and references therein.

(6) The upfield C_3H nmr shift excludes alternative salt structures (I, X = R′). Minor equilibrium amounts of such species could still, however, be present in solution.

(7) D. Vörlander, *Chem. Ber.*, **34**, 1645 (1901).

(8) The known IVa [G. Schroeter and O. Eisleb, *Ann.*, **367**, 101 (1909)] was similarly made by heating IIa, R′ = OMe.

(9) J. Davoll and D. H. Laney, *J. Chem. Soc.*, 314 (1960).

(10) N. A. Lange and F. E. Sheibley, *J. Amer. Chem. Soc.*, **55**, 2113 (1933).

(11) For logic of base choice see: R. A. Olofson, S. W. Walinsky, J. P. Marino, and J. L. Jernow, *ibid.*, **90**, 6554 (1968).