On the Barrier to Inversion of Cyclooctatetraene. The Thermal Decomposition of Dibenzo[*e*,*g*][1,4]diazocine[1]

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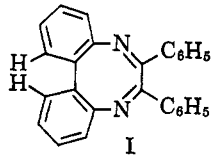
An attempt was made to measure the barrier to inversion of a cyclooctatetraene derivative by the thermal racemization of optically active dimethyl dibenzo[*e*.*g*][1,4]diazocine-3,10-dicarboxylate. At above 240° the compound fragmented to yield dimethyl 6-phenylphenanthridine-3,8-dicarboxylate and benzonitrile. The rate of the fragmentation reaction allowed estimation of the barrier to inversion of cyclooctatetraene as greater than 17 kcal./mole.

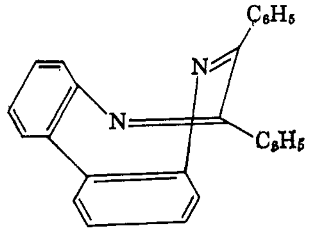
Cyclooctatetraene is known to possess a tub-like configuration (D_{2d}) with alternating long and short bonds,[2] while the most detailed quantum mechanical calculations published on the system (Pariser-Parr approximation)[3] indicate that the planar structure with alternating long and short bonds (D_{4h}) should be slightly more stable. More recently better approximations have indicated[4] that the D_{2d} structure should indeed be the more stable, but only by a few kcal./mole. An experimental determination of the difference in energy between these two forms was considered desirable, so that the accuracy of the theoretical calculations might be assessed. [The energy of the symmetrical (D_{8h}) structure of all equivalent bond lengths is calculated to be of such high energy that it is not being considered here although an experimental measurement of the $D_{2d} \rightarrow D_{8h}$ change has been reported.[5]]

An experimental method was devised for setting a lower limit for the energy of the change from the D_{2d} form to the D_{4h} form. While in principle the energy could have been found, in fact the system underwent instead another reaction, which appears to be of a previously unknown type. While some modification of the system could probably have been made so as to give the desired results, an independent measurement of the desired quantity by another group[6] has made it unnecessary to pursue the problem further, and therefore only a lower limit to the energy for the change is reported here.

Instead of studying cyclooctatetraene itself, the system I was examined. This compound contains a (modified) cyclooctatetraene system which appeared to be sufficient for our purposes. This particular system was chosen because an optically active derivative of it was already known.[7] While this molecule has an apparent plane of symmetry in a planar projection, it is really a cyclooctatetraene derivative and should have the three dimensional structure (A), and hence is potentially optically active. If the eight-membered ring becomes planar as in I, any optical activity would be lost. Now (A) contains a derivative of the D_{2d} system of cyclooctatetraene, while the planar form contains a derivative of the D_{4h} system, and therefore measurement of the rate of racemization of an optically active derivative of I as a function of temperature would enable one to calculate the energy of activation (ΔH^*) for the racemization reaction, and the latter is a measure of the desired energy, with some minor complications. The only complication which appears to be of real significance is that caused by the van der Waals' interaction of the two hydrogens shown in the planar form. From the geometry of planar I, most of which can be rather accurately assumed, the distance between these hydrogens (assuming normal bond angles and lengths for the C–H bonds) was determined (see Appendix). Their van der Waals repulsion was calculated by the method of Hill[8] and found to be enormous (over 200 kcal./mole). Obviously the aromatic C–H bond angles would deform to move the hydrogens further apart and hence lower this energy. The energy required for such a deformation was calculated, and the deformation was allowed to proceed until the total energy (van der Waals plus bond deformation) was minimized.[9] The minimum total interaction energy of the hydrogens occurred when they were moved apart by distorting each C–C–H angle 23° from its normal value, and still amounted to 46 kcal./mole. Since this energy is still very large, further smaller effects were taken into account, specifically the bending of the angles in the eight-membered ring and the compression of the C–H bonds. These quantities, together with the angular distortion and van der Waals energies mentioned previously, were all simultaneously adjusted so as to minimize the total energy. The total interaction energy obtained in this way was 20 kcal./mole, and this value is used for subsequent calculations.



I



(A)

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[1] This research was supported by a grant from the National Science Foundation.

[2] O. Bastiansen, L. Hedberg, and K. Hedberg, *J. Chem. Phys.*, **27**, 1311 (1957).

[3] N. L. Allinger, *J. Org. Chem.*, **27**, 443 (1962).

[4] M. A. Miller, unpublished results.

[5] F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 671 (1962).

[6] K. Mislow and H. D. Perlmutter, *ibid.*, **84**, 3591 (1962).

[7] F. Bell, *J. Chem. Soc.*, 1527 (1952).

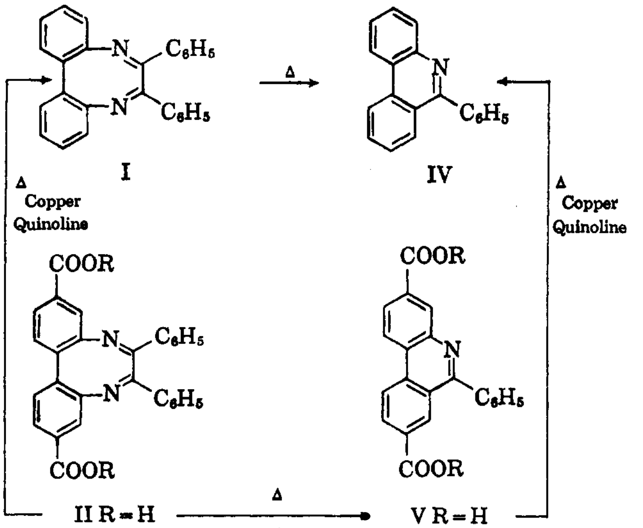
[8] T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

[9] F. H. Westheimer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, New York, N. Y., 1956, p. 523.

This total energy would be included in the experimental ΔH^*; so to find the energy change $D_{2d} \rightarrow D_{4h}$ it is necessary to subtract it from the observed ΔH^*. It was felt that this interaction was desirable from an experimental point of view in that it would raise the value of ΔH^* sufficiently to make the material reasonably stable with respect to racemization. Without this interaction the value of ΔH^* would be lower, and there was no guarantee that such a compound would even be resolvable.

An optically active derivative of I is II, the synthesis of which was reported some years ago.[7] For the present work, (−)-II was obtained with some small modifications of the published procedures. So as to avoid possible intermolecular reactions between the imine linkages and the carboxyl groups, which might present an alternative path for racemization, the ester III was first studied. When (−)-III was heated at 200° in mesitylene solvent for twenty-four hours, no racemization or reaction took place as judged by the lack of change in the optical rotation. At 242° the optical activity was lost at a conveniently measurable rate. The reaction was first order to 50% completion, and the first-order rate constant was found to be 1.56×10^{-6} sec.$^{-1}$.

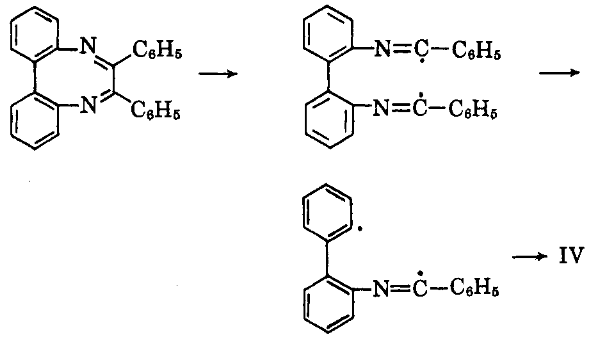
When (−)-III was heated in mesitylene at 278° for seventy-two hours on a preparative scale, an optically inactive compound, which was subsequently shown to be VI, was isolated in good yield. Under the same conditions racemic III also gave VI and in a similar manner II was converted to V. Under the same conditions it was then found that I was converted to IV. The latter is a known compound and the identification was by comparison with an authentic sample.



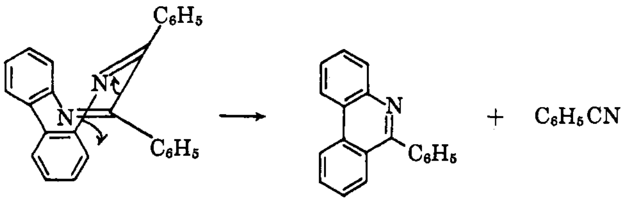
Compound VI was identified by analysis, molecular weight and infrared spectrum, and by hydrolysis to give V, which was also obtained by the thermal decomposition of II. Compound V was identified by analysis, infrared, and by decarboxylation to yield IV. These interconversions are summarized on the flow sheet.

The other product of the thermal fragmentation indicated by the stoichiometry was benzonitrile. This compound proved to be difficult to isolate under the reaction conditions, so a sample of III was placed in a small flask and heated until decomposition set in. A volatile material distilled which was identified as benzonitrile by the superimposability of its infrared spectrum with that of an authentic sample, and by hydrolysis to benzoic acid.

The mechanism of the thermal reaction is of interest, and since the reaction goes at high temperature in a hydrocarbon solvent, and since the rate of reaction is essentially the same in III when powerful electron-withdrawing groups are present, and in I, a reaction lacking in intermediates having a large charge separation is indicated. The reaction can be written as proceeding *via* a radical path.



Evidence that this mechanism is at least a reasonable possibility comes from the fact that biphenyl, benzaldehyde and polymeric material were isolated from the thermal decomposition of the dianil of benzil, as one would predict from a mechanism similar to that shown. This latter reaction occurred at a much slower rate than did the decomposition of I, however, and only traces of benzonitrile could be detected. The mechanism may also be written as a bond switching.



It has been shown that both the photolysis[10] and thermal decomposition[10] of cyclooctatetraene give benzene and acetylene, and the decomposition of I would seem to be a closely analogous reaction.

The thermal elimination reaction defeated the attempt to find the barrier to inversion, since it was shown that when the thermal decomposition of III was allowed to proceed to 50% completion, the starting material and product could be cleanly separated by chromatography. The recovered III was found to have the same optical rotation as the starting material. Since the racemic III is higher melting and less soluble than the pure enantiomer, very little racemic III was present. If the racemic compound were present in the recovered starting material to the extent of 1% or more it would easily have been detectable. The rate constant for the racemization must, therefore, be no larger than 1.56×10^{-8} sec.$^{-1}$ at 242°. From the

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(10) (a) I. Tanaka and M. Okuda, *J. Chem. Phys.*, **22**, 1780 (1954); (b) I. Tanaka, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **75**, 212 (1954).

Eyring equation then, ΔF^* is greater than 48 kcal./mole.

A summary of racemization data for hindered biphenyls[11] shows that these compounds have values of ΔS^* which range from +9 to −21 e.u. The very negative values are obtained when an *ortho* substituent is present which can rotate rather freely in the ground state but very slightly in the transition state. The restriction of the two phenyl substituents is less severe in this case and it would seem safe to say that the value for ΔS^* expected is no more negative than −21 e.u. At the observed temperature this corresponds to a value for $T\Delta S$ of −11 kcal./mole. The value for ΔF^* (greater than 48 kcal./mole), therefore, corresponds to a ΔH^* of greater than 37 kcal./mole.

The energy of the steric interaction between the interfering hydrogens in I, when minimized as previously indicated, amounted to 20 kcal./mole, and when this value was subtracted from the calculated value of ΔH^*, a difference was found which was greater than 17 kcal./mole, and this represents an estimate of a *minimum* value for the energy of the cyclooctatetraene $D_{2d} \rightarrow D_{4h}$ transition.[12] This minimum value is consistent with the other value (27 kcal./mole) reported[6] for the activation energy for this type of change. The theory indicates that this energy should be less than that for the $D_{2d} \rightarrow D_{8h}$ change (14 kcal./mole). The comparison of theory and experiment leaves something to be desired, however, and substantial improvements in the theoretical quantities are also possible. Our future efforts will be limited to improving the theory.

Experimental[13]

6,7-Diphenyldibenzo[*e,g*][1,4]diazocine (I).—This compound was prepared in 80% yield according to a published procedure,[14] yellow plates, m.p. 236–238° (lit.[14] m.p. 236–237°).

2,2′-Dinitro-4,4′-diphenyldicarboxylic Acid.—Twenty grams of 4,4′-diphenyldicarboxylic acid[15] was suspended in 200 ml. of concentrated sulfuric acid and 40 ml. of fuming (90%) nitric acid was added dropwise with stirring. The temperature was not allowed to rise above 60°. After stirring for 4 hr., the mixture was poured onto 2 kg. of crushed ice. The product was filtered and washed with water until the washings were neutral. After trituration with 50 ml. of hot methanol, 20 g. (73%) of a pale yellow powder was obtained, m.p. 341–343° (lit.[16] m.p. 335–337°).

The methyl ester was prepared by the Fischer esterification method and had m.p. 159–161° (lit.[17] m.p. 159–160°).

2,2′-Diamino-4,4′-diphenyldicarboxylic Acid.—The diamine was prepared according to the procedure of F. Bell.[7] The material was used without purification m.p. 306–309° (lit.[7] m.p. 307–309°).

Dibenzo[*e,g*][1,4]diazocine-3,10-dicarboxylic Acid (II).—A mixture of 10 g. of 2,2′-diamino-4,4′-diphenyldicarboxylic acid and 10 g. of benzil in 300 ml. of glacial acetic acid was heated under reflux for 24 hr. After cooling the solution, the resulting product was collected and washed with small portions of pentane. After recrystallization from ethanol, 12 g. (73%) of a pale yellow solid was obtained, m.p. 348–352° (lit.[7] m.p. 348°).[18]

The methyl and ethyl esters were prepared by the Fischer esterification method. The methyl ester (III) formed plates from methyl alcohol, m.p. 177–179°.

Anal. Calcd. for $C_{30}H_{22}N_2O_4$: C, 75.93; H, 4.67; N, 5.91. Found: C, 75.68; H, 4.70; N, 6.04.

The ethyl ester formed plates from ethyl alcohol, m.p. 177–179°.

Anal. Calcd. for $C_{32}H_{26}N_2O_4$: C, 76.47; H, 5.22; N, 5.58. Found: C, 76.54; H, 5.39; N, 5.66.

Resolution of Dibenzo[*e,g*][1,4]diazocine-3,10-dicarboxylic Acid (II).—Diacid II was resolved as the brucine salt as described by F. Bell.[7] From 10 g. of the brucine salt, 2.8 g. (56%) of optically active acid (II) was obtained. After several crystallizations from ethanol–water, yellow needles were obtained, m.p. 223–225°, M^{19}_{D} −1384° (diglyme, *c* 0.530).

Anal. Calcd. for $C_{28}H_{18}N_2O_4$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.03; H, 4.17; N, 6.26.

Fischer esterification of the resolved acid with methanol gave the optically active methyl ester (−III). Crystallization from methyl alcohol afforded plates m.p. 130–135°, M^{20}_{D} −1531° (*c* 0.420).

Anal. Calcd. for $C_{30}H_{22}N_2O_4$: C, 75.93; H, 4.67; N, 5.91. Found: C, 76.07; H, 4.86; N, 5.74.

Kinetics of Thermal Decomposition Methyl (−)-dibenzo[*e,g.*]-[1,4]diazocine-3,10-dicarboxylate, (−)-III.—Small pyrex glass tubes were filled three-quarters full (*ca.* 4 ml.) with a solution of (−)-III in mesitylene (4.2 mg./ml.) and sealed. The samples were placed in a constant temperature furnace at 242° ± 2°. Samples were removed at time intervals (zero time, 5 min. after placing samples in furnace) and the specific rotations were observed. First-order kinetics were observed for the first 50% of the reaction.

TABLE I

KINETIC DATA FOR THE REACTION III ⟶ VI AT 242° IN MESITYLENE SOLVENT

Time, hr.	$-\alpha_{obsd}$
0	6.625
25	5.750
49	5.047
73	4.400
167	2.576

Identification of Products from the Thermal Rearrangement of (−)-III.—A solution of 131 mg. of (−)-III in 20 ml. of mesitylene was sealed in a Pyrex tube and heated at 278° for 72 hr. The solvent was removed *in vacuo*. Chromatography of the residue on 5 g. of neutral alumina using benzene as eluent gave two products. The first product eluted, 60 mg. (69%), was optically inactive and had m.p. 240.5–242.5 and was identified as dimethyl 6-phenylphenanthridine-3,8-dicarboxylate (VI).

Anal. Calcd.: C, 74.38; H, 4.62; N, 3.77; O, 17.23; mol. wt., 371. Found: C, 74.33; H, 4.72; N, 3.80; O, 16.81; mol. wt., 362.

A similar experiment carried out with optically inactive III also gave VI, m.p. 240.5–242.5°, which did not depress when mixed with the product arising from (−)-III. The second product from the chromatography, 20 mg. (15%), proved to be starting material. After recrystallization from benzene it melted at 129–134° and it was not depressed upon admixture with authentic (−)-III. Its molecular rotation was unchanged, M^{20}_{D} −1528° (*c* 0.530). The benzene was evaporated from the filtrate and the rotation of the residue was measured, M^{20}_{D} −1518°. No racemization was detectable.

A further experiment was carried out to isolate the other organic fragment arising from the decomposition of III. In a small distillation apparatus was placed 1.5 g. of (±)-III. The compound when heated above its melting point gave as one product a clear liquid (0.5 g.) which had an infrared spectrum that was superimposable on that of phenylcyanide. Acid hydrolysis of this liquid gave an acid, m.p. 120–122°, after recrystallization from water, and which was undepressed when mixed with authentic benzoic acid.

Rearrangement of 6,7-diphenyldibenzo[*e,g*][1,4]diazocine (I) to 9-Phenylphenanthridine (IV).—A solution of 1.0 g. of I in 20 ml. of mesitylene was sealed in a Pyrex tube and heated at 278° for 7 days. The mesitylene was removed and the residue was crystallized from ethyl alcohol to give 0.5 g. (69%) of 9-phenyl-

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[11] D. M. Hall and M. H. Harris, *J. Chem. Soc.*, 490 (1960).

[12] There are a good many uncertainties which enter into this calculation, some of which are difficult to estimate. Even if all of the errors the authors are able to imagine were to enter into the calculation in the same direction, it seems unlikely that the actual enthalpy for the inversion of 1,4-diazacyclooctatetraene could be less than 10 kcal./mole.

[13] All melting points are uncorrected.

[14] N. L. Allinger and G. A. Youngdale, *J. Org. Chem.*, **24**, 306 (1959).

[15] The authors are indebted to the Dow Chemical Company for furnishing a supply of this compound.

[16] Z. v. Jakubowski and St. v. Niemtowski, *Ber.*, **42**, 634 (1909).

[17] F. Ullmann and J. Bielecki, *ibid.*, **34**, 2174 (1901).

[18] This compound also was prepared by the method described by F. Bell, see ref. 7. Mixture melting point showed no depression.

phenanthridine, m.p. 103–104°. A mixture melting point with authentic material prepared as described[19] showed m.p. 103–105°. The infrared spectra of the two compounds were superimposable.

Decarboxylation of II to Give I.—A mixture of 1 g. of II and 1 g. of copper powder in 25 ml. of quinoline was heated under reflux for 3 hr. The mixture was filtered, 50 ml. of chloroform was added, and the organic phase was washed in turn with *N* hydrochloric acid and water. The organic phase was dried and the solvent was removed. The yellow solid was recrystallized from acetic acid to give 0.6 g. (75%) of I, m.p. 235–238°. A mixture melting point with I showed no depression.

Thermal Rearrangement of II.—When II was heated in mesitylene at 278° for 5 days an acid (V) which did not melt below 360° was obtained. The infrared spectrum of this acid was identical with that of the acid obtained by hydrolysis of VI.

Anal. Calcd. for $C_{21}H_{13}NO_4$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.09; H, 3.78; N, 3.98.

Decarboxylation of V to IV.—The acid V, 60 mg., and 100 mg. of copper powder in 2 ml. of quinoline were refluxed 3 hr. After filtration the quinoline was removed by heating *in vacuo* and the residue was recrystallized from ethanol to give 10 mg., of solid, m.p. 103–106°. The melting point was undepressed when mixed with authentic 9-phenylphenanthridine.[19]

Preparation and Thermal Rearrangement of Benzil Dianil.—A mixture of 4.2 g. of benzil, 4 g. of aniline, 0.5 g. of *p*-toluenesulfonic acid, and 60 ml. of toluene was heated under reflux for 2 days. The water which was formed from the reaction was removed with a water separator.

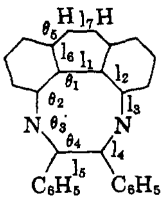
The cooled solution was filtered to remove the *p*-toluenesulfonic acid, and the solvent was removed *in vacuo*. The residues were recrystallized twice from an ether–pentane mixture, 5 g. (69%), m.p. 140–142° (lit.[20] m.p. 141–142°).

A solution of 100 mg. of benzil dianil in 20 ml. of mesitylene was heated in a sealed tube at 280° for 24 hr. Upon evaporation of the mesitylene only starting material (90 mg.) was isolated, m.p. 139–142°. A solution of 1 g. of benzil dianil and 20 ml. of benzene was heated in a sealed tube at 278° for 8 days. After the benzene was removed the residues were chromatographed on acid-washed alumina. The first product eluted with pentane was biphenyl (100 mg.), m.p. 68–76°, which was undepressed when mixed with an authentic sample. The second fraction contained about 50 mg. of benzaldehyde, characterized as its 2,4-dinitrophenylhydrazone, m.p. 236–237°. The third fraction (300 mg.), m.p. 139–142°, was eluted with a 50–50 pentane–ether mixture and was shown to be starting material by a mixture melting point determination. The largest fraction of material (500 mg.) was eluted with ether and appeared to be a noncrystalline polymer containing some starting material. The last product (about 5 mg.) was obtained by elution with methanol and was a deep purple water-soluble substance which was not characterized.

It was noted that, when the pure benzil dianil was heated above 400° in a small glass tube, traces of benzonitrile could be detected from the infrared spectrum of the distillate and by odor.

Appendix

For the energy calculation, the initial geometry of the molecule in the planar form was assumed using normal bond lengths[21] and these minimally deformed angles.



l_1 1.520 Å.	θ_1 134°
l_2 1.390 Å.	θ_2 136°
l_3 1.475 Å.	θ_3 134°
l_4 1.350 Å.	θ_4 137°
l_5 1.450 Å	θ_5 120°
l_6 1.09 Å	
l_7 0.70 Å	

The stretching and bending constants used are those given by Westheimer[9] for the aromatic hydrogen and for ethylene. The ethylene bending constant was used in this calculation for all angles not involving the aromatic hydrogen. The energy of the system was minimized with respect to θ_1, θ_2, θ_3, θ_4, θ_5, l_6, and l_7, simultaneously and in the minimum energy form these quantities had the values: $\theta_1 = 129°$, $\theta_2 = 138°$, $\theta_3 = 141°$, $\theta_4 = 132°$, $\theta_5 = 111°$, $l_6 = 1.04$ Å., and $l_7 = 1.53$ Å.

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[19] A. Pictet and A. Hubert, *Ber.*, **29**, 1182 (1896).

[20] M. Siegfeld *Ber.* **25**, 2600 (1892).

[21] Tables of interatomic distances and configurations in molecules and ions, special publication no. 11, the Chemical Society, London (1958).

The Rearrangement of 2-Amino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxides with Acetic Anhydride

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2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I) gave 2-acetamido-3-acetoxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (II), 10-acetyl-7-chloro-2-methyl-5-phenyl-10*H*-oxazolo[4,5-*b*]-1,4-benzodiazepine (V), and 2-acetamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-3-one (VI) upon treatment with acetic anhydride under varying conditions. The structures of the products were established by chemical and spectroscopic evidence. The 2-methylamino analog of I also was studied.

The rearrangement of 1,3-dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-one 4-oxides[1] with acid anhydrides resulting in 3-acyloxy-1,3-dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-ones recently has been reported from this laboratory.[2] In a similar manner, 2-amino-5-aryl-3*H*-1,4-benzodiazepine 4-oxides[3] have undergone rearrangements upon treatment with acid anhydrides. In some instances, however, several other products were isolated, the relative amounts often depending upon the conditions of the reactions.

The reaction of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I) with acetic anhydride gave three rearranged products (II, V, VI). 2-Acetamido-3-acetoxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (II), the expected compound, was hydrolyzed

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[1] (a) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961); (b) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).

[2] S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962).

[3] (a) L. H. Sternbach, U. S. Patent 2,893,992 (1959); (b) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961); and (c) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).