[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

Stability of Di- and Trimethyl-1,5-benzodiazepines and their Salts

BY J. O. HALFORD AND ROBERT M. FITCH

RECEIVED SEPTEMBER 11, 1962

Introduction of a third methyl group at the 3-position of 2,4-dimethyl-1,5-benzodiazepine slightly destabilizes the base and causes somewhat greater destabilization of the monohydrochloride. In the 1-position the third methyl group completely destabilizes the base and severely destabilizes the salt. From these effects, which appear to reflect energetically small steric strains, it follows that the apparently stable dimethylbenzodiazepine and its monohydrochloride have minimal competitive stability. The cation, however, is stabilized by 55–60 kcal./mole of delocalization energy, an amount comparable to the assignable resonance energy of naphthalene or quinoline.

Colorless 2,4-dimethyl-1,5-benzodiazepine and its deep purple, almost black, monohydrochloride were originally synthesized by Thiele and Steimmig[1] by rapid precipitation reactions at room temperature from *o*-phenylenediamine and acetylacetone. Both base and salt are stable in moist air and in moderately strong acidic or basic solutions at ordinary temperatures. Warming with acid, however, effects decomposition to 2-methylbenzimidazole and acetone. Gaseous HCl converts the monohydrochloride to a colorless dihydrochloride which readily drops the second HCl in aqueous solution or in the solid state.

In contrast to the behavior of 2,4-dimethyl-1,5-benzodiazepine, the usual experience has been that azepines and diazepines resist synthesis and appear to be unstable structures. We find, however, that a third methyl group at position 1 or 3 causes moderate to severe steric destabilization of the base and salt.

After verifying the results of Thiele and Steimmig, Vaisman[2] synthesized 2,3,4-trimethyl-1,5-benzodiazepine from *o*-phenylenediamine and methylacetylacetone (3-methylpentane-2,4-dione). His attempt to synthesize a tetramethyl derivative from the diamine and dimethylacetylacetone produced a yellow base which formed a red hydrochloride but was not a benzodiazepine. Barltrop, Richards, Russell, and Ryback[3] have reported the synthesis of a series of 1,5-benzodiazepines and related derivatives of 3,6-diaza-4,5-benzotropone.

We have verified prior reports on the 2,4-dimethyl- and 2,3,4-trimethyl-1,5-benzodiazepines and on the attempted synthesis of 2,3,3,4-tetramethyl-1,5-benzodiazepine. The yield of crude 2,3,4-trimethyl-1,5-benzodiazepine is lower (65%) under comparable conditions than that of 2,4-dimethyl-1,5-benzodiazepine (83%) and the crude trimethyl derivative contains substantial amounts of 2-methylbenzimidazole. We have carried out the expected hydrolytic decomposition of the trimethyl derivative to 2-methylbenzimidazole and methyl ethyl ketone. Under the same conditions Vaisman's yellow base and red salt do not decompose.

Conductometric titration yields accurate consistent equivalent weights for the diazepine bases and an equivalent weight of 274 for Vaisman's yellow base. Base strength constants, obtained with the glass electrode in approximately 0.02 molal aqueous solution, are 3.1×10^{-7} for 2,3,4-trimethyl-1,5-benzodiazepine and 1.1×10^{-8} for 2,4-dimethyl-1,5-benzodiazepine. With the hydrogen electrode, at higher concentration, Schwarzenbach and Lutz[4] measured $K_B = 10^{-9.5}$ for the latter compound.

(1) J. Thiele and G. Steimmig, *Ber.*, **40**, 955 (1907).

(2) S. Vaisman, *Trudy Inst. Khim. Kharikov. Gosudarst. Univ.*, **5**, 57 (1940).

(3) J. A. Barltrop, C. G. Richards, D. M. Russell, and G. Ryback, *J. Chem. Soc.*, 1132 (1959).

(4) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1147 (1940).

The original structure assignment by Thiele and Steimmig was strongly indicated by the visible color of the cation and is fully supported by the ultraviolet and infrared spectra. The lack of selective ultraviolet absorption by the diazepine bases is inconsistent with alternative structures. The benzodiazepine cation, but not the free base, shows an NH stretching frequency in the infrared.

Benzimidazolines have not appeared as intermediates or end products. The fragmentation observed in some preparations and in the hydrolytic decomposition to a benzimidazole and a ketone indicates that the 3-acylbenzimidazoline structure is unstable.

The monodeuteriochloride obtained by rapid precipitation from a benzene solution of the 2,4-dimethyl base by gaseous DCl shows both the NH and ND frequencies but not the CD frequency. It is possible under these conditions that individual cation units have deuterium on one nitrogen and protium (ordinary hydrogen) on the other.

A scale model of the 2,3,3,4-tetramethyl-1,5-benzodiazepine which Vaisman failed to obtain shows penetration of one of the 3-methyl groups into the benzene π-orbital region. The resultant strain is evidently not relieved by the assumption of a more nearly planar conformation. If the failure of the tetramethylbenzodiazepine to appear is due to the energetic rather than the kinetic factor, it follows that the energy required to strain the diazepine ring into the planar conformation is considerable, probably 5 kcal./mole or more. Since this strain should be offset by increased interaction of the CN bonds with the ring, the net strain without interaction, pertinent to a later discussion, would be larger, probably of the order 10 kcal./mole.

It is likely that a monoanil is first formed and subsequently removed by one of two cyclizations, to the benzimidazole or to the benzodiazepine. If the ratio of specific rates of the two ring closures is not sensitive to the level of methyl substitution, the relative amounts of benzimidazole and benzodiazepine formed could still be sensitive to the thermodynamic factors controlling the equilibrium concentrations of diazepine, diazepine salt, and the monoanil precursor.

This equilibrium hypothesis suggests possible improvement of the chance of obtaining the missing 2,3,-3,4-tetramethyl base by displacement of the equilibrium toward the diazepine base or salt by removing water as it forms. Therefore, with benzene substituted as solvent, we have pumped out water during the reaction. This procedure, tried out with 2,3,4-trimethyl-1,5-benzodiazepine, increases the yield of crude product from 65 to 85%, a result which supports the equilibrium hypothesis. As might be expected, however, from the estimated strain energy, the revised procedure still fails to produce the missing tetramethyl base.

The correct choice between the tautomeric 1H and 3H structures for the base and cations has been evi-

dent from the outset[1] and has received subsequent experimental support.[3,4] The base and dication are taken to have minimally strained nonplanar 3H dianil forms while a planar resonance-stabilized 1H structure can be assigned to the singly charged cation. Vaisman's projected but apparently unstable tetramethyl base would have to be a dianil which could not be protonated to a 1H cation. With the pertinent atomic p-orbital axes in the bases inclined at more than 60° in parallel planes, styrene-like interaction with the benzene ring should be small and is probably negligible.

Strong selective absorption by the cation in the visible and ultraviolet suggests a delocalized orbital system which implies a planar conformation for the entire bicyclic skeleton. In order to stabilize this conformation, the delocalization energy, relative to a hypothetical planar cation with localized double bonds in both rings, should be large enough to compensate for tautomerization and strain terms, and will include the benzene resonance energy for a total above 50 kcal./mole.

We have extended the series of methylated 1,5-benzodiazepines to include the cation of the 1,2,4-trimethyl-1,5-benzodiazepine, obtained in two steps from acetylacetone and N-methyl-*o*-phenylenediamine. Reaction under the conditions used by Thiele and Steimmig produces the intermediate anil, 4-N-(*o*-methylaminophenyl)-iminopentanone-2, contaminated with 1,2-dimethylbenzimidazole, but yields no diazepine salt. Attempted cyclization of the monoanil in hydroxylic solvents produces transitory color suggesting cyclization, but results in practically complete conversion to 1,2-dimethylbenzimidazole. The cyclization occurs, however, at lower temperatures in benzene with HCl present, and with simultaneous removal of water under reduced pressure. The crude diazepine salt, the residue after evaporation of the solvent under reduced pressure, eludes direct purification by recrystallization or sublimation.

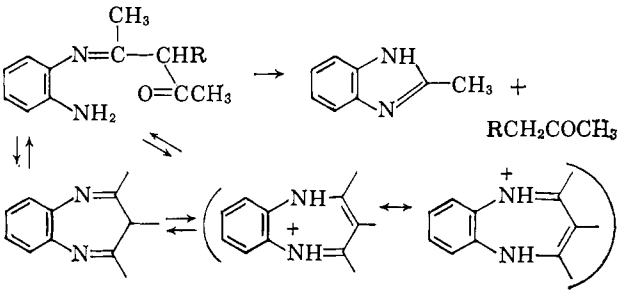
In the other cases, purified salt was obtained by precipitating the base and reconverting to the hydrochloride. Here, the base, which would have to assume the less stable 1H enamine form, is not obtained. Instead, the attempt to precipitate a diazepine base from the crude salt yields a mixture of the monoanil precursor and 1,2-dimethylbenzimidazole.

The mean equivalent weight of the crude salt, by conductometric titration in water, is 234. If the only impurity is uncyclized monoanil salt, this indicates 30 to 40% cyclization. The ultraviolet absorption, however, after adjustment of intensities, is almost identical, in alcohol, with that of the 2,3,4-trimethyl-1,5-benzodiazepine hydrochloride, indicating much more nearly complete cyclization. Both the visible absorption and the main double ultraviolet maximum at 263, 269 mμ show clearly the presence of a high relative concentration of a benzodiazepine salt.

A secondary maximum appears in the trimethylbenzodiazepine salt spectra at 237 mμ, but is less intense and lies at a lower wave length (<228) in the dimethyl case. The absorption curve for the cations has an interesting similarity to the azulene spectrum.

For analytical purposes, since the hydrochloride eluded purification, the bis-3,5-dinitrobenzoate was prepared. A slightly low carbon percentage indicates that the analytical sample may have contained as much as 20% of a bis-dinitrobenzoate of 1,2-dimethylbenzimidazole.

From the isolation of the intermediate monoanil in the 1,2,4-trimethyl-1,5-benzodiazepine salt synthesis, and the sensitivity of the yields of 1,2,4-trimethyl- and 2,3,4-trimethyl-1,5-benzodiazepine salts to the removal of water during the cyclization, the following reaction scheme appears to be valid for the 2,4-dimethyl and 2,3,4-trimethyl cases



It appears, however, that the formation of 1,2-dimethylbenzimidazole from N-methyl-*o*-phenylenediamine and acetylacetone proceeds through the benzodiazepine salt with subsequent ring opening at the NH site to give a transitory isomeric monoanil in the enamine form which then cyclizes to the benzimidazole. This reaction route is indicated by the formation of a transitory color, presumably the benzodiazepine cation, in the conversion of the monoanil to 1,2-dimethylbenzimidazole by alcoholic HCl at room temperature.

In each case studied the seven-ring cyclization appears to be intrinsically more rapid than the competing cyclization to a benzimidazole. Equilibrium between the monoanil and the base–salt combination of the diazepine is rapidly established and is readily displaced toward the diazepine by the removal of water. In the preparation of 2,4-dimethyl-1,5-benzodiazepine, the lack of appreciable contamination by 2-methylbenzimidazole can be taken as evidence of a low equilibrium concentration of the monoanil which slows down the five ring cyclization. The monoanil concentration and the amount of 2-methylbenzimidazole formed are higher in the case of 2,3,4-trimethyl-1,5-benzodiazepine.

In the 1,2,4-trimethyl-1,5-benzodiazepine formation the equilibrium concentration of monoanil is high and the direct formation of 1,2-dimethylbenzimidazole has been largely eliminated by a retarding effect of the N-methyl group. Cyclization to the benzodiazepine salt may also have been retarded, but it is still quite rapid under benzene when water is simultaneously removed. Consequently the main product from N-methyl-*o*-phenylenediamine and acetylacetone is the monoanil.

Steric destabilization results from placing three methyl groups on successive carbon atoms in the 2,3,4-trimethyl derivatives. The effect is smallest and could be negligible in the monoanil intermediate, it should be larger in the nonplanar benzodiazepine base, and will be most pronounced in the planar cation where the distance of closest approach of hydrogens on adjacent methyl groups is near 1.2 Å. The base strength constants of the 2,4-dimethyl and 2,3,4-trimethyl bases indicate that the third methyl group has destabilized the cation more than the base by about 2 kcal./mole. This follows from the relation $\Delta F^\circ = -RT \ln K$, which shows the high sensitivity of K to small energy changes. Colorless 2,4-dimethyl-1,5-benzodiazepine is quite stable in air, but the 2,3,4-trimethyl base is obtained colorless only in the absence of oxygen and rapidly acquires a yellow color when exposed to air. This difference could be due to a decrease in activation energy of the reaction with oxygen produced by a small steric destabilization caused by the third methyl group. The relatively small decrease in the initial yield of the base indicates that the destabilization on the energy scale is quite small.

Crowding by the N-methyl group is more serious because of the greater proximity of hydrogens occasioned by the shorter CN bonds and the inability of the rigidly fixed benzene hydrogen to participate in a strain-relieving cooperative internal rotation. The resulting destabilization has made the 1,2,4-trimethyl-1,5-benzodiazepine salt difficult to isolate and characterize.

The greater destabilization of the missing 2,3,3,4-tetramethyl-1,5-benzodiazepine has already been discussed.

It is inferred that, barring the intervention of new factors, the parent compound, 1,5-benzodiazepine, should be stable. An attempted synthesis from *o*-phenylenediamine and malonaldehyde diacetal in water or water–alcohol solutions, however, resulted only in polymeric products. If the acetal was hydrolyzed before the introduction of the diamine, colors suggesting diazepine salt formation were produced, but neither a diazepine base nor salt was successfully identified or isolated.

Strain effects introduced with the third methyl group have produced moderate to severe decreases in competitive stability. Since the strains in energy units should not be large, it can be inferred that the apparently stable 2,4-dimethyl-1,5-benzodiazepine and its salts cannot have much more than the minimum thermodynamic stability required to account for their observed properties.

Low competitive stability argues against classification of any of the 1,5-benzodiazepines or their salts as aromatic. Such classification of the salts, however, is not inconsistent with the ultraviolet and visible absorption or with the delocalization energy, which is comparable with that of naphthalene or quinoline and exceeds by a wide margin the value (28) estimated by Turner, *et al.*,[5] for azulene.

Resonance Stabilization of the Cation.—It is feasible to make a more accurate evaluation of the resonance energy of the 1,5-benzodiazepine cations relative to hypothetical planar cations with localized double bonds in both rings. Except for the omission for obvious practical reasons of correction for the compression effect, the resonance energy so defined is a true delocalization energy.

The energies of the actual and reference cations, respectively, are evaluated relative to the base, and the derived resonance energy is obtained by difference. From the measured base strength of the 2,4-dimethyl-1,5-benzodiazepine, $K_B = 1.1 \times 10^{-8}$, the heat of protonation to the real cation is $\Delta H = -8.2 + T\Delta S_1$ kcal./mole. The base is tautomerized to the 1H form, protonated to a hypothetical nonplanar cation, then strained into the planar conformation of the defined reference cation.

Bond energies from the Pauling table as given by Branch and Calvin[6] are used to obtain the tautomerization energy, 7.6 kcal./mole. For the protonation step we first note a measurement by Freeman[7] of the relative strength in acetonitrile of aniline and the stilbene-like benzylidene-aniline. Transfer of the relative strength unchanged to the water scale yields a base strength constant of 10^{-12} for the anil. We would guess that the base strength of our hypothetical diazepine with its isolated imino linkage would not be significantly different, but we have sought independent confirmation.

For this purpose an estimate of the free energy of further protonation of the cation to the dication is made. The dihydrochloride is formed under HCl at one atmosphere and is readily hydrolyzed to the monohydrochloride in moderately acidic solutions. Known activities of aqueous HCl together with reasonable assumptions about the extent of protonation in each limiting situation indicate that the standard free energy of the second protonation should not be significantly different from 2.0 kcal. The free energy of double protonation of the nonplanar 3H base to the presumably nonplanar 3H dication becomes −6.2 kcal. With the anil linkages assumed to be isolated, the free energy of the first hypothetical step to a nonplanar 3H singly charged cation should be $-(3.1 + RT \ln 2)$ kcal./mole. For the hypothetical 1H tautomer with a single isolated anil linkage, the corresponding figure is −3.1, indicating a base strength constant of 2×10^{-12} and giving $\Delta H = -3.1 + T\Delta S_2$.

A check on the elusive strain energy required for planarity, already estimated at about 10 kcal./mole, can be obtained by assigning relative values to the pertinent force constants for angle distortion. Frequencies chosen[8] for rocking motions indicate that the force constants for HCC angle distortion are nearly the same in ethane and ethylene. A like equality is assumed for CCC, CCN, and CNC angles, making the strain in the first approximation dependent only upon deviations from normal valence angles. The dependence of strain upon angle is based upon a value for cyclobutane presented by Branch and Calvin,[9] 4.0 kcal./mole per CH_2 group. Of the total 70° angular deviation in the diazepine ring, one-twelfth is assigned to each of the bridgehead angles and one-sixth to each of the remaining five angles. With the limiting assumption of harmonic forces, the total strain energy is estimated to be 2.15 times the value per corner in cyclobutane, or 8.6 kcal./mole, in good agreement with the earlier estimate of 10. Increases could be proposed because of anharmonicity or different separation of hydrogens on adjacent atoms in the compounds involved, but an error in the assumption of equality of force constants would be likely to call for a decrease, as would also the presence of nitrogen atoms in the ring. Since a result which included adjustment for such factors in a necessarily dubious manner would be no more clearly defensible than the uncorrected preliminary one, the value 8.6 is used in the resonance energy summation.

For the defined planar reference state with localized double bonds in both rings, the energy relative to the real base is taken to be the sum of the benzene value, 36 kcal./mole, and the increments estimated for tautomerization protonation, and strain, a total of $49.1 + T\Delta S_2$ kcal./mole. The real cation differs from the base by $-8.2 + T\Delta S_1$, which is subtracted to give the defined resonance energy of the real cation. If the entropies of the two similar protonations on endocyclic nitrogens are taken to be nearly equal, the entropy effects cancel and the net estimated resonance energy of the cation is 57.3 kcal./mole.

There is no evident reliable basis for a quantitative evaluation of the uncertainty. Substitution of the Schwarzenbach–Lutz base strength would produce a decrease of 1.0 kcal., and the strain energy might be in error by ±2.0 kcal. Inclusion of an increase of perhaps 2.0 kcal. because of possible styrene-like interaction in the base might be justified, and correction of the base strength of the hypothetical monoanil for

(5) R. B. Turner, *et al.*, *J. Am. Chem. Soc.*, **79**, 4127 (1957).

(6) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1941, p. 289.

(7) S. K. Freeman, *Anal. Chem.*, **25**, 1750 (1953).

(8) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1945, pp. 107, 346 ff.

(9) Reference 6, p. 279.

neglected electrostatic repulsion in the dication could cause a decrease of about 2.0 kcal. Although these suggested adjustments delimit a range of nearly 10 kcal., it is unlikely that the uncorrected result is in error by more than 3.0 kcal./mole.

It is evident that the Hückel $2 + 4n$ rule, derived for simple monocyclic alternant polyenes, is not in general defensibly applicable to bicyclic structures with heteroatoms. Nevertheless, we can look for indications that our 12-electron structure might show signs of a corresponding $4n$ destabilization. The related 11-orbital, 12-electron carbocyclic system would be particularly vulnerable to this kind of destabilization because the highest occupied orbital is in the antibonding region in the monocyclic case. The bicyclic system should be more stable but an opposed destabilizing effect could be expected from the nitrogen atoms.

On the CCβ scale, the calculated stabilization is about 0.30 per electron, as compared with 0.33 for benzene, 0.37 for naphthalene, 0.30 calculated for a planar cyclodecapentaene, and 0.24 for the hypothetical planar $4n$ electron structure cyclododecahexaene. There is in these numbers no indication of the inheritance by the diazepine cation of any instability derived from the factors responsible for the $2 + 4n$ generalization.

There is evidently, on the empirical experience basis, a $2 + 4n$ effect of broad scope which is not readily traced to the causes behind the Hückel rule. By experience, stable $4n$ compounds are extremely rare. In general, $4n$ compounds will have unfavorable ring sizes which, as in the 1,5-benzodiazepines, may leave them vulnerable to competition from less strained alternative structures and decomposition products.

The significant accuracy of a delocalization energy computed by the simple MO method for a 12-electron bicyclic heterocycle is seriously open to question. The inherent uncertainty of the variation method, the effect of the cationic charge, and the question of choice of coulombic and exchange constants for the heteroatoms tend to undermine confidence in the calculated result. Nevertheless the result of an attempted evaluation by the LCAO–MO method is interesting enough for inclusion here.

Computations are first made for two extreme limits. At one limit the carbon coulombic and exchange energies are applied to nitrogen without correction; at the other the CN exchange constant is set equal to zero. In the latter limit the calculated resonance energy is independent of the nitrogen coulombic value. The results are, respectively, 4.22 and 2.83β (CCβ), delimiting a range within which a defensibly accurate value should lie. Since the extreme situations are physically unreal, it is reasonable to expect that the significant answer lies within the inner half of the range, at $3.53 \pm 0.35\beta$. If this arbitrary limitation of range is accepted, the result is about as close to significant accuracy as can be expected by available methods.

A useful check on this result, which suggests a slightly lower value within narrower limits, has been obtained in the following manner. With the coulombic term uncorrected, a new CN exchange constant is introduced. This device, which is equivalent to multiplicative correction of both constants in a fixed ratio, cannot give accurate individual levels, but should yield an acceptable resonance energy. A new CN constant between 0.5 and 0.7β yields resonance energies for pyrrole between 20 and 30 kcal./mole. For the benzodiazepine cation, the same range of constants gives $3.41 \pm 0.18\beta$ for the resonance energy. With a constant which holds pyridine between 30 and 36 kcal./mole, the indicated result for the benzodiazepine cation is $3.60 \pm 0.35\beta$.

A rounded value of 3.5β, in conjunction with the resonance energy of 57.3 kcal./mole estimated from the base strength and other constants, gives 16.4 for β, which is close to the exchange constant derivable from more recent estimates for naphthalene.[10]

Estimates by the more complex valence bond method, although not yet in completely supportable form, point toward a result close to the values obtained by the other methods.

Experimental

2,4-Dimethyl-1,5-benzodiazepine monohydrochloride, prepared as described by Thiele and Steimmig (83% yield), was purified by vacuum sublimation, m.p. 204–206°. The free base, by vacuum sublimation at 71° (47 μ), melted at 129–130° (Thiele and Steimmig, 131–132°); equivalent weight, conductometric, aqueous solution, 171.7 ± 0.6; calcd. 172.2; base constant, glass electrode, aqueous solution, 1.1×10^{-8}.

2,3,4-Trimethyl-1,5-benzodiazepine.—Vaisman's preparation, following Thiele and Steimmig, gave a 65% yield of crude product contaminated with 2-methylbenzimidazole. Fitch[11] used a procedure which improved yield and purity and demonstrated reversibility of the cyclization. *o*-Phenylenediamine hydrochloride reacted with methylacetylacetone in benzene under reflux with removal of water vapor by suction; yield, crude product, 85%. The hydrochloride, after resublimation, melted at 214°; equiv. wt. 220.3 ± 0.4, calcd. 222.7.

The crude yellow base was converted by sublimation under reduced nitrogen pressure to colorless prisms, which turned yellow upon exposure to air; base strength constant, 3.1×10^{-7}.

2,3,3,4-Tetramethyl-1,5-benzodiazepine (Attempted Synthesis).—Nine attempts were made to synthesize this compound or its hydrochloride under a variety of conditions from *o*-phenylenediamine and 3,3-dimethylpentanedione-2,4. Reaction was always incomplete and the mixtures produced contained 2-methylbenzimidazole. In some cases a small amount of a yellow base convertible to a red hydrochloride and a dihydrochloride, evidently Vaisman's product, was obtained. This was definitely not a benzodiazepine. A rough material balance on one attempt revealed evolution of 2 moles of water for each mole of either starting material used up in the reaction. The bright yellow base did not give a readily interpreted analysis, but had an equivalent weight about 274, and a molecular weight below 700. A likely composition is $C_{17}H_{20}N_4$.

4N-(*o*-Methylaminophenyl)-iminopentanone-2.—To 6.5 g. of N-methyl-*o*-phenylenediamine dissolved in a solution of 8 ml. of acetic acid in 25 ml. of alcohol was added dropwise, with vigorous stirring, at 0°, 5.33 g. of acetylacetone. The solution turned a deep orange-red, and a pale green product soon precipitated as fine needles which were filtered off and washed rapidly with cold alcohol. The product sublimed without losing its color at 70° (40 μ).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.58; H, 7.90; N, 13.76; equiv. wt., 204.2. Found: C, 70.47; H, 7.84; N, 14.33; equiv. wt. (conductometric), 202.5.

When 4N-(*o*-methylaminophenyl)-iminopentanone-2 was treated with acid in alcohol or other hydroxylic media, color changes were observed which indicated transitory formation of a benzodiazepine salt. The salt, however, was not successfully obtained from such solutions, even at temperatures as low as −80°. It therefore appears that 1,2,4-trimethyl-1,5-benzodiazepine salts are much less stable than the corresponding salts of 2,4-dimethyl-1,5-benzodiazepine which are reasonably stable in alcohol or aqueous solutions.

Introduction of dry HCl gas, at 0°, into a solution of 4N-(*o*-methylaminophenyl)-iminopentanone-2 in dry benzene produced a colorless precipitated salt which slowly assumed a red color. The reaction flask was quickly evacuated with the water aspirator and was evaporated to dryness *in vacuo* with gentle heating to leave a pale red residue. This residue, dissolved in absolute alcohol, gave an ultraviolet absorption closely similar to that of 2,3,4-trimethyl-1,5-benzodiazepine hydrochloride, indicating the presence of a high concentration of 1,2,4-trimethyl-1,5-benzodiazepine hydrochloride. The equivalent weight, however, was high: found 234, calcd. for $C_{12}H_{14}N_2 \cdot HCl$ 223.

Analytical evidence was obtained for the 1,2,4-trimethyl-1,5-benzodiazepine structure in the form of a bis-3,5-dinitrobenzoate.

1,2,4-Trimethyl-1,5-benzodiazepine Bis-3,5-dinitrobenzoate.—A solution of 13.1 g. 3,5-dinitrobenzoic acid in anhydrous alcohol,

(10) Reference 5, pp. 4131–4132.

(11) R. M. Fitch, *Dissertation Abstr.*, **15**, 499 (1955); *Chem. Abstr.*, **49**, 9663 (1955).

made up to be slightly supersaturated at room temperature, was cooled to 0°, and before crystallization could occur, 4.2 g. of finely powdered 4-N-(*o*-methylaminophenyl)-iminopentanone-2 was rapidly added. An immediate deep red-orange coloration followed, and in a few minutes a salt crystallized out, which was filtered off after the addition of an equal volume of dry benzene; yield, 5.8 g. Attempts to purify this orange-colored product by crystallization or sublimation resulted in decomposition. The material was washed with dry benzene, dried for 5 hr. at 106° (0.1 mm.) and analyzed.

Anal. Calcd. for $C_{26}H_{22}N_6O_{12}$: C, 51.15; H, 3.63; N, 13.77. Found: C, 50.52; H, 3.60; N, 13.99.

[CONTRIBUTION FROM THE RESEARCH DIVISION OF PHILLIPS PETROLEUM CO., BARTLESVILLE, OKLA.]

Relative Reactivities of Positions on Biphenyl in the Generation of Reactive Species by Electron Irradiation and in Subsequent Ring Substitution

BY W. M. HUTCHINSON, P. S. HUDSON, AND R. C. DOSS

RECEIVED NOVEMBER 19, 1962

A model is proposed to separate the relative reactivities of the three different positions on biphenyl in the generation of reactive species by ionizing radiation and the relative reactivities of the same positions on biphenyl in its substitution by the reactive species. The method depends on quantitative analysis of the six isomeric quaterphenyl products. Relative yields of these products from irradiation of biphenyl with electrons at 80 and 300° have been obtained and used to check the model. The model fits the experimental data well. Results indicate that the net production of reactive species is not random; that most reactive species are free radicals but that some species more *para*- and less *ortho*-selective than free radicals are also formed; and that there is considerable hindrance to *ortho*-substitution at 300°

Introduction

Quantitative analyses have been made of the six isomeric quaterphenyls produced from biphenyl by ionizing radiation. The relative yields of the isomers are related here to the relative reactivities or partial rate factors of biphenyl both in the generation of reactive species by radiation and in substitution of biphenyl molecules by these species. To our knowledge, partial rate factors for the generation of reactive species by ionizing radiation have not been reported. These factors or reactivities should allude to the nature of the radiative generation processes. The partial rate factors for substitution of the molecule by reactive species are obtained simultaneously. These will be averages for substitution of biphenyl by its free radicals, ion-molecules, excited molecules, etc. Deviation of the averages from partial rate factors obtained with free radicals alone will depend on the frequency with which other reactive species occur and on their selectivity. The partial rate factors of biphenyl in its substitution by the three isomeric biphenylyl free radicals were obtained by irradiation with ultraviolet light of dilute solutions of the respective iodobiphenyls in biphenyl.

The relative reactivities or partial rate factors of the three different positions on biphenyl to substitution by free radicals such as phenyl have been extensively investigated.[1] Substitution of the benzene ring by a free phenyl radical appears to proceed through an intermediate containing a tetrahedral carbon attached to its original hydrogen atom and to the entering group.[2] This intermediate, although it may be classed as a radical, does not appear active enough to substitute a benzene ring because no terphenyls are produced from benzene and phenyl free radicals. The main reaction of the intermediate is disproportionation into biphenyl and dihydrobiphenyl. The intermediate appears to a lesser extent to dimerize to form tetrahydroquaterphenyl. 1,1′,4,4′-Tetrahydro-4,4′-diphenylbiphenyl and 1,4-dihydrobiphenyl have been isolated from the products of a reaction between benzene and benzoyl peroxide from which air was excluded.[3] In the disproportionation reaction, deuterium appeared to be removed less readily than hydrogen from the tetrahedral carbon.[4] Orientation (*ortho*, *meta*, and *para*) of the entering group might similarly affect which intermediates were reduced and which were aromatized in the disproportionation reactions. This raised doubt[4] that the isomer ratios of only the aromatic products represented the relative frequencies (partial rate factors) with which the initial additions occurred at the various positions on the aromatic ring. Indeed the use of isomer ratios for this purpose has been questioned.[5] The yield of biphenyl (distinguished from dihydrobiphenyl) was increased by the presence of molecular oxygen.[6] Dimerization of the intermediate was inhibited by cupric ions.[7] The distribution of aromatic products from substitution of various aromatics by free radicals were found to be unaffected by the presence of oxygen.[8] These authors[8] were of the opinion that the entering aryl group would not affect the course of the disproportionation reactions and that the relative yields of isomeric aromatic products reflected the frequencies or partial rate factors of the addition reactions.

In the work reported herein, conversions were limited to very low levels, the hydroaromatic products were found to be rapidly aromatized in air, and little dimerization product or tar was detected. In the case of complete aromatization of all the radical substitution products, any influence of the entering group on disproportionation reactions would not appear to affect the isomer distribution unless some rearrangement or back reaction of the intermediate occurred. Back reaction is believed to be unlikely energetically. Rearrangement of the intermediate would not be detected by methods employed in the present work and could affect the net distribution of products. Such perturbations could be important in explanations of differences in reactivity of the various positions on an aromatic ring.

The Model.—The chemical processes occurring during the irradiation of biphenyl are divided into two independent events.

Event 1 (generation of reactive species)

(1) (a) D. R. Augood and G. H. Williams, *Chem. Rev.*, **57**, 123 (1957); (b) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 482–486.

(2) G. W. Wheland, *J. Am. Chem. Soc.*, **64**, 900 (1942).

(3) D. F. DeTar and R. A. J. Long, *ibid.*, **80**, 4742 (1958).

(4) E. L. Eliel, S. Mayerson, Z. Welvart, and S. H. Wilen, *ibid.*, **82**, 2936 (1960).

(5) D. F. DeTar, *ibid.*, **83**, 1014 (1961).

(6) M. Eberhardt and E. L. Eliel, *J. Org. Chem.*, **27**, 2289 (1962).

(7) S. C. Dickerman and G. B. Vermont, *J. Am. Chem. Soc.*, **84**, 4150 (1962).

(8) R. T. Morrison, J. Cazes, N. Samkoff, and C. A. Howe, *ibid.*, **84**, 4152 (1962).