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# The Bromination of 2-Pyrone

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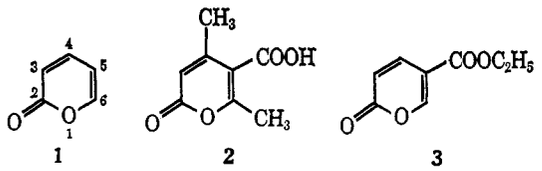
Substituted 2-pyrones are known to undergo substitutive halogenation and other apparently electrophilic substitution reactions. Herein is reported the results of a study of the bromination of unsubstituted 2-pyrone, which has been found to react by an addition–elimination sequence rather than by direct electrophilic substitution. Several intermediate bromine addition products have been isolated and their chemistry has been studied. Several of the addition–elimination products are of particular interest since they are precursors of specifically deuterated 2-pyrones. Chlorination of 2-pyrone also appears to proceed *via* an addition–elimination sequence rather than by direct substitution.

Although the 2-pyrone chromophore, which is common to many naturally occurring physiologically active substances, has been known for quite some time, only recently has the chemistry of the parent compound **1** been the subject of extensive investigation. These investigations include the behavior of 2-pyrone toward light,[2-5] nucleophiles,[6-8] and dienophiles.[9-11] However, no reports of electrophilic substitution reactions upon the parent compound have appeared,[12] although the literature does contain several instances of what seem to be electrophilic substitution reactions upon substituted 2-pyrones. For example, Shusherina, *et al.*, claim to have nitrated,[13] chloromethylated,[14] and chlorosulfonated[15] several 5,6-disubstituted 2-pyrones; however, the proposed structures of the products were not documented as fully as might be desired. Additionally, it seems to be accepted that substituted 2-pyrones can undergo substitutive halogenation. Feist[16,17] found that bromination of isodehydroacetic acid (**2**) or ethyl coumalate (**3**) leads to the 3-substituted bromo derivatives. The Russian workers have employed Feist's studies to assign, by analogy, the structures of the products derived from nitration, chlorosulfonation, and chloromethylation of substituted 2-pyrones. The assumption that these reactions are all mechanistically similar seems implicit in such an approach and is unjustifiable. A sequence involving bromine addition and subsequent elimination of hydrogen bromide could equally well lead to the substitutive bromination observed by Feist, yet need not necessarily give rise to the same products as might aromaticlike electrophilic substitution. This paper reports the results of a study of the halogenation of parent 2-pyrone in which an effort has been made to distinguish between addition–elimination and direct aromaticlike electrophilic substitution pathways.




1 2 3

## Results and Discussion

**Bromination Studies.**—Upon addition of an equimolar amount of bromine to a carbon tetrachloride solution of 2-pyrone, an exothermic reaction ensues and a viscous orange oil separates from solution. Judging from its nmr spectrum,[18] this oil is composed of a complex mixture of brominated pyrones. Overnight

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(2) P. de Mayo and R. W. Yip, *Proc. Chem. Soc.*, 84, (1964).

(3) E. J. Corey and J. Streith, *J. Amer. Chem. Soc.*, **86**, 950 (1964).

(4) A. Padwa and R. Hartman, *ibid.*, **88**, 1518 (1966).

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(6) R. Gompper and O. Christmann, *Chem. Ber.*, **94**, 1784, 1795 (1961).

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(8) G. Vogel, *J. Org. Chem.*, **30**, 203 (1965).

(9) O. Diels and K. Alder, *Ann.*, **490**, 257 (1931).

(10) H. E. Zimmerman and R. M. Paufler, *J. Amer. Chem. Soc.*, **82**, 1514 (1960).

(11) A. B. Evnin and D. Seyferth, *ibid.*, **89**, 952 (1967).

(12) See, however, W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, in press.

(13) N. P. Shusherina, N. D. Dmitrieva, T. F. Kozlova, and R. Y. Levina, *Zh. Obshch. Khim.*, **30**, 2829 (1960).

(14) N. P. Shusherina, N. D. Dmitrieva, and R. Y. Levina, *ibid.*, **31**, 2794 (1961).

(15) N. P. Shusherina, N. D. Dmitrieva, and R. Y. Levina, *Dokl. Akad. Nauk SSSR*, **135**, 1406 (1960).

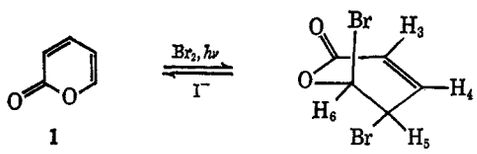
(16) F. Feist, *Ber.*, **26**, 747 (1893).

(17) F. Feist, *ibid.*, **34**, 1996 (1901).

(18) Nmr spectroscopy is most helpful in assigning structures to substituted 2-pyrones since the location of substituents is easily inferred from the magnitudes of the spin–spin coupling constants observed for the remaining ring protons. See W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, **6**, 1 (1969).

heating causes this mixture to evolve slowly hydrogen bromide with concomitant disappearance of bromine. Isolable from this reaction is a major crystalline product having the composition $C_5H_3BrO_2$ and exhibiting nmr and infrared spectra in accord with its formulation as 3-bromo-2-pyrone (**4**). This structural assignment is supported by the demonstration that zinc dust–deuterioacetic acid reduction of **8** produces 2-pyrone-3-*d* whose nmr parameters correspond well with those of unlabeled 2-pyrone.[18]

However, this isolable product, 3-bromo-2-pyrone, is not initially present in the complex bromination product mixture. One of the components of this initial mixture can be prepared in high yield and purity by an alternate procedure. At −78°, addition of an equivalent amount of bromine to a solution of 2-pyrone in methylene chloride produces no apparent reaction. However, when the cold solution is irradiated with visible light, rapid photobromination occurs, a 1:1 adduct being the sole reaction product. This adduct, clearly the product of free-radical bromination, is always a major product of the thermal bromination of 2-pyrone even when all reagents are carefully purified, degassed, and the reaction carried out in the dark. Possibly, the adduct arises *via* an ionic mechanism as well as by a radical pathway. Treatment of photodibromide, $C_5H_4Br_2O_2$, with either zinc dust or sodium iodide, results in debromination and 2-pyrone is regenerated. Accordingly, it is clear that the photodibromide has an intact ring and is either the product of 1,2 or 1,4 addition of a molecule of bromine. Analysis of the nmr spectrum[18] of the adduct leads to the assignment of its structure as *dl-trans*-5,6-dibromo-5,6-dihydro-2-pyrone (**5**). The

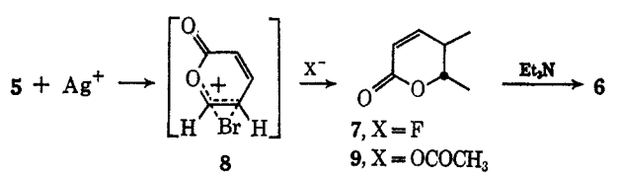



1 5

presence of a 9.7-Hz coupling constant points to retention of the $C_3$–$C_4$ double bond, and the observation of long-range coupling between $H_4$ and $H_6$ is readily explained if **5** has *trans* diaxial bromines, thereby placing $H_4$, $C_4$, $C_5$, $C_6$, and $H_6$ in a near planar situation. Such a planar "W" arrangement often leads to observable four-bond coupling.[19] Moreover, a *trans* arrangement of the bromines might be expected to preclude facile *trans* elimination of hydrogen bromide. While **5** is sufficiently stable to allow distillation at *ca.* 100° and 0.2 Torr, it can be dehydrobrominated with triethylamine to produce a new $C_5H_3BrO_2$ isomer, whose nmr spectrum indicates it to be 5-bromo-2-pyrone (**6**), consistent with the observation that zinc dust–deuterioacetic acid reduction of **6** yields 2-pyrone-5-*d*. Further, the production of **6** upon dehydrobromination of **5** lends support to the structure assigned to the photodibromide.

Treatment of photodibromide **5** with silver fluoroborate yields a product, $C_5H_4BrFO_2$, identified as *dl-trans*-5-bromo-6-fluoro-5,6-dihydro-2-pyrone (**7**) from the similarity of its proton nmr spectrum to that of photodibromide **5**, and from its ready conversion into 5-bromo-2-pyrone upon dehydrofluorination with triethylamine. The $^{19}F$ nmr spectrum of **7** is consistent with this assignment, showing but one resonance (112.8 ppm upfield from internal fluorotrichloromethane) split by coupling constants of 51.0 and 6.0 Hz. These splittings are observed in the proton nmr as well and arise from coupling between fluorine and $H_6$ and $H_5$, respectively.

Compound **7** presumably arises from backside attack of fluoride ion upon bridged ion **8**.[20] Silver acetate reacts with photodibromide **5** to afford an analogous product *dl-trans*-5-bromo-6-acetoxy-5,6-dihydro-2-pyrone (**9**) in which acetate rather than fluoride ion has




replaced the $C_6$ bromine. Treatment of **9** with triethylamine leads to 5-bromo-2-pyrone. The conversion of both **7** and **9** into 5-bromo-2-pyrone clearly indicates the location of bromine in these compounds.

While photodibromide **5** is sufficiently stable to allow purification and storage (in the cold), it does undergo gradual decomposition to produce, surprisingly, 3-bromo-2-pyrone. It seemed likely that the formation of **5** from 2-pyrone and bromine is a reversible reaction. If so, then a minor bromination reaction leading to 3-bromo-2-pyrone (or a precursor of this compound) could eventually proceed to an appreciable extent, particularly if an irreversible step (such as loss of hydrogen bromide) were included in the sequence. The formation of photodibromide **5** is reversible; heating a cyclohexene solution of purified photodibromide results in the formation of 2-pyrone and 1,2-dibromocyclohexane.[21] The debromination of photodibromide **5** is promoted by both iodide and bromide ions. Acetonitrile solutions 0.1 *M* in **5** and 1.0 *M* in cyclohexene undergo only slow conversion at 50° into 1,2-dibromocyclohexane and 2-pyrone unless a small quantity of tetra-*n*-butylammonium bromide or sodium iodide is added. These salts profoundly accelerate the debromination of photodibromide **5** and the formation of 1,2-dibromocyclohexane.

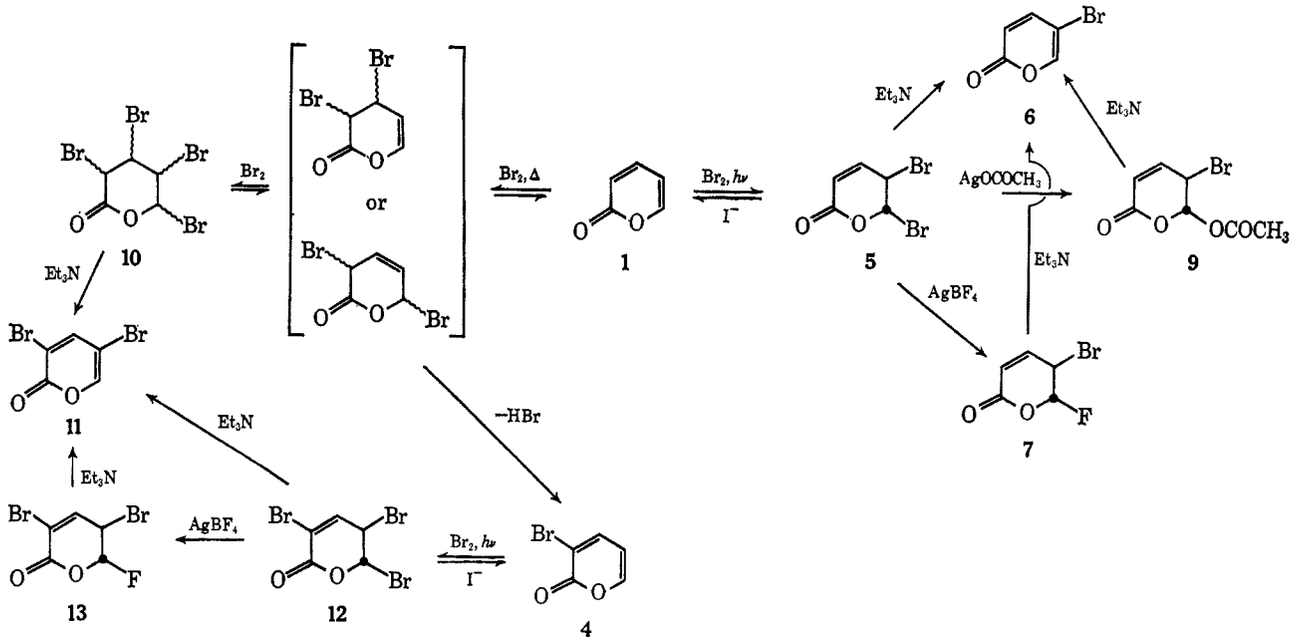
Significantly, purified photodibromide **5** undergoes neither thermal nor photochemical bromination unless hydrogen bromide is added to the reaction mixture. Under these conditions, an additional molar equivalent of bromine is consumed and *dl*-3,4,5,6-tetrabromo-3,4,5,6-tetrahydro-2-pyrone (**10**) is produced. Although the nmr spectrum of **10** has not been completely analyzed, the appearance of two multiplets at $\delta$ 6.7 and 4.6–5.4 having relative areas of 1:3 is consistent with the

(19) See, for instance, K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(20) Examples of fluoroborate ion acting as a source of nucleophilic fluoride are rare; see, for instance, P. Beak, R. J. Trancik, J. B. Mooberry, and P. Y. Johnson, *ibid.*, **88**, 4288 (1966).

(21) In order to verify that this reaction results from liberation of bromine from **5** prior to bromination of cyclohexene rather than by bimolecular bromination of cyclohexene by **5**, the following simple kinetic experiment was undertaken. Diglyme solutions, 0.10 *M* in photodibromide and containing 10- and 20-fold molar excesses of cyclohexene, were maintained at 54.98 ± 0.02°; aliquots were periodically withdrawn; and the formation of 1,2-dibromocyclohexane was followed by vpc analysis. The reaction, proceeding slowly under these conditions, followed smooth first-order kinetics over 2.5 half-lives, having identical rate constants of $7.6 \times 10^{-4}$/min. This result demonstrates that slow first-order debromination of **5** is followed by rapid bromination of cyclohexene by the liberated bromine.

SCHEME I

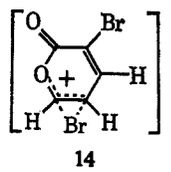


proposed structure. More direct evidence supporting this structural assignment follows from the result of exhaustive dehydrobromination with triethylamine. From this reaction, a crystalline dibromo-2-pyrone may be isolated which is believed to be 3,5-dibromo-2-pyrone (**11**). This structural assignment is based on an nmr spectrum strikingly similar to that of 3,5-dichloro-2-pyrone and further substantiated by the observation that reduction of dibromopyrone **11** with zinc dust in deuterioacetic acid affords 2-pyrone-3,5-$d_2$.

Even in the absence of added hydrogen bromide, addition of 2.2 molar equiv of bromine to a chloroform solution of 2-pyrone produces **10**. However, since small quantities of hydrogen bromide are evolved from this reaction and since it is known that photodibromide **5** cannot be further brominated except in the presence of hydrogen bromide, one may infer that the tetrabromide **10** arises from initial 1,2 addition of bromine to the 3,4 double bond of 2-pyrone (or by 1,4 addition at $C_3$ and $C_6$) followed by the addition of the second mole of bromine. Presumably, a trace of hydrogen bromide arises from dehydrobromination of some dibromide and serves to facilitate the regeneration of 2-pyrone from the rapidly formed photodibromide **5** (which cannot undergo further bromination) and hence ultimately allows complete conversion into tetrabromide **10**.

Although there are several possible stereoisomers of tetrabromide **10**, the *trans,trans,trans* isomer (having all bromine atoms equatorial) is thought to be the major isomer since it should possess the least nonbonded interaction between bromine atoms. Because the all-*trans* equatorial isomer cannot undergo *trans* elimination of hydrogen bromide, it would be expected to be less labile than other stereoisomers of **10**. This compound is relatively stable and can be stored for weeks at 0° with apparently little decomposition. On standing at room temperature or upon warming, the tetrabromide slowly loses hydrogen bromide to form crystalline $C_5H_3Br_3O_2$, formulated as *dl-trans*-3,5,6-tribromo-5,6-dihydro-2-pyrone (**12**) on the basis of the similarity of its nmr parameters to those of photodibromide **5** and its conversion into 3-bromo-2-pyrone by the action of zinc dust or iodide ion, or upon heating with cyclohexene.[22] This tribromide **12** is readily converted into 3,5-dibromo-2-pyrone upon dehydrobromination with triethylamine. Photoaddition of 1 mol of bromine to 3-bromo-2-pyrone also leads to the formation of tribromide **12**.

Addition of an ethylene dichloride solution of silver fluoroborate to tribromo-2-pyrone **12** affords a fluorodibromodihydro-2-pyrone analogous to the formation of fluorobromodihydro-2-pyrone **7** from photodibromide **5** with the same reagent. This compound is assigned the structure *dl-trans*-3,5-dibromo-3,5-dihydro-3-fluoro-2-pyrone (**13**) principally on the basis of its $^{19}F$ and proton nmr spectra. The fluorine resonance (a doublet of doublets with splittings of 51.0 and 6.0 Hz) falls at 113.1 ppm upfield from internal fluorotrichloromethane. The striking similarity of the nmr spectrum of **13** to those of 5-bromo-6-fluoro-5,6-dihydro-2-pyrone and 3,5,6-tribromo-5,6-dihydro-2-pyrone allows confident structural assignment of **13**. A bridged bromonium ion (**14**) is postulated to be the reaction intermediate.



**14**

Summarized in Scheme I are the interrelated bromination reactions thus far discussed.

The formation of dihydropyrones **7**, **9**, and **13** from the postulated intermediate bridged ions **8** and **14** deserves further comment. In typical electrophilic aromatic substitutions, the $\sigma$ complex (an onium ion which may be either a distinct intermediate or a transition state) initially formed may either revert to starting materials or deprotonate to yield the substitution product. To the extent that the action of silver(I) ion

(22) An analogous tribromide has been reported to arise on bromination of 4,6-diphenyl-2-pyrone; see F. Arndt and B. Eistert, *Ber.*, **58**, 2318 (1925).

upon photodibromide **5** or tribromide **12** affords an onium ion intermediate, and to the extent that this onium ion intermediate resembles a $\sigma$ complex, one may contrast the behavior of 2-pyrone with that of aromatic substances. In the case of the pyrone, the intermediacy of onium ions **7** and **14** seems reasonable; the products obtained are most readily rationalized as arising from the trapping of these ions by nucleophiles. The observed products require that the trapping reactions be much faster than deprotonation or reversible loss of cationic bromine. This behavior is atypical of aromatic systems where $\sigma$ complexes cannot normally be trapped, but such trapping is not unusual in the reactions of olefins with electrophiles. Thus the failure of 2-pyrone to undergo electrophilic substitution reactions may well be a consequence not of a failure to generate a $\sigma$ complex, but rather of a failure of the $\sigma$ complex to deprotonate competitively with nucleophilic attack.

**Chlorination of 2-Pyrone.**—The chlorination of 2-pyrone, studied less extensively than was bromination, leads one to the conclusion that, in most respects, chlorination sequences parallel those of bromination. The exhaustive photochemically initiated chlorination of 2-pyrone at low temperatures leads to a tetrachlorotetrahydro-2-pyrone **15** whose nmr spectrum is nearly superimposable upon that of the tetrabromotetrahydro-2-pyrone **10**. When the reaction course is followed by nmr spectroscopy, the accumulation of an intermediate whose splitting pattern very closely matches that of photodibromide **5** is observed. Other intermediates are also formed, all eventually yielding the tetrachlorotetrahydro-2-pyrone. This product is readily converted into the known 3,5-dichloro-2-pyrone upon exhaustive dehydrochlorination with triethylamine.

## Experimental Section

Reagent grade chemicals were used without further purification unless so specified. All nmr spectra were determined on Varian A-60, A-56/60A, or A-60A spectrometers using *ca.* 15% solutions in deuteriochloroform with tetramethylsilane and fluorotrichloromethane as internal standards. Infrared spectra were run on a Perkin-Elmer 521 spectrophotometer using 10% carbon tetrachloride solutions unless otherwise noted. Ultraviolet spectra were determined on a Perkin-Elmer 202 instrument. Melting points were taken on a Reichert block and are uncorrected, as are boiling points. Indices of refraction were measured on a Carl Zeiss refractometer. Analyses were conducted by Mr. J. Nemeth and his associates of these laboratories; mass spectra were obtained by Mr. J. Wrona using an Atlas CH-4 spectrometer.

**2-Pyrone** (1).—Coumalic acid was decarboxylated[23] to yield 2-pyrone, bp 110° (15 mm), bp 210–211° (760 mm), $n^{25}$D 1.5262 [lit.[22] bp 206–209°, $n^{25}$D 1.5272]. Prior to usage, 2-pyrone was either distilled or chromatographed on silica gel, since it tends to darken and resinify unless stored under nitrogen or below its melting point (*ca.* 0°).

**3-Bromo-2-pyrone** (4). **A. From the Thermal Decomposition of Photodibromide 5.**—The dark gum which resulted when 0.968 g of photodibromide **5** was allowed to stand at room temperature for 20 days was triturated with methylene chloride and the soluble material was chromatographed on silical gel to yield 0.645 g of 3-bromo-2-pyrone of mp 62°. After sublimation at 50° (0.1 mm), the white crystals had mp 63.5–64°. The carbonyl stretching frequency for the compound occurs at 1748 cm$^{-1}$, and two sharp peaks are also observed at 1631 and 1535 cm$^{-1}$. The ultraviolet spectrum of the compound shows $\lambda_{max}^{CCl_4}$ 300 m$\mu$ ($\epsilon$ 5750). Three equal area quartets can be observed in the compound's nmr spectrum, falling at $\delta$ 6.23, 7.56, and 7.77.

(23) H. E. Zimmerman, G. L. Grunewald, and R. N. Paufler, *Org. Syn.*, **46**, 101 (1966).

*Anal.* Calcd for $C_5H_3BrO_2$: C, 34.40; H, 1.71; mol wt, 174.94. Found: C, 34.21; H, 1.78; mol wt, 175 (mass spectrometric).

**B. From the Direct Action of Bromine on 2-Pyrone.**—To a solution of 12.0 g of bromine in 100 ml of carbon tetrachloride was added 7.5 ml of 2-pyrone (0.09 mol) and the resulting mixture heated to reflux for 14 hr. While hot, the supernatant was decanted from the dark gummy residue and concentrated to half-volume at reduced pressure and cooled, whereupon long needles of 3-bromo-2-pyrone crystallized and were collected. Trituration of the dark gum with hot carbon tetrachloride yielded additional product. After two recrystallizations from carbon tetrachloride, 5.98 g of 3-bromo-2-pyrone of mp 64–65° was obtained. An additional 2.5–3 g of material was isolated from the mother liquors upon fractional sublimation.

**C. From 3,5,6-Tribromo-5,6-dihydro-2-pyrone (12) and Cyclohexene.**—To an nmr tube was added 0.40 ml of a 25% solution of **12** in cyclohexene, and the tube sealed and placed in a steam bath for 30 hr. Examination of the contents by nmr spectroscopy revealed them to be 3-bromo-2-pyrone and 1,2-dibromocyclohexane in a 1:1 mole ratio, plus excess cyclohexene. Subsequent work-up of the products from the nmr tube (fractional sublimation) resulted in the isolation of 25 mg of 3-bromo-2-pyrone, mp 61–63°.

**D. From Treatment of Tribomide 12 with Zinc.**—A solution of 1.40 g of recrystallized tribromide in 40 ml of ethyl ether was treated with *ca.* 2 g of zinc dust at room temperature for 5 hr. The solution was filtered and the residue washed with ether; the combined filtrates were evaporated to dryness at reduced pressure. Upon silica gel chromatography, the residual straw-colored syrup yielded 0.550 g of crystalline product, mp 63–66°, which has an infrared spectrum superimposable with that of an authentic sample of 3-bromo-2-pyrone.

**5,6-Dibromo-5,6-dihydro-2-pyrone** (5).—In a typical preparation, 5.42 g (0.0565 mol) of freshly distilled 2-pyrone was dissolved in 200 ml of methylene chloride and cooled to −78° in a Dry Ice–isopropyl alcohol bath while a stream of dry nitrogen was bubbled through the solution. Bromine, 9.2 g (0.0575 mol), in *ca.* 20 ml of methylene chloride, was slowly introduced into the cold solution and the mixture irradiated with a 400-W tungsten projector bulb until the bromine had been consumed (3–5 min). After the solvent had been removed (rotary evaporator), the amount of yellow clear oil obtained, 14.6 g, corresponded to quantitative formation of a 1:1 adduct. This adduct was purified by chromatography upon Brinkmann silica gel with methylene chloride and yielded 13.5 g of a clear oil, $n^{23}$D 1.5933, which, although it can be stored unchanged for several weeks at −20°, evolves hydrogen bromide at room temperature. An imperfect elemental analysis reflects this difficulty. The infrared spectrum shows carbonyl stretching at 1760–70 cm$^{-1}$ and no other bands between 1400 and 1700 cm$^{-1}$. The ultraviolet spectrum of an ethanolic solution of **5** shows only end absorbtion. In the nmr spectrum of **5**, four equal area multiplets are apparent at $\delta$ 5.15 (quartet), 6.20 (doublet), 6.90 (quartet), and 7.20 (octet).

*Anal.* Calcd for $C_5H_4O_2Br_2$: C, 23.45; H, 1.56; mol wt, 255.92. Found: C, 24.01; H, 1.62; mol wt, 256 (mass spectrometric).

**Titration of Active Bromine from Photodibromide 5.**—To a solution of 0.212 g ($8.3 \times 10^{-4}$ mol) of freshly purified (chromatography on silica gel) photodibromide in *ca.* 5 ml of acetonitrile was added *ca.* 0.5 g of powdered potassium iodide in 5 ml of water. The magnetically stirred slurry was titrated with 15.48 ml of 0.1076 *N* sodium thiosulfate solution to the starch end point. This value corresponds to 1.0 mol of active bromine per mole of photodibromide **5**.

**Debromination of Photodibromide 5 with Zinc.**—Photodibromide (100 mg) in 1 ml of methylene chloride was treated with *ca.* 0.2 g of zinc dust. After 15 min at 35–40°, the solution was filtered through glass wool into an nmr tube and found, by nmr, to contain only 2-pyrone.

**Reaction of Photodibromide 5 with Cyclohexene.**—A 25-ml ampoule was sealed after addition of 4.424 g (0.0172 mol) of **5** and 10.0 ml of cyclohexene. After 24 hr in a steam bath, the ampoule was opened. An assay of the products (tlc, nmr) showed that no photodibromide remained. The excess cyclohexene was removed (rotary evaporator), the residue was chromatographed on a column of silica gel with methylene chloride as eluent, and nine 15-ml fractions were taken. Through comparisons with an authentic sample of 1,2-dibromocyclohexane (indices of refraction, boiling

point, infrared spectra, and tlc) fractions 1–3 were shown to be pure 1,2-dibromocyclohexane (3.112 g, 0.0129 mol). Fraction 4 (0.500 g) proved (tlc, infrared spectrum) to be 2-pyrone and 1,2-dibromocyclohexane with the former in preponderance. Fractions 5–9 (1.276 g) were shown by similar methods to be solely 2-pyrone.

**Kinetics of the Debromination of 5 in the Presence of Cyclohexene.**—Two 10-ml portions of a solution 0.10 *M* in freshly chromatographed photodibromide in diglyme (distilled from sodium) were pipetted into 25-ml volumetric flasks and rubber serum caps affixed. Into these flasks was injected 0.80 ml (0.01 mol) and 1.60 ml (0.20 mol), respectively, of cyclohexene which had been passed through alumina and then distilled. A small quantity (100 mg) of nitrobenzene was added to each flask to serve as an internal vpc standard. Both flasks were immersed in a constant-temperature bath maintained at 54.98 ± 0.02° and aliquots periodically withdrawn and injected into an Aerograph A90-P3 chromatograph using a 5 ft × 0.25 in. column packed with 20% SE-30 on 60/80 Chromosorb W and operating at 130°. The appearance of 1,2-dibromocyclohexane was noted as a function of time. In both cases, identical first-order rate constants of $7.6 \times 10^{-4}$/min were obtained.

**5-Bromo-2-pyrone (6).**—A magnetically stirred solution of 1.010 g of photodibromide **5** in 15 ml of methylene chloride was treated dropwise with a solution of 0.60 ml of triethylamine in methylene chloride (5 ml). After 5 min, the solvent was evaporated and the residue extracted with ether, leaving behind most of the triethylamine hydrobromide. The orange slush (0.794 g) left after evaporation of the ether was chromatographed on silica gel with ether as eluent to yield 0.726 g (91%) of white crystalline 5-bromo-2-pyrone, which, after sublimation at 50° and 0.1 Torr, melted at 60–61°. The carbonyl absorption in the infrared spectrum of this product occurs at 1750–1754 $cm^{-1}$, with two less intense absorptions at 1613 and 1533 $cm^{-1}$. The ultraviolet spectrum of **6** shows $\lambda_{max}^{CCl_4}$ 307 mμ (ε 5430). Three equal area quartets were observed in the nmr spectrum of **6**, falling at δ 6.2, 7.3, and 7.5.

*Anal.* Calcd for $C_5H_3O_2Br$: C, 34.40; H, 1.71; mol wt, 174.94. Found: C, 34.72; H, 1.90; mol wt, 175 (mass spectrometric).

**5-Bromo-6-fluoro-5,6-dihydro-2-pyrone (7).**—While dry nitrogen was bubbled through a solution of 1.030 g of photodibromide **5** in 50 ml of ethylene dichloride, 4.4 ml of a 1 *M* silver fluoroborate solution in ethylene dichloride was added dropwise with consequent precipitation of silver bromide and evolution of boron trifluoride fumes. After 10 min, the reaction mixture was filtered and the silver bromide washed once with 10 ml of ethylene dichloride. After drying at 110°, the silver bromide weighted 0.644 g (86%). The combined filtrates were dried over anhydrous sodium sulfate and stripped of solvent to leave 0.849 g of colorless oil. This material was chromatographed through a short silica gel column with ether, with consequent isolation of 0.719 g (91%) of **7** as a colorless oil. The product was molecularly distilled prior to elemental and spectral analysis. The infrared spectrum of **7** shows a broad carbonyl absorption centered at *ca.* 1740 $cm^{-1}$ with a low-intensity spike at 1627 $cm^{-1}$. Only end absorption is observable in its ultraviolet spectrum. The pmr spectrum of **7** contains four equal area multiplets centered at δ 4.7, 6.2, 6.3, and 7.0. The fluorine nmr spectrum consists of a quartet centered at 124 ppm upfield of fluorotrichloromethane.

*Anal.* Calcd for $C_5H_4BrFO_2$: C, 30.77; H, 2.05; mol wt, 194.95. Found: C, 30.82; H, 1.97; mol wt, 195 (mass spectrometric).

**5-Bromo-6-acetoxy-5,6-dihydro-2-pyrone (9).**—To a slurry of *ca.* 4 g of silver acetate in 25 ml of methylene chloride, 1.502 g of photodibromide **5** was added, and the resulting heterogeneous reaction mixture magnetically stirred at room temperature for 3 days. The mixture was then filtered and the filtrate passed through a column of silica gel with methylene chloride as eluent. A total of 0.817 g of a yellow solid was eluted which after fractional sublimation gave, as the third sublimation fraction, 0.708 g of white crystalline material melting at 75–77°. A broad band at 1705–1750 $cm^{-1}$ was apparent in the infrared spectrum of the product. Only end absorption is observed in the ultraviolet spectrum of **9** and its nmr spectrum shows four one-proton multiplets at δ 4.70 (quartet), 6.17 (doublet), 6.72 (quartet), and 7.10 (octet), and a three-proton singlet at δ 2.12.

*Anal.* Calcd for $C_7H_7BrO_4$: C, 35.74; H, 2.97; mol wt, 234.05. Found: C, 35.75; H, 2.93; mol wt, 234 (mass spectrometric).

**5-Bromo-2-pyrone (4) from 9.**—To a solution of 0.096 g of **9** in 5 ml of methylene chloride, 1 ml of triethylamine was added dropwise, the reaction being worked up in the same manner as was that in which 5-bromo-2-pyrone was prepared from the photodibromide **5**. The product thus obtained (0.057 g) was shown to be identical with the 5-bromo-2-pyrone obtained from **5**.

**3,4,5,6-Tetrabromo-3,4,5,6-tetrahydro-2-pyrone (10). A. From the Thermal Bromination of 5.**—Dry hydrogen bromide was bubbled into a stirred solution of 1.025 g of photodibromide and 0.25 ml (0.0049 mol) of bromine in methylene chloride (25 ml). After 12 hr, the solvent was evaporated to leave 1.698 g of a reddish oil which was chromatographed with methylene chloride upon a column of silica gel to yield 1.517 g of tetrabromide **10** as a colorless oil. Since it was apparent that at 25° this oil was slowly decomposing with evolution of hydrogen bromide, spectra and elemental analyses were obtained without further purification. This oil shows infrared absorption at 1790 $cm^{-1}$ with no other bands between 1400 and 1800 $cm^{-1}$. The nmr spectrum of the product consists of two multiplets having area ratios of 3:1. The larger multiplet is complex, centered at about δ 5.0; the smaller appears to be a doublet centered at δ 6.7.

*Anal.* Calcd for $C_5H_4Br_4O_2$: C, 14.44; H, 0.96. Found: C, 15.14; H, 1.12.

**B. From the Thermal Bromination of 2-Pyrone.**—Addition of 2 molar equiv of bromine to a hot solution of 1.655 g of 2-pyrone in 25 ml of chloroform causes evolution of small quantities of hydrogen bromide and consumption of the bromine. After 1 hr, the only product isolated from a work-up identical with that outlined in A was 5.648 g (80%) of **10**, as judged by comparison of infrared and nmr spectra.

**3,5,6-Tribromo-5,6-dihydro-2-pyrone (12). A. From Tetrabromide 10.**—Tetrabromide (5.390 g) in 20 ml of carbon tetrachloride was heated to reflux overnight with consequent evolution of copious amounts of hydrogen bromide. Overnight chilling (0°) of the solution resulted in the deposition of 2.237 g of white crystals of tribromide **12** which were collected and washed with cold carbon tetrachloride. After two sublimations at 100° and 0.01 Torr, the product had mp 92.5–93.0°; it shows bands in its infrared spectrum at 1787, 1772, and 1617 $cm^{-1}$. The nmr spectrum of **12** is composed of three equal area quartets at δ 5.0, 6.80, and 7.45.

*Anal.* Calcd for $C_5H_3Br_3O_2$: C, 17.94; H, 0.90; mol wt, 334.83. Found: C, 18.17; H, 1.02; mol wt, 335 (mass spectrometric).

**B. From the Photobromination of 3-Bromo-2-pyrone (4).**—A solution of 0.743 g of 3-bromo-2-pyrone and 0.680 g of bromine in 200 ml of methylene chloride was irradiated at −78° with a 400-W tungsten projector bulb for 25 min. Upon removal of the solvent, 1.420 g of yellowish crystalline material, mp 87–89°, was obtained. Sublimation under conditions described above raised the melting point to 92–93°. Infrared and nmr spectra of the products of procedures A and B were superimposable.

**3,5-Dibromo-2-pyrone (11). A. From 3,5,6-Tribromo-5,6-dihydro-2-pyrone (12).**—To a solution of 0.124 g of **12** in 15 ml of methylene chloride was added (dropwise and with stirring) a solution of 1 ml of triethylamine in 5 ml of methylene chloride. After 10 min, the reaction mixture was evaporated to dryness and the solid residue extracted several times with small volumes of methylene chloride. The combined extracts (25 ml) were stripped of solvent and passed through a short silica gel column with ether, eventually yielding 0.087 g of crystalline dibromide **11** which after a single sublimation (50°, 0.1 Torr) melted at 66–67°. The infrared spectrum of a 5% chloroform solution of **11** shows carbonyl absorption at 1755 $cm^{-1}$ and two sharp peaks at 1620 and 1530 $cm^{-1}$. Ultraviolet absorption, $\lambda_{max}^{CH_2Cl_2}$ 315 mμ (ε 8100), is also noted. The nmr spectrum of **11** shows an AB quartet, the two doublets centered at δ 7.63 and 7.80.

*Anal.* Calcd for $C_5H_2Br_2O_2$: C, 23.62; H, 0.79; mol wt, 253.90. Found: C, 23.74; H, 0.94; mol wt, 254 (mass spectrometric).

**B. From 3,4,5,6-Tetrabromo-3,4,5,6-tetrahydro-2-pyrone (10).**—The same procedure as described above was applied to 0.433 g of tetrabromide **10**, and resulted in the isolation of a single product (0.087 g) having mp 64–65° (oil bath) and infrared and nmr spectra identical with those of **11**.

**2-Pyrone-3,5-$d_2$.**—To a solution of 2.47 g of 3,5-dibromo-2-pyrone (0.00975 mol) in 15 ml of deuterioacetic acid was added *ca.* 25 g of zinc dust and the nitrogen-blanketed mixture heated on a steam bath for 3 days. The reaction mixture was diluted with 75 ml of warm water and, after the residual zinc was pulverized,

the solution was filtered. The zinc was washed once more with 50 ml of hot water and the extracts were combined. Finally, the zinc was washed with two 75-ml portions of warm methylene chloride and these washings were used to extract the combined aqueous filtrates. The combined methylene chloride extracts were rinsed twice with 50 ml of dilute sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the solvent by evaporation left 0.308 g (33%) of 2-pyrone-3,5-$d_2$ which was further purified by molecular distillation. The nmr spectrum of the pyrone contains two equal area doublets centered at $\delta$ 7.47 and 7.62, both split by 2.4 Hz. Mass spectral analysis showed the product to be 79% doubly deuterated, 20% singly deuterated, and about 1% unlabeled.

**3,5-Dibromo-6-fluoro-5,6-dihydro-2-pyrone (13).**—Dry nitrogen was bubbled through a solution of 0.927 g of silver fluoroborate in 30 ml of ethylene dichloride while a solution of 1.58 g of 3,5,6-tribromo-5,6-dihydro-2-pyrone (12) in 5 ml of ethylene dichloride was added dropwise. After *ca.* 15 min, evolution of boron trifluoride fumes subsided and the reaction mixture was filtered; the remaining silver bromide was washed with 10 ml of ethylene dichloride. Removal of the solvent from the combined filtrates left 0.946 g of oil which crystallized on standing. After a single recrystallization from carbon tetrachloride, the white crystalline 13 melted at 75–76°. The infrared spectrum (chloroform) of 13 has broad carbonyl absorption at 1745–1775 $cm^{-1}$. The pmr spectrum is composed of three equal area multiplets centered at $\delta$ 4.73, 6.25 (split by 51.0 Hz), and 7.37. The fluorine nmr spectrum shows a quartet centered at 113 ppm upfield of internal fluorotrichloromethane.

*Anal.* Calcd for $C_5H_3Br_2FO_2$: C, 21.91; H, 1.10. Found: C, 22.21; H, 1.33.

**3,4,5,6-Tetrachloro-3,4,5,6-tetrahydro-2-pyrone (15).**—While irradiating with a GE 275-W sun lamp, chlorine was slowly bubbled into a solution of 1.979 g of 2-pyrone (0.0207 mol) in 100 ml of methylene chloride which was cooled to −78° in a Dry Ice–acetone bath. After *ca.* 1 hr, the reaction was allowed to warm to −35°, since condensed chlorine was increasing the solution volume. After 1.5 hr at −35°, the solvent and excess chlorine were evaporated to leave *ca.* 5 g of a clear oil ($n^{23}D$ 1.5212) having no noticeable odor of chlorine or hydrogen chloride. The nmr spectrum of the compound is composed of a multiplet at $\delta$ 4.4–5.15 (3 H) and a doublet centered at 4.33 (1 H).

*Anal.* Calcd for $C_5H_4Cl_4O_2$: C, 25.21; H, 1.68. Found: C, 25.20; H, 1.72.

**3,5-Dichloro-2-pyrone.**—To a solution of 1.776 g of tetrachloride 15 in ether was added dropwise 2 ml of triethylamine in 5 ml of ether. After 5 min, the solution was filtered and the filtrate stripped of solvent, leaving 0.948 g of discolored solid. Chromatography of this product on silica gel resulted in the isolation of 0.735 g of crystalline 3,5-dichloro-2-pyrone melting at 67–70°. After a single sublimation (50°, 0.05 Torr) the melting point was raised to 72.5–73.5° (lit.[24] mp 71–73°).

**Registry No.**—**1**, 504-31-4; **4**, 19978-32-6; **5**, 19988-79-5; **6**, 19978-33-7; **7**, 19988-77-3; **9**, 19988-78-4; **10**, 19988-73-9; **11**, 19978-41-7; **12**, 19988-74-0; **13**, 19988-75-1; **15**, 19988-76-2.

(24) A. Roedig and G. Markl, *Ann.*, **631**, 1 (1960).

# The Synthesis of 9,13b-Dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-6-one

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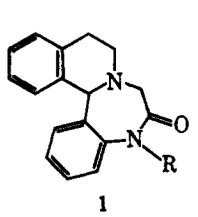
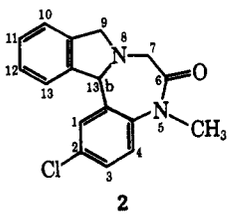
Two independent syntheses for the new isoindolo[2,1-*d*][1,4]benzodiazepine ring system are described. In one approach 2′-bromomethyl-5-chloro-2-nitrobenzophenone is allowed to react with glycine ethyl ester and the reaction product is reduced with zinc in acetic acid yielding 2-chloro-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]-benzodiazepin-6(7H)-one. The second approach begins with 3-(5-chloro-2-methylaminophenyl)isoindolin-1-one, which on electrolytic reduction followed by alkylation with ethyl bromoacetate and cyclization on heating in acetic acid gives rise to 2-chloro-5-methyl-9,13b-dihydro-5H-isoindolo[2,1-*d*][1,4]benzodiazepin-6(7H)-one. The syntheses of the respective starting materials are reported. The electrolytic reduction in deuterated solvents is also described.

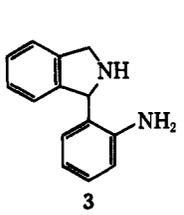
In an earlier publication[1] we reported on the synthesis and the pharmacological activities of tetracyclic benzodiazepines of type **1**. We now[2] wish to report the synthesis of the isoindoline analog **2**, a previously unreported ring system.



**1**



**2**



**3**

In this instance a similar synthetic sequence to that used for the synthesis of **1** would require an N-unsubstituted 1-(*o*-aminophenyl)isoindoline, *e.g.*, **3**, as an intermediate since N alkylation on the isoindoline of this with ethyl bromoacetate and subsequent cyclization would lead to the desired system. Although the synthesis of 1-phenylisoindolines has been described by Veber and Lwowski,[3] we considered **3** not readily available by their reaction sequence. We therefore initially decided to develop a synthesis of **2** not involving the intermediate **3**. This synthesis is outlined in Scheme I.

The structure assigned to **8** is supported by its ir spectrum which showed a strong carbonyl peak at 1740 $cm^{-1}$ and lacked NH or OH absorptions. The nmr spectrum of the crude material was also as expected, showing aromatic and O-ethyl protons as well as an AB quartet for the $NCH_2CO$ protons centered at $\delta$ 4.78 ($J_{AB}$ = 16 Hz).

Since larger quantities of **2** were required a second, more economical, sequence was developed as outlined in Scheme II.

The physical characteristics of the intermediate **13** are in accordance with the structure shown rather than with the corresponding benzophenone imine tautomer (no C=N absorption in ir spectrum). Compound **13**

(1) H. Ott, G. E. Hardtmann, M. Denzer, A. J. Frey, J. H. Gogerty, G. H. Leslie, and J. Trapold, *J. Med. Chem.*, **11**, 777 (1968).

(2) Part of the work described in this paper was published in U. S. Patent 3,375,246 (1968) (to G. E. Hardtmann and H. Ott).

(3) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **85**, 646 (1963).