Derivatives of 3,6-Endoxo-5-methyl-Δ^4-tetrahydrophthalic Acid. Structural Assignments by Nuclear Magnetic Resonance Spectroscopy

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Received December 20, 1965

During the course of nmr studies regarding the detection of long-range couplings in bicyclic systems under such conditions that the relative signs of the coupling constants could be determined, the synthesis of two different bromolactonic acids was carried out.

The reaction of 3-methylfuran (I) with maleic acid (II) in deuterium oxide showed, by nmr spectroscopy, the simultaneous formation of *endo* and *exo* adduct (III and IV) (see Scheme I). If equimolecular amounts of I and II in deuterium oxide are left under continuous agitation for 3 days the composition of the reaction mixture, after this period of time, is: maleic acid (II) (35.5%), *exo* adduct IV (24.7%), and *endo* adduct III (39.8%). These values are obtained from the nmr spectrum by measuring the integrals for the vinyl protons of maleic acid (δ = 6.40 ppm), the C-4 protons of *exo* adduct IV (δ = 6.00 ppm), and the C-4 proton of *endo* adduct III (δ = 6.21 ppm). A complete study of this Diels–Alder addition is under way in our laboratories since it presents some peculiarities that will be reported in due time.

Addition of bromine to the reaction mixture, with the composition described above, results in the formation of a white precipitate, the bromolactonic acid VI. The identification and structural assignments of the latter compound was made by elemental analysis and nmr spectroscopy. Formation of VI can only be rationalized by means of an *exo* addition of bromine to adduct III and subsequent lactonization with participation of the corresponding carboxyl group.[1,2] No appreciable amount of bromolactonic acid XII could be detected in the preparation of compound VI. The nmr spectrum of compound XII is expected to be different from compound VI, especially in the region of the C-4 *exo* proton, since this proton should be coupled to the proton on the neighboring bridgehead carbon atom.[3,4] The course of the lactonization process may be explained if one takes into account the inductive effect of the 5-methyl group which causes the charge distribution, on the bromonium ion, to be asymmetric and determines the attack at the 5 position by the 1-*endo* carboxyl group. The fact that VI is a monolactone was proved by its chemical properties and by the preparation of the ester VII on treatment of VI with diazomethane. Under the described conditions, no bromination product was observed of the *exo* adduct IV, either in the precipitated solid or in the mother liquor of the reaction mixture.

The pure *exo* adduct IV, from the diene synthesis in benzene,[5] on dissolving in alkali and treating with bromine gave a white precipitate. This solid was identified, by its nmr spectrum, as bromolactonic acid XI. The formation of XI may suggest an *exo* addition of bromine with subsequent migration of the bond between carbon atoms 1 and 6, to form an ion intermediate X which in turn gives bromolactonic acid XI. The spectrum of the latter compound is discussed below and, in addition to its great interest from the nmr viewpoint, is in complete agreement with the proposed structure. The presence of an alternate reaction product, bromolactonic acid XIII, which may occur by migration of the bond between carbon atoms 2 and 3, was not detected. The reason why the latter reaction path is not followed may be found by analogy with the bromolactonic acid XII, discussed above. Here again, the expected spectral differences of compounds XI and XIII leave no doubt in the structural assignment for the compound obtained, since compound XIII is expected to show the known $J_{3,4}$ ($\simeq$ 4 cps) characteristic of these compounds.[3,4]

Despite the low probability of formation of an *endo* bromination product, a study was made of the nmr spectra of all the possible compounds of this type which may have occurred. It seems safe to conclude that none of them would have exhibited the nmr spectra observed in the products studied here.

The nmr spectra of bromolactonic acid VI has been interpreted by analogy with spectra of similar compounds studied previously.[3,6] The C-1 and C-2 protons form an AB-type spectrum[7] ($\delta_{1,2}$ = 13.7 cps, $J_{1,2}$ = 10.1 cps) centered at δ = 3.28 ppm. The C-1 proton is also coupled to the C-6 proton ($J_{1,6}$ = 4.5 cps) and the C-2 proton is coupled to the C-3 proton ($J_{2,3}$ = 4.4 cps) giving rise to additional splittings. Furthermore, the C-1 proton presents a long-range coupling with the C-3 proton ($J_{1,3}$ = 0.7 cps) which can be verified in the region of the spectrum corresponding to the C-3 proton. Although the existence of the latter coupling has been predicted,[8] it hasn't been possible to detect it in this type of compound. The band at δ = 5.01 ppm has been assigned to the C-3 proton; it consists of a doublet of triplets, where the following coupling constants can be measured: $J_{1,3}$, $J_{2,3}$, and $J_{3,6}$ = 1.2 cps. Centered at δ = 5.28 ppm appears a doublet of doublets due to the C-6 proton and originated by $J_{3,6}$ and $J_{1,6}$. Finally, the C-4 proton gives rise to a sharp singlet at δ = 4.96 ppm. Both, the structure and the position of this band are critical in the structural assignment of the molecule since its sharpness shows the absence of any couplings and hence, this proton must be located at an *endo* position geminal to the bromine atom. This fact discards structure XII as a possible one. The 5-methyl group shows a singlet at δ = 1.74 ppm. Conversion of bromolactonic acid VI into ester VII does not introduce any important changes in the spectrum, except

(1) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).
(2) J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953); **76**, 4060 (1954).
(3) D. Gagnaire and E. Payo, *Bull. Soc. Chim. France*, 2627 (1963).
(4) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
(5) I. J. Rinkes, *Rec. Trav. Chim.*, **50**, 1131 (1931).
(6) E. Payo, These d'Université, Grenoble, France, 1964.
(7) The spectra have been analyzed on a first-order basis, and the recorded coupling constants are the observed splittings.
(8) J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961).

SCHEME I

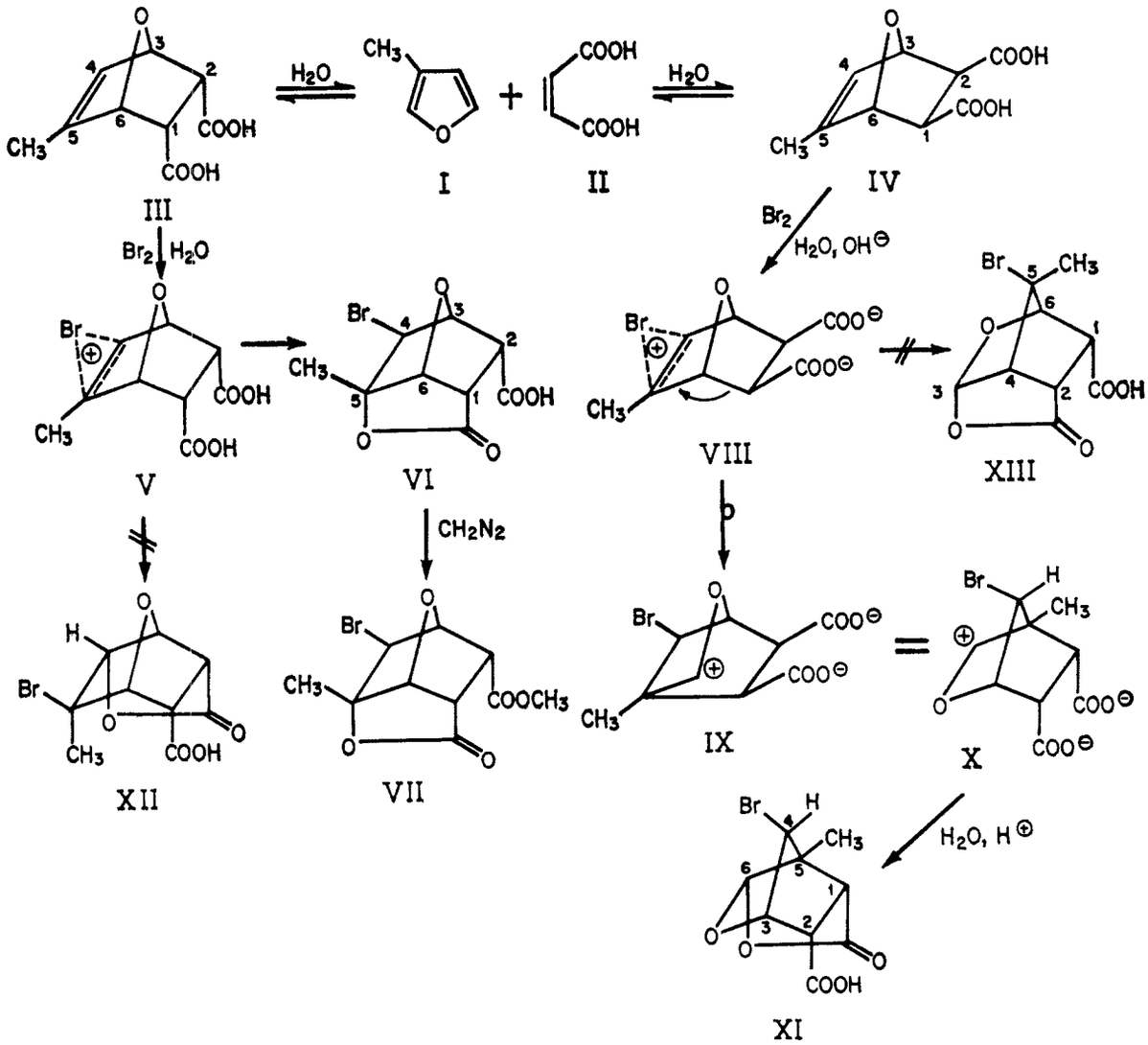

TABLE I

NMR SPECTRAL DATA ON BROMOLACTONIC ACID VI

Protons	Chemical shift, ppm	Integral protons	Multiplicity[a]	Coupling constant,[b] cps
C-1,2	3.28	2	m (AB)	$J_{1,2} = 10.1$
				$J_{1,6} = 4.5$
				$J_{2,3} = 4.4$
				$J_{1,3} = 0.7$
C-3	5.01	1	m	$J_{2,3} = 4.4$
				$J_{3,6} = 1.2$
				$J_{1,3} = 0.7$
C-4	4.96	1	s	
5-CH_3	1.74	3	s	
C-6	5.28	1	q	$J_{3,6} = 1.2$
				$J_{1,6} = 4.5$

[a] m, multiplet; q, quartet; s, singlet. [b] See ref 7.

TABLE II

NMR SPECTRAL DATA ON BROMOLACTONIC ACID XI

Protons	Chemical shift, ppm	Integral protons	Multiplicity	Coupling constant, cps
C-1,2	3.19	2	m (AB)	$J_{1,2} = 10.4$
				$J_{1,6} = 1.2$
				$J_{1,3} = 0.5$
				$J_{2,3} = 1.4$
C-3	4.78	1	m	
C-4	4.53	1	m	
5-CH_3	1.45	3	s	
C-6	5.88	1	q	$J_{1,6} = 1.2$
				$J_{3,6} = 0.5$

the appearance of the methyl band of the ester at $\delta = 3.80$ ppm.

The nmr spectrum of bromolactonic acid XI shows two broad bands, which could not be resolved with the instrument available, for the C-3 ($\delta = 4.78$ ppm) and C-4 ($\delta = 4.53$ ppm) protons. This handicap prevents the exact measure of the coupling constant $J_{3,4}$. The spectrum originated by the C-1, C-2, and C-6 protons allows the structural assignment to be made in an unequivocal way. The C-1 and C-2 protons give rise to an AB-type spectrum ($\delta_{1,2} = 15.0$ cps; $J_{1,2} = 10.4$ cps) centered at $\delta = 3.19$ ppm. The C-1 proton is also coupled to C-6 ($J_{1,6} = 1.2$ cps) and C-3 ($J_{1,3} = 0.5$ cps) protons. The C-2 proton at the same time is coupled to the C-3 proton ($J_{2,3} = 1.4$ cps.). The C-6 proton is responsible for the doublet of doublets at $\delta = 5.88$ ppm as it couples with the C-1 and C-3 protons ($J_{3,6} = 0.5$ cps). The 5-methyl group shows a singlet at $\delta = 1.45$ ppm. The described spectrum is in agreement with the structure XI. Structure XIII can be discarded on the basis of the following evidence. First,

the C-4 proton would be coupled ($J \simeq 4$ cps) to the C-2 and C-3 protons;[4] this is not observed in the spectrum. Second, the same proton of structure XIII should appear at lower field ($\delta \simeq 3$ ppm) which is not observed. Tables I and II present in a condensed form all of the nmr data for compounds VI and XI.

Experimental Section

3-Methylfuran (I) was prepared as described elsewhere[9] and was distilled before use, bp 56° (622 mm).[10]

Bromolactonic Acid VI.—A mixture of 18.1 g (0.22 mole) of 3-methylfuran (I) and 19.7 g (0.10 mole) of maleic anhydride dissolved in 100 ml of water was stirred vigorously at room temperature for 72 hr. The layers were separated and the water layer was treated with bromine until the dark color persisted. The mixture was filtered and the white solid was washed with cold water to yield 14.0 g of bromolactonic acid VI (25% over-all from maleic anhydride). Recrystallization from water gave white creamish plates, mp 212–215°.

Anal.[11] Calcd for $C_9H_9BrO_5$: C, 39.01; H, 3.27. Found: C, 38.98; H, 3.18.

Bromolactone Methyl Ester VII.—A suspension of 3.0 g (0.0108 mole) of bromolactonic acid VI in 100 ml of ether was esterified with an excess of distilled diazomethane in ether. The solid remaining in suspension was filtered off, washed with ether, and dried to yield 2.8 g (89%) of bromolactone methyl ester VII, mp 162–163°.

***exo-cis*-3,6-Endoxo-5-methyl-Δ^4-tetrahydrophthalic anhydride** was prepared according to the procedure of Rinkes[5] with slight modifications. To a warm solution of 7.3 g (0.074 mole) of maleic anhydride in 9 ml of dry benzene was added 6.15 g (0.075 mole) of compound I. The reaction mixture was refrigerated for 30 min. The solvent was then removed at room temperature. The crude solid was washed with ether and dried to yield 13.0 g (98%) of the anhydride of compound IV, mp 77–79°,[12] which showed no traces of the *endo* adduct. This compound was used without any further purification.

Bromolactonic Acid XI.—To a solution of 5.0 g (0.028 mole) of the anhydride of compound IV in 60 ml of 1 *N* sodium hydroxide solution was slowly added an excess of bromine. After addition was complete, a white solid formed and the reaction mixture was acidified to assure complete precipitation. Recrystallization from water gave 4.5 g (58%) of bromolactonic acid XI, mp 232–245° dec.

Anal. Calcd for $C_9H_9BrO_5$: C, 39.01; H, 3.27. Found: C, 38.68; H, 3.12.

Nmr spectra were measured at approximately 30° with a Varian A-60 nmr spectrometer. TMS was used as an external standard. The spectra for all substances were measured in K_2CO_3–D_2O solutions except for compound VII which was measured in $CDCl_3$.

(9) D. M. Burnes, "Organic Syntheses", Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 628.

(10) All boiling and melting points are uncorrected.

(11) The microanalyses were performed by Franz Pascher, Mikroanalytisches Laboratorium, Bonn, Germany.

(12) Rinkes[5] reports mp 82° after two recrystallizations from ether.

Potential Folic Acid Antagonists. II. Deaza Analogs of Methotrexate. II.[1] 2,4-Diamino-6-methyl-3-deazapteridine

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Received January 17, 1966

The preparation of 2,4-diamino-6-methyl-3-deazapteridine (6,8-diamino-2-methylpyrido[2,3-*b*]pyrazine, XVI) was accomplished by a 10-step synthesis from diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (Ia). A key step in the sequence was the preparation of ethyl 6-chloro-4-[(diphenylmethyl)amino]-5-nitro-2-pyridinecarbamate (VIII). Unsuccessful routes to XVI are also discussed.

Our interest in the structural requirements for binding to and, therefore, inhibiting the enzymes involved in folic acid metabolism led us to attempt the synthesis of deaza analogs of aminopterin and methotrexate.[2] The synthesis of such diaminodeaza compounds are, however, fraught with more difficulties than are the syntheses of the parent pteridines, since four rather than two isomers can be formed in the reactions usually employed in the synthesis of folic acid and pteridine analogs.[3] Because of this additional complication, we chose, and have described in a previous publication,[2] an unambiguous method for the synthesis of 2,4-diamino-6-methyl-1-deazapteridine (5,7-diamino-3-methylpyrido[3,4-*b*]-pyrazine), a possible intermediate in the synthesis of 1-deazaaminopterin or 1-deazamethotrexate. Briefly, this method involved the reaction of aminoacetone semicarbazone with diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (Ia)[2] followed by hydrolysis of the semicarbazone and then reduction of the nitro group. The intermediate aminoketopyridine thus formed cyclized spontaneously to the dihydro 1-deazapteridine which was oxidized to the desired ring system. A suitable modification of this reaction sequence has now been used for the preparation of the isomeric 2,4-diamino-6-methyl-3-deazapteridine (6,8-diamino-2-methylpyrido[2,3-*b*]pyrazine, XVI).

Several early attempts to synthesize the desired 3-deazapteridine ring system were based on building the pyrazine ring from the vicinal nitrogen atoms in compound Ia (Scheme I). The alkylation of Ia with chloroacetone to give Ib was considered as a starting point for the synthesis of the 3-deazapteridine XVI. Our inability to isolate Ib, however, precluded this approach. Another scheme involved the preparation of the 2,3-diaminopyridine IIIb and condensation of the latter with pyruvaldehyde to give XVa. Reaction of Ia with aminodiphenylmethane in methanol containing sodium acetate gave diethyl 4-[(diphenylmethyl)amino]-3-nitro-2,6-pyridinedicarbamate (IIa), the urethan groups of which were hydrolyzed with methanolic ammonia at 139° to give 2,6-diamino-4-[(diphenylmethyl)amino]-3-nitropyridine (IIb). Reduction of the nitro group of IIb to give IIIb was attempted with Raney nickel; however, hydrogen uptake was incomplete and a complex mixture of products was

(1) This work was supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51.

(2) For part I of this series, see J. A. Montgomery and N. Wood, *J. Org. Chem.*, **29**, 734 (1964).

(3) Many of these reactions are described by E. L. R. Stokstad, *Vitamins* (N. Y.), **3**, 91 (1954).