the filtrate was taken to dryness. The infrared spectrum at this stage showed two carbonyl bands of moderate strength at 1877 and 1727 $cm^{-1}$ [4] indicating that the residue was essentially hexadecylketene lactone dimer formed in very high yield.

On cautious crystallization from methanol the lactone was freed of traces of other carbonyl components to give purified lactone: mp 64°; ultraviolet transparent, $\tilde{\nu}_{max}^{CS_2}$ 1877, 1727, 839 $cm^{-1}$; yield 91%.

*Anal.* Calcd for $C_{36}H_{68}O_2$: C, 81.13; H, 12.85. Found: C, 81.08; H, 12.90.

**Methyl 2-Hexadecyl-3-oxoarachidate (17-Carbomethoxy Stearone) (III).**—A sample of hexadecylketene lactone dimer was recrystallized from methanol one time without change but a repetition of the operation from boiling methanol gave complete conversion to the methanolytic ring-opened product: mp 63°; $\tilde{\nu}_{max}^{CS_2}$ 1748 (COOMe), 1718 (CO), 1165, 1198, 1262 $cm^{-1}$; nmr δ 3.55 ($OCH_3$), 0.86, 1.21, 2.09, 2.20. A trace of alkali catalyses the methanolysis markedly.

*Anal.* Calcd for $C_{37}H_{72}O_3$: C, 78.66; H, 12.85. Found: C, 78.74; H, 12.85.

**Direct Conversion of Hexadecylketene Lactone Dimer to Stearone. A.**—The lactone (60 mg) was refluxed in pure methanol for 1 hr without undergoing change but when a trace of potassium hydroxide was added the methanolysis product was obtained after an additional 1 hr of reflux. The solution was then made acid with diluted hydrochloric acid. The product, [stearone (45 mg) isolated by ether extraction] was identical in every respect to an authentic specimen.

**B.**—Chromatography of hexadecylketene lactone dimer on Florisil "dried" at 180° for 72 hr gave "hydrolysis" to stearone. The first two cuts eluted with pentane showed traces of unreacted lactone followed by a trace of contaminant methyl stearate. The stearone eluted with methylene chloride.

**Distearoylhydroxamic Acid and Tristearoylhydroxamic Acid.**—Stearoyl chloride (3 molar equiv), 1 equiv of hydroxylamine hydrochloride, and 100 ml of dry (over Linde Molecular Sieve 4A) pyridine were refluxed for 7 hr. Much of the excess pyridine was removed under reduced pressure, and the residue was taken up in chloroform and rapidly washed with ice water and dried by quick filtration through a column of sodium sulfate. The solvent was removed under reduced pressure, and the residue dissolved in pentane, was rapidly filtered through a short inefficient column of Florisil in order to decolorize. The residue, 790 g, mp 65.5–66.0 with refractile material persisting up to 92°, was essentially tristearoylhydroxylamine with a small distearoylhydroxylamine contamination. Fractional crystallization from pentane (discarding the least soluble small first crop) gave 748 g of pure tristearoyl hydroxamic acid: mp 66°, $\tilde{\nu}_{max}^{CS_2}$ 1799, 1722, 1166 $cm^{-1}$.

*Anal.* Calcd for $C_{54}H_{105}NO_4$: C, 77.91; H, 12.72; N, 1.68; mol wt, 832. Found: C, 78.18; H, 12.78; N, 1.61; mol wt, 753–889 thermistor method, 829 *vs.* benzil standard in chloroform.

The remaining material, whose infrared spectrum showed that the material was essentially the tristearoyl derivative, was dissolved in methylene chloride and chromatographed on dried Florisil. Methylene chloride elution gave 20% of the original weight of recovered tristearoyl hydroxamic acid. Elution with 1:1 absolute ethyl ether–methylene chloride gave distearoylhydroxamic acid, mp 107–108°, melting point unchanged by recrystallization. The distearoylhydroxamic acid is a very insoluble material.

*Anal.* Calcd for $C_{36}H_{71}NO_3$: C, 76.40; H, 12.65; N, 2.48. Found: C, 76.57; H, 12.46; N, 2.44.

**Registry No.**—II, 10126-68-8; III, 10126-69-9; distearoylhydroxamic acid, 10126-70-2; tristearoylhydroxamic acid, 10126-71-3.

**Acknowledgment.**—The author wishes to express his appreciation to C. T. Leander for infrared and ultraviolet spectra, R. J. Szamborski for nmr spectra, Miss C. Tylenda for technical assistance, and L. Scroggins and K. Davis for microanalyses.

(4) The authors of ref 3 report 1852 and 1706 $cm^{-1}$ for a phenyl ketene lactone dimer.

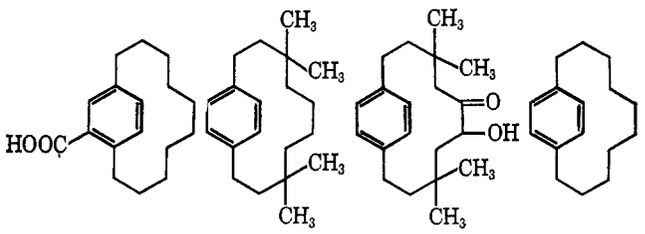
# Many-Membered Carbon Rings. XXV. Derivatives of 3,3,8,8-Tetramethyl[10]paracyclophane[1,2]

A. T. BLOMQUIST AND BRANDES H. SMITH[3]

*Baker Laboratory of Chemistry, Cornell University, Ithaca, New York*

*Received September 1, 1966*

In the course of studies[4] leading to the resolution of [10]paracyclophane-12-carboxylic acid (I), we had occasion to examine the related system, 3,3,8,8-tetramethyl[10]paracyclophane (II), whose acyloin precursor, 3,3,8,8-tetramethyl-6-hydroxy[10]paracyclophan-5-one (III), has been reported .[5] Work with this tetramethyl system was deemed desirable at the time




I II III IV

since the phenomenon of bridge migration in the parent [10]paracyclophane (IV) had not been fully elucidated.[4] Once success had been achieved with the simpler system I, further study of the tetramethyl compound became needless. We do, however, wish to report these partial studies as they further illustrate certain elements of behavior which are characteristic of many of these bridged systems. Additional and extensive background may be found elsewhere.[4,5]

When problems arose in the substitution and resolution studies on the hydrocarbon IV, it was decided to replace hydrogen by methyl at four positions as in II. This was done so as to create bulk in the bridge with attendant restriction of rotation about its carbon–carbon single bonds. This course of action presented several challenging syntheses, not the least of which was the intramolecular acyloin cyclization of the diester, dimethyl *p*-phenylenebis(β,β-dimethyl-δ-valerate). Only by continued refinement of technique was a 38% yield obtained. Clemmensen-type reductions of acyloin functions are well known[6] to produce hydrocarbon and ketone, conditions in general dictating which. However, subjection of the acyloin III to strenuous Clemmensen conditions repeatedly resulted only in incomplete reduction to the ketone, 3,3,8,8-tetramethyl-

(1) Abstracted from part of the dissertation presented by B. H. Smith in June, 1960, to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) The nomenclature used throughout is discussed more fully by B. H. Smith, "Bridged Aromatic Compounds," Academic Press Inc., New York, N. Y., 1964, pp 8–22.

(3) Proctor and Gamble Fellow, Cornell University, 1958–1959. Esso Research and Engineering Co., Linden, N. J.

(4) A. T. Blomquist, R. E. Stahl, Y. C. Meinwald, and B. H. Smith, *J. Org. Chem.*, **26**, 1687 (1961).

(5) A. T. Blomquist and F. Jaffe, *J. Am. Chem. Soc.*, **80**, 3405 (1958).

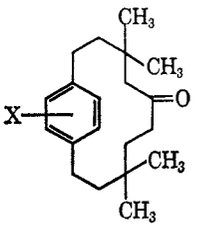
(6) V. Prelog, L. Frankiel, M. Kobelt, and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947); D. J. Cram and H. U. Daeniker, *J. Am. Chem. Soc.*, **76**, 2743 (1954); *Org. Syn.*, **36**, 14; K. L. Wiesner, D. M. MacDonald, E. B. Ingraham, and R. B. Kelly, *Can. J. Res.*, **28B**, 561 (1950).

[10]paracyclophan-5-one (Va); the hydrocarbon II was never detected. Other reduction techniques produced comparable results (see Table I). There seems to us little doubt that the explanation of incomplete reduction has steric origins.

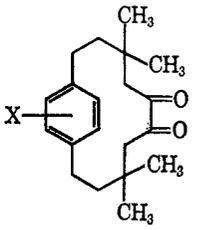
TABLE I

| Starting material | Reagents | Temp, °C | Time | Products, % |
|---|---|---|---|---|
| III | Zn–HCl–HOAc | Reflux | 3.5 hr | Va, 61 |
| | Zn–Cu(OAc)$_2$–HCl–HOAc | Reflux | 9 hr | Va, 28 |
| | Zn–Cu(OAc)$_2$–HCl–HOAc | Reflux | 8 days | Va, 27 |
| Va | Zn(Hg)–HCl–HOAc–toluene | Reflux | 60 hr | Va, 97 |
| | $Na_2SO_4$–$ZnCl_2$–benzene–$(CH_2SH)_2$ | 25 | 7 days | Va, 88 |
| | KOH–$(CH_2OH)_2$–85% $N_2H_4$ | 170 (1 hr), 200 (10.5 hr), and 300 (4 hr) | | Va, 32 |
| | 95% EtOH–85% $N_2H_4$ | Reflux | 11 hr | Va, 100 |
| | 95% EtOH–95+% $N_2H_4$ | Reflux | 6 hr | |
| | Absolute EtOH–95+% $N_2H_4$ | Reflux | 46 hr | Azine of Va |

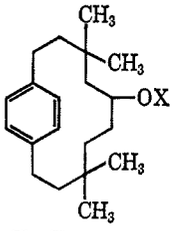
Less direct methods to the synthesis of a potentially resolvable compound thus became necessary. Four routes were examined; none was totally successful.



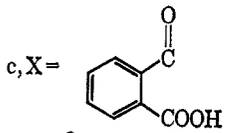
Va, X = H
b, X = Br
c, X = $SO_2NH_2$

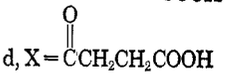


VIa, X = H
b, X = Br
c, X = Cl



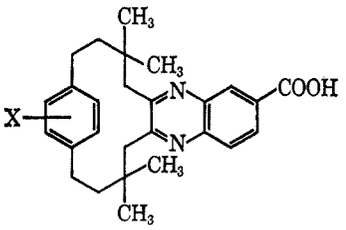
VIIa, X = H
b, X = $SO_2$—$C_6H_5$





d, X = $CCH_2CH_2COOH$

Because of the ready availability, in our laboratory, of numerous reagents for the resolution of optically active carboxylic acids, two carboxy-substituted quinoxalines were chosen for the initial resolution studies. These were 6,7,8,9,14,15,16,17-octahydro-7,7,16,16-tetramethyl-10,13-ethenocyclotetradeca[*b*]quinoxaline-2-carboxylic acid (VIIIa) and its 11(12)-bromo (VIIIb) and 11(12)-chloro (VIIIc) derivatives. Pertinent syntheses were straightforward and details are included in the Experimental Section. Although it was possible to condense the unsubstituted diketone VIa with 3,4-diaminobenzoic acid to give the quinoxaline VIIIa, its *ortho*-halo derivatives VIb and c were inert under the same standard conditions,[7] and even under more vigorous ones.



VIIIa, X = H
b, X = Br
c, X = Cl

This extreme difference in reactivity between the substituted and unsubstituted diketones is strange since the point of substitution is far removed from the diketone function. While no complete explanation is available, the reason surely has steric origins. Barton and co-workers[8] have reported the observance of long-range effects ("conformational transmission") on mutarotation in systems of fairly rigid conformation. This is far from the complete lack of reactivity as observed here. However, it is possible to invoke a form of conformational transmission if we assume that the introduction of the large-volume halogen atom forces rotation of the benzene ring about the two *para* bonds, thus "locking" its conformation. This would result in the two adjacent benzene hydrogens butting against the diketone function, and severely inhibiting reaction.

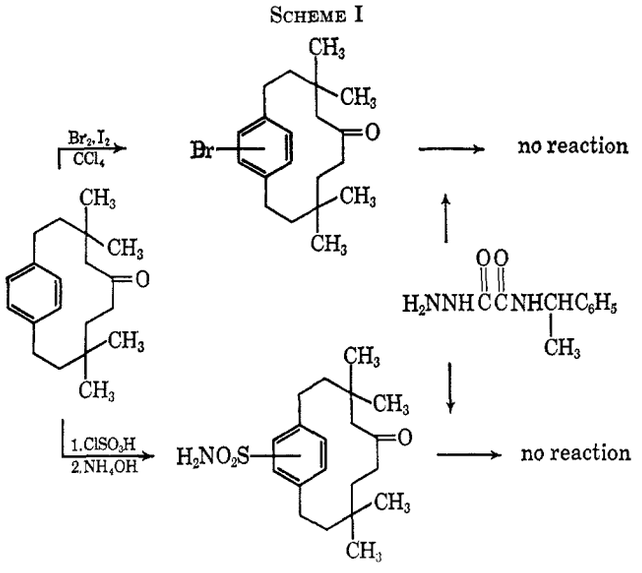
Further attempts at preparation of the substituted quinoxalines VIIIb and c by halogenation of the parent species VIIIa resulted in the formation of inseparable mixtures. One would expect the carboxyl group to deactivate the heterocyclic quinoxaline system with substitution then taking place solely in the paracyclophane moiety. Results show this assumption to be incorrect.

Other resolution attempts involved the bromo and sulfamido derivatives of the monoketone Va. These were prepared by standard methods[9] and formation of suitable carbonyl derivatives[10] was attempted as outlined in Scheme I. All attempts at semioxamazone formation failed and the method was abandoned.

Formation of carbon–hydrogen bonds by hydride displacement on tosylate derivatives of alcohols is well known.[11] Lithium aluminum hydride reduction to the ketone Va gave the alcohol 3,3,8,8-tetramethyl[10]-paracyclophan-5-ol (VIIa) in fair yield. The tosylate, acid phthalate, and acid succinate derivatives, which could be used further, could not be formed. It is interesting to note that the postulate of increasing steric hindrance proposed for the ketone Va should be even more forceful here, and in addition has supporting spec-

(7) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).
(8) D. H. R. Barton and A. J. Head, *J. Chem. Soc.*, 932 (1956); D. H. R. Barton, A. J. Head, and P. J. May, *ibid.*, 935 (1957).
(9) W. J. Hickinbottom, "Reactions of Organic Compounds," 3rd ed, Longmans Green and Co., New York, N. Y., 1957, p 82.
(10) N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, **15**, 42 (1950).
(11) Norman G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp 855–873.

SCHEME I




troscopic evidence. The expanded infrared spectrum[12] in the region 3550–3700 $cm^{-1}$ clearly indicates a nonsymmetrical triplet with $\lambda_{max}^{CCl_4}$ 3625.1 $cm^{-1}$ and $\lambda_{shoulder}^{CCl_4}$ 3640.3 and 3601.8 $cm^{-1}$. This behavior is characteristic of a sterically hindered hydroxyl group rather than due to hydrogen bonding.[13] The 3625-$cm^{-1}$ peak is characteristic of secondary alcohols, while the 3640-$cm^{-1}$ shoulder can be attributed to steric hindrance. The 3601-$cm^{-1}$ shoulder cannot be assigned with certainty, but were it due to hydrogen bonding a larger shift than observed would be expected.

### Experimental Section[14]

**3,3,8,8-Tetramethyl-6-hydroxy[10]paracyclophan-5-one (III).**—This compound was prepared by the acyloin cyclization of dimethyl *p*-phenylenebis(β,β-dimethyl-δ-valerate).[5] Prior to addition of the diester, the sodium dispersion was stirred vigorously for 2 hr. Yields of 35–38% were obtained and the distilled mixture of acyloin and diketone was used directly in subsequent reactions.

**Reduction of the Acyloin III by Zinc Dust and Hydrochloric Acid.**—The reduction of the acyloin III was carried out using the method of Prelog.[6] A mixture of 4.0 g (13 mmoles) of the acyloin–diketone mixture, 10.0 g (15 mg-atoms) of zinc dust, and 70 ml of glacial acetic acid was brought to reflux with stirring and 50 ml of concentrated hydrochloric acid was added dropwise. At 90-min intervals, two more 50-ml portions of concentrated hydrochloric acid were added. Refluxing and stirring were continued for 30 min beyond the final addition. The reaction mixture was filtered hot and the filtrate was poured into 350 ml of saturated sodium chloride solution. The filtered insolubles were washed with ether and the aqueous mixture was extracted with ether. The combined organic portions were washed successively with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution, and dried over magnesium sulfate. Following this, the ether was distilled, leaving a white, waxy solid. This solid was sublimed at 100° (0.5 mm) to give 2.3 g (61%) of white needles, mp 135–136°. The spectrum showed strong carbonyl absorption at 5.84 μ and no hydroxyl absorption in the 2.8–3.1-μ region. This and the analysis confirmed the solid as the monoketone Va.

*Anal.* Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56; mol wt, 286. Found: C, 84.14, 84.05; H, 10.78, 10.61; mol wt, 275.

The **2,4-dinitrophenylhydrazone derivative** was prepared in the regular manner,[15] mp 219.5–220° (ethanol–ethyl acetate).

*Anal.* Calcd for $C_{26}H_{34}N_4O_4$: C, 66.93; H, 7.35; N, 12.01. Found: C, 67.07; H, 7.48; N, 11.85.

The ketone was oxidized by the usual sodium dichromate–aqueous sulfuric acid method[16] giving terephthalic acid (identified as the dimethyl ester).

**Reduction of the Acyloin III Using Hydrochloric Acid and a Zinc–Copper Couple.**—A mixture of 3.6 g (12 mmoles) of the acyloin–diketone product, 20.0 g (300 mg-atoms) of zinc dust, 0.5 g of cupric acetate, and 50 ml of glacial acetic acid was brought to reflux with stirring and 240 ml of concentrated hydrochloric acid added over a 7-hr period. Heating and stirring were continued for 30 min beyond the end of the addition. The reaction mixture was filtered cold. Work-up as described in the previous method gave 1.05 g (28%) of the ketone Va, mp 134–136°. No trace of hydrocarbon was detected. Another attempt as above, but utilizing 700 ml of concentrated hydrochloric acid over a 7-day reflux period, gave 1.02 g (27%) of the same ketone.

**Attempted Reduction of the Ketone Va Using Amalgamated Zinc in a Mixed-Solvent System.**[17]—A mixture of 20.0 g (300 mg-atoms) of zinc dust (amalgamated with 4.0 g of mercuric chloride),[18] 30 ml of water, 60 ml of concentrated hydrochloric acid, 60 ml of toluene, and 3.0 g of the ketone Va was brought to reflux with stirring. At 12-hr intervals four 30-ml portions of concentrated hydrochloric acid were added and the reflux period was continued for 12 hr beyond the final addition. Work-up as in the first attempt left a solid residue of the ketone, 2.9 g (97% recovery).

**Attempted Reduction of the Ketone Va by Reductive Desulfurization.**—A mixture of 0.25 g (0.87 mmole) of the ketone Va, 1.0 g (7.1 mmoles) of sodium sulfate, 0.20 g (1.5 mmoles) of freshly fused zinc chloride, 0.15 g (1.6 mmoles) of ethanedithiol, and 15 ml of anhydrous benzene was left in a tightly stoppered erlenmeyer flask at room temperature. Periodically, it was shaken. After 7 days the insolubles were filtered and washed thoroughly with benzene. The organic filtrates were combined and evaporated to dryness. The solid residue was then dissolved in 50 ml of 95% ethanol and 5.0 g of W-2 Raney nickel catalyst[19] added. After a 3-hr reflux, the mixture was filtered hot and the solvent was evaporated leaving 0.22 g (88%) of the ketone Va.

**Attempted Wolff–Kishner Reduction of the Ketone Va. A.**—The method used was that described in *Organic Reactions*.[20] The usual work-up left a residue of 0.32 g (73% recovery) of the ketone.

**B.**—The basic procedure used in a second attempt was that of Zelinskii and Elagina,[21] but difficulties in the formation of the hydrazone required some modification of their method. The regular method, and a modification using 95% ethanol and 95+% hydrazine with the usual work-up both gave a near quantitative return of unchanged ketone. This unchanged ketone was then refluxed for 46 hr with a mixture of 10 ml of absolute ethanol and 25 ml of 95+% hydrazine which, following the usual work-up, gave a tan solid, mp 210–227°. Chromatography using neutral aluminum oxide gave, with a 50% petroleum ether (bp 60–70°)–50% benzene eluent, a tan solid, mp 233–240°. After five recrystallizations (ethyl acetate) the melting point had been increased to 245–248° (sealed tube). The usual test for nitrogen was positive and a peak at 6.1 μ in the infrared spectrum supported the formation of a carbon–nitrogen double bond. Nitrogen–hydrogen stretching absorption in the region 2.86–3.04 μ was absent.

*Anal.* Calcd for $C_{20}H_{32}N_2$: C, 79.94; H, 10.74; N, 9.33; mol wt, 300. Found: C, 84.70; H, 10.48; N, 4.88; mol wt, 569. Calcd for $C_{40}H_{60}N_2$: C, 84.44; H, 10.63; N, 4.93; mol wt, 569.

(12) In carbon tetrachloride, using a lithium fluoride prism.

(13) We are indebted to Dr. P. von R. Schleyer for this spectrum and for helpful interpretation of it. See also, J. C. Cook and I. H. Reece, *Australian J. Chem.*, **14**, 211 (1961), for further discussion.

(14) All melting points and boiling points are uncorrected. Infrared spectra were determined with Perkin-Elmer double-beam spectrophotometers, Models 21 and 137. Ultraviolet spectra were determined with a Beckman DK recording spectrophotometer.

(15) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 219.

(16) Reference 15, p 250.

(17) S. Harris and J. S. Pierce, *J. Am. Chem. Soc.*, **62**, 2223 (1940); W. E. Bachmann and E. O. Edgerton, *ibid.*, **62**, 2219 (1940).

(18) E. L. Martin, *Org. Reactions*, **1**, 155 (1942), specifically p 163.

(19) R. Mozingo, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(20) D. Dodd, *Org. Reactions*, **4**, 378 (1948), specifically pp 385 and 391.

(21) N. D. Zelinskii and N. V. Elagina, *Compt. Rend. Acad. Sci. USSR*, **49**, 568 (1945).

The elemental analysis and spectral data are consistent with the solids being 3,3,8,8-tetramethyl[10]paracyclophan-5-one azine, the diylidene derivative of the ketone Va.

**3,3,8,8-Tetramethyl[10]paracyclophan-5-ol (VIIa).**—A mixture of 50 ml of anhydrous diethyl ether and 1.1 g of 95+% lithium aluminum hydride, protected from moisture, was cooled to −10° by an external ice–acetone bath and the system swept with dry, high-purity nitrogen. A solution of 1.0 g (35 mmoles) of the ketone Va, in 30 ml of anhydrous diethyl ether, was added slowly with cooling and continued nitrogen flow. The mixture was stirred at room temperature for 48 hr. An additional portion of 50 ml of anhydrous diethyl ether was added, the system cooled to −10°, and hydrolysis was accomplished with 10% aqueous hydrochloric acid. The usual work-up followed by chromatography using neutral aluminum oxide as adsorbent gave, with a 50% petroleum ether (bp 30–60°)–50% benzene eluent, 0.56 g (51%) of a white solid, mp 132–148°. Three recrystallizations [petroleum ether (bp 60–70°)] gave pure alcohol, mp 153–153.5°.

*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18; mol wt, 288. Found: C, 83.54; H, 11.07; mol wt, 271.

**Attempted Preparation of 3,3,8,8-Tetramethyl[10]paracyclophan-5-ol Tosylate (VIIb).**—The method used was that of Tipson.[22] The usual work-up gave 0.065 g (93%) of unreacted alcohol.

**Attempted Preparation of 3,3,8,8-Tetramethyl[10]paracyclophan-6-ol Acid Phthalate (VIIc).**—A mixture of 0.050 g (0.17 mmole) of the alcohol VIIa, 0.030 g (0.20 mmole) of phthalic anhydride, and 10 ml of anhydrous toluene was heated at 110° for 37 hr. Standard work-up gave 47 mg (94%) of unreacted alcohol. In a second attempt, a mixture of 0.50 g (1.7 mmoles) of the alcohol VIIa, 1.0 g (6.7 mmoles) of phthalic anhydride, and 25 ml of anhydrous xylene was refluxed vigorously for 48 hr. Chromatography of the crude material using neutral aluminum oxide as the adsorbent gave, with 80% petroleum ether (bp 30–60°)–20% diethyl ether as eluent, 0.11 g (22%) of unreacted alcohol.

**Attempted Preparation of 3,3,8,8-Tetramethyl[10]paracyclophan-5-ol Acid Succinate (VIId).**—A mixture of 0.10 g (0.34 mmole) of the alcohol VIIa, 0.050 g (0.49 mmole) of carefully purified succinic anhydride,[23] and 12 ml of anhydrous xylene was refluxed for 11 hr. Usual work-up gave 0.075 g (75%) of unreacted alcohol.

**3,3,8,8-Tetramethyl[10]paracyclophane-5,6-dione (VIa).**—The bismuth oxide procedure of Rigby was used.[24] A mixture of 500 ml of glacial acetic acid, 46.5 g (100 mmoles) of bismuth oxide, and 9.8 g (32 mmoles) of the crude acyloin–diketone product was refluxed for 5 hr, cooled, and filtered. The filtrate was poured into 2 l. of cold water and the mixture was extracted with benzene and with ether. The combined organic extracts were washed with cold water and with saturated sodium bicarbonate solution and dried. The solvent was distilled leaving an orange-yellow residue. Two recrystallizations (ethanol–water) gave 9.5 g (98.6%) of the diketone as yellow needles, mp 135.8–136.5°.

*Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; mol wt, 300. Found: C, 80.11; H, 9.40; mol wt, 307.

**6,7,8,9,14,15,16,17-Octahydro-7,7,16,16-tetramethyl-10,13-ethenolcyclotetradeca[*b*]quinoxaline-2-carboxylic Acid (VIIIa).**—The method of Leonard and Mader[8] was used. A mixture of 1.0 g (3 mmoles) of the diketone VIa, 0.51 g (3.3 mmoles) of 3,4-diaminobenzoic acid, and 25 ml of glacial acetic acid was refluxed for 4 hr, cooled to room temperature, poured into 500 ml of cold water, and allowed to stand for 4 hr. The precipitated solid was filtered and dried *in vacuo* at room temperature. Recrystallization, once from a chloroform–petroleum ether (bp 60–70°) mixture and five times from ethanol–water, gave 0.74 g (49%) of the quinoxaline as an amorphous tan solid, mp 246–248°.

*Anal.* Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73; mol wt, 417. Found: C, 78.12; H, 7.82; N, 6.88; mol wt, 407.

The ultraviolet spectrum in 95% ethanol gave the following peaks: $\lambda_{max}$ 213 (log $\epsilon$ 4.44), 243 (4.35), 315 (3.70), and 329 m$\mu$ (3.75); $\lambda_{shoulder}$ 233 (log $\epsilon$ 4.29), 271.5 (3.79), 293 (3.57), and 300 m$\mu$ (3.53).

**12-Bromo-3,3,8,8-tetramethyl[10]paracyclophane-5,6-dione (VIb).**—A black flask was charged with 25 ml of carbon tetrachloride, 0.400 g (1.33 mmoles) of the diketone VIa, and a small crystal of iodine. This was stirred for 15 min by means of a magnetic stirring apparatus. A solution of 0.210 g (1.34 mmoles) of bromine in 10 ml of carbon tetrachloride was added over a 5-min period. An immediate evolution of hydrogen bromide was noted. The reaction mixture was stirred overnight, poured into 100 ml of 1 *M* sodium bisulfite solution, and stirred again until the dark color of excess bromine had disappeared. The organic layer was separated, washed with cold water, and dried. Removal of the solvent under reduced pressure at room temperature left a yellow residue. Recrystallization (ethanol–water) gave 0.350 g (69%) of the bromo diketone VIb as yellow needles, mp 166.5–167.5°.

*Anal.* Calcd for $C_{20}H_{27}BrO_2$; C, 63.32; H, 7.17; Br, 21.07; mol wt, 379. Found: C, 63.52; H, 7.27; Br, 21.33; mol wt, 369.

The usual sodium iodide in acetone and alcoholic silver nitrate tests[25] confirmed that the halogen was in the aromatic nucleus.

**Attempted Preparation of 11(12)-Bromo-6,7,8,9,14,15,16,17-octahydro-7,7,16,16-tetramethyl-10,13-ethenocyclotetradeca[*b*]-quinoxaline-2-carboxylic Acid (VIIIb).**—A mixture of 0.252 g (0.66 mmole) of the bromo diketone VIb, 0.101 g (0.67 mmole) of 3,4-diaminobenzoic acid, and 12 ml of glacial acetic acid was refluxed for 9 hr. The usual work-up gave 0.184 g of unreacted bromo diketone.

**Bromination of the Quinoxaline VIIIa.**—A mixture of 25 ml of carbon disulfide, 0.245 g (0.6 mmole) of the quinoxaline VIIIa, and a crystal of iodine was placed in a black flask and stirred for 15 min. A solution of 0.94 g (0.6 mmole) of bromine of 5 ml of carbon disulfide was introduced over a 5-min period. The mixture was stirred for 24 hr, then poured into 75 ml of 1 *M* sodium bisulfite solution, and stirred until the dark color of excess bromine had disappeared. The organic layer was washed with cold water, dried, and the solvent was removed *in vacuo* at room temperature to leave a tan residue, mp 185–215° with decomposition. Numerous recrystallizations (ethanol–water) gave light tan crystals, mp 172–175° with partial decomposition, 193–202° with total decomposition. The elemental analysis was incorrect for either a mono- or dibromo derivative. No further purification was attempted.

*Anal.* Calcd for $C_{27}H_{31}BrN_2O_2$: C, 65.45; H, 6.31; Br, 16.13; N, 5.66; mol wt, 495. Found: C, 63.00; H, 6.39; Br, 21.31; N, 4.39; mol wt, 202.

**12-Chloro-3,3,8,8-tetramethyl[10]paracyclophane-5,6-dione (VIc).**—The method of Keefer and Andrews[26] was used. A mixture of 0.60 g (2.0 mmoles) of the diketone VIa, 0.65 g (2.4 mmoles) of iodobenzene dichloride,[27] and 80 ml of glacial acetic acid was stirred for 20 hr while protected from light. The reaction mixture was poured into 250 ml of cold water and allowed to stand for 4 hr. The solid was filtered and dried in air to yield 0.59 g of a yellow solid, mp 150–162°. Two recrystallizations (ethanol–water) gave the chlorodiketone as yellow needles, mp 166–167°.

*Anal.* Calcd for $C_{20}H_{27}ClO_2$: C, 71.73; H, 8.13; Cl, 10.59; mol wt, 335. Found: C, 71.83; H, 8.22; Cl, 10.45; mol wt, 322.

The usual tests[25] confirmed that the halogen was in the aromatic nucleus.

**Attempted Preparation of 11(12)-Chloro-6,7,8,9,14,15,16,17-octahydro-7,7,16,16-tetramethyl-10,13-ethenocyclotetradeca[*b*]-quinoxaline-2-carboxylic Acid (VIIIc).**—Again the method of Leonard and Mader[8] was employed. The usual work-up and subsequent recrystallization (ethanol–water) gave 0.205 g of unreacted chloro diketone.

**Chlorination of the Quinoxaline VIIIa.**—A mixture of 0.300 g (0.72 mmole) of the quinoxaline VIIIa, 0.198 g (0.72 mmole) of iodobenzene dichloride,[27] and 50 ml of glacial acetic acid was placed in a black flask and stirred for 20 hr. The reaction mixture was poured into cold water and allowed to stand for 1 hr. The solid was filtered and dried in the air. Two recrystallizations (ethanol–water) gave 0.215 g (66%) of chlorinated product, mp 172–175°, with sintering at 166°. Elemental analysis was incorrect for either a mono- or dichloro derivative although the usual tests[25] supported the fact that the halogen was in an aromatic nucleus. No further purification was attempted.

(22) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(23) R. L. Shiner and H. C. Struck, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 561.

(24) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(25) Reference 15, pp 136–137, 158–160.

(26) R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **79**, 4348 (1957).

(27) Reference 19, p 482.

*Anal.* Calcd for $C_{27}H_{31}ClN_2O_2$: C, 71.90; H, 6.93; Cl, 7.86; N, 6.21; mol wt, 451. Found: C, 71.82; H, 7.08; Cl, 10.24; N, 6.25; mol wt, 345.

**12(13)-Bromo-3,3,8,8-tetramethyl[10]paracyclophan-5-one (Vb).**—A mixture of 25 ml of carbon tetrachloride, 0.286 g (1 mmole) of the ketone Va, and a crystal of iodine was placed in a black flask and stirred for 15 min. A solution of 0.160 g (1 mmole) of bromine in 15 ml of carbon tetrachloride was added over a 5-min period and the entire mixture was stirred for 22 hr. The solution was poured into 100 ml of 1 *M* sodium bisulfite solution and stirred until colorless. The organic layer was washed with cold water, dried, and the solvent was evaporated, leaving a white solid, mp 150–155°. Three recrystallizations (ethanol–water) gave 0.300 g (84%) of the bromo ketone as white needles, mp 169–168°.

*Anal.* Calcd for $C_{20}H_{29}BrO$: C, 65.75; H, 8.00; Br, 21.87; mol wt, 365. Found: C, 65.97; H, 8.16; Br, 22.14; mol wt, 367.

The usual tests[25] supported the fact that the halogen was in the aromatic nucleus.

**3,3,8,8-Tetramethyl-5-oxo[10]paracyclophane-12(13)-sulfonamide (Vc).**—A solution of 0.50 g (1.7 mmoles) of the ketone Va in 2 ml of anhydrous chloroform was cooled to 0° and 10 ml of chlorosulfonic acid added all at once. The reaction mixture was allowed to warm to room temperature over the course of 1 hr, then poured over ice, and finally extracted with chloroform. The chloroform solution was placed in an erlenmeyer flask, 20 ml of concentrated ammonium hydroxide was added, and the entire mixture was stirred at 50° for 4 hr. The dried chloroform layer was evaporated leaving a tan solid, mp 165–175°. Three recrystallizations [petroleum ether (bp 90–100°)–benzene] gave a light tan solid, mp 174.5–175.5°.

*Anal.* Calcd for $C_{20}H_{31}NO_3S$: C, 65.71; H, 8.55; N, 3.83; S, 8.77. Found: C, 65.96; H, 8.55; N, 3.70; S, 8.75.

Attempts to form the **semioxamazone derivative** by the method Leonard and Boyer[11] using *d*-5-(α-phenylethyl)semioxamazide failed to yield a derivative.

**Registry No.**—Va, 10197-52-1; 2,4-dinitrophenylhydrazone of Va, 10197-53-2; Vb 11 isomer, 10235-62-8; Vb 12 isomer, 10197-54-3; Vc 12 isomer, 10197-55-4; Vc 11 isomer, 10239-63-1; VIa, 10197-56-5; VIb, 10197-57-6; VIc, 10197-58-7; VIIa, 10197-59-8; VIIIa, 10197-60-1; VIIIc 12 isomer, 10197-61-2; VIIIc 11 isomer, 10197-62-3; 3,3,8,8-tetramethyl[10]parcyclophan-5-one azine, 10197-63-4.

## Nucleotides. VII.[1] Preparation and Optical Rotatory Dispersion of Some 9β-D-Ribofuranosyl-3,5′-purine Cyclonucleosides[2]

ALEXANDER HAMPTON AND A. W. NICHOL[3]

*Cancer Research Unit (McEachern Laboratory) and Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada*

*Received December 28, 1966*

Cyclization of purine and pyrimidine ribonucleosides to 3,5′- and 2,2′-cyclonucleosides, respectively, has until recently been restricted to intramolecular alkylation involving 5′- or 2′-tosyl or -iodo derivatives of the nucleosides.[4] However, Fox, *et al.*,[5] have prepared 2,2′-anhydro-1-β-D-arabinofuranosyluracil directly by treatment of uridine with thiocarbonyldiimidazole. A similar reaction between uridine and diphenyl carbonate is also useful for production of the same 2,2′-cyclonucleoside.[6] Diphenyl carbonate converts adenosine and inosine to the 2′,3′ cyclic carbonates[6] and under appropriate conditions can also convert inosine to bis(inosine 5′-)carbonate.[1] The present communication describes the reactions of this reagent with other nucleosides. An interesting finding was that xanthosine can be smoothly converted, *via* a 2′,3′-carbonate, to 3,5′-cycloxanthosine.

The preparation of 2,2′-anhydro-1-β-D-arabinofuranosylcytosine by treatment of cytidine with polyphosphoric acid has been described.[7] Treatment of $N^4,O^{3'},O^{5'}$-triacetylcytidine with *p*-toluenesulfonyl chloride yields $N^4,O^{3'},O^{5'}$-triacetyl-1-β-D-arabinofuranosylcytosine, presumably through the corresponding 2,2′-cyclonucleoside.[8] Attempts to prepare a 2,2′-cyclonucleoside by reaction of cytidine, 5′-O-tritylcytidine[9] or $N^4$-benzoylcytidine[10] with diphenyl carbonate yielded mixtures of at least six products.[11] Similar results were obtained when the above compounds were treated with *p*-nitrophenoxycarbonyl chloride in pyridine.

Reaction of xanthosine (**1**) with diphenyl carbonate yielded a product which analyzed as the 2′,3′-carbonate of 3,5′-cycloxanthosine (**2**). In accord with the proposed structure the compound did not react with periodate in the manner of a *cis*-α-glycol, but showed carbonyl absorption in the region 1830 $cm^{-1}$ typical of organic five-membered cyclic carbonates.[12] On mild alkaline hydrolysis a compound was obtained which showed properties identical with 3,5′-cycloxanthosine (**3**) recently prepared[13] from 2′,3′-O-isopropylidene-3,5′-cycloguanosine by successive alkaline and acidic treatments. Diazotization of 2′,3′-O-isopropylidene-3,5′-cycloguanosine (**4**) followed by deblocking produced the same cycloxanthosine. The conversion of **4** to **3** occurred in low over-all yield,[14] but served to add to the already substantial evidence[13] that cyclization is at the 3 position. (See Scheme I.) As expected, the $pK_a$ (9.4) of **3** was similar to that (10.1)[15] of 3,9-dimethylxanthine. The conversion of **1** to **2** probably involves attack by N-3 on a 5′-carbonate derivative of xanthosine 2′,3′-carbonate because under similar conditions diphenyl carbonate converts inosine to bis(inosine 2′,3′-carbonate 5′-)carbonate *via* inosine 2′,3′-carbonate[1] and it also appears to convert isopropylideneguanosine to a 5′-carbonate derivative (see below).

Attempts to prepare 3,5′-cycloguanosine by reac-

(1) Part VI: A. Hampton and A. W. Nichol, *J. Org. Chem.*, **31**, 3402 (1966).

(2) This work was supported by funds from the National Cancer Institute of Canada and the Medical Research Council of Canada (Grant MA-1591).

(3) Institute of Medical Research, Royal North Shore Hospital, Sydney, Australia.

(4) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press Inc., New York, N. Y., 1963, pp 15–23.

(5) J. J. Fox and I. Wempen, *Tetrahedron Letters*, 643 (1965); J. J. Fox, N. Miller, and I. Wempen, *J. Med. Chem.*, **9**, 101 (1966).

(6) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).

(7) E. R. Walwick, W. K. Roberts, and C. A. Dekker, *Proc. Chem. Soc.*, 84 (1959).

(8) H. P. M. Fromageot and C. B. Reese, *Tetrahedron Letters*, 3499 (1966).

(9) H. Bredereck, *Z. Physiol. Chem.*, **223**, 61 (1934).

(10) D. H. Rammler and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 3112 (1962).

(11) The conditions used were those of ref 6, with $NaHCO_3$ as catalyst. With cytidine, 1.2 molar equiv of phenol was also used as catalyst (*cf.* the conversion of adenosine to adenosine 2′,3′-carbonate[6]).

(12) L. Hough, J. E. Priddle, and R. S. Theobald, *J. Chem. Soc.*, 1934 (1962).

(13) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28**, 3483 (1963).

(14) 3-Methylguanine is also resistant to diazotization: G. B. Elion, *ibid.*, **27**, 2478 (1962); L. B. Townsend and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 3008 (1962).

(15) W. Pfleiderer and G. Nübel, *Ann.*, **647**, 155 (1961).