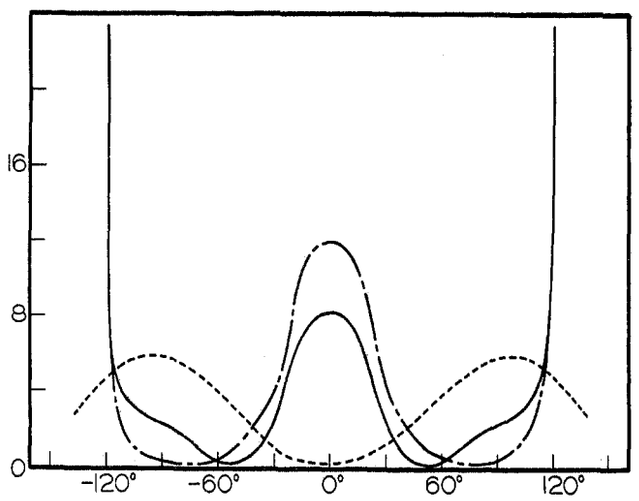

Figure 1.—Energy profiles as a function of the twist angle ϕ, for diamide III (half-molecule): — — —, nonbonded atoms interactions; – – – –, conjugative energy; ————, relative conformational energy. The 0° position is that where the carbonyl bisects the cyclopropane ring (maximum orbitals overlap).

However, if it is true that the geometrical arrangement with the amide (or thioamide) unit bisecting the cyclopropane ring meets the Walsh[1] requirements for the maximum overlap of cyclopropyl and carbonyl orbitals, an inspection of molecular models reveals that the nonbonded atom interactions are very unfavorable. As a consequence, a preferred conformation has to be assessed taking into account both conjugative and steric factors.

The conjugative ability of cyclopropane and carbonyl groups at the "maximum overlap" conditions has been estimated[4,5] to be about 6.0 kcal/mol in cyclopropanecarboxaldehyde, a system reasonably free from steric restraints. Assuming[4,5] a cosine[2] dependence of the conjugative energy from the angle of twist ϕ, the latter energy can be calculated for each ϕ value.

In Figure 1 are reported, as a function of the twist angle ϕ, the nonbonded interactions,[13] the conjugative energy, and the resultant relative conformational energy curves, relative to the half-molecule of diamide III.

It is apparent that the conformational minima are removed about 50–60° from the maximum-overlap position; this would still allow more than one-half of the maximum conjugative energy to be present.

This simple analysis appears to provide a more realistic basis to rationalize the transmission of electronic effects observed in the case of diamide III. Thus, it is not necessary to have coincidence between the maximum orbital overlap and the actual preferred conformation in order to get a sizable conjugative interaction and, therefore, the transmission of electronic effects through the cyclopropane ring.

Experimental Section

Spectra were recorded on a Jasco-Durrum ORD/CD/UV-5 spectropolarimeter; concentration 10^{-2}–10^{-3} M, cell length 0.1–1.0 mm, temperature 20–25°. All ORD/CD data are given in deg cm²/dmole of substrate.

Tetramethylenesulfone (Aldrich Chemical Co.) and methanesulfonic acid (Eastman Kodak Co.) were used without further purification.

(−)-(1*R*,2*R*)-*trans*-2-Phenylcyclopropanecarboxylic Acid (I).—(−)-(1*R*,2*R*)-*trans*-2-Phenylcyclopropanecarboxylic acid (I) was prepared as previously described:[15] mp 48.5–49.5° [petroleum ether (bp 30–60°)]; $[\alpha]^{20}D$ −410° ($CHCl_3$, 1.0 g/dl) [lit.[14a] mp 51–52°; $[\alpha]^{24}D$ −368° ($CHCl_3$, 0.931 g/dl)].

Bis-1,4-[(−)-(1*R*,2*R*)-2-phenylcyclopropanecarbonyl]-2,5-dimethylpiperazine (III).—(−)-(*R*)-*trans*-2-Phenylcyclopropanecarboxylic acid and a catalytic amount of anhydrous zinc chloride were added to thionyl chloride (120% excess relative to carboxyl groups) at room temperature. The mixture was stirred at 40° for 3 hr. The excess thionyl chloride was then removed under reduced pressure and the residue was fractionated to afford an 85% yield of the acid chloride, bp 80° (0.25 mm).

A mixture of 0.193 g (1.69 mmol) of *trans*-2,5-dimethylpiperazine (DMPIP), 9.32 ml (3.63 mmol) of 0.4 N aqueous NaOH solution, and 35.5 ml of methylene chloride was precooled to 0° in a Waring semimicro blender. This mixture was cooled in ice and vigorously stirred during the addition of 0.641 g of acid chloride and for an additional 10 min. The reaction mixture was filtered through a medium sintered glass funnel and the methylene chloride phase was separated and evaporated to dryness to afford 0.68 g (~100% based on DMPIP) of crude III which was purified by column chromatography (Florisil 60–100 mesh and 160 ml, MeOH 60 ml/hr, room temperature, retention volume 140–200 ml) and two recrystallizations from *n*-hexane, mp 120–121°.

Anal. Calcd for $(C_{10}H_9O_2)_2(C_6H_{12}N_2)$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.76; H, 7.64; N, 6.84.

Registry No.—I, 3471-10-1; I (acid chloride), 37107-48-5; III, 37107-49-6.

Acknowledgments.—The authors wish to thank Dr. Y. Shimokawa for his help in the preparation of compounds I and II and are grateful for financial support by the Department of the Army, Research Office (Durham), under Grant DAHCO-4-69-C-0050.

(13) The nonbonded atoms interactions were estimated using pertinent literature data on interatomic distances and bond angles.[5] Coefficients for the pair-wise Lennord-Jones potential functions and for angular deformations were taken from Scott and Scheraga.[14]

(14) R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, **45**, 2091 (1966); T. Ooi, R. Scott, G. Vanderkooi, and H. A. Scheraga, *ibid.*, **46**, 4410 (1967).

(15) (a) H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.*, **83**, 2138 (1961); (b) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).

A Convenient Synthesis of β-Halopyruvaldoximes

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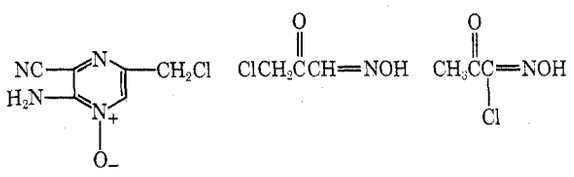
In order to further our recent studies on unequivocal syntheses of 6-substituted pteridines,[1,2] we required large quantities of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**1**), obtained in good yield by condensation of aminomalononitrile with β-chloropyruvaldoxime (**2**). The preparation of **2** had previously been accomplished by chlorination of pyruvaldoxime in dilute chloroform solution,[3] but this proved to be a tedious and unpredictable reaction. Major problems

(1) E. C. Taylor in "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Ltd., Tokyo, 1970, pp 79–93.

(2) E. C. Taylor, K. L. Perlman, I. P. Sword, M. Séquin-Frey, and P. A. Jacobi, *J. Org. Chem.*, submitted for publication.

(3) J. Armand, J-P. Guette, and F. Valentini, *C. R. Acad. Sci., Ser. C*, **263**, 1388 (1966).

were the consistently poor yields, concomitant formation of the isomeric hydroxamoyl chloride (**3**), the in-

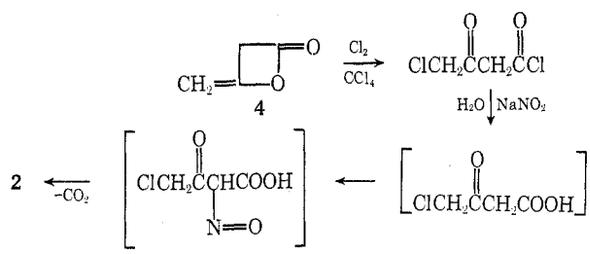


1 **2** **3**

stability of the desired product **2** in the acidic reaction medium, and a mysterious dependence of results on unknown variables in the nature and water content of the solvent.

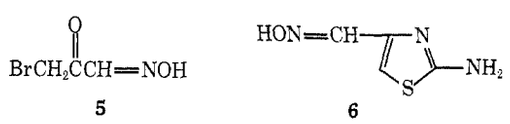
In preference to identifying and standardizing the many variables in the chlorination of pyruvaldoxime, we sought an alternate route to **2**. An attractive possibility was to employ a derivative of γ-chloroacetoacetic acid which could be hydrolyzed, nitrosated, and decarboxylated without jeopardizing the fragile chloromethyl group. Chlorination of diketene (**4**) provided us with γ-chloroacetoacetyl chloride[4] which was converted in one step into **2** in a two-phase system of ether–aqueous sodium nitrite (Scheme I). The de-

SCHEME I



sired β-chloropyruvaldoxime was isolated in 60% yield (based on diketene) from the organic layer. Proof of structure was obtained by spectroscopic data, by comparison with an authentic sample,[3] and by conversion into **1** *via* standard procedures.[5]

Similarly, β-bromopyruvaldoxime[6] (**5**) was prepared in 66% yield by bromination of diketene[7] followed by an analogous hydrolysis–nitrosation–decarboxylation sequence. Proof of structure was obtained for this product from spectral data and microanalysis, and by its facile reaction with thiourea[8] to give 2-amino-5-isonitrosomethylthiazole (**6**).



5 **6**

Both of the β-halopyruvaldoximes prepared by the above method are highly lachrymatory, and the chloro compound (**2**) has been found to produce severe skin irritation in some individuals after sensitization from long exposure. These halo oximes are unstable to storage at room temperature, especially when impure; decomposition is accompanied by the evolution of hydrogen cyanide. Although they are more stable at −20°, it is recommended that they be utilized immediately after preparation.

Experimental Section

β-Chloropyruvaldoxime (**2**).—In a 500-ml, three-neck flask equipped with thermometer, gas inlet tube, drying tube, and magnetic stirring bar was placed a solution of 33.6 g of freshly distilled diketene in 300 ml of dry CCl_4. The flask was weighed and then cooled to 0° (Dry Ice–acetone at −20°). Then 28.4 g of chlorine was bubbled into the solution with efficient stirring (about 1–2 g/min) while the temperature was maintained at −2 to +2°. After the solution had absorbed the required weight of chlorine (checked by intermittent weighing), the solvent was removed on a rotary evaporator and the residue was dissolved in 300 ml of absolute ether.

A solution of 27.6 g of $NaNO_2$ in 300 ml of water was placed in a 1-l., three-neck flask and cooled to 0° (salt–ice bath). Then, with efficient mechanical stirring, the ethereal solution of γ-chloroacetoacetyl chloride (see above) was added dropwise while the temperature was maintained below 5°. After complete addition of the acid chloride, the two-phase mixture was stirred an additional 15 min at room temperature. The layers were separated, and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether layers were dried over Na_2SO_4 and concentrated on a rotary evaporator (less then 25°). The resulting cream-colored waxy solid was recrystallized from carbon tetrachloride and dried *in vacuo* to yield 29.1 g (60%) of white plates, mp 98–100° (lit.[3] mp 98–102°). This material was identical in every way with an authentic sample of **2** prepared by chlorination of pyruvaldoxime,[3] and could be used without further purification for the preparation of **1**: nmr (DMSO-d_6) δ 4.78 (2, s, $-CH_2Cl$), 7.65 (1, s, CH=NOH), 12.75 (1, s, =NOH).

β-Bromopyruvaldoxime (**5**).—In a 100-ml, three-neck flask equipped with dropping funnel, thermometer, and magnetic stirring bar was placed a solution of 4.2 g of freshly distilled diketene in 50 ml of CCl_4. The solution was cooled to −2° (Dry Ice–acetone) and a solution of 8.0 g of bromine in 20 ml of CCl_4 was added slowly with stirring while maintaining the temperature at −2 to +2°. The bromine was added especially slowly near the equivalence point, where bromine decolorization was very slow. After complete addition of the bromine, the solvent was removed on a rotary evaporator, and the residue was dissolved in 50 ml of absolute ether.

β-Bromopyruvaldoxime was prepared from the ethereal solution of the acid bromide by the procedure described above for β-chloropyruvaldoxime. The resulting waxy tan solid was recrystallized from carbon tetrachloride and dried *in vacuo* to yield 5.5 g of white plates (66%): mp 78–79° (lit.[7] mp 89–90°);[9] nmr (DMSO-d_6) δ 4.50 (2, s, $-CH_2Br$), 7.63 (1, s, CH=NOH), 12.75 (1, s, =NOH).

Anal. Calcd for $C_3H_4NO_2Br$: C, 21.71; H, 2.43; N, 8.44. Found: C, 21.68; H, 2.28; N, 8.31.

This compound was identified by conversion into **2-amino-5-isonitrosomethylthiazole** (**6**) as follows: A solution of 0.5 g of β-bromopyruvaldoxime and 0.25 g of thiourea in 10 ml of methanol was allowed to stand overnight at room temperature. The methanol was removed on a rotary evaporator, and the residue was dissolved in 10 ml of water. The solution was made basic with Na_2CO_3, and the resulting light yellow crystals were collected by filtration and recrystallized from ethanol (charcoal). The yield of colorless needles, mp 178–179°, was 0.11 g (39%). The analytical sample was prepared by two further recrystallizations from ethanol without change in the melting point: nmr (DMSO-d_6) δ 6.85 (1, s, C_5–H), 7.10 (2, s, $-NH_2$), 7.91 (1, s, CH=NOH), 11.05 (1, s, =NOH).

(4) C. D. Hurd and J. L. Abernethy, *J. Amer. Chem. Soc.*, **62**, 1147 (1940).

(5) E. C. Taylor and T. Kobayashi, manscript in preparation.

(6) G. C. Singhal and M. M. Bokadin, *J. Indian Chem. Soc.*, **35**, 898 (1958).

(7) N. T. M. Wilsmore and F. Chick, *J. Chem. Soc.*, 1978 (1910).

(8) B. G. Chatterjee and R. F. Abdulla, *Z. Naturforsch. B*, **24**, 1120 (1969).

(9) The melting point of this compound could not be raised above 78–79° even by repeated recrystallizations.

Anal. Calcd for $C_4H_5N_3OS$: C, 33.56; H, 3.52; N, 29.35. Found: C, 33.30; H, 3.55; N, 29.55.

Registry No.—**2**, 14337-41-8; **5**, 37150-52-0; **6**, 37150-53-1.

Acknowledgment.—We are gratful to the FMC Corporation, Princeton, N. J., for a generous gift of diketene.

A Simple Synthesis of the Cis,cis and Trans,trans Isomers of Tetrabenzo[*a*,*c*,*g*,*i*]cyclododecene (*sym*-Tetrabenz[12]annulene)[1]

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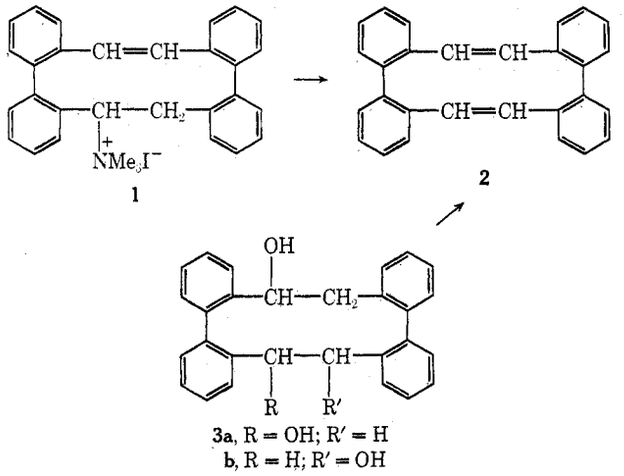
The stereoisomeric tetrabenzo[*a*,*c*,*g*,*i*]cyclododecenes (*sym*-tetrabenz[12]annulenes) (**2**) are interesting compounds, about which there has been some confusion in the literature. In 1955, Wittig, *et al.*,[3] reported that Hofmann degradation of *cis*-**1** leads to two isomers of **2**, mp 297.5–298 and 163–164°, to which they ascribed the cis,cis and trans,trans stereochemistry, respectively. Very recently, it has been shown by Irngartinger[4] and by Wittig and Skipka[5] that the lower melting isomer in fact has the cis,trans configuration, and we independently came to the same conclusion by repetition of Wittig's synthesis.[3] Moreover, Wittig and Skipka[5] have shown that dehydration of **3a** and **3b** gives rise to



3a, R = OH; R′ = H
b, R = H; R′ = OH

three stereoisomers of **2**, mp (corrected) 306–306.5, 253.5, and 301–301.5°; the first of these proved to be the cis,cis compound obtained previously, the second appears to be another cis,cis isomer, while the third is the trans,trans isomer.

(1) Unsaturated Macrocyclic Compounds. XCVIII. Part XCVII: P. D. Howes and F. Sondheimer, *J. Amer. Chem. Soc.*, **94**, 8261 (1972).

(2) On leave from the University of Connecticut, Storrs, Conn.

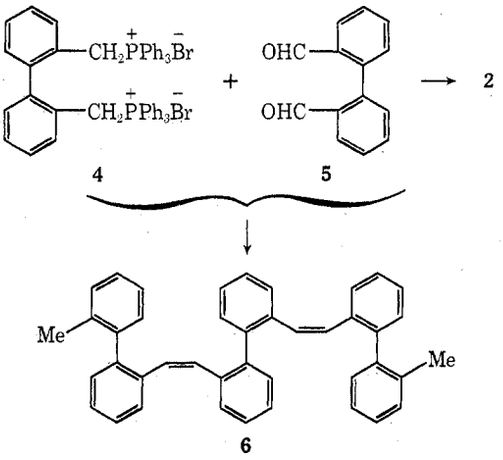
(3) G. Wittig, G. Koenig, and R. Clauss, *Justus Liebigs Ann. Chem.*, **593**, 127 (1955).

(4) H. Irngartinger, *Chem. Ber.* **105**, 2068 (1972).

(5) G. Wittig and G. Skipka, *Justus Liebigs Ann. Chem.*, in press.

Several years ago we required the tetrabenz[12]annulene **2** as a synthetic intermediate, and we devised a simple synthesis through the Wittig reaction between 2,2′-bis(triphenylphosphoniomethyl)biphenyl dibromide (**4**)[6] and 2,2′-biphenyldicarboxaldehyde (**5**).[7] This led in low yield to an isomer of **2**, mp 296–297°, which we considered[8] to be Wittig's cis,cis compound[3] in view of the correspondence of the melting points, ir spectra, and uv spectra.[9] The reaction between **4** and **5** has also been investigated by Bergmann, *et al.*,[5,10] who apparently obtained Wittig's cis,trans and trans,trans isomers of **2**. No details of the reaction between **4** and **5** have been published previously, and Staab, *et al.*,[11] thereby could obtain only traces of **2**.

We now report the details of a reinvestigation of the Wittig reaction between **4** and **5**. When the reaction was carried out with lithium methoxide in methanol under relatively high dilution conditions, both *cis,cis*-**2**, mp 296–297° (1.1%), and *trans,trans*-**2**, mp 302–303° (4.2%), could be isolated by chromatography and fractional crystallization. The structures and stereochemistry of these products are based on their spectral



properties, and are confirmed by the correspondence of the spectra and melting points with those reported by Wittig, *et al.*[3,5] In the case of *cis,cis*-**2**, direct comparison with a sample obtained from *cis*-**1** confirmed their identity.

The reaction between **4** and **5** also gave rise to the all-cis tri(biphenyl) derivative **6**, mp 181–182° (1.5%), the structure of which is based on the spectral data. The all-cis stereochemistry follows from the absence of a strong trans ethylene band at ~960 cm^{-1} in the ir spectrum; it is confirmed by the fact that the olefinic protons resonate as a singlet at τ 3.88 in the nmr spectrum, showing both double bonds to have the same

(6) D. M. Hall and B. Prakobsantisukh, *J. Chem. Soc.*, 6311 (1965); H. J. Bestmann, H. Häberlein, H. Wagner, and O. Kratzer, *Chem. Ber.*, **99**, 2848 (1966); E. D. Bergmann, P. Bracha, I. Agranat, and M. A. Kraus, *J. Chem. Soc. C*, 328 (1967).

(7) P. S. Bailey and R. E. Erickson, *Org. Syn.*, **41**, 41 (1961).

(8) See R. H. Mitchell and F. Sondheimer, *Tetrahedron Lett.*, 2873 (1968), footnote 6.

(9) Wittig and Skipka (ref 5, footnote 15) state that the uv spectrum of this substance, according to a personal communication from Dr. Grohmann, corresponds to the trans,trans isomer. This is a misunderstanding, since the uv spectral data given by Dr. Grohmann to Professor Wittig were not those of the substance considered by us to be *cis,cis*-**2**, but of another product (now known to be *trans,trans*-**2**).

(10) See E. D. Bergmann, *Bull. Soc. Chim. Fr.*, 2681 (1965); E. D. Bergmann, I. Agranat, and M. Kraus, *Israel J. Chem.*, **3**, 48p (1965).

(11) H. A. Staab, E. Wehringer, and W. Thorwart, *Chem. Ber.*, **105**, 2290 (1972).