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Cyclic Diacyl Diimides. II. 1,4-Phthalazinedione, 3,6-Pyridazinedione, and 4,5-Dihydro-3,6-pyridazinedione

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The generation of the cyclic diacyl diimides, 3,6-pyridazinedione and 4,5-dihydro-3,6-pyridazinedione, from 1,2-dihydro-3,6-pyridazinedione and 1,2,4,5-tetrahydro-3,6-pyridazinedione, respectively, and their *in situ* reactions with butadiene are described. Also described are the *in situ* reactions of these cyclic diacyl diimides and of 1,4-phthalazinedione with anthracene. The lack of reactivity of 1,4-phthalazinedione toward a variety of unsaturated substrates is reported.

A previous publication[1] reported the generation of the unstable cyclic diacyl diimide 1,4-phthalazinedione (*2a*) from the corresponding cyclic hydrazide (*1a*) and its reaction, *in situ*, with butadiene in the sense of Equations 1 and 2. In this paper are described similar generations and *in situ* reactions with butadiene of 3,6-pyridazinedione (*2b*) and 4,5-dihydro-3,6-pyridazinedione (*2c*). Reactions of the three cyclic diacyl diimides *2*, *in situ*, with anthracene according to Equation 3 are also described as are structure proofs and incidental reactions of the adducts *3* and *4*.

The cyclic diacyl diimides *2a*, *2b*, and 4,5-difluoro-3,6-pyridazinedione and their reactions with a variety of dienes has recently been reported by Kealy[2] who prepared the cyclic diacyl diimides by oxidation with *t*-butyl hypochlorite of the sodium salts of the corresponding cyclic hydrazides. Kealy's procedure permits the preparation of essentially pure solutions of cyclic diacyl diimides; however, when the objective is the preparation of Diels-Alder adducts of the cyclic diacyl diimides, our procedure is more convenient and appears to provide higher yields.

In previous work,[1] the preparation of 1,4-phthalazinedione was carried out in acetonitrile, but subsequent work has established that acetone and methylene chloride are also suitable solvents for the general type of oxidation represented by Equation 1. Acetonitrile and acetone have the virtue of providing reasonably stable solutions of cyclic diacyl diimides, and when oxidations are attempted in these media, the color of the solution (diacyl diimides are intensely colored) provides a convenient qualitative test for successful reaction. In methylene chloride, all the cyclic diacyl diimides we have tested are very unstable; however, they are generated very quickly and react very rapidly with dienes, which, for this reason and because of the ease of isolation of product makes methylene chloride the preferred medium for the *in situ* preparation of Diels-Alder adducts of cyclic diacyl diimides by the sequence of Equations 1 and 2.

When 1,2-dihydro-3,6-pyridazinedione (*1b*) was treated with lead tetraacetate in acetone, the solution assumed a slight yellow-green tint, suggesting successful oxidation to the cyclic diacyl diimide *2b* which, however, was very reactive toward further oxidation as attested by the evolution of gas (nitrogen). The same test, applied to 1,2,4,5-tetrahydro-3,6-pyridazinedione[3,4] (*1c*) produced an intense blue color, attributable to the cyclic diacyl diimide *2c*, which was rather stable.

In confirmation of these observations, the oxidation of *1b* with lead tetraacetate in methylene chloride in the presence of butadiene produced a 76% yield of the Diels-Alder adduct, 6,9-dihydro-

(1) R. A. Clement, *J. Org. Chem.*, **25**, 1724 (1960).
(2) T. J. Kealy, *J. Am. Chem. Soc.*, **84**, 966 (1962).
(3) H. Feuer, G. B. Bachman, and E. H. White, *J. Am. Chem. Soc.*, **73**, 4716 (1951).
(4) R. L. Hinman and R. J. Landborg, *J. Org. Chem.*, **24**, 724 (1959).

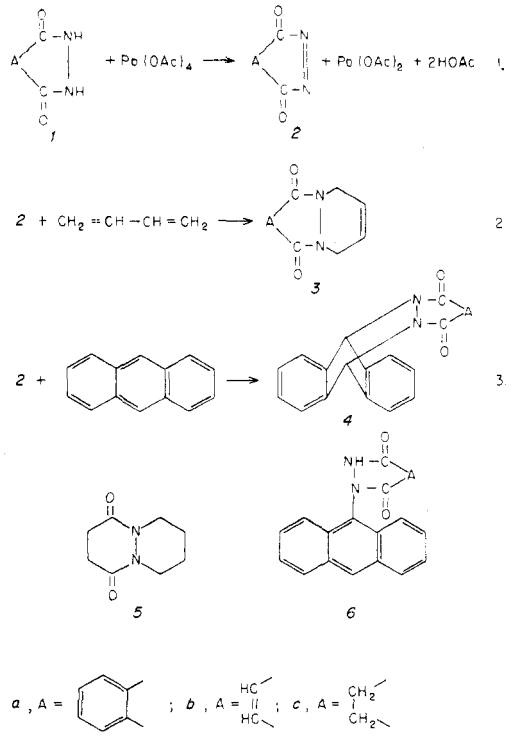

Fig. 1. Some reactions of, and structures from, cyclic diacyl diimides

pyridazino[1,2-*a*]pyridazine-1,4-dione (*3b*). Similarly, there was produced a 54% yield of 2,3,6,9-tetrahydropyridazino[1,2 - *a*]pyridazine - 1,4-dione (*3c*) from *1c*.

The structure of the adduct *3b* was proved by its identity with the product of reaction between maleic anhydride and 1,2,3,6-tetrahydropyridazine, and by its physical properties, which were in agreement with the assigned structure and with the literature.[2] Further, *3b* was reduced to 2,3,6,-7,8,9 - hexahydropyridazino[1,2 - *a*]pyridazine-1,4-dione (*5*), the structure of which was indicated by its physical properties which were as expected and in agreement with the literature.[2,5]

The structure of the adduct *3c* was suggested by its physical properties and proved by its reduction to *5*.

The most noteworthy characteristic of cyclic diacyl diimides is their extraordinary reactivity as dienophiles in Diels-Alder reactions. To test the reactivities of the three cyclic diacyl diimides *2* toward an inactive diene, the three cyclic hydrazides *1* were oxidized by lead tetraacetate in the presence of anthracene. In all three cases the anthracene adduct was formed: 5,14-dihydro-5,14-*o*-benzenophthalazino[2,3-*b*]phthalazine-7,12-dione (*4a*) from *1a;* 6,11-dihydro-6,11-*o*-benzenopyridazino[1,2-*b*]phthalazine-1,4-dione (*4b*) from *1b;* and 2,3,6,11-tetrahydro-6,11-*o*-benzenopyridazino-[1,2-*b*]phthalazine-1,4-dione (*4c*) from *1c*. The adducts *4a* and *4b* were produced in acceptable yields of 71% and 23%, respectively, while the adduct *4c* was obtained in only 3% yield. In the case of cyclic hydrazide *1a*, oxidation to the cyclic diacyl diimide *2a*, proceeded rapidly, and the latter reacted very rapidly with anthracene. Cyclic hydrazide *1b* was oxidized rather slowly to *2b*, but the latter reacted rapidly with anthracene, being only slightly less selective (addition to anthracene *vs.* further oxidation and decomposition) than *2a*. The cyclic hydrazide *1c* was oxidized very rapidly to the cyclic diacyl diimide *2c* which, however, reacted very slowly with anthracene, most of *2c* being further oxidized by lead tetraacetate under the reaction conditions.

The structures of the three adducts *4* could not be established by independent syntheses or by degradations, but the evidence for their validities is strong. None possessed an hydrazide N—H bond as judged by their insolubilities in aqueous base and their infrared spectra. In the ultraviolet, none showed the multiple long wave length absorption characteristic of the anthracene chromophore.[6] The NMR spectra of *4b* and *4c* possessed singlets at $\tau = 3.23$, which must be assigned to the benzylic bridgehead hydrogen atoms in those structures. (Unfortunately, this signal was absent in the NMR spectrum of *4a*, doubtless because it was shifted downfield, into the region of multiplet absorption by the aromatic hydrogen atoms, due to ring-current deshielding of the benzylic bridgehead hydrogen atoms by the additional aromatic system.)[7]

The anthracene adducts *4a* and *4b* were also converted to 2-(9-anthryl)-2,3-dihydro-1,4-phthalazinedione (*6a*) and 1-(9-anthryl)-1,2-dihydro-3,6-pyridazinedione (*6b*), respectively, in rearrangements analogous to that observed with the adduct between anthracene and azocarboxylic ester.[8] (Insufficient *4c* was at hand to test its behavior.) The structures *6a* and *6b* were indicated by their solubilities in aqueous base, and by their ultraviolet spectra which showed the multiple long-wave length absorption characteristic of the anthracene chromophore.[6]

To test the dienophenolic and enophilic character of 1,4-phthalazinedione (*2a*), the oxidation of *1a* by lead tetraacetate was carried out in the presence of a variety of unsaturated substrates, and the reaction products were examined carefully by chromatography and by infrared spectroscopy. The unsaturated substrates so employed were: thiophene, naphthalene, hexamethylbenzene, anisole, and bicyclo[2.2.1]hept-2-ene. In no case was there any indication of the formation of an adduct between the unsaturated substrate and *2a*. Thus,

(5) H. Stetter and H. Spangenberger, *Chem. Ber.*, **91**, 1982 (1958).

(6) J. C. J. MacKenzie, A. Rodgman, and G. F. Wright, *J. Org. Chem.*, **17**, 1666 (1952).

(7) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, 1959, p. 18.

(8) K. Alder and H. Niklas, *Ann.*, **585**, 81 (1954).

the dienophilic character of cyclic diacyl diimides is not without limit, and enophilic character is apparently lacking.

EXPERIMENTAL[9]

General procedure for the preparation of Diels-Alder adducts of cyclic diacyl diimides. The reagents, cyclic hydrazide (10 mmoles) and diene (at least 10 mmoles), were slurried in methylene chloride (*ca.* 50 ml.) containing *ca.* 1 ml. of acetic acid (to suppress hydrolysis of lead tetraacetate in the early stages of reaction) at room temperature. A molar equivalent (Equation 1) of lead tetraacetate was added, in small increments, as fast as it was consumed.[10] After addition of the lead tetraacetate, 7 g. of Woelm neutral alumina was added to the reaction flask, and the total mixture was evaporated to dryness under reduced pressure at < 40°. The resulting solid was then packed on top of a chromatographic column composed of 50 g. of Woelm neutral alumina which had been deactivated with 10% by weight of water, and the chromatogram was developed, starting with carbon tetrachloride as the solvent. The adduct was generally eluted in good state of purity by mixtures of methylene chloride in carbon tetrachloride, and was further purified by crystallization from the appropriate solvent.

In large scale experiments and where the product was formed in good yield, the reaction mixture was transferred to a separatory funnel and washed with water to remove lead acetate. The methylene chloride phase, after drying, was evaporated under reduced pressure to yield crude adduct which was purified by crystallizations from the appropriate solvent.

Adducts prepared in this manner, along with their physical properties, are listed below. Yields are based on the amount of cyclic hydrazide taken and were determined by chromatographic examination of the reaction mixtures as described above.

6,9-Dihydropyridazino[1,2-a]pyridazine-1,4-dione (*3b*) from *1b* and butadiene in 76% yield, was obtained pure (from benzene–petroleum ether) as pale yellow blades, m.p. 156–157° (lit.,[2] m.p. 157–159°). In the infrared it showed acyl absorption at 1628 cm.$^{-1}$, and in the ultraviolet (chloroform) it had λ_{max} 340 mμ (ε 2500) and λ_{min} 266 mμ (ε 250). By the criteria of mixture melting point and infrared spectral comparison, it was identical with material formed by the reaction of 1,2,3,6-tetrahydropyridazine[11] with maleic anhydride under conditions similar to those in an analogous reaction previously described.[1]

2,3,6,9-Tetrahydropyridazino[1,2-a]pyridazine-1,4-dione (*3c*) from *1c* and butadiene in 54% yield, was obtained pure (from ethanol) as white prisms, m.p. 190–193°. In the infrared it showed acyl absorption at 1655 cm.$^{-1}$, and in the ultraviolet (chloroform) it had no maxima above 270 mμ.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07. Found: C, 57 98; H, 6.13.

5,14-Dihydro-5,14-o-benzenophthalazino[2,3-b]phthalazine-7,12-dione (*4a*) from *1a* and anthracene in 71% yield, was obtained pure (from toluene) as white needles, m.p. 295–298° dec. (sealed cap.) when inserted in the bath at 290°. In the infrared it showed acyl absorption at 1637 cm.$^{-1}$, and in the ultraviolet (chloroform) it had λ_{max} 314 mμ (ε 6400), λ_{min} 259 mμ (ε 2600), and shoulders at 273 (ε 3300) and 278 mμ (ε 3500). Its NMR signals consisted of two ill-defined multiplets, τ = 1.68–2.00 and 2.26–2.93, respectively.

Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17. Found: C, 78.22; H, 4.17.

6,11-Dihydro-6,11-o-benzenopyridazino[1,2-b]phthalazine-1,4-dione (*4b*) from *1b* and anthracene in 23% yield, was obtained pure (from 1-propanol) as pale yellow leaflets, m.p. > 300°. In the infrared it showed acyl absorption at 1631 cm.$^{-1}$ and in the ultraviolet (chloroform) it had λ_{max} 347 mμ (ε 4000), λ_{min} 284 mμ (ε 700), and shoulders at 267 (ε 1200), 274 (ε 1000), and 380 mμ (ε 1900). Its NMR signals consisted of a singlet (6,11-benzylic bridgehead hydrogens) at τ = 3.23, and a complex multiplet (olefinic and aromatic hydrogens) at τ = 2.29–2.86.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20. Found: C, 74.96; H, 4.11.

2,3,6,11-Tetrahydro-6,11-o-benzenopyridazino[1,2-b]phthalazine-1,4-dione (*4c*) from *1c* and anthracene in 3% yield, was obtained pure (from 1-propanol) as white needles, m.p. > 300°. In the infrared it had acyl absorption at 1664 cm.$^{-1}$, and in the ultraviolet (chloroform) it showed no maxima above 260 mμ, although there were shoulders at 267 (ε 4700) and 276 mμ (ε 3100). Its NMR signals consisted of a singlet (2,3-aliphatic hydrogens) at τ 7.54, a singlet (6,11-benzylic bridgehead hydrogens) at τ = 3.23, and a complex multiplet (aromatic hydrogens) at τ = 2.43–2.94.

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86. Found: C, 74.59; H, 5.03.

2,3,6,7,8,9-Hexahydropyridazino[1,2-a]pyridazine-1,4-dione (*5*). A. *From 6,9-dihydropyridazino[1,2-a]pyridazine-1,4-dione* (*3b*). Hydrogenation of *3b* (1.05 g.) was accomplished at atmospheric pressure and room temperature in water (40 ml.) with 10% palladium-on-charcoal (0.20 g.) as the catalyst and over a period of 7 hr. Hydrogen absorption amounted to 103% of theory for two moles, and there was isolated, after a single crystallization from ethyl acetate–*n*-heptane, *5* (0.63 g., 59%), m.p. 175.5–176.5°. The pure sample, white blades, had m.p. 176–177° (lit., m.p. 174–177°,[2] 179–180°[5]) and in the infrared exhibited acyl absorption at 1658 cm.$^{-1}$.

B. *From 2,3,6,9-tetrahydropyridazino[1,2-a]pyridazine-1,4-dione* (*3c*). Hydrogenation was conducted as for *3b*, hydrogen amounting to 101% of theory for 1 mole being absorbed over the course of 1.5 hr., and *5* (m.p. 175–176°) being obtained in 75% yield after a single crystallization from ethyl acetate–*n*-heptane. By the criteria of mixture melting point and infrared spectral comparison, it was identical with *5* as obtained from *3b*.

2-(9-Anthryl)-2,3-dihydro-1,4-phthalazinedione (*6a*) *by rearrangement of 5,14-dihydro-5,14-o-benzenophthalazino[2,3-b]-phthalazine-7,12-dione* (*4a*). A solution of *4a* (3.21 g.), glacial acetic acid (50 ml.), and concd. hydrochloric acid (2 ml.) was heated under reflux for 1 hr., water (50 ml.) was added, and the solution was cooled. The precipitate was suspended in water, the *p*H of the solution was adjusted to 14, and the resulting yellow solution was filtered to remove a small amount of insoluble material. Addition of acetic acid to the filtrate produced a pale yellow powder which was crystallized once from 1-propanol to yield pure *6a* (1.96 g., 61%), m.p. > 300°, as a pale yellow microcrystalline powder. In the infrared, *6a* exhibited H-stretching absorption (broad, weak, ambiguous) at 3060 cm.$^{-1}$, acyl absorption at 1642 cm.$^{-1}$, and a very intense doublet at

(9) Melting points were taken on a calibrated Fisher-Johns melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 21 infrared spectrophotometer, ultraviolet spectra on a Bausch and Lomb Spectronic 505 spectrophotometer, and NMR spectra on a Varian Associates 40-mc. dual purpose spectrophotometer. Compounds were dispersed in potassium bromide pellets for the recording of infrared spectra, and dissolved as 5% solutions in deuterochloroform for the recording of NMR spectra which were calibrated against tetramethylsilane as an internal standard. I am indebted to Mr. W. Saschek of this department for the elemental analyses.

(10) A convenient spot test for lead tetraacetate involves moistening a filter paper with the solution, permitting solvent to evaporate, and then moistening with water. The formation of a brown spot (lead dioxide) indicates unchanged lead tetraacetate.

(11) P. Baranger and J. Levisalles, *Bull. soc. chim. France*, 704 (1957).

1574 and 1553 cm.$^{-1}$. In the ultraviolet (0.02 *N* sodium hydroxide), *6a* had λ_{max} 252 (ϵ 132,000), 317 (ϵ 6800), 331 (ϵ 7400), 347 (ϵ 9300), 365 (ϵ 11,200), and 384 mμ (ϵ 9400), and λ_{min} 226 (ϵ 24,000), 279 (ϵ 4000), 322 (ϵ 6800), 338 (ϵ 6800), 355 (ϵ 6700), and 375 mμ (ϵ 5100).

Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17. Found: C, 78.03; H, 4.35.

1-(9-Anthryl)-1,2-dihydro-3,6-pyridazinedione (6b) by rearrangement of 6,11-dihydro-6,11-o-benzenopyridazino[1,2-b]phthalazine-1,4-dione (4b). A solution of *4b*, (1.33 g.), glacial acetic acid (50 ml.), and concd. hydrochloric acid (3 ml.) was stirred at room temperature for 4 hr. The yellow precipitate which formed was removed by filtration, and washed with acetic acid and water. It amounted to 1.24 g. (93%) of *6b* which was obtained pure, as yellow cubes, m.p. > 300°, after a single crystallization from dimethylformamide–water. In the infrared, *6b* exhibited H-stretching absorption (broad, weak, ambiguous) at 2960–2340 cm.$^{-1}$, acyl absorption at 1661 cm.$^{-1}$, and intense absorption at 1563 and 1497 cm.$^{-1}$. In the ultraviolet (0.02 *N* sodium hydroxide), *6b* had λ_{max} 252 (ϵ 148,000), 333 (ϵ 5300), 348 (ϵ 7800), 365 (ϵ 10,700), and 385 mμ (ϵ 9100) and λ_{min} 226 (ϵ 23,300), 282 (ϵ 1300), 336 (ϵ 5300), 355 (ϵ 6400), and 375 mμ (ϵ 5100). It was soluble in 0.01 *N* sodium hydroxide.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20. Found: C, 75.12; H, 4.42.

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CHICAGO 37, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF MICHIGAN]

Experiments Directed toward the Total Synthesis of Terpenes. II. The Synthesis of *dl*-6-Keto-5,5,9-trimethyl-2-methylene-*trans*-decalyl-1α-acetic Acid and Derivatives[1]

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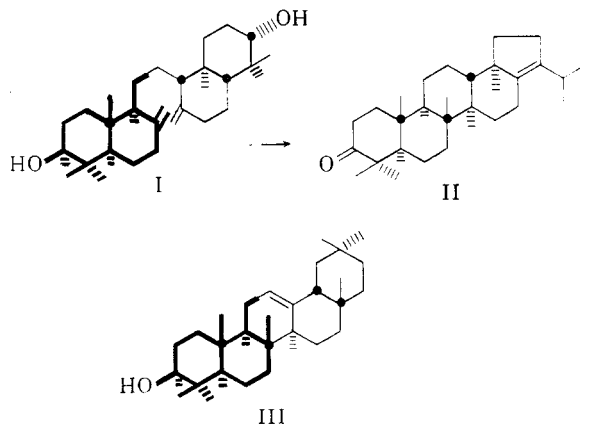
Utilization of the alkoxymethylene grouping allowed the conversion of 6,6-ethylenedioxy-5,5,9-trimethyl-*trans*-decalone-1 (*2*) to the corresponding keto alcohol (*7*). Pyrolysis of the vinyl ether prepared from this alcohol generated an acetaldehyde derivative that was readily oxidized to the title compound (*10*), a potentially useful intermediate in triterpene total synthesis. The acid (*10*) was converted into the keto acid (*12*), a key intermediate in the total synthesis of α-onocerin. Studies in the 6-desoxydecalone-1 series demonstrated the axial character of the acetaldehyde residue introduced by the Claisen rearrangement.

One approach to the total synthesis of pentacyclic triterpenes that has been under investigation in these laboratories[4] is the coupling of two dicyclic moieties, followed by acid-catalyzed cyclization of the resulting tetracyclic system—*i.e.*, the ABDEC scheme. The success of such a plan has recently been amply demonstrated by the construction of such model pentacyclic systems as pentacyclosqualene by Corey[5] and Eschenmoser[6] and olean-11,12; 13,18-diene by Corey.[7] The most notable result of this plan has been the total synthesis of α-onocerin (I)[26] announced by Stork and coworkers.[8] In view of the earlier conversion[9] of α-onocerin (I) to hopenone-I(II), this latter total synthesis represents the first total synthesis of a naturally occurring pentacyclic triterpene.



The symmetry of the α-onocerin molecule makes the task of constructing the appropriate dicyclic moieties somewhat easier, and it is not surprising that it has been the first of the polycyclic triterpenes to be conquered by the synthetic organic chemist. Indeed, it is possible that an appro-

(1) A preliminary account of this work has appeared in *Tetrahedron Letters*, 34 (1961); taken in part from the Ph.D. thesis of R. F. Church, University of Michigan, 1961.

(2) Dow Chemical Company Fellow, 1958–1959; Sun Oil Company Fellow, 1959–1960.

(3) Public Health Service Research Fellow of the National Heart Institute, 1958–1960.

(4) R. E. Ireland and J. A. Marshall, *J. Org. Chem., in press.*

(5) E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, 81, 1739 (1959).

(6) A. Eschenmoser, P. A. Stadler, A. Nechvatal, and A. J. Frey, *Helv. Chim. Acta*, 40, 1900 (1957).

(7) E. J. Corey, H. Hess, and S. Proskow, *J. Am. Chem. Soc.*, 81, 5258 (1959).

(8) G. Stork, J. E. Davies, and A. Meisels, *ibid.*, 81, 5516 (1959).

(9) K. Schaffner, O. Jeger, L. Caglioti, and D. Arigoni, *Helv. Chim. Acta*, 41, 152 (1958).