Synthesis of 1-Aryl-3-formyl-3-methyltriazenes, Potential Metabolites of 1-Aryl-3,3-dimethyltriazenes

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Abstract □ Some *para*-substituted 1-aryl-3,3-dimethyltriazenes were oxidized with *tert*-butyl hydroperoxide in the presence of vanadium pentoxide as a catalyst. Under these conditions, the corresponding 1-aryl-3-formyl-3-methyltriazenes, 1-aryl-3-*tert*-butylperoxymethyl-3-methyltriazenes, and *p*-nitrobenzenes were obtained. The 1-aryl-3-formyl-3-methyltriazenes might play a role in the metabolic oxidation of the 1-aryl-3,3-dimethyltriazenes, which are active as mutagenic, carcinogenic, and antitumor agents.

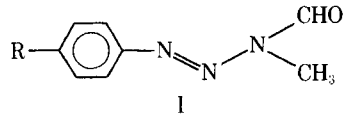
Keyphrases □ 1-Aryl-3-formyl-3-methyltriazenes—synthesis as potential metabolites of 1-aryl-3,3-dimethyltriazenes □ Antitumor agents—1-aryl-3,3-dimethyltriazenes, synthesis of 1-aryl-3-formyl-3-methyltriazenes as potential metabolites □ Metabolites, potential—1-aryl-3-formyl-3-methyltriazenes, synthesis as oxidation products of 1-aryl-3,3-dimethyltriazenes

Dimethyltriazenes have been reported to cause mutagenic (1), carcinogenic (2), and antineoplastic (3) effects, and their mechanism of action has been investigated. Their local carcinogenic effects have been attributed to aryldiazonium cations generated by hydrolysis (4), whereas their antitumor and systemic carcinogenic effects have been attributed to the methylation of cellular components by monomethyltriazenes (5) produced by microsomal oxidative *N*-demethylation (4, 6).

BACKGROUND

However, it is possible that some biological effects observed for dimethyltriazenes are due to other metabolites formed by oxidation of the nitrogen atoms or methyl groups in the triazene moiety. The *N*-hydroxymethyltriazenes suggested as intermediates in the microsomal *N*-demethylation of dimethyltriazenes (6) recently were synthesized (7) and isolated as metabolites (8). Therefore, it seemed interesting to attempt the chemical oxidation of dimethylaryltriazenes because of the potential of the resulting compounds as possible metabolites or as antitumor agents themselves.

The possibility of performing the oxidation without the destructive reactions reported using Udenfried's system (9) was investigated. Of the several attempts using hydrogen peroxide, oxygen, *m*-chloroperoxybenzoic acid, and *tert*-butyl hydroperoxide in the presence of molybdenum dioxyacetylacetonate (10) or vanadium pentoxide, only the latter combination of oxidizing agent and catalyst was successful and gave satisfactory yields. In this way, the *N*-formyl derivatives (I*a*–I*d*), peroxides (II*a*–II*d*), and *p*-nitrobenzenes resulting from the oxidative breakdown of the triazene function were obtained.



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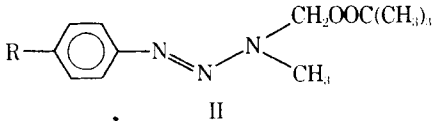

II

I*a* and II*a*: R = NO_2
I*b* and II*b*: R = Cl
I*c* and II*c*: R = Br
I*d* and II*d*: R = I

The reported structures were assigned on the basis of elemental analyses as well as NMR, IR, and mass spectral data. For I*a*–I*d*, the presence of a formyl group and a single methyl group was indicated by a singlet at δ ~9.30 for one proton and a singlet at δ ~5.40 for three protons, respectively. Furthermore, a strong band at ~1700 cm^{-1}, attributable to C=O stretching, was observed in the IR spectra. For II*a*–II*d*, the NMR spectra showed the presence of a singlet for nine protons at δ ~1.25, a singlet for three protons at δ ~3.30, and a singlet for two protons at δ ~5.50. Further investigation is in progress to evaluate the antitumor effect of these formyltriazenes and their possible role in the metabolism of dimethyltriazenes.

EXPERIMENTAL[1]

General Procedure—A 3,3-dimethyl-1-aryltriazene (5 mmoles) and vanadium pentoxide (50 mg) were suspended in 25 ml of benzene, and 6 ml of 80% *tert*-butyl hydroperoxide (47 mmoles) was added dropwise with stirring. The temperature was raised to 45°, and stirring was maintained for 26–30 hr, or for 50 hr for I*d* and II*d*, to ensure complete disappearance of the starting triazene. The starting material was detected by TLC on silica gel plates developed with 5% hexane in benzene (v/v) or 30% ethyl acetate in hexane for II*b*. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure.

Compounds I*a* and II*a*—The residue dissolved in 2 ml of acetone was chromatographed on silica gel. The elution with 1% acetone in benzene (v/v) afforded three fractions detected by TLC. The first fraction, which contained only 1,4-dinitrobenzene, was discarded. The second fraction, after evaporation of the solvent under reduced pressure, gave 30 mg of II*a*. The third fraction, which contained a mixture of I*a* and II*a*, was chromatographed again, after evaporation, on silica gel with ethyl acetate in hexane (1:2 v/v) as the eluent.

The first fraction yielded 350 mg of 1-(4-nitrophenyl)-3-*tert*-butylperoxymethyl-3-methyltriazene (II*a*), mp 86°, after crystallization from hexane; UV: 345 nm; NMR: δ 1.24 (s, 9H), 3.32 (s, 3H), 5.48 (s, 2H), and 7.45–8.35 (m, 4H); mass spectrum: *m/e* 282 (M).

Anal.—Calc. for $C_{12}H_{18}N_4O_4$: C, 51.05; H, 6.42; N, 19.84. Found: C, 51.08; H, 6.40; N, 19.81.

The second fraction, after evaporation, yielded 200 mg of 1-(4-nitrophenyl)-3-formyl-3-methyltriazene (I*a*) after crystallization from methanol, mp 117–119°; UV: 215 and 302 nm; IR: 1700–1720 (C=O) cm^{-1}; NMR: δ 3.44 (s, 3H), 7.73–8.44 (m, 4H), and 9.35 (s, 1H); mass spectrum: *m/e* 208 (M).

Anal.—Calc. for $C_8H_8N_4O_3$: C, 46.15; H, 3.87; N, 26.91. Found: C, 46.03; H, 3.85; N, 26.95.

Compounds I*b* and II*b*—To obtain I*b*, the residue was dissolved in 2 ml of benzene and chromatographed on silica gel. Elution with 5% hexane in benzene (v/v) afforded three fractions detected by TLC. The first fraction, which contained *p*-chloronitrobenzene, was discarded. The second fraction contained II*b*, and the third fraction, after evaporation under reduced pressure, gave 150 mg of 1-(4-chlorophenyl)-3-formyl-3-methyltriazene (I*b*) as a crystalline residue, mp 89°, after crystallization twice from methanol; UV: 223 and 283 nm; IR: 1733 (C=O) cm^{-1}; NMR: δ 3.36 (s, 3H), 7.28–7.72 (m, 4H), and 9.26 (s, 1H).

Anal.—Calc. for $C_8H_8ClN_3O$: C, 48.62; H, 4.08; N, 21.26. Found: C, 48.65; H, 4.11; N, 21.28.

[1] Melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. IR spectra were obtained as potassium bromide disks with a Perkin-Elmer model 225 spectrometer. UV spectra of methanol solutions were determined on a Hitachi Perkin-Elmer model 124 spectrometer. NMR spectra were recorded on a Perkin-Elmer R12B spectrometer, in deuterochloroform, with tetramethylsilane as the internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L spectrometer. Silica gel (Merck) of 230–240 mesh activated 5 hr at 200° and HF (254 + 366) were used for column chromatography and TLC, respectively.

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To obtain IIb, the residue dissolved in 2 ml of benzene was chromatographed on silica gel. The elution with hexane–ether (7:1 v/v) afforded a first fraction containing a mixture of *p*-chloronitrobenzene and IIb. The second fraction was evaporated under reduced pressure. The residue, after crystallization from hexane chilled in a dry ice–acetone bath to avoid losses, gave 150 mg of 1-(4-chlorophenyl)-3-*tert*-butylperoxymethyl-3-methyltriazene (IIb), mp 44.5°; UV (ethanol): 218, 222, and 282 nm; NMR: δ 1.23 (s, 9H), 3.30 (s, 3H), 5.52 (s, 2H), and 7.35–7.43 (m, 4H).

Anal.—Calc. for $C_{12}H_{18}ClN_3O_2$: C, 53.04; H, 6.68; N, 15.46. Found: C, 53.03; H, 6.64; N, 15.50.

Compounds Ic and IIc—The residue dissolved in 2 ml of benzene was chromatographed on silica gel. Three fractions resulted from elution with 5% hexane in benzene (v/v). The first fraction was *p*-bromonitrobenzene. The second fraction, after evaporation of the solvent under reduced pressure, gave 200 mg of 1-(4-bromophenyl)-3-*tert*-butylperoxymethyl-3-methyltriazene (IIc), mp 54°; UV: 218, 222, and 281 nm.

Anal.—Calc. for $C_{12}H_{18}BrN_3O_2$: C, 45.58; H, 5.74; N, 13.29. Found: C, 45.80; H, 5.84; N, 13.10.

The third fraction gave 200 mg of 1-(4-bromophenyl)-3-formyl-3-methyltriazene (Ic), mp 102–104°, after crystallization from methanol and from hexane; UV: 224 and 284 nm; IR: 1733 (C=O) cm^{-1}; NMR: δ 3.37 (s, 3H), 7.55 (m, 4H), and 9.24 (s, 1H).

Anal.—Calc. for $C_8H_8BrN_3O$: C, 39.69; H, 3.33; N, 17.36. Found: C, 39.63; H, 3.30; N, 17.30.

Compounds Id and IId—The residue was suspended in 2 ml of methanol and filtered. The filtrate was chromatographed on silica gel, and elution with 5% hexane in benzene gave three fractions. The first fraction, which contained *p*-iodonitrobenzene, was discarded. The second fraction, after evaporation of the solvent, gave 250 mg of 1-(4-iodophenyl)-3-*tert*-butylperoxymethyl-3-methyltriazene (IId), mp 56°; UV: 224 and 284 nm.

Anal.—Calc. for $C_{12}H_{18}IN_3O_2$: C, 39.68; H, 4.99; N, 11.57. Found: C, 39.80; H, 4.93; N, 11.30.

The third fraction gave 50 mg of 1-(4-iodophenyl)-3-formyl-3-methyltriazene (Id), mp 123–124°, after crystallization from methanol; UV: 230 and 293 nm; IR: 1700 (C=O) cm^{-1}; NMR: δ 3.38 (s, 3H), 7.25–7.95 (m, 4H), and 9.30 (s, 1H).

Anal.—Calc. for $C_8H_8IN_3O$: C, 33.24; H, 2.79; N, 14.54. Found: C, 33.23; H, 2.69; N, 14.45.

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Stability of Solid Drugs: Degradation of Ergocalciferol (Vitamin D_2) and Cholecalciferol (Vitamin D_3) at High Humidities and Elevated Temperatures

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Abstract □ Ergocalciferol and cholecalciferol powders were studied at 25 and 40° and at different humidities. Ergocalciferol decomposed rapidly at 25 and 40° when stored in dry air. Decomposition of ergocalciferol led to the formation of products of higher polarity. Cholecalciferol was not as labile under dry conditions, but decomposed rapidly at high temperature.

Keyphrases □ Vitamin D—ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), effects of temperature and humidity on decomposition □ Stability—ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), effects of humidity and temperature □ Ergocalciferol—stability, effects of temperature and humidity □ Cholecalciferol—stability, effects of temperature and humidity

Ergocalciferol and cholecalciferol are fat-soluble vitamins essential for their antirachitic activity. The adverse effects of light, air, and temperature on solutions of these 9,10-secosterols are well documented (1–4).

Previous studies on the solid-state decomposition of ergocalciferol (initially a white, crystalline powder) showed the formation of a yellow powder having a lowered melting point (5). These observations also were made in this laboratory. GLC analysis of ergocalciferol and cholecalciferol resulted in the decomposition of the parent product, with the formation of two peaks (6). These two peaks were identified as pyro- and isopyro vitamin D[1], formed as a result of thermal cyclization of vitamin D (6). The decomposition of ergocalciferol in powder preparations was reported to depend directly on the surface acidity of the excipients and their ability to adsorb moisture (7).

These studies on the decomposition of vitamin D are valuable but do not predict its stability under normal storage conditions. A labile reference material such as vitamin D must be stored at optimum conditions. Therefore, to determine these conditions, the effects of temperature and humidity on the stability of ergocalciferol and cholecalciferol in the absence of light were investigated.

[1] Vitamin D refers to vitamins D_2 and D_3.

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