104946-87-4; **7** (methyl ester), 104975-65-7; **8**, 104946-88-5; **9**, 4390-94-7; **9** (diol), 76579-69-6; **10a**, 104947-29-7; **10b**, 85546-02-7; **11a**, 104947-30-0; **11b**, 104946-95-4; **12a**, 104947-31-1; **12b**, 104946-96-5; **13**, 104947-34-4; **14a**, 104994-60-7; **14a** (acetylthio deriv), 104947-37-7; **14b**, 104946-98-7; **14b** (acetylthio deriv), 104946-97-6; **15a**, 104946-99-8; **15b**, 104947-00-4; **15c**, 104947-01-5; **15d**, 104947-02-6; **15e**, 104947-38-8; **16a**, 104947-03-7; **16b**, 104947-04-8; **16c**, 104947-05-9; **16d**, 104947-06-0; **16e**, 104947-07-1; **16f**, 104947-39-9; **16f** (NBD deriv), 104947-13-9; **If**, 104947-17-3; **Ig**, 104947-18-4; **Ih**, 104947-20-8; **Ih** (THP deriv), 104947-19-5; **Ii**, 104947-21-9; **Ij**, 104947-22-0; **Ik**, 104947-24-2; **Ik** (THP deriv), 104947-23-1; **Il**, 104946-93-2; **Im**, 104946-90-9; **Im** (THP deriv), 104946-89-6; **In**, 104946-92-1; **In** (THP deriv), 104946-91-0; **Io**, 104946-94-3; **IIf**, 104947-26-4; **IIf** (benzyl deriv), 104947-25-3; **IIg**, 104947-28-6; **IIg** (benzyl deriv), 104947-27-5; **III** (Y = 4, X = 3-nitrophthalic anhydride), 104947-40-2; **IIIf**, 104947-33-3; **III** (di(t-BuMe$_2$Si ether)), 104947-32-2; **IIIg**, 104947-36-6; **IIIg** (ethylvinyl ether deriv), 104947-35-5; **IIIh**, 104947-08-2; **IIIi**, 104947-09-3; **IIIj**, 104947-10-6; **IIIk**, 104947-11-7; **IIIl**, 104947-12-8; **IIIm**, 104947-14-0; **IIIn**, 104947-41-3; **IIIo**, 104947-43-5; **IIIo** (ethylvinyl deriv), 104947-42-4; **IIIp**, 104975-78-2; *i*, 104947-15-1; dansyl-Cl, 605-65-2; NBD-Cl, 10199-89-0; 4-MeC$_6$H$_4$SO$_2$Cl, 98-59-9; t-BuMe$_2$SiCl, 18162-48-6; MePh$_3$PBr, 1779-49-3; MeCOSH, 507-09-5; H$_2$C = CHCN, 107-13-1; Br(CH$_2$)$_3$CN, 5332-06-9; Br(CH$_2$)$_4$CN, 5414-21-1; Br(CH$_2$)$_5$CN, 6621-59-6; MeI, 74-88-4; PhCH$_2$Br, 100-39-0; i (diol), 76412-01-6; i (hexestrol monoallyl ether), 76411-99-9; BuSH, 109-79-5; PhCH$_2$Cl, 100-44-7; EtOCH=CH$_2$, 109-92-2; MeSO$_2$Cl, 124-63-0; Br(CH$_2$)$_6$CN, 20965-27-9; potassium phthalimide, 1074-82-4; 3-nitrophthalic anhydride, 641-70-3; ethylenimine, 151-56-4; dihydropyran, 25512-65-6; 2,4-dinitrofluorobenzene, 70-34-8; 2,2′-dichlorodiethyl ether, 111-44-4.

Supplementary Material Available: Complete experimental procedures and spectroscopic characterizations of the following compounds: i, **1**, If–k, **7**, IIf, **8**, IIg, **10a**, **11a**, **12a**, IIIf, **13**, IIIg, **14a**, **15e**, **16f**, IIIn, IIIo, and IIIp (18 pages). Ordering information is given on any current masthead page.

Double-Headed Haptens with Pyrocatechol (Poison Ivy like) and Methylene Lactone Functional Groups: A Search for Skin-Tolerance Inducers

Henri Mattes and Claude Benezra*

Laboratoire de Dermato-Chimie, Associé au CNRS (UA 31), Université Louis Pasteur, Clinique Dermatologique, CHU, 67091 Strasbourg, France. *Received May 12, 1986*

In order to develop new theories for desensitization, a potential skin sensitizer, **1**, with two different haptenic ends, (a) a pyrocatechol group and (b) an α-methylene-γ-butyrolactone moiety, separated by a straight nine-carbon-atom chain has been prepared and used to sensitize guinea pigs. A "monohapten" **8** containing an electrophylic α-methylene-γ-butyrolactone, connected to a dimethoxybenzene group, has also been prepared. Both the "bihapten" **1** and the "monohapten" **8** were shown to be sensitizers. Bihapten **1** sensitized animals recognized only bihapten **1** (and not the lactone **8**) while monohapten **8** sensitized guinea pigs reacted to both **8** and **1**. Bihapten **1** treated animals were further sensitized to monohapten **8** and challenged to the latter: the skin intensity reaction was significantly lower than the test to **8** in **8**-sensitized animals. Bihapten **1** seems therefore to "tolerize" against the α-methylene-γ-butyrolactone end.

Molecular aspects of allergic contact dermatitis (ACD) are now better understood, thanks to structure–activity relationships studies.[1,2] In particular, it seems that induction of sensitization is dependent on the ability of the sensitizer to form covalent bonds with epidermal proteins; most of the skin haptens are therefore electrophilic.[2] However, apparently nonelectrophilic skin sensitizers do exist;[3,4] their activity can be rationalized either by an in vivo transformation into electrophiles (in this case they are called prohaptens) or their capacity to form strong hydrophobic bonds, in particular by insertion into cell membranes.

Once that bond is formed, accessory cells (Langerhans cells, LC[5]) have to take up the foreign complete antigen (hapten + carrier protein), process them, and present them on their surface in association with Ia.[6] LC are essential to the induction of a contact allergy by an epicutaneous pathway.[7] It appears that a specific tolerance may be induced by application of a hapten to a skin area in which a fair number of LC are either absent naturally (mouse tail skin)[8] or artificially (anti-Ia antisera and complement)[7] or

Scheme I. Retrosynthetic Scheme

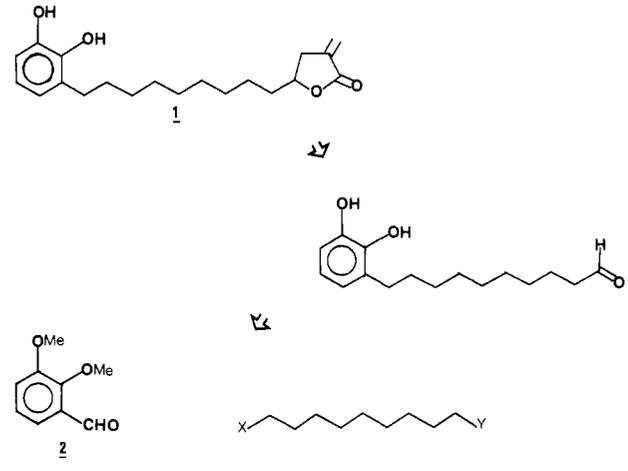

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Table I. Results of Open Epicutaneous Tests on Guinea Pigs

sensitizer[a]	compd tested[b]	skin reaction[c] 3	2	1	0.5	0	av skin reaction[d]	no. of positive animals
bihapten 1	bihapten 1	0	0	8	0	0	1	8/8
	lactone 8	0	0	0	0	0	0	0/8
lactone 8	bihapten 1	0	5	3	0	0	1.6	8/8
	lactone 8	8	0	0	0	0	3	8/8
lactone 8 (pretreated with bihapten 1)	bihapten 1	0	0	8	0	0	1	8/8
	lactone 8	0	0	2	6	0	0.6	8/8

[a] Sensitized by the FCAT method, using three injections (each other day) of a 1:1 FCA/saline emulsion of the hapten (2.5% w/v). [b] Open epicutaneous test using a 4:1 acetone/olive oil solution of the hapten (2% w/v). [c] The scale used is the following: 0 = no reaction, 0.5 = slight erythema not covering the whole test area, 1 = definite erythema covering the whole test area, 2 = erythema plus swelling of the test area, 3 = erythema plus swelling going well beyond the test area. The figures represent the number of animals responding with a 0, 0.5, 1, 2, or 3 skin intensity test. [d] The average skin intensity is obtained by adding all the test scores and dividing by the number of animals tested.

are "incapacitated", after destruction (UV irradiation)[9] or disappearance (prior processing of a first hapten)[10,11] of the membranous ATPase system.

An obvious question resulting from the last concept is the following: is it possible to introduce at the same time both the sensitizer and the tolerance inducer by linking two different haptens connected through a hydrocarbon chain? A preliminary answer to this question was provided by a previous work from this Laboratory: in a bihapten containing a pyrocatechol end and an α-methylene-γ-butyrolactone end, only the pyrocatechol part of the molecule was recognized.[12] The question raised by this finding was therefore: would animals, thus sensitized to pyrocatechol, be tolerized (or immunized) against the other hapten (the methylene lactone)? Such a property could be utilized for therapeutic purposes.

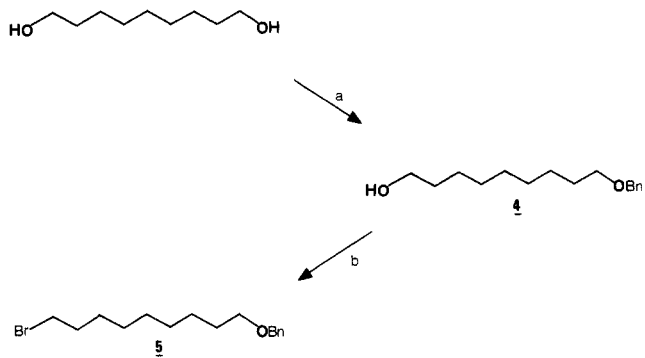
To answer this question, a new bihapten containing pyrocatechol and methylene lactone ends has been synthesized and its tolerance-inducing activity examined in guinea pigs. The pyrocatechol end was chosen by analogy with pentadecylcatechol (PDC), one of the haptens from poison ivy urushiol. The latter is known to cause ACD in 60% of the U.S. population.[13,14] The other end, an α-methylene-γ-butyrolactone, is a moiety present in a number of Compositae and other plants.[15] Their sensitizing capacity is also well-documented.

Chemistry

The general synthetic strategy designed for bihapten 1 is illustrated in Scheme I. An appropriate synthon seemed to be the bifunctional compound 2, which could be linked to *o*-veratraldehyde by Grignard reaction and, after oxidation and deprotection, further reacted with the Reformatsky reagent 3.

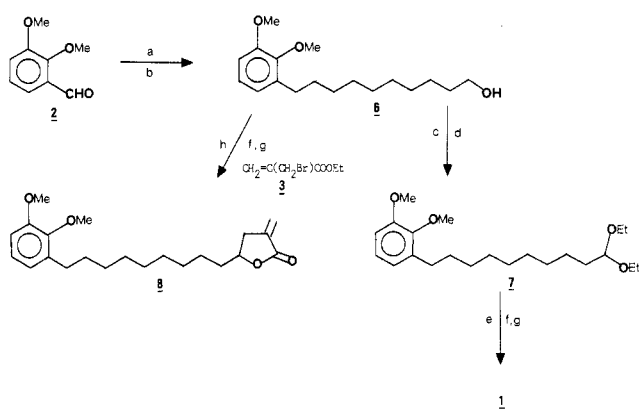
Monoprotection[16] of butanediol with benzyl chloride followed by bromination using carbon tetrabromide and triphenylphosphine afforded bromide 5 (the latter reaction in 90% yield) (Scheme II). Sonication of 5 with magnesium in THF and subsequent trapping with *o*-veratraldehyde produced a benzylic alcohol, which could be hydrogenolyzed over palladium (Scheme III). The alcohol 6 thus obtained in 66% yield was oxidized with a chromium oxide–pyridine complex in dichloromethane[17] and the aldehyde ketalized without further purification with EtOH and H_2SO_4 to give 7 (70% yield). Further deprotection of both methyl ethers and ketal with BBr_3[18,19] and subsequent Reformatsky-type reaction with ester 3 using our recently described improved procedure[20] in aqueous media produced, after acid-catalyzed lactonization, the required bihapten 1 (47% yield).

Scheme II[a]



[a] (a) Na, $PhCH_2Cl$, xylene, 120 °C (30% yield), (b) CBr_4, PPh_3, CH_3CN, room temperature, (90% yield).

Scheme III[a]



[a] (a) **5**, Mg, THF, (b) H_2, Pd/C 10%, EtOH, HCl catalyst, room temperature (66% yield), (c) CrO_3, pyr, CH_2Cl_2, room temperature, (d) EtOH, H_2SO_4 catalyst, room temperature (70% yield), (e) BBr_3, CH_2Cl_2, −78 °C, (f) **3**, Zn, NH_4Cl/THF (5:2), 60 °C, (g) *p*-TsOH catalyst, Et_2O, room temperature (47% yield), (h) CrO_3, pyr, CH_2Cl_2, room temperature.

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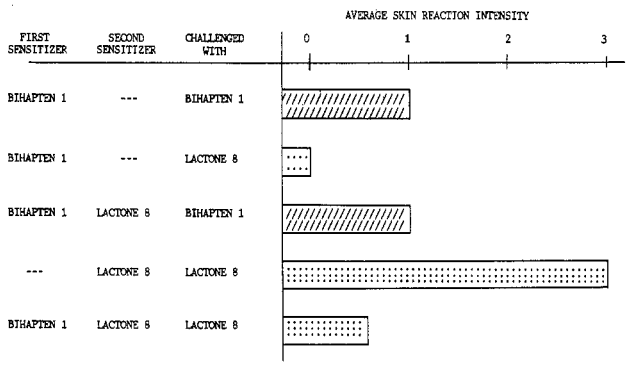

Figure 1. Compared skin sensitivity to lactone 8 and bihapten 1 for naive and bihapten-pretreated animals.

We have also prepared the dimethoxy derivative 8 by oxidation of alcohols 6 followed by Reformatsky reaction with ester 3 and lactonization[20] in an overall 32% yield from veratraldehyde.

Results

The biological activity of compounds 1 and 8 was determined by experimental skin sensitization of guinea pigs. Results of epicutaneous tests are given in table I.

Sensitization. The first striking result emerging from the data in Table I is the stronger sensitizing activity exhibited by the monohapten 8 (only the α-methylene-γ-butyrolactone end should be active) as compared to that of the bihapten: 3.0 average skin reaction in the former score vs. 1.0 in the latter.

A second remarkable finding is that, while monohapten 8 is not recognized in bihapten 1 sensitized animals, monohapten 8 sensitized guinea pigs reacted to bihapten 1, presumably through its α-methylene-γ-butyrolactone end. This is at variance with previous results from this laboratory where a similar double-headed hapten (the immunogenic ends being separated by six methylene groups) was prepared by another longer synthetic pathway and examined for its skin-sensitizing capacity.[15] While double-headed hapten sensitized animals did not recognize the monohaptenic methylene lactone (as in this study), monohapten (containing the lactone ring) sensitized animals did not react to the bihapten. The number of methylene groups connecting the two haptenic ends is certainly important in determining reaction to two, one, or no end.

Tolerance. A question raised at the inception of this study was: is the nonreaction to one haptenic end an active tolerance? If this latter hypothesis is correct, prior treatment with bihapten should immunize (or induce tolerance) against the nonexpressed part of the molecule. Table I results seem to favor this hypothesis: bihapten 1 sensitized animals were sensitized to monohaptenic α-methylene-γ-butyrolactone 8. The result was striking: the average skin reaction to 8 dropped from 3.0 in the control group, which had only undergone sensitization to monohapten 8, to 0.6 in the group that had previously been treated with bihapten 1 (Figure I).

Discussion

Simultaneous introduction of two haptens into a living organism can result in what is known as antigenic competition.[21] In this paper, sensitization to a compound with two immunogenic functions only evoked reactivity to one of the two ends of the molecule, in this case, the pyrocatechol ("poison ivy like") end. In a previous paper, we interpreted this result as being due to the "shielding" of the hydrophobic part of the molecule (the α-methylene-γ-butyrolactone part) and expression at the T-cell receptors of only the hydrophilic (pyrocatechol) part. It seems however that the γ-lactone is probably not as deeply "shielded" as thought previously and T-cell receptors from a monohaptenic α-methylene-γ-butyrolactone can indeed recognize it. This one-way recognition could also explain that some tolerance to this γ-lactone end can be induced in the animals undergoing previous treatment with the double-headed hapten 1. If this result (induction of tolerance) is general, then therapeutic applications are in sight. More work along these lines is in progress.

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Experimental Section

General Methods. Proton NMR spectra were recorded on a Perkin-Elmer 60-MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with respect to Me_4Si as internal standard. Coupling constants (J) are expressed in hertz. Multiplicities are indicated by a (singlet), d (doublet), t (triplet), and m (multiplet). Infrared spectra were obtained on a Beckman Acculab spectrometer using $CHCl_3$ solutions; peaks are reported in reciprocal centimeters. Melting points were determined on a Büchi Tottoli 510 apparatus and are uncorrected.

Dry solvents were freshly distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Dichloromethane and acetonitrile were distilled from P_2O_5. All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon.

Ethyl (Bromomethyl)acrylate (3). A solution of (bromomethyl)acrylic acid (5.43 g, 32.9 mmol) in benzene (150 mL), EtOH (110 mL), and concentrated H_2SO_4 (10 drops) was heated at reflux in a Soxhlet containing $MgSO_4$. Reflux was maintained for 3 days, and then the solvents were carefully removed in vacuo. Ether (60 mL) and 10% K_2CO_3 (40 mL) were added to the mixture. The ether layer was separated, dried, filtered, and evaporated. Flash chromatography of the resulting liquid afforded 3 (4.77 g, 75% yield) which was identical with an authentic sample.[12]

9-(Benzyloxy)-1-bromononane (5). Triphenylphosphine (10.68 g, 40.7 mmol) was added in small portions under argon at 0 °C to a stirred solution of 9-(benzyloxy)-1-nonanol (4; 9.29 g, 37.1 mmol) and carbon tetrabromide (13.50 g, 40.7 mmol) in dry CH_3CN (40 mL). The mixture was stirred at room temperature for 1.5 h and evaporated. The resulting oil was taken up in ether (100 mL), filtered, and evaporated. Flash chromatography of the residue (AcOEt/hexane, 5:95) afforded 5 as an oil (10.32 g, 90% yield): NMR δ 7.23 (5 H, br s, Ar H), 4.41 (2 H, s, Ar CH_2O), 3.41 (2 H, t, J = 6 Hz), 3.35 (2 H, t, J = 6 Hz), 1.30 (14 H, m). Anal. ($C_{16}H_{25}OBr$) C, H.

3-(10-Hydroxydecyl)veratrole 6. To a solution of [9-(benzyloxy)-1-nonyl]magnesium bromide, prepared with sonication from 5 (10.11 g, 32.2 mmol) and magnesium (2.11 g, 32.2 mmol) in dry THF (10 mL), was added dropwise a solution of *o*-veratraldehyde (4.29 g, 25.8 mmol) in dry THF (15 mL) under argon at 0 °C. Stirring of the solution was continued overnight at 25 °C and the reaction was quenched by the addition of a saturated ammonium chloride solution (30 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL), dried, filtered, and evaporated. The residue was dissolved in EtOH (30 mL) containing concentrated HCl (3 drops) and hydrogenated over 10% Pd/C (0.15 g) for 3 weeks. Evaporation followed by flash chromatography provided alcohol 6 as an oil (5.02 g, 66% yield): IR 3610, 3600–3200 cm^{-1}; NMR δ 7.10–6.60 (3 H, m, Ar H), 3.81 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.50 (2 H, t, J = 6, CH_2O), 2.61 (2 H, t, J = 6.6, Ar CH_2), 1.30 (16 H, m). Anal. ($C_{18}H_{30}O_3$) C, H.

3-(10,10-Diethoxydecyl)veratrole (7). A solution of 6 (2.51 g, 8.5 mmol) in CH_2Cl_2 (10 mL) was rapidly added to a suspension of CrO_3 (5.13 g, 51.3 mmol) in CH_2Cl_2 (130 mL) containing pyridine (8.29 mL, 102.6 mmol) at 25 °C. After stirring for 15 min, the reaction mixture was filtered through silica gel (20 g) and washed with AcOEt (150 mL). The clear pale yellow filtrates were combined and evaporated. The residue was dissolved in EtOH (10 mL) containing a few drops of concentrated H_2SO_4. After the mixture was stirred overnight at 25 °C, 10% aqueous K_2CO_3 (5 mL) was added and the solution was stirred for 1 h before addition of ether (20 mL) and water (10 mL). The ether

layer was separated dried, filtered, and evaporated. Flash chromatography of the residue (Et_2O/hexane, 2:8) afforded **7** (2.19 g, 70% yield) as an oil: IR 3000, 1200 cm^{-1}; NMR δ 6.78 (3 H, m, Ar *H*), 4.46 (1 H, t, *J* = 6, C*H*(OEt)$_2$), 3.78 (6 H, s, OCH_3), 3.6–3.3 (4 H, m, OCH_2), 2.60 (2 H, t, *J* = 6.6, Ar CH_2), 1.3 (16 H, br s), 1.19 (6 H, t, J = 6 Hz, CH_3). Anal. ($C_{22}H_{38}O_4$) C, H.

5-[9-(2,3-Dihydroxyphenyl)nonyl]-3-methylene-2-dihydrofuranone (1). A solution of BBr_3 (13.50 mL, 13.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise at −78 °C under argon to a solution of **7** (1.64 g, 4.5 mmol) in dry CH_2Cl_2 (10 mL). After 3 h of stirring at −78 °C, ether (10 mL) and water (15 mL) were added, and the resulting solution was filtered. The ether layer was separated, dried, filtered, and evaporated to give a viscous oil. This oil was dissolved in THF (2 mL) and added to a saturated NH_4Cl solution (5 mL) containing Zn (0.35 g, 5.4 mmol) and ethyl (bromomethyl)acrylate (**3**; 1.04 g, 5.4 mmol). The resulting mixture was heated at 60 °C for 4 h and then cooled to room temperature. Ether (30 mL) was added and the ether layer separated. To this layer was added *p*-TsOH (0.10 g, 0.6 mmol) and the resulting solution was stirred at 25 °C for 2.5 h. After evaporation, the yellow oil was chromatographed (Et_2O/hexane, 7:3) to yield crystalline bihapten **1** (0.70 g, 47% yield): IR 3620, 3600–3200, 1755 cm^{-1}; NMR δ 6.60 (3 H, br, s, Ar *H*), 6.14 (1 H, m, C=C*H*), 5.65 (1 H, m, C=C*H*), 5.37 (2 H, br s, O*H*), 4.46 (1 H, m, C*H*O), 2–4 (4 H, m), 1.22 (16 H, br s); mp 58–60 °C. Anal. ($C_{20}H_{28}O_4$) C, H.

5-[9-(2,3-Dimethoxyphenyl)nonyl]-3-methylene-2-dihydrofuranone (8). A solution of **6** (2.51 g, 8.5 mmol) in CH_2Cl_2 (3 mL) was rapidly added to a suspension of CrO_3 (5.12 g, 51.0 mmol) in CH_2Cl_2 (25 mL) containing pyridine (8.29 mL) at 25 °C. After stirring for 15 min, the reaction mixture was filtered through silica gel (15 g) and washed with AcOEt (100 mL). The clear pale filtrates were combined and evaporated. The residue was dissolved in THF (4 mL) and added to a saturated NH_4Cl solution (10 mL) containing Zn (0.67 g, 10.2 mmol) and **3** (1.98 g, 10.2 mmol). The resulting mixture was heated at 60 °C for 4 h before being cooled. Ether (50 mL) was added and the ether layer separated. To this layer, *p*-TsOH (0.20 g, 1.2 mmol) was added and the solution was stirred at 25 °C for 2.5 h. After evaporation, the oil was chromatographed (Et_2O/hexane, 5:5) to give **8** as an oil (1.48 g, 48% yield): IR 1755, 1205 cm^{-1}; NMR δ 6.74 (3 H, m, Ar H), 6.11 (1 H, m, C=C*H*), 5.52 (1 H, m, C=C*H*), 4.54 (1 H, m, C*H*O), 3.79 (6 H, s, OCH_3), 3.0–2.5 (4 H, m), 1.28 (16 H, br s). Anal. ($C_{22}H_{32}O_4$) C, H.

Biological Assays. Albino Himalayan spotted Füllingsdorf (from Hoffman-La Roche, Basel) female guinea pigs weighing from 300 to 500 g were sensitized as described by Klečak.[22] On alternate days, the hapten, emulsified in Freund's complete adjuvant (FCA), was injected intradermally (0.1 mL) in the shaved nuchal region of the animal (in all, three injections, five after boost). After 15 days of rest, the elicitation was conducted by an open epicutaneous test (OET): 25 μL of a 4:1 acetone/olive oil solution of hapten was deposited on the shaved flank of the animal (on a 2-cm^2 surface with a standard circular stamp). Tests were read at the 48th hour, using the following scale: 0 = no reaction, 0.5 = slight erythema not covering the whole test area, 1 = erythema covering all the test area, 2 = erythema plus swelling of the test area, 3 = erythema plus swelling going well beyond the test area. Before any sensitization, irritation thresholds (primary toxicity) were determined on FCA-injected controls (same procedure as above for elicitation). Concentrations up to 2% in 4:1 acetone/olive oil of Bihapten were nontoxic. Control groups of eight animals (FCA treated) were used in each experiment.

Registry No. **1**, 104876-09-7; **2**, 86-51-1; **3**, 17435-72-2; **3** (acid), 72707-66-5; **4**, 104876-10-0; **5**, 104876-11-1; **6**, 104876-12-2; **6** (adlehyde), 104876-13-3; **7**, 104876-14-4; **7** (adlehyde) (deprotected), 104876-15-5; **8**, 104876-16-6.

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Preparation and Antitumor Activity of New Mitomycin A Analogues

Salah M. Sami,[†] Bhashyam S. Iyengar,[†] William A. Remers,*[†] and William T. Bradner[‡]

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, Arizona 85721, and Bristol-Myers Company, Syracuse, New York 13221. *Received May 1, 1986*

A series of 26 mitomycin A analogues including 23 new ones was prepared by a variety of methods. The most useful methods were alkoxide exchange on mitomycin A and treatment of 7-hydroxymitosane with 3-substituted 1-phenyltriazenes. Many of the new analogues were superior to mitomycin C in the P388 leukemia assay and the more stringent subcutaneous B16 melanoma assay both in mice. Four of them gave long-term survivors in the latter assay. Quantitative correlations between log *P* and antitumor activity were not possible, but some guidelines for future analogue development are proposed.

Although hundreds of mitomycin C analogues (7-aminomitosanes) have been prepared and tested for antitumor activity, only a small number of mitomycin A analogues (7-methoxymitosanes) are known. The latter include naturally occurring compounds mitomycin A (**1**),[1] mitomycin F (N^{1a}-methylmitomycin A),[2] and a group of 16 semisynthetic analogues.[3] Of the semisynthetic compounds, 14 had the 7-methoxy group replaced by other simple alkoxy groups. All 16 were active against sarcoma-180 in mice. There are a few other naturally occurring 7-methoxy compounds in the mitomycin family, but they are placed in other subgroups.[2] For example, mitomycins B and J (B group) are epimeric at C-9 from the mitomycin A group, and mitomycins H and K (G group) have a 9,10-methylene group.

Our interest in mitomycin A analogues is based on the group of semisynthetic compounds plus our observation that mitomycin A is highly potent (in terms of minimal effective dose, MED) against P388 leukemia in mice.[4] Thus, it is 4 times as potent as mitomycin C, although it is less effective in prolonging life than mitomycin C at their optimal doses (OD). As described below, we prepared a series of 26 mitomycin A analogues, including 23 new ones that were different from the simple 7-alkoxy types. They contained such functionalities as double and triple bond,

[†] University of Arizona.
[‡] Bristol-Myers Company.

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