Table I (*Continued*)

Compd	Formula	Mp, °C (recrystn solvent)	Yield, %	Antileukemic activity: P388 Dose, mg/kg	P388 Survival	P388 Wt diff	P388 T/C, %	L1210 Dose, mg/kg	L1210 Survival	L1210 Wt diff	L1210 T/C, %
9	$C_{22}H_{23}NO_5$	140–142	83	160	6/6	−1.6	59				
				80	6/6	−1.0	90				
				40	6/6	+2.0	100				
				20	6/6	+0.5	154				
				10	6/6	−0.2	173				
				5	6/6	−0.5	127				
10a	$C_{21}H_{24}INO_4$	158–160 dec (MeOH–Et_2O)	83					400	1/6		
								200	4/6	+0.5	95
								100	6/6	+0.8	98
								50	12/12	−0.7	106
								25	6/6	+0.5	102
								12.5	6/6	−0.0	104
10b	$C_{22}H_{26}BrNO_4$	165–167 dec (EtOH–Et_2O)	89	200	0/6			200	2/6		
				100	5/6	−0.5	104	100	6/6	−0.2	98
				50	6/6	+0.7	90	50	5/6	−0.4	115
								25	6/6	−0.4	94
11	$C_{24}H_{27}NO_9S$	277–279 dec (MeOH)	68					200	0/6		
								100	10/12	−4.1	116
								50	6/6	−5.6	107
								25	5/6	−4.6	104

[a] For general screening procedure and data interpretation, *cf.* R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3** (2), 1 (1972); Instruction Booklet 14, "Screening Data Summary Interpretation," Drug Research and Development, Chemotherapy, National Cancer Institute, Bethesda, Md., 1972. [b] 1–2 cures in groups of six to ten mice were occasionally observed at doses of 25–200 mg/kg. [c] 1–3 cures against B16 melanocarcinoma in groups of ten mice were noted at doses of 12.5–200 mg/kg. [d] The corresponding chloride salt was prepared in 85% yield, mp 292–294° dec. [e] Cell culture (KB): ED_{50} at 1.0×10^{-1} μg/ml. Activity confirmed. [f] One cure each in one group of six mice was observed at doses of 12.5 and 8.33 mg/kg. [g] The corresponding chloride salt was prepared in 85% yield, mp 252–254° dec. [h] Two cures in one group of six mice were observed at dose of 100 mg/kg. [i] The corresponding chloride salt was prepared in 85% yield, mp 235–237° dec. [j] Cell culture (KB): ED_{50} at 2.2×10^{-1} μg/ml. Activity confirmed. [k] The corresponding nitrate salt was prepared in 80% yield, mp 303–305° dec.

ine and CH_3I in a manner similar to that described for **10b**. *Anal.* ($C_{21}H_{24}INO_4$) C, H, N.

5,6-Dihydro-8-methyl-2,3,10,11-tetramethoxydibenzo[*a*,*g*]-quinolizinium acetosulfate (11), mp 277–279° dec, was prepared from dihydropapaverine (**5**, R_1, R_2, R_3, R_4 = OCH_3) in a manner similar to that used for the preparation of coralyne. Uv absorption of this compound is similar to that of dehydro-α-coralydine.[11] *Anal.* ($C_{24}H_{27}NO_9S$) C, H, N.

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9,11-Seco Steroids. An Attempt to Separate Biological Activities *via* Ring Cleavage

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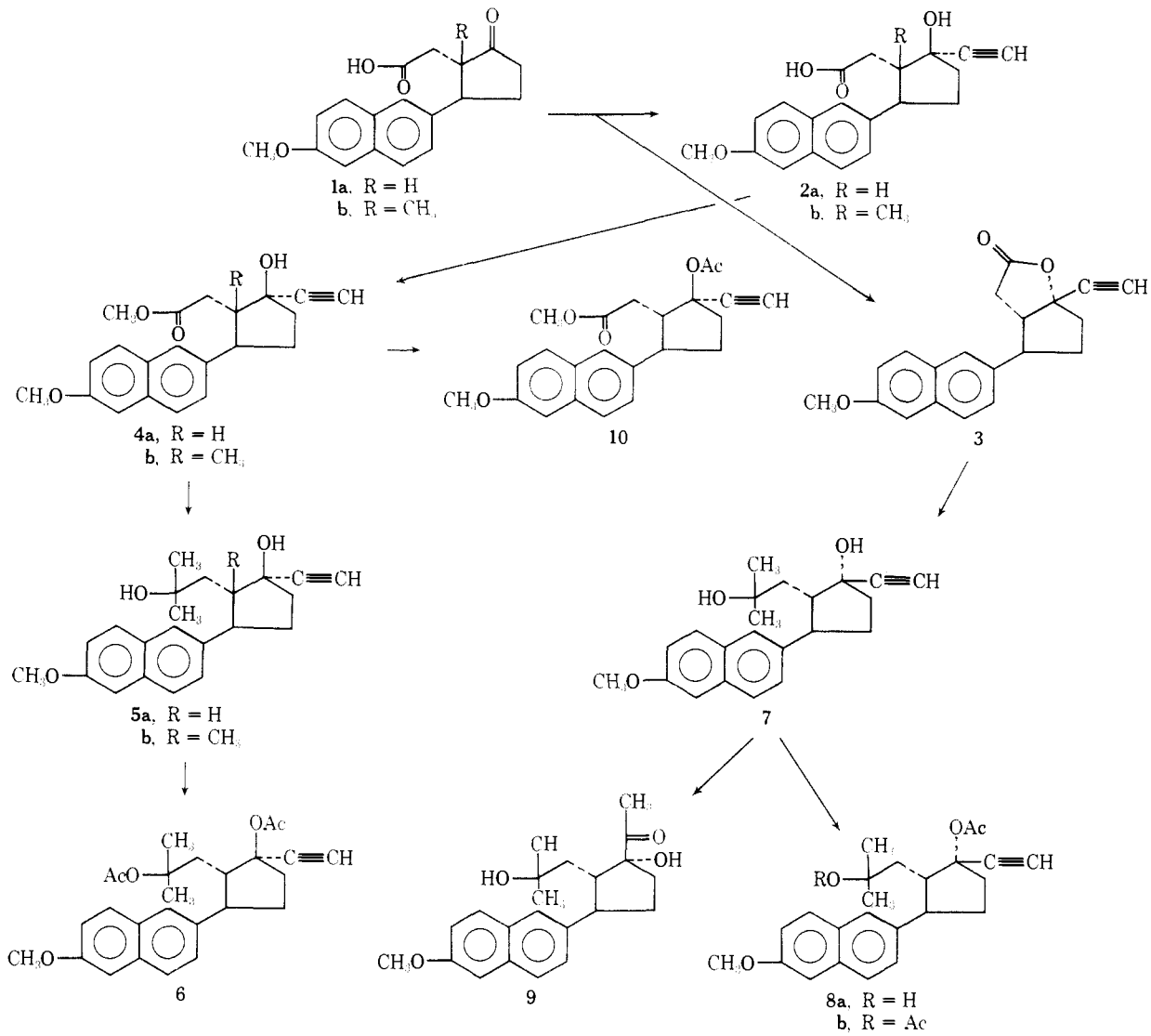
A series of seco steroids with rings A and B aromatic was synthesized in order to determine the effect which scission of the 9,11 bond has on biological activities. One compound, **5a**, was found to have antiestrogen, antifertility, and antiinflammatory properties, with an estrogenic activity approximately 0.003% that of estrone.

Molecular modification has been employed as a means of enhancing specific biological activities while reducing or eliminating less desirable effects. Application of this process has led to the successful development of potent antiinflammatory steroids,[1] anabolic agents with reduced androgenic properties,[2] orally active progestins,[3] and long acting estrogens.[4]

Of the four classes of steroid hormones (corticosteroids,

Scheme I



androgens, progestins, and estrogens), the estrogens are structurally the least specific. A variety of nonsteroidal substances show feminizing activity.[5]

The naturally occurring steroid estrogens have also been reported to possess hypocholesterolemic, antiinflammatory, and calcium-retaining effects.[6] These effects are useful in the treatment of certain diseases. However, the potent feminizing property of the estrogens often militates against their use as therapeutic agents.

Suppression of the feminizing effect of the estrogens without concomitant loss of other biological activities would be highly desirable. As an extension of work which had previously been reported,[7] we prepared a series of 9,11-seco steroids in order to determine whether rupture of the 9,11 bond would produce the desired result.

It was our hope that ring cleavage ("entropy effect"[8]) would alter the substrate-receptor interaction in the uterus[9] as to provide a favorable separation of activities.

Each of the compounds studied contained a *gem*-dimethyl function at C-11 (steroid numbering). The purpose of inserting two methyl groups into that position was to prevent the molecule from adopting the nearly planar conformation of the natural estrogens, thereby reducing the possibility of the compound being estrogenic.

The starting substance, *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid (1a), was treated with ethynylmagnesium bromide to afford a mixture of *trans-anti*-2-(6-methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetic acid (2a)† and *trans-syn*-2-(6-methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetic acid lactone (3) in a ratio of 2:3. In contrast, the reaction of ethynylmagnesium bromide with the homologous 1-methylketo acid 1b proceeded stereoselectively to give the *trans-anti* acid 2b as the sole product.[10] Esterification of 2a followed by treatment with methylmagnesium bromide yielded *trans-anti*-2-(2-hydroxy-2-methylpropyl)-1-ethynyl-3-(6-methoxy-2-naphthyl)cyclopentanol (5a). In a similar manner, 2b afforded 5b.[10] When 5a was heated at 95° with acetic anhydride and pyridine, the diacetate 6 was obtained.

Conversion of the lactone 3 to *trans-syn*-2-(2-hydroxy-2-methylpropyl)-1-ethynyl-3-(6-methoxy-2-naphthyl)cyclopentanol (7) was accomplished directly with methylmagnesium bromide. Compound 7 was converted into a mixture of the monoacetate 8a and the diacetate 8b by warming at 60° with acetic anhydride and pyridine.

Hydration of the triple bond of the *trans-syn*-ethynylcyclopentanol 7 furnished *trans-syn*-1-acetyl-2-(2-hydroxy-2-methylpropyl)-3-(6-methoxy-2-naphthyl)cyclopentanol (9) (Scheme I).

The estrogenicity of the seco steroids was determined in

†In this paper the configuration is designated on the basis of the relative spatial orientation of the following three groups attached to the cyclopentane ring and in this order: methoxynaphthyl ring, hydroxyalkyl or the acetic acid moiety, and hydroxyl group. Unless specified otherwise the compounds are racemic.

immature (22–25 days old) mice. A total of 1 mg of each compound was administered subcutaneously in corn oil over a period of 3 days. Increase in uterine weight in the 72-hr interval was employed as the index for activity. A compound inactive at this dose has less than 0.01% the activity of estrone.[11]

All of the compounds were tested for estrogenic activity. Only two compounds, namely, **6** and **9**, showed activity at the 1-mg dose level. In view of their estrogenic response, the ability of these two compounds to antagonize estrone-stimulated uterine growth was also studied. Only **9** showed estrogen antagonism when given subcutaneously in oil at a total dose of 1 mg in 3 days simultaneously with a total dose of 0.3 μg of estrone. Estrogen-stimulated uterine growth can be antagonized by progesterone;[12] the antiestrogen activity of **9** corresponds to 5–10% that of progesterone.

While **6** and **9** possess side chains which are characteristic of the progestins, neither compound showed progestational or antiprogestational activity in immature female rabbits primed with 5 μg of 17β-estradiol daily for 6 days.[13]

Although the diacetate **6** was inactive as an estrogen antagonist, the corresponding diol **5a** was found to be active. In a control group of ten mice, each treated only with 0.3 μg of estrone, the average uterine weight was 74.2 mg. Subcutaneous administration of a total of 1 mg of **5a**, as described above, reduced the average uterine weight to 52.9 mg of the estrone-treated animals (ten in the group). To establish whether this effect might possibly be due to **5a** being an agonist, the estrogenicity of **5a** was determined at 2 and 4 mg, as well as at the 1-mg dose level. The diol **5a** was found to be active at 4 mg but not at 1 or 2 mg. Surprisingly, the optically active, homologous diol **5b**,[10] which possesses the same stereochemistry as the natural estrogens, was inactive as an estrogen or as an antiestrogen at 1 mg.

The diol **5a** displayed antifertility activity in reducing the number of rats with normal-size fetuses 15 days after mating when these rats were given 4 mg/day of the compound daily for 7 days following mating.[14] No other compounds in this series showed this activity.

When given 4 mg/day of **5a** subcutaneously, only one out of five rats became pregnant. At the same dose level but administered orally, **5a** prevented pregnancy in three out of five rats. In the untreated group of animals, 80% or more were pregnant. The ED_{50} values for **5a** are 3.1 (subcutaneously) and 3.3 mg (orally). The corresponding subcutaneous and oral values for estrone are 3 and 360 μg, respectively.

5a showed neither progestational or antiprogestational activity. However, it did exhibit antiinflammatory activity. It was found to be active in the carrageenin-induced foot edema rat assay[15] at 40 mg/kg and in the mycobacterium butyricum-induced polyarthritic, hypersensitive rat test[16] at 25 mg/kg.

With the exception of the acetoxy methyl ester **10**, which was obtained by acetylating **4a**, none of the compounds in this series was found to be active in reducing the plasma cholesterol level of male rats made hypercholesterolemic and hypothyroid with propylthiouracil[17] when the test compound was administered at 10 mg/kg daily for 10 days.

In the eight animals employed as control, the average plasma cholesterol concentration was 86.7 mg %. The value for the eight rats treated orally with compound **10** was 78.7 mg %.

Although the present study cannot be regarded as definitive, the results appear sufficiently interesting to us that we have undertaken further studies on the seco steroids.

Experimental Section†

Melting points were determined on a Fisher-Johns melting block and are corrected. Nmr spectra were taken on a Varian A-60 instrument in deuteriochloroform (unless specified otherwise) with tetramethylsilane as the standard.

(±)-*trans-anti*-2-(6-Methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetic Acid (2a) and **(±)-*trans-syn*-2-(6-Methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetic Acid Lactone (3).** To 820 ml of redistilled THF saturated with acetylene was added with stirring at 20° 330 ml of 3 *M* EtMgBr in THF over a period of 75 min. Acetylene was continuously passed into the mixture. The reaction mixture was cooled in an ice bath and while acetylene was continually being passed into the mixture, a solution of 16.4 g of *trans*-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid (**1a**)[7] in 190 ml of THF was added portionwise over a period of 50 min. The reaction mixture was stirred in the ice bath for an additional 2 hr and then allowed to come to room temperature over the course of 15 hr with stirring. The reaction mixture was concentrated under reduced pressure. The residue was acidified with 300 ml of 7 *N* H_2SO_4, and the resultant mixture was extracted with ether. The ether extract in turn was extracted with successive portions of H_2O, 5% $NaHCO_3$, and H_2O again. The ether solution was dried (Na_2SO_4) and distilled to dryness under reduced pressure to afford *ca.* 9.7 g of the crude lactone **3**. The crude product was chromatographed on 1500 g of SiO_2. The column was eluted with C_6H_6–EtOAc. Elution with 1% EtOAc in C_6H_6, followed by crystallization from pentane, gave 6.8 g of **3**, mp 78–80°. Another crystallization from pentane raised the melting point to 82–84°; nmr (Hz) multiplet 425.5–468, 233, 164.5. *Anal.* ($C_{20}H_{18}O_3$) C, H.

The combined bicarbonate extracts were acidified with 6 *N* HCl. The acidified mixture was extracted with ether. The ether extract was washed with H_2O, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford *ca.* 6.8 g of the crude acid **2a**. The crude acid was chromatographed on 980 g of SiO_2. The column was eluted with C_6H_6–EtOAc. Elution with 5% EtOAc in C_6H_6, followed by crystallization from chloroform–pentane, furnished 5.3 g of the acid **2a**: mp 132–134°; nmr (Hz) multiplet 423–474, 233.5, 158.

(±)-Methyl *trans-anti*-2-(6-Methoxy-2-naphthyl)-5-ethynyl-5-hydroxycyclopentaneacetate (4a). To a solution of 889 mg of the acid **2a** in 15 ml of ether, cooled in an ice bath, was added 20 ml of an ethereal solution of diazomethane (prepared from 3.5 g of *N*-nitrosomethylurea, 40 ml of ether, .7 g of KOH, and 7 ml of H_2O). The reaction mixture was allowed to stand at 5° for 3 hr. Then it was evaporated to dryness to afford a viscous yellow oil. The viscous oil was crystallized from ether–pentane to afford 565 mg of the ester **4a**: mp 102.5–105°; nmr (Hz) multiplet 427–468, 235, 214, 158.5.

(±)-*trans-anti*-2-(2-Hydroxy-2-methylpropyl)-1-ethynyl-3-(6-methoxy-2-naphthyl)cyclopentanol (5a). To 30 ml of 1 *M* MeMgBr in diethyl ether, stirred and heated under reflux, was added over a period of 5 min a solution of 443 mg of the ester **4a** in 30 ml of ether. The reaction mixture was stirred and heated under reflux for 7 hr. The cooled reaction mixture was treated with a saturated solution of NH_4Cl. The ether phase was separated, washed successively with H_2O and saturated NaCl, dried (Na_2SO_4), and distilled to dryness under reduced pressure. The residual viscous yellow oil was crystallized from ether–pentane to afford 396 mg of a crystalline product, mp 164.5–167.5°. Two more crystallizations from ether–pentane gave 318 mg of **5a**: mp 167.5–168°; nmr [Hz, $(CD_3)_2SO$] multiplet 424–473, 234, 207, 201 (one of the two signals belongs to H_2O), 64, 56. *Anal.* ($C_{22}H_{26}O_3$) C, H.

(±)-*trans-anti*-2-(2-Hydroxy-2-methylpropyl)-1-ethynyl-3-(6-methoxy-2-naphthyl)cyclopentanol Diacetate (6). A solution of 880 mg of the diol **5a**, 10 ml of C_5H_5N, and 10 ml of Ac_2O was maintained at 95° for 36 hr in an N_2 atmosphere. The cooled reaction mixture was poured into ice H_2O. The resultant mixture was extracted with ether. The ether extract was washed with H_2O, dried (Na_2SO_4), and evaporated to a small volume. The residue was diluted with hexane whereupon the product **6** crystallized out of the mixture: yield 887 mg; mp 119.5–121.5°. Another crystallization from ether–hexane raised the melting point to 122–123°; nmr (Hz) multiplet 426–467.5, 233.5, 165, 124, 95.5, 79, 77. *Anal.* ($C_{26}H_{30}O_5$) C, H.

(±)-*trans-syn*-2-(2-Hydroxy-2-methylpropyl)-1-ethynyl-3-(6-

methoxy-2-naphthyl)cyclopentanol (7). To 210 ml of 1 *M* MeMgBr in diethyl ether, stirred and heated under reflux, was added over a period of 25 min a solution of 2.93 g of the lactone 3 in 200 ml of ether. The reaction mixture was stirred and heated under reflux for 3.5 hr. The cooled reaction mixture was treated with a dilute solution of NH_4Cl. The ether phase was separated, washed successively with H_2O and saturated NaCl, dried (Na_2SO_4), and concentrated to a small volume by distillation under reduced pressure. The residue, which contained a crystalline product, was allowed to stand at 0° for 1 hr. The solid was collected by filtration: yield 1.78 g; mp 178–180°. From the mother liquor, an additional 0.67 g of 7, mp 173–184.5°, was obtained. Crystallization of 7, mp 178–180°, from acetone–hexane raised the melting point to 179.5–182.5°; nmr [Hz, $(CD_3)_2SO$] multiplet 422–471.5, 232.5, 199.5, 60.5, 49. *Anal.* ($C_{22}H_{26}O_3$) C, H.

(±)-*trans-syn*-2-(2-Hydroxy-2-methylpropyl)-1-ethynyl-3-(6-methoxy-2-naphthyl)cyclopentanol 1-Acetate (8a) and (±)-*trans-syn*-2-(2-Hydroxy-2-methylpropyl)-1-ethynyl-3-(6-methoxy-2-naphthyl)cyclopentanol Diacetate (8b). A mixture of 412 mg of the diol 7, 5 ml of C_5H_5N, and 5 ml of Ac_2O was maintained at 60° in an N_2 atmosphere for 36 hr. The cooled reaction mixture was poured into ice H_2O and rubbed. The resultant gum was collected by filtration, washed with H_2O, and dried. Then it was crystallized from ether–pentane to afford 328 mg of a crystalline product, mp 119.5–130°.

A 249-mg sample of this product was chromatographed on 8 g of SiO_2. The column was eluted with C_6H_6–EtOAc. Elution with 10% EtOAc in C_6H_6 gave initially a solid product which was crystallized from ether–pentane to afford 68 mg of the diacetate 8b, mp 135.5–137°. Further crystallization from ether–pentane raised the melting point to 137–138.5°; nmr (Hz) multiplet 424.5–466, 234.5, 158.5, 127, 93, 76. *Anal.* ($C_{26}H_{30}O_5$) C, H.

Continued elution of the column with 10% EtOAc in C_6H_6 gave a second solid product which was crystallized from ether–pentane to afford 45 mg of 8a, 137–138.5°. Admixed with 8b, it melted at 124–137.5°; nmr (Hz) multiplet 425–468, 234.5, 164, 127.5, 61, 53. *Anal.* ($C_{24}H_{28}O_4$) C, H.

When a mixture of 1.8 g of the diol 7, 30 ml of C_5H_5N, and 30 ml of Ac_2O was heated under reflux in an N_2 atmosphere for 6.5 hr and worked up in the usual manner, 1.36 g of the diacetate 8b was obtained: mp 134–138°.

(±)-*trans-syn*-1-Acetyl-2-(2-hydroxy-2-methylpropyl)-3-(6-methoxy-2-naphthyl)cyclopentanol (9). A mixture of 285 mg of the ethynyl diol 7, 70 mg of HgO, 6 ml of MeOH, and 0.4 ml of BF_3-Et_2O was stirred at room temperature for 2 hr. Afterward a 2-ml solution of aqueous–methanolic HCl (prepared from 2 ml of 6 *N* HCl, 13 ml of H_2O, and 7 ml of MeOH) was added to the reaction mixture. Stirring at room temperature was continued for an additional 1.5 hr. The reaction mixture was then diluted with 30 ml of 2% $NaHCO_3$. The resultant mixture was allowed to stand at 0° for 1 hr. The gum which formed was collected by filtration, washed with H_2O, and dried. Crystallization from ether–pentane afforded 145 mg of 9, mp 114.5–117°. Another crystallization from ether–pentane raised the melting point to 116–117.5°; λ^{KBr} 2.82, 2.96, 5.87, 6.13, 6.23 μ. *Anal.* ($C_{22}H_{28}O_4$) C, H.

(±)-Methyl *trans-anti*-2-(6-Methoxy-2-naphthyl)-5-ethynyl-5-acetoxycyclopentaneacetate (10). A solution of 1.5 g of the hydroxy ester 4a, 12 ml of C_5H_5N, and 12 ml of Ac_2O was maintained at 60° for 66 hr in an N_2 atmosphere, after which time it was poured into ice H_2O. The resultant solid was collected by filtration, washed with water, and dried: yield 1.52 g; mp 143.5–145.5°. Crystallization from ether–pentane afforded 1.32 g of 10: mp 148.5–149°; λ^{KBr} 3.03, 4.72, 5.73, 6.12, 6.22, 8.07 μ. *Anal.* ($C_{23}H_{24}O_5$) C, H.

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