The methosulfate of compound **75** was prepared and converted to the methide in the same manner to give a solid melting at 89–91°. The latter was unstable and decomposed on standing 1 week.

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Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1,2] 5. Bis-Basic Ethers of Anthraquinone and Bisalkamine Esters of Anthraquinonedicarboxylic Acids

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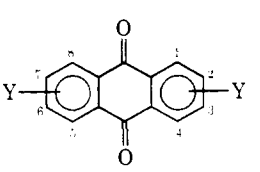
2,6-Bis[2-(diethylamino)ethoxy]-9,10-anthracenedione dihydrochloride (**10**, RMI 10,024DA) was found to prolong survival of mice infected with lethal challenges of encephalomyocarditis (EMC) virus. It was effective by oral as well as subcutaneous administration and showed broad spectrum antiviral activity. It was selected for preclinical evaluation from a series of congeners that were synthesized to determine structure–activity correlations. These indicated that the 2,6- and 2,7-position isomers showed much greater activity than the 1,4, 1,5, or 1,8 isomers and that elongation of the side chains and increase of molecular weight of the dialkylamine substituent led to decreased oral activity. The congeners **5**, **6**, **11**, and **15** also showed high antiviral activity. Bis(3-dibutylaminopropyl) 9,10-dihydro-9,10-dioxoanthracene-2,6-dicarboxylate dihydrochloride (**4**) and 9,10-dibutylidene-2,6-bis[2-(diethylamino)ethoxy]-9,10-dihydroanthracene dihydrochloride (**26**) showed antiviral activity on subcutaneous administration.

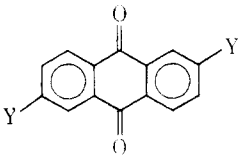
The preceding paper of this series[2] described the synthesis and biological evaluation of the anthraquinonesulfonamides I. Earlier, the antiviral activity of several fluorenone derivatives,[2–5] including tilorone hydrochloride,[4,6,7] was reported from our laboratories. Since these included bis-basic esters[3] and ethers,[4] the synthesis of the corresponding anthraquinone derivatives II and III was undertaken.

Chemistry. The bisalkamine esters of 9,10-dihydro-9,10-dioxoanthracene-1,5-, 1,8-, and 2,6-dicarboxylic acid



I, Y = $-SO_2NH(CH_2)_nNR_2$
II, Y = $-CO_2(CH_2)_nNR_2$
III, Y = $-O(CH_2)_nNR_2$

were prepared from the corresponding acids and dialkylaminoalkyl chlorides in 2-propanol in the presence of benzyltrimethylammonium chloride, as described in the Experimental Section. 9,10-Dihydro-9,10-dioxoanthracene-2,6-dicarboxylic acid (VII)[8] was obtained in good yield by hydrolysis of the dicarbonitrile VI. VI was obtained from the dichloride V which was prepared from IV by the method reported by Nepras, *et al.*[9]



IV, Y = SO_3Na
V, Y = Cl
VI, Y = CN
VII, Y = COOH

The bis-basic ethers III were prepared from the dihydroxyanthraquinones. As noted by Wenner,[10] who prepared the 1,4, 1,5, and 1,8 isomers, special reaction conditions are required to effect ether formation of both hydroxy functions. In addition to Wenner's procedure in which the anhydrous dipotassium salt is formed by refluxing a concentrated aqueous solution with xylene under a Dean-Stark trap, three alternate procedures were developed and examples are described in the Experimental Section. Compound **24** (Table I) was obtained by lithium aluminum hydride reduction of **10** and compounds **25** and **26** by reaction of **10** with large excesses of methylmagnesium iodide or butyllithium, respectively.

Biological Evaluations and Structure–Activity Relationships. The compounds listed in Table I were evaluated for their effectiveness in protecting mice against encephalomyocarditis (EMC) virus infections. As defined in the Experimental Section, antiviral activity is expressed as the survival time ratio (STR), *i.e.*, the mean day of death of a treated group of ten mice divided by the mean day of death of a simultaneously infected but untreated control group. An STR of 1.30 and above indicates high activity. The test compounds were administered in single or multiple doses, prior and subsequent to virus challenge.

Compounds **5**, **6**, **10**, **11**, and **15** showed highest oral activity (STR greater than 1.80). In addition, compounds **4**, **21**, **22**, **23**, and **26** showed high activity on subcutaneous administration.

Of the four bisalkamine esters of anthraquinonedicarboxylic acids, only the 3-(dibutylamino)propyl ester of the 2,6 isomer **4** showed activity on subcutaneous administration. It was less active than the corresponding fluorenone-2,7-dicarboxylic acid ester reported earlier.[3]

Of the bis-basic ethers of anthraquinone (**5**–**23**) the 2,6 and 2,7 isomers showed much greater antiviral activity than the 1,4, 1,5, and 1,8 isomers. The latter had been synthesized earlier by Wenner[10] and 1,4-bis[2-(diethylamino)ethoxy]-9,10-anthracenedionedihydrochloride (**7**, Ro 2-9009) was reported to have anthelmintic activity.[11] This compound showed no antiviral activity on oral administration; on subcutaneous administration, it showed only moderate antiviral activity at high doses, which also produced toxic effects. Similar superiority of 2,6 and 2,7 position isomers was found earlier in bis-basic sulfonamides of anthraquinone.[2] Lengthening of the alkylene chain separating O and N atoms (**5** *vs.* **21**, **10** *vs.* **22**) resulted in a reduction of oral activity. Similarly, an increase of the molecular weight of the *N*-dialkyl groups above that of a diethylamino group (**10** *vs.* **15**, **17**, **18**, and **19**; **11** *vs.* **12**, **16**, and **20**) resulted in decreased oral activity. These findings parallel those obtained with bis-basic ethers of fluorenone.[4]

Compounds **24** and **25**, in which the anthraquinone carbonyl groups of **10** are reduced, were found to have reduced activity; compound **25** that cannot be oxidized metabolically to the corresponding anthraquinone was inactive. The 9,10-dibutylidene-substituted compound **26**, on the other hand, showed high subcutaneous antiviral activity. This finding is interesting when compared to results obtained earlier with bis(aminoacyl)fluorenes and -fluorenones.[5] There it was found that antiviral activity required at least one conjugated carbonyl function either at the 9 position of the fluorene nucleus or in the side chains, and it was postulated that the conjugated carbonyl imparts properties to the fluorene nucleus that are favorable to the interaction of the molecule with the biological receptor site. The present findings further support this interpretation and show, in addition, that the carbonyl group can be replaced by an alkylidene group.

Compound **10** (RMI 10,024DA) also showed oral antiviral activity against another EMC strain, Mengo (STR 1.77) in mice. It was effective in mice against other RNA viruses, including the myxoviruses Influenza A Equine/New Mexico (STR 1.28) and Influenza B/Massachusetts (STR 1.18), the arbovirus Semliki Forest virus (STR 1.69), and vesicular stomatitis virus (50% reduction in tail lesion severity). It was also effective against nonlethal doses of vaccinia IHD, a DNA virus, as indicated by a 65% decrease in severity of tail lesions. Compound **10** was found to induce high blood titers of interferon in mice.[12] Compound **10** has been selected for additional biologic, pathologic, and toxicologic evaluation.

Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are uncorrected. Ir and uv spectra of all compounds in Table I were obtained and absorptions were as expected; microanalytical results obtained were within ±0.4% of theoretical values. Neutralization equivalents (NE) were determined by nonaqueous titration with $HClO_4$ in AcOH with $Hg(OAc)_2$ added and Crystal Violet or *p*-Naphtholbenzein as indicator [USP XVIII, 836(1970)].

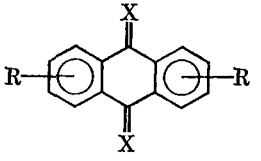
Antiviral Evaluation Method. The anti-EMC virus activity of compounds in this study was determined in CF-1 male mice, 15–17 g each, at the several dose levels indicated in Table I. Ten mice were used for each dose level of a compound, and the control group for each compound was 20–30 untreated mice. The test compound was dissolved or suspended in 0.15% hydroxyethylcellulose in H_2O and injected subcutaneously in the nape of the neck or administered orally by gavage. For each dose level, the indicated dose was given 28, 22, and 2 hr before and 2 hr after inoculation with virus. In oral evaluations, the 250 mg/kg dose was a single dose administered 22–28 hr prior to virus infection.

The EMC virus was administered subcutaneously in the groin at infective doses in the range of 4–62 LD_{50}. Simultaneously untreated control mice were infected with the same viral challenge. The mice were observed for 10 days after inoculation. Deaths were recorded twice daily and the mean day of death of the group was determined. A score of 11 was assigned to each survivor and used in determining the mean. A survival time ratio (STR), which is the mean day of death of the treated group divided by the mean day of death of the controls, was calculated for each dose level.

Activity is interpreted on the basis of parameters derived from standard deviations of the mean of control groups. An STR of less than 0.90 indicates that early deaths were observed; a ratio of 0.90–1.09 indicates that there was no activity; a ratio of 1.10–1.19 indicates low or weak activity (p = 0.2–0.05 by Student's t test); a ratio of 1.20–1.29 indicates medium activity (p = 0.1 to <0.001); and a ratio of 1.30 or greater indicates high activity (p = 0.05 to <0.001).

Bis(3-dibutylaminopropyl) 9,10-Dihydro-9,10-dioxoanthracene-2,6-dicarboxylate Dihydrochloride Hemihydrate (4). A mixture of 18.2 g (0.065 mol) of 2,6-dichloroanthraquinone (V) and 14.5 g (0.162 mol) of Cu_2CN_2 in 55 g of diphenylacetonitrile was

Table I. Chemical and Antiviral Properties of Bisalkamine Esters of Anthraquinonedicarboxylic Acids and of Bis-Basic Ethers of Anthraquinone



No.	X	R	Mp, °C	Recrystn solvent[a]	Yield, %	Formula[b]	STR *vs.* EMC virus in mice at various doses (mg/kg)[c]						
							sc administration				po administration		
							250	50	10	2	250[d]	50	10
1	O	2,6-$CO_2(CH_2)_3NEt_2$	264–265 dec	C	29	$C_{30}H_{38}N_2O_6 \cdot 2HCl$	1.15	1.14	1.12				
2	O	1,5-$CO_2(CH_2)_3NBu_2$	199–207	D–G	55	$C_{38}H_{54}N_2O_6 \cdot 2HCl$		1.14	0.94				
3	O	1,8-$CO_2(CH_2)_3NBu_2$	136–138	F	27	$C_{38}H_{54}N_2O_6 \cdot 2HCl \cdot 0.5H_2O$[e]	0.90	1.14	0.90				
4	O	2,6-$CO_2(CH_2)_3NBu_2$	199–200	D	26	$C_{38}H_{54}N_2O_6 \cdot 2HCl \cdot 0.5H_2O$[e]	1.48[f]	1.26	1.17		0.88	0.96	0.92
5	O	2,6-$O(CH_2)_2NMe_2$	278–280	D	9	$C_{22}H_{26}N_2O_4 \cdot 2HCl$	0.82[f,g]	1.80	1.11		2.30	1.77	
6	O	2,7-$O(CH_2)_2NMe_2$	230–233	B–E	28	$C_{22}H_{26}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	2.04	2.26	1.17		1.83	1.83	
7[h,i]	O	1,4-$O(CH_2)_2NEt_2$	240–242 dec			$C_{26}H_{34}N_2O_4 \cdot 2HCl \cdot 2H_2O$[e]	1.35[f]	1.10			1.00	0.96	0.93
8[h]	O	1,5-$O(CH_2)_2NEt_2$	253–255 dec	B–E	31	$C_{26}H_{34}N_2O_4 \cdot 2HCl$	Lethal	0.87[d,f]	1.18		1.00[f]	1.22	1.04
9[h]	O	1,8-$O(CH_2)_2NEt_2$	231–233	C	18	$C_{26}H_{34}N_2O_4 \cdot 2HCl \cdot H_2O$	1.15	1.13	1.09		1.15	0.93	
10[j]	O	2,6-$O(CH_2)_2NEt_2$	274–275	C	49	$C_{26}H_{34}N_2O_4 \cdot 2HCl$	1.00[f]	1.82[k]	1.34[k]	1.27[k]	2.20	1.75	1.11
11	O	2,7-$O(CH_2)_2NEt_2$	232–234	C	72	$C_{26}H_{34}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	2.44	2.11	1.22		2.24	1.78	1.46
12	O	2,7-$O(CH_2)_2$-pyrrolidino	286–288	B–A	24	$C_{26}G_{30}N_2O_4 \cdot 2HCl$	Lethal	Lethal	1.25[f,g]		Lethal	1.39	
13[h]	O	1,5-$O(CH_2)_2$-piperidino	250–252	B–D	89	$C_{28}H_{34}N_2O_4 \cdot 2HCl \cdot H_2O$	Lethal	1.38			1.31	1.05	1.04
14[h]	O	1,8-$O(CH_2)_2$-piperidino	270–272 dec	B–D	37	$C_{28}H_{34}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	1.45[f,l]	1.07[f]	1.02		1.05[f]	1.05	
15	O	2,6-$O(CH_2)_2$-piperidino	285–287	B–A	32	$C_{28}H_{34}N_2O_4 \cdot 2HCl$	Lethal	0.93[d,f]	1.12		0.70[f]	2.02	1.24
16	O	2,7-$O(CH_2)_2$-piperidino	275–277	B–E	29	$C_{28}H_{34}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	Lethal	1.30[d,f]	1.04		1.47	1.53	1.24
17	O	2,6-$O(CH_2)_2$-morpholino	288–290 dec	D–A	12	$C_{26}H_{30}N_2O_6 \cdot 2HCl$	1.35[l]	1.11	0.98		1.48	1.20	
18	O	2,6-$O(CH_2)_2N$-*i*-Pr_2	254–256	D–A	29	$C_{30}H_{42}N_2O_4 \cdot 2HCl$	1.45	1.15	1.19		1.66	1.40[f]	
19	O	2,6-$O(CH_2)_2NBu_2$	210–212	D–A	26	$C_{34}H_{50}N_2O_4 \cdot 2HCl$	1.02	1.00	0.94		0.89	0.98	
20	O	2,7-$O(CH_2)_2NBu_2$	180–182	B–E	67	$C_{34}H_{50}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	1.21[f]	1.26	1.04		1.00	1.11	
21	O	2,6-$O(CH_2)_3NMe_2$	280–281	B–A	29	$C_{24}H_{30}N_2O_4 \cdot 2HCl$	1.79[f,l]	2.09	1.15		1.77	1.28	
22	O	2,6-$O(CH_2)_3NEt_2$	273–275	C	14	$C_{28}H_{38}N_2O_4 \cdot 2HCl$		2.02	1.26	1.07	1.59	1.32	1.12
23	O	2,6-$O(CH_2)_3NBu_2$	206–208	D	28	$C_{36}H_{54}N_2O_4 \cdot 2HCl$	1.96[f]	1.74	1.62	1.10	1.07	1.05	1.05
24[m]	H, OH	2,6-$O(CH_2)_2NEt_2$	102–115	F–I	31	$C_{26}H_{38}N_2O_4$	Lethal[n]	0.83[d,f,n]	0.87[n]		1.20[n]	1.33[n]	
25[m]	Me, OH	2,6-$O(CH_2)_2NEt_2$	110–135	H	57	$C_{28}H_{42}N_2O_4$	Lethal[n]	Lethal[n]	1.09[n]		0.72[f,n]	0.93[d,n]	0.96[n]
26[m]	$CH(CH_2)_2CH_3$	2,6-$O(CH_2)_2NEt_2$	234–235	B–G	31	$C_{34}H_{50}N_2O_2 \cdot 2HCl$	1.76	1.71	1.20		0.98	0.98	
Tilorone hydrochloride[o]							Lethal	1.95	1.37	1.21	2.27	1.83	1.26

[a] A = H_2O, B = MeOH, C = EtOH, D = *i*-PrOH, E = EtCOMe, F = EtOAc, G = Et_2O, H = C_7H_{16}, I = C_5H_{12}. [b] All compounds were analyzed for the elements C, H, and Cl (or N), and microanalytical results were within ±0.4% of calculated values. [c] STR, survival time ratio, is defined in the description of the test method in the Experimental Section. [d] Single dose administered 22–28 hr before virus inoculation. [e] Neutralization equivalent (NE) agreed with calculated values within 1%. [f] Early deaths were observed, which indicated toxicity at specified dose. [g] Only first two doses of standard regimen given. [h] Reference 10. [i] Ro 2-9009, ref 11. [j] RMI 10,024DA. [k] Tested in 20-g mice. [l] Only first three doses of standard regimen given. [m] Probably a mixture of geometric isomers. [n] 10% Tween 80 added to usual compound diluent (see Experimental Section). [o] Reference 4.

stirred at 320–330° for 20 min. The mixture was cooled to 115°; the solid was collected and washed with 75 ml of benzyl cyanide and with acetone to give 15.1 g (89%) of 2,6-dicyanoanthraquinone (VI): mp >310°; ir (KBr) 2230 cm^{-1}.

A suspension of 17.9 g (0.069 mol) of VI in 22 ml of H_2O and 68 ml of concentrated H_2SO_4 was stirred and heated at 215° for a period of 15 min. The reaction mixture was cooled and the precipitate was collected. It was dissolved in a slight excess of 0.1 *N* KOH, filtered, and reprecipitated by addition of concentrated HCl. The product was washed with H_2O and Me_2CO to give 13.2 g (64%) of VII: mp >300° (lit.[8] mp >460°); ir (KBr) 1680, 1700 cm^{-1}.

A mixture of 6.5 g (0.022 mol) of VII, 10.7 g (0.052 mol) of 3-di(*n*-butyl)aminopropyl chloride, and 0.2 ml of 60% aqueous benzyltrimethylammonium chloride in 225 ml of *i*-PrOH was stirred for 24 hr at reflux temperature. The mixture was allowed to cool and solids were collected by filtration. The filtrate was treated with anhydrous Et_2O and the resulting precipitate was collected and added to the previously obtained solids. These were treated with 2 *N* HCl and filtered to remove unreacted VII, and the filtrate was made alkaline with 5 *N* NaOH. The product was extracted into Et_2O; the extract was washed (H_2O), dried (Na_2SO_4), decolorized (charcoal), and treated with ethereal HCl. The resulting oil was separated by decantation and was crystallized from EtOAc and recrystallized twice from *i*-PrOH to give 4.1 g (26%) of 4 with the properties listed in Table I.

2,6-Bis[2-(diethylamino)ethoxy]-9,10-anthracenedione Dihydrochloride (10). To a solution of 144 g (0.6 mol) of 2,6-dihydroxyanthraquinonein 1.2 l. of ClC_6H_5 was added a solution of 412 g (2.4 mol) of 2-(diethylamino)ethyl chloride hydrochloride in 350 ml of H_2O and a solution of 264 g (4.0 mol) of 85% KOH pellets in 350 ml of H_2O, and the resulting mixture was stirred and refluxed for 15 hr. The mixture was allowed to cool, 500 ml of H_2O was added, and insolubles were removed by filtration. To aid separation of phases, 400 ml of $CHCl_3$ was added, the aqueous phase was separated and washed with 400 ml of $CHCl_3$, the combined organic phases were washed (H_2O) and dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was taken up in 95% EtOH and was acidified to Congo Red with alcoholic HCl. The mixture was cooled in an ice bath and the product was collected, washed with cold EtOH, and dried to give 150.1 g (49%): mp 264–267°; recrystallizations from *i*-PrOH gave **10** with the properties listed in Table I.

2,7-Bis[2-(diethylamino)ethoxy]-9,10-anthracenedione Dihydrochloride Hemihydrate (11). A mixture of 5.0 g (0.02 mol) of 2,7-dihydroxyanthraquinone[13] and 100 ml of 0.4 *N* KOH was heated to 100° overnight and the resulting solution was evaporated to dryness. The residue was washed with acetone and was dried for 24 hr at 100° in a vacuum oven. The material was powdered and suspended in 100 ml of xylene. A solution of 2-(diethylamino)ethyl chloride, prepared from 35.0 g (0.2 mol) of the hydrochloride salt in xylene, was added and the mixture was refluxed under a Dean-Stark trap for 24 hr. The nearly black solution was filtered and evaporated to dryness. The residue was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and acidified with ethereal HCl. The yellow precipitate was recrystallized from EtOH and gave 5.0 g of 11 (Table I); a second crop of 2.5 g was recovered from the mother liquor.

2,6-Bis[3-(dibutylamino)propoxy]-9,10-anthracenedione Dihydrochloride (23). A mixture of 12.0 g (0.05 mol) of 2,6-dihydroxyanthraquinone, 22.6 g (0.11 mol) of 3-(dibutylamino)propyl chloride, 48 ml of a 10% NaOH solution, and 100 ml of DMSO was stirred and heated on a steam bath for 4 hr. The mixture was poured into 500 ml of H_2O and the resulting precipitate was collected. It was dissolved in Et_2O–CH_2Cl_2 and the solution was dried ($MgSO_4$) and acidified with ethereal HCl. Several recrystallizations from *i*-PrOH gave **23** (Table I).

2,6-Bis[2-(diethylamino)ethoxy]-9,10-dihydroanthracene-9,10-diol (24). A suspension of 12.4 g (28.3 mmol) of **10** (free base) in 200 ml of THF was added to 2.5 g (66 mmol) of $LiAlH_4$ in 100 ml of THF under N_2 and the mixture was refluxed for 2 hr. Excess reagent was decomposed by careful addition of moist THF and 300 ml of H_2O, and the resulting precipitate was removed by filtration and was thoroughly washed with THF. The filtrate was freed of THF and was extracted with $CHCl_3$. The extract was washed (H_2O) and dried (Na_2SO_4) and the solvent was evaporated. Crystallization from MeOH gave 2.8 g of starting material. The filtrate was freed of solvent and the residue recrystallized twice from EtOAc–pentane to give **24** (Table I).

2,6-Bis[2-(diethylamino)ethoxy]-9,10-dihydro-9,10-dimethylanthracene-9,10-diol (25). To methylmagnesium iodide prepared from 45.0 g (0.317 mol) of methyl iodide in 100 ml of Et_2O was added 10.0 g (0.0228 mol) of **10** (free base) and 400 ml of dry THF, and the mixture was boiled to remove Et_2O, refluxed for 4 hr, and allowed to stand overnight. To the mixture was added 200 ml of 2 *N* NH_4Cl and the product was extracted into Et_2O. The extract was washed (H_2O) and dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in 100 ml of MeOH, cooled, and filtered, and the filtrate was evaporated to dryness. The residue was triturated with pentane and recrystallized twice from heptane to give 6.1 g of **25** (Table I). One of the geometric isomers of **25** was obtained from the mother liquors and was recrystallized from hexane: mp 141–143°; nmr ($CDCl_3$) δ 1.03 (t, 12, J = 7 Hz), 1.51 (s, 6), 2.54 (q, 8, J = 7 Hz), 2.70 (m, 4), 3.36 (s, 2), 3.86 (m, 4), 6.82 (q, 2, J = 8.5, 2.5 Hz), 7.19 (d, 2, J = 2.5 Hz), 7.68 ppm (d, 2, J = 8.5 Hz). *Anal.* ($C_{28}H_{42}N_2O_4$), C, H, N. The nmr spectrum of the mixture of isomers differed primarily by having an additional singlet at δ 1.80 ppm.

9,10-Dibutylidene-2,6-bis[2-(diethylamino)ethoxy]-9,10-dihydroanthracene Dihydrochloride (26). To *n*-butyllithium, freshly prepared 64.8 g (0.70 mol) of *n*-butyl choride and 13.9 g of Li in 600 ml of THF at −25° under N_2 was added 8.5 g (0.019 mol) of **10** (free base) and the mixture was stirred for 2 hr at −25° and allowed to warm to room temperature overnight in a water bath. Water was added and the product was extracted into Et_2O. The extract was washed (H_2O), dried (Na_2SO_4), and acidified with ethereal HCl. The oil that separated was crystallized from MeOH–Me_2CO and recrystallized from MeOH–Et_2O to give **26** (Table I).

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