MeOH was refluxed for 4 hr and allowed to stand for 3 days. Water was added, and the mixt was extd with Et_2O. The Et_2O soln was washed (dil HCl, dil $NaHCO_3$, H_2O, and satd NaCl) and dried (Na_2SO_4). After filtration and evaporation of the solvent, the product was distd giving 36.8 g of solid, bp 152° (0.1 mm). A sample was recrystallized from *i*-PrOH giving white crystals, mp 81–83°. *Anal.* C, H, Cl.

2′-Chloro-2-(*o*-chlorophenyl)-3-(1-pyrrolidinyl)propiophenone Hydrochloride (21). A mixt of 35 g (0.126 mole) of 2′-chloro-2-(*o*-chlorophenyl)acrylophenone and 12 ml (0.15 mole) of pyrrolidine was warmed to effect soln and allowed to stand for 4 days. The resulting oil was dissolved in Et_2O, washed (H_2O, satd NaCl), and dried (Na_2SO_4). After filtration, the soln was acidified with ethanolic HCl, and the resulting solid was crystallized from EtCOMe yielding 19.6 g of white crystals, mp 135–136°.

4′-Chloro-2-(*p*-chlorophenyl)acrylophenone. This was prepd as described above for the ortho isomer from 10 g (0.0378 mole) of 4-chloro-2-*p*-chlorophenyl)acetophenone,[13] 8.8 ml (0.11 mole) of 37% CH_2O, and 0.19 ml of piperidine in 35 ml of MeOH. The product was not distilled but was recrystallized from hexane yielding 7.2 g (69%) of white crystals, mp 80–83°. *Anal.* C, H, Cl

Benzyl Indol-3-yl Ketone. A soln of 287.6 g of *N,N*-dimethylphenylacetamide in 300 ml of PhH was cooled under N_2 to 10° and 108 ml of $POCl_3$ was added dropwise with stirring. After warming to 20°, 102.9 g (0.878 mole) of indole was slowly added keeping the temp below 48° by cooling. The mixt was then refluxed for 2 hr, cooled, and poured into 6 l. of H_2O. A soln of 307.5 g of NaOH in 914 ml of H_2O was added, and the mixt was stirred for 1 hr. The product was extd with Et_2O, washed (H_2O, satd NaCl), and evapd *in vacuo*. The residue was mixed with 200 g of NaOAc in 200 ml of H_2O and 3 l. of MeOH, refluxed for 3 hr, and cooled to near 0°. The solid was collected, washed (MeOH), and dried yielding 122.6 g of product, mp 206.5–209°. An addnl 45.5 g (total 81.5%) was obtained by concn of the filtrate. A sample was recrystd from EtOAc, mp 208–209°. *Anal.* C, H, N.

Method C. 1-(Indol-3-yl)-2-phenyl-1-propenone and 1-(Indol-3-yl)-2-phenyl-3-(1-piperidinyl)-1-propanone (29). A mixt (prepared under N_2 with cooling) of 50 ml of AcOH, 4.9 ml (0.05 mole) of piperidine, 11.76 g (0.05 mole) of benzyl indol-3-yl ketone, and 2 g (0.0666 mole) of paraformaldehyde was stirred at 100–110° for 3–5 hr, cooled, and concd *in vacuo* to half its vol. This was poured into ice water and the solid was collected, washed (H_2O), and dried giving 4.68 g of 1-(indol-3-yl)-2-phenyl-1-propenone, mp 175–181.5°. Recrystallization from EtOAc–hexane gave 1.17 g of crystals, mp 195–196.5°. *Anal.* C, H, N.

The aqueous filtrate was basified with NaOH giving free base which was collected, dried, and recrystallized from EtOAc yielding 8.99 g (54%) of **29**, mp 171.5–172.5°. Recrystallization from EtOAc–hexane raised the mp to 172.5–173.5°.

1-(Indol-3-yl)-3-(4-methyl-1-piperazinyl)-2-phenyl-1-propanone (31). A mixt of 6.33 g (0.0266 mole) of 1-(indol-3-yl)-2-phenyl-1-propenone and 20 ml of 1-methylpiperazine was heated under N_2 at 100° for 3 hr and poured into ice water. The resulting solid was dissolved in $CHCl_3$ and extd with dil HCl. The acid soln was basified with NaOH giving solid which was collected, washed (H_2O), dried, and recrystallized first from EtCOMe–cyclohexane and then from EtOAc–hexane yielding 4.3 g of **31**, mp 183.5–184.5°.

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Potential Bioreductive Alkylating Agents. 1. Benzoquinone Derivatives

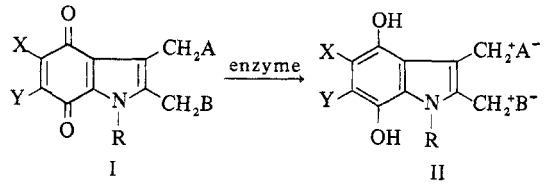
Ai Jeng Lin,* Lucille A. Cosby, Charles W. Shansky, and Alan C. Sartorelli

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510. *Received June 14, 1972*

A series of benzoquinone derivatives with one or two side chains potentially capable of alkylation after bioreduction was synthesized. These compounds showed growth-inhibitory activity against adenocarcinoma 755 ascites cells and greatly prolonged the life-span of such tumor-bearing mice. Compounds of this series were also found to be potent inhibitors of the synthesis of both DNA and RNA in these neoplastic cells.

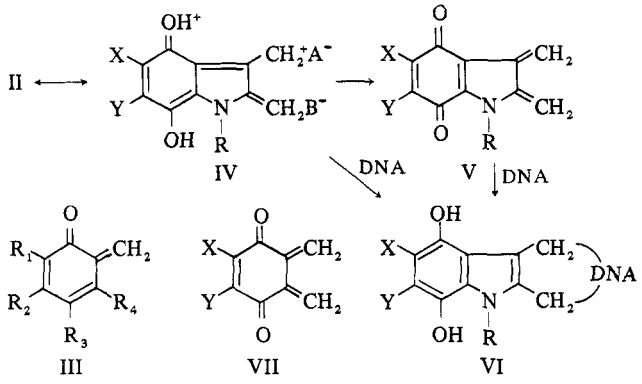
Mitomycin C, an antineoplastic agent active against tumors of both animals and man, has been shown to be a strong inhibitor of the synthesis of the nucleic acids.[1] Iyer and Szybalsky[2] presented evidence to indicate that mitomycins act as bifunctional alkylating agents which add across both strands of the DNA double helix to cause cross-linking. Schwartz, *et al.*,[3] demonstrated that the reduction of the benzoquinone ring of the mitomycins to dihydrobenzoquinone was an essential step for biological activity and Iyer and Szybalsky[4] showed that a NADPH (reduced form of nicotinamide-adenine dinucleotide phosphate) dependent quinone reductase system was involved in the reductive activation step. Recently, Kinoshita and coworkers[5] reported a positive correlation between both antineoplastic and antimicrobial activity of a series of mitomycin derivatives and their reduction potentials. These investigators[5] also provided evidence that the carbamyl group and the aziridine ring of the mitomycins were not essential for biological activity. The essential portions of the mitomycins were proposed to be the structures shown in formulas I and II (Scheme I). It is possible that charge delocalization of the dihydroquinone hydroxyl

Scheme I



groups of II results in *o*-quinone methide (III) like intermediates IV and V, which are the forms that act to alkylate DNA (Scheme II).

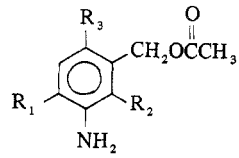
Scheme II



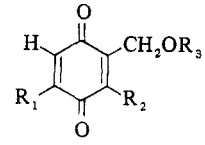
o-Quinone methides (III) have been reported to be active intermediates in several chemical reactions; indications for their possible involvement in a number of biochemical processes have also been published.[6] In view of the structural similarity and possible chemical reactivity between the presumed active form (V) of the mitomycin analogs and the quinone methides (III), it was anticipated that bis(*o*-quinone methides) (VII), generated *in vivo*, would have the potential to alkylate DNA, as well as other structures, and thereby perhaps be effective tumor-inhibitory agents. Based upon this concept, a series of benzoquinones with one or two side chains with the potential to alkylate was prepared.

Since the NADPH-dependent enzyme system which reduced the mitomycins *in vivo* apparently has little specificity,[5] conceivably the same quinone reductase system will convert the benzoquinones of this series to the corresponding dihydrobenzoquinones, a reaction essential for the expression of alkylating potential. Furthermore, since Cater and Phillips[7] reported a significantly lower oxidation-reduction potential for tumor tissue relative to most normal tissues, it is conceivable that a therapeutic differential will exist between normal tissues and some cancers with compounds requiring bioreduction.

Chemistry. Compounds **2a** and **2b** were prepared in one step by the oxidation of the amine **1a** with sodium dichromate in an acidic medium. The formation of **2b** was apparently the result of ester hydrolysis of compound **2a**. The *o*-benzoquinone isomer of **2a**, which was also a probable product from the oxidation of amine **1a**, was not found in the reaction mixture. The structures of **2a** and **2b** were identified by nmr. Long-range coupling (J = 1.5 Hz) between the methyl protons and the ring proton at the 2 position of **2a** and **2b** was observed. Similarly the methylene protons were found to couple (J = 1.6 Hz) with the ring proton at the 5 position of both **2a** and **2b**. Reports of such long-range coupling of benzoquinones have been documented.[8] Compound **2c** was prepared by the oxidation of 3-acetoxymethyl-2,4,6-trimethoxyaniline (**1b**) with chromic acid.

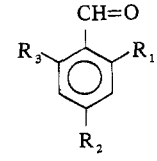


1a, $R_1 = CH_3$; $R_2 = H$; $R_3 = H$
b, $R_1 = OCH_3$; $R_2 = OCH_3$; $R_3 = OCH_3$



2a, $R_1 = CH_3$; $R_2 = H$; $R_3 = C(=O)CH_3$
b, $R_1 = CH_3$; $R_2 = H$; $R_3 = H$
c, $R_1 = OCH_3$; $R_2 = OCH_3$; $R_3 = C(=O)CH_3$
d, $R_1 = H$; $R_2 = H$; $R_3 = H$
e, $R_1 = H$; $R_2 = H$; $R_3 = C(=O)CH_3$

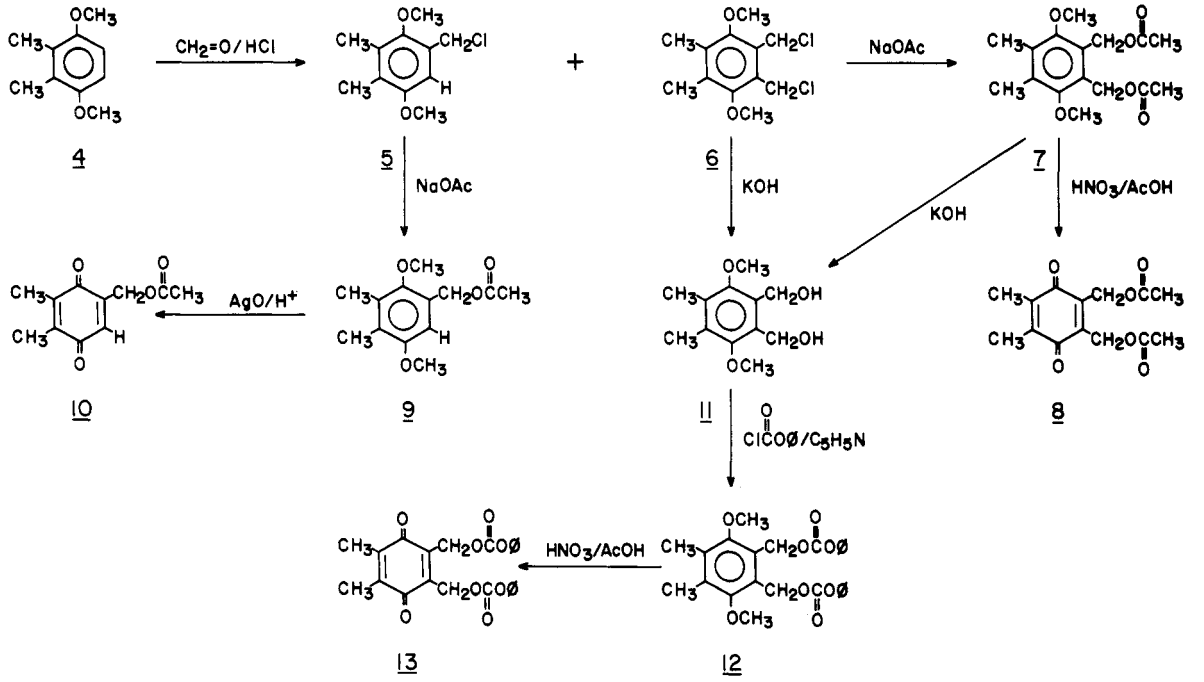
The anilines **1a** and **1b** are compounds in which the amino group is meta to the acetoxymethyl group. The corresponding ortho isomers, which also result in the same product after oxidation, are not expected to be stable, since they are good precursors of *o*-quinomonomethane imines which are, like *o*-quinone methides, reactive species. The other reason for not using ortho isomers of **1a** and **1b** is that the amino group and the ester group are so close to each other that intramolecular transacylation may take place. The preparation of amines **1a** and **1b** involved nitration and reduction of aldehydes **3a** and **3b**. Nitration of 3,4,5-trimethoxybenzyl alcohol acetate and 2,4,5-trimethoxybenzaldehyde under similar conditions, however, did not give the desired nitro compounds. In the case of 2,4,5-trimethoxybenzaldehyde, nitration was also attempted at 50–60°, using $Cu(NO_3)_2 \cdot 3H_2O$ as the nitrating agent.[9] The product isolated was identified by ir and nmr as 2,3,6-trimethoxynitrobenzene. Conceivably, the desired nitro compound was an intermediate which further oxidized to the corresponding carboxylic acid and then decarboxylated at the elevated temperature.



3a, $R_1 = H$; $R_2 = CH_3$; $R_3 = H$
b, $R_1 = OCH_3$; $R_2 = OCH_3$; $R_3 = OCH_3$

The preparation of the bifunctional alkylating agents is shown in Scheme III. The starting material, *o*-xylohydroquinone and its dimethyl ether 4, was prepared by a modification of the procedure of Smith.[10] Chloromethylation of *o*-xylohydroquinone dimethyl ether **4** with an equimolar quantity of formaldehyde was reported to give mainly 2,5-dimethoxy-3,4-dimethylbenzyl chloride (**5**).[10] However, if excess formaldehyde was used the main product was the bis(chloromethyl) compound **6**. Treatment of **6** with an excess of sodium acetate in glacial acetic acid gave the corresponding diacetoxy compound **7** in good yield. Although boron tribromide[11] has been reported to be a mild and selective reagent for dealkylation of phenyl ethers, application of this reagent to remove the methyl group of the dimethoxy compound **7** did not give the desired product. Demethylation and oxidation of **7** to benzoquinone **8** was achieved in good yield using a mixture of fuming nitric acid and acetic acid at room temperature. This reagent was first employed by Szeki[12] to prepare 2-methoxy-5-meconylbenzoquinone. It proved valuable in synthesizing compounds **8** and **13** which are extremely difficult to obtain by other approaches. Conversion of compound **9** to **10** was accomplished using AgO/H^+, an active oxidizing agent

Scheme III

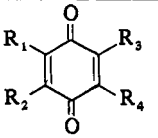


originally found useful for the oxidation of benzylic alcohol or activated methyl groups to corresponding aldehydes.[13] Recently the application of this reagent to the synthesis of naphthoquinones has been reported.[14]

Biological Evaluation. The inhibitory activities of these agents on the synthesis of DNA and RNA were evaluated *in vitro* using adenocarcinoma 755 ascites cells. The results indicated that all benzoquinones of this series were inhibitory to varying degrees to the synthesis of both DNA and RNA (Table I). All hydroquinone dimethyl ethers were noninhibitory, and acetoxymethylbenzoquinones showed equal or greater activity than the corresponding hydroxymethyl analogs in inhibiting the synthesis of both DNA and RNA. Whether the inhibitory activity of these compounds is the result of alkylation of the nucleic acids awaits further study. However, our results indicate that a direct S_N2 displacement reaction, without the involvement of a bioreductive activation step as has been shown for mitomycin C, is not likely to be the action mechanism, since both the ethers (7 and 12) and the quinones possessed alkylating side chains. That only compounds with the benzoquinone ring were inhibitory to nucleic acid synthesis suggests a mitomycin-like reaction mechanism. The finding that acetoxymethyl benzoquinones were either more active or at least equal in activity to the corresponding hydroxymethyl analogs can be explained by the fact that the acetoxy group is in general a better leaving group than the hydroxyl group. The bifunctional agent 8 appeared to be a slightly stronger inhibitor of both DNA and RNA biosynthesis than the single armed agents and all but one compound showed greater inhibition of the synthesis of DNA than of RNA, which is in accord with previous findings with mitomycin.[1]

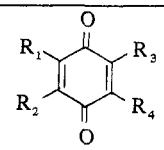
The antitumor activity of these compounds was measured against the growth of adenocarcinoma 755 ascites cells. It was found that all compounds of this series, except 13, were potent inhibitors of the growth of adenocarcinoma 755 *in vivo* (Table II), profoundly prolonging the life-span of tumor-bearing mice. However, substantial host toxicity, as measured by body weight loss of host mice during the treatment period, was observed with all compounds except 13. Such toxicity resulted in decreased survival time of tumor-bearing animals at the largest drug doses employed. With two bulky carbophenoxy groups in the molecule, compound 13 is relatively water insoluble and only sparingly soluble in organic solvents. The lack of

Table I. 50% Inhibitory Concentration (ID_{50}) of Quinone Derivatives on DNA and RNA Synthesis *in Vitro* in Adenocarcinoma 755 Cells



Compd	R_1	R_2	R_3	R_4	ID_{50}, $M \times 10^{-5}$ DNA	RNA
2a	H	CH_3	$CH_2OC(O)CH_3$	H	0.9	1.5
2b	H	CH_3	CH_2OH	H	2	4
2e	H	H	$CH_2OC(O)CH_3$	H	2	3.5
2d	H	H	CH_2OH	H	2	4.5
10	CH_3	CH_3	$CH_2OC(O)CH_3$	H	0.8	1.0
8	CH_3	CH_3	$CH_2OC(O)CH_3$	$CH_2OC(O)CH_3$	0.5	0.6
13	CH_3	CH_3	$CH_2OCO_2C_6H_5$	$CH_2OCO_2C_6H_5$	1.3	2.2
2c	H	OCH_3	$CH_2OC(O)CH_3$	OCH_3	1.5	1.5

Table II. Effect of Quinone Derivatives on the Survival Time of Mice Bearing Adenocarcinoma 755 Ascites Cells



Compd	R_1	R_2	R_3	R_4	Daily dosage, mg/kg[a]	Av Δ wt, g[b]	Av survival, days ± S.E.	No. of 50-day survivors[c]
Control						+13.2	13.3 ± 0.4	0/30
2a	H	CH_3	$CH_2OC(O)CH_3$	H	2.5	+3.9	13.0 ± 1.0	0/10
					5.0	−11.8	29.0 ± 3.0	3/20
					7.5	−24.7	5.2 ± 2.0	0/5
2b	H	CH_3	CH_2OH	H	5.0	−10.2	34.0 ± 3.0	0/5
2e	H	H	$CH_2OC(O)CH_3$	H	2.5	−2.4	35.2 ± 9.1	3/5
					5.0	−10.0	39.8 ± 3.3	2/9
					10.0	+23.0	12.6 ± 6.1	0/5
2d	H	H	CH_2OH	H	2.5	+6.6	11.6 ± 1.2	0/10
					5.0	−9.4	32.1 ± 3.9	4/15
					10.0	−11.7	16.2 ± 0.8	0/5
10	CH_3	CH_3	$CH_2OC(O)CH_3$	H	2.5	−4.5	9.8 ± 1.4	0/5
					5.0	−15.6	37.0 ± 4.0	3/9
					10.0		4.0 ± 1.0	0/5
8	CH_3	CH_3	$CH_2OC(O)CH_3$	$CH_2OC(O)CH_3$	2.5	−2.2	19.2 ± 3.0	2/19
					5.0	−11.9	28.7 ± 2.8	4/23
					7.5	−15.3	14.9 ± 2.0	0/15
13	CH_3	CH_3	$CH_2OCO_2C_6H_5$	$CH_2OCO_2C_6H_5$	5	+32.0	14.0 ± 0.6	0/5
					10	+14.1	11.0 ± 1.0	0/5
					20	+8.0	11.2 ± 0.8	0/5
					30	+15.2	11.2 ± 0.2	0/5
2c	H	OCH_3	$CH_2OC(O)CH_3$	OCH_3	2.5	−2.0	22.8 ± 4.8	2/10
					5.0	−13.2	38.3 ± 3.4	7/15
					7.5	−22.9	11.0 ± 4.7	0/5

[a] Administered once daily for 6 consecutive days, beginning 24 hr after tumor implantation. [b] Average weight change from onset to termination of drug treatment. [c] Mice surviving over 50 days were calculated as 50-day survivors in determination of the average survival time.

solubility in both organic solvents and water may be partially responsible for its lack of activity *in vivo*. Compound 8 with two alkylating side chains, despite its being the strongest inhibitor of this series of DNA and RNA synthesis *in vitro*, did not show superior advantage over the single armed compounds in prolonging the life-span of mice bearing adenocarcinoma 755 ascites cells. Studies of the biological action mechanism of this series of compounds are in progress.

Experimental Section

Biological Methods. Antineoplastic Activity. Compounds were tested for antineoplastic activity in BDF_1 mice bearing adenocarcinoma 755 ascites cells. Complete details of the biological methods have been described earlier.[15]

Studies of DNA and RNA Inhibition. One-tenth gram wet weight of 6-day-old adenocarcinoma 755 ascites cells was incubated in Fischer's medium minus horse serum at 37° for 30 min in a total volume of 10 ml containing either 80 μg of [^{3}H]thymidine (1.6×10^5 cpm) or [^{3}H]uridine (1.6×10^5 cpm) to measure the synthesis of DNA and RNA, respectively. Quinones were either dissolved in 0.9% sodium chloride or were solubilized using concentrations of dimethyl sulfoxide no greater than 4%; these levels of dimethyl sulfoxide were not inhibitory. Incorporation was terminated by the addition of 70% $HClO_4$ to give a final concentration of 0.4 *M*. The precipitate was collected by centrifugation at 1600*g*, washed 3× with cold 0.4 *M* $HClO_4$, and hydrolyzed by heating for 30 min at 95° with 0.4 *M* $HClO_4$. An aliquot of the supernatant was then analyzed for radioactivity using a Tri-Carb liquid scintillation spectrometer.

Chemical Methods. All melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by the Baron Consulting Co., Orange, Conn. Spectral data were obtained using a Perkin-Elmer 257 grating ir spectrophotometer, and Varian A-60 and A-60A spectrometers. The latter instrument used Me_4Si as an internal standard. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

3-Nitro-4-methylbenzyl Alcohol Acetate. 3-Nitro-4-methylbenzyl alcohol[16] (8.3 g, 0.05 mole), Ac_2O (8 ml), and C_5H_5N (8 ml) in C_6H_6 (100 ml) were heated at 60° for 1 hr. The soln was cooled and washed with aqueous NaOH and H_2O, dried over Na_2SO_4, and evapd to dryness. The oil obtained crystd from C_6H_6 and petr ether to give white needles (8 g, 77%): mp 34–36°. *Anal.* ($C_{10}H_{11}NO_4$) C, H, N.

4-Acetoxymethyltoluquinone (2a) and 4-Hydroxymethyltoluquinone (2b). 3-Nitro-4-methylbenzyl alcohol acetate (10 g, 0.048 mole) was dissolved in 200 ml of 95% EtOH. To the soln was added 1 g of 5% Rh-Al_2O_3 and the mixt was hydrogenated under 10 psi pressure for 2 hr. The soln was filtered to remove the catalyst, and the EtOH was evapd to dryness under reduced pressure. The oily residue was dissolved in ether (50 ml) and cooled in an ice bath while HCl gas was passed to form the HCl salt (6.1 g). The amine HCl salt was dissolved in 40% H_2SO_4 (60.9 ml) and cooled to −15°. To the cooled soln was added slowly an aqueous $Na_2Cr_2O_7$ soln (10.9 g in 36 ml of H_2O), which was stirred at the same temp for 4 hr. After being allowed to stand at room temp overnight, the reaction mixt was extd with ether (100 ml × 5). The ether exts were combined, dried (Na_2SO_4), and evapd to dryness to give a powder. The crude product was dissolved in a small amount of ether and applied to an alumina column (45 × 4.5 cm, neutral, deactivated with 10% H_2O). The column was washed with ether to give a red solid which was then added to a silica gel column (45 × 4.5 cm) and eluted with a mixt of C_6H_6 and EtOAc (8.5 : 1.5, v/v) to give two major products. The first yellow fraction was evapd to give yellow crystals (1.0 g) which were identified as compound **2a**: mp 92–93°; nmr ($CDCl_3$) δ 2.07 (d, 3, J = 1.7 Hz), 2.15 (s, 3), 5.00 (d, 2, J = 1.9 Hz), 6.68 (m, 2). *Anal.* ($C_{10}H_{10}O_4$) C, H.

The second yellow fraction gave long needles (150 mg) after recrystn from hexanes, mp 74–76°. It was identified as **2b**: nmr ($CDCl_3$) δ 2.05 (d, 3, J = 1.5 Hz), 3.05 (t, 1, J = 6 Hz), 4.53 (q, J = 2 and 6 Hz), 6.59 (q, 1, J = 1.5 Hz), 6.81 (t, 1, J = 2 Hz). *Anal.* ($C_8H_8O_3$) C, H.

3-Nitro-2,4,6-trimethoxybenzaldehyde. 2,4,6-Trimethoxybenzaldehyde (4 g, 0.02 mole) was added in small portions to 6 ml of fuming HNO_3 which was cooled to 10°. The soln was stirred for an addnl 10 min and then poured into 50 ml of ice water. The yellow ppt was collected, washed with H_2O, and recrystd from EtOH twice to yield pale needles (4.5 g, 91%): mp 144–145°. *Anal.* ($C_{10}H_{11}NO_6$) C, H, N.

3-Nitro-2,4,6-trimethoxybenzyl Alcohol. 2,4,6-Trimethoxybenzaldehyde (4.5 g, 0.018 mole) in 150 ml of MeOH was cooled to 5° with an ice bath. To the soln was added, in small portions with stirring, $NaBH_4$ powder (1.5 g). The soln was stirred at room temp for an addnl hr and evapd to dryness to leave a yellow solid. Recrystn from H_2O and EtOH gave yellow needles (3 g, 67%): mp 122–124°. *Anal.* ($C_{10}H_{13}NO_6$) C, H, N.

3-Nitro-2,4,6-trimethoxybenzyl Alcohol Acetate. 3-Nitro-2,4,6-trimethoxybenzyl alcohol (2 g, 8.2 mmoles), Ac_2O (2 ml), and C_5H_5N (2 ml) were refluxed in 20 ml of C_6H_6 for 4 hr. The soln was cooled to room temp and washed successively with 5% HCl, aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evapd to dryness. The oil obtained crystd from C_6H_6 and hexanes to give pale yellow crystals (1.5 g, 65%): mp 91–93°. *Anal.* ($C_{12}H_{15}NO_7$) C, H, N.

2,6-Dimethoxy-3-acetoxymethyl-1,4-benzoquinone (2c). 3-Nitro-2,4,6-trimethoxybenzyl alcohol acetate (1 g) was dissolved in 20 ml of EtOH. To the soln was added 0.25 g of 5% Rh/carbon and hydrogenation was accomplished under 10-psi pressure. The catalyst was removed by filtration and the filtrate evapd to dryness under reduced pressure. The oily residue was dissolved in 20 ml of anhyd ether and HCl gas was passed through the soln. The amine HCl salt (0.7 g) was collected, dried, and dissolved in 50 ml of H_2O. The aqueous soln was added dropwise with stirring to a CrO_3 soln (2 g in 75 ml of H_2O) which was cooled to 6–9°. The soln was slowly warmed to 60° and allowed to stand at room temp for 4 hr. The mixt was then extd several times with ether. The ether exts were combined, dried, and evapd to dryness under reduced pressure to give yellow crystals (0.25 g): mp 90–94°. The crude product was purified by chromatography on an alumina column (neutral) using EtOAc as eluent to give yellow needles (mp 93–95°) after recrystn from EtOAc and hexanes. *Anal.* ($C_{11}H_{12}O_6$) C, H.

2-(Acetoxymethyl)-1,4-benzoquinone (2e). To 2-hydroxymethyl-1,4-benzoquinone (**2d**)[17] (0.7 g, 5 mmoles) in 25 ml of C_6H_6 was added Ac_2O (2 ml) and C_5H_5N (2 ml). The soln was allowed to stand at room temp overnight and then heated on a steam bath for 15 min. After cooling, the soln was washed with dil HCl and H_2O, dried over Na_2SO_4, and evapd to dryness under reduced pressure to provide 0.5 g of pale yellow crystals: mp 124–126° (lit.[18] 128°), after recrystn from C_6H_6 and petr ether.

***o*-Xylohydroquinone.** Sodium nitrite (4 g) in 10 ml of H_2O was added slowly to a chilled slurry of sulfanilic acid (10 g) in 50 ml of H_2O and 10 ml of concd HCl. The suspension was stirred for 1 hr in an ice bath and was added with stirring to a cold mixt of 2,3-dimethylphenol (6 g, 0.05 mole) and NaOH (8 g) in 50 ml of H_2O. The red soln was allowed to stand at room temp overnight. After cooling with an ice bath, the soln was acidified with concd HCl and the azo compd was collected and dried. The azo compd was suspended in 200 ml of EtOH and hydrogenated under 30-psi pressure for 1 hr using 10% Pd/C (1 g) as catalyst. The resulting suspension was filtered, and the ppt washed with EtOH. The filtrate and washings were combined and evapd to dryness to give a dark amorphous aminophenol that was added to a cold acid soln which contained 27 ml of 12 *N* H_2SO_4 and 400 ml of ice H_2O. To this mixt was added a cold soln of 157 ml of 10% $Na_2Cr_2O_7$ and 42 ml of 12 *N* H_2SO_4. The soln was extd repeatedly with $CHCl_3$, and the exts were combined and evapd to dryness to give a red oil. The oil was dissolved in 100 ml of EtOH and 10% Pd/C (1 g) was added. The suspension was hydrogenated with a Parr Shaker under 30 psi pressure for 30 min to give, after recrystn from C_6H_6, white crystals (4 g, 49%): mp 225–226° dec (lit.[10] 223–224° dec).

***o*-Xylohydroquinone Dimethyl Ether (4).** This compound was synthesized according to the procedure of Smith.[10]

3,6-Dimethoxy-4,5-dimethyl-1,2-bis(chloromethyl)benzene (6). *o*-Xylohydroquinone dimethyl ether (9.3 g, 0.056 mole) was suspended in 40 ml of concd HCl and 30 ml of 40% formalin. The suspension was rapidly stirred while HCl gas was passed through the soln. After an hour the mixt was warmed gently on an oil bath for 1.5 hr. The resulting cooled mixt was extd with ether twice, and the ether exts were combined and washed with H_2O until the wash H_2O remained neutral (litmus). The ether layer was dried (Na_2SO_4) and evapd to dryness under reduced pressure. The cryst residue was recrystd from petr ether to give 5 g (34%) of white crystals: mp 98–100°. *Anal.* ($C_{12}H_{16}O_2Cl_2$) C, H.

3,6-Dimethoxy-4,5-dimethyl-1,2-bis(acetoxymethyl)benzene (7). The bis(chloromethyl) compound **6** (4.5 g, 0.017 mole) and NaOAc (10 g, 0.12 mole) were refluxed in 100 ml of AcOH for 8 hr. The AcOH was evapd to dryness under reduced pressure to give an oil to which 20 ml of H_2O was added and extd several times with ether. The ether exts were combined, washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evapd to dryness. The oil was crystd from benzene and hexanes to give white needles (4 g, 75%): mp 110–112°. *Anal.* ($C_{16}H_{22}O_6$) C, H.

2,3-Dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone (8). The dimethyl ether 7 (0.4 g, 1.3 mmoles) was dissolved in 2 ml of AcOH. To the soln was added 0.5 ml of an acid mixt (fuming HNO_3 and AcOH, 1:1, v/v) and it was stirred at room temp for 8 hr. Water (20 ml) was added and the mixt was extd with ether 3 times. The ether exts were combined, washed with aqueous $NaHCO_3$, and dried (Na_2SO_4). After evapn, the residue was recrystd from C_6H_6 and hexanes to give yellow needles (0.25 g, 70%): mp 91–93°. *Anal.* ($C_{14}H_{16}O_6$) C, H.

2,5-Dimethoxy-3,4-dimethyl-1-acetoxymethylbenzene (9). 2,5-Dimethoxy-3,4-dimethylbenzyl chloride[19] (3 g, 0.014 mole) and anhyd NaOAc (3 g, 0.036 mole) were refluxed in 10 ml of AcOH for 10 hr. The soln was evapd under reduced pressure to dryness. To the gummy residue was added 20 ml of H_2O and the mixt was extd 3 times with an equal volume of ether. The ether exts were combined, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evapd to dryness under reduced pressure to give an oil which crystd in petr ether. Recrystn from petr ether gave white needles (2.5 g, 76%): mp 43–45°. *Anal.* ($C_{13}H_{18}O_4$) C, H.

2,3-Dimethyl-5-acetoxymethyl-1,4-benzoquinone (10). To compound 9 (2.1 g, 8.4 mmoles) in 30 ml of *p*-dioxane was added AgO (4.2 g, 33.3 mmoles) and 6 *N* HNO_3 (8.4 ml). The suspension was stirred at room temp for 1.5 hr. Water (50 ml) was added, and the mixt was extd with ether twice. The ether exts were combined, washed with H_2O, dried over Na_2SO_4, and evapd to dryness. The yellow oil was chromatographed on an alumina column using as eluent EtOAc and petr ether (1:3, v/v). The first yellow band gave yellow leaflet crystals (0.5 g, 30%): after recrystn from petr ether, mp 53–55°. *Anal.* ($C_{11}H_{12}O_4$) C, H.

3,6-Dimethoxy-4,5-dimethyl-1,2-bis(hydroxymethyl)benzene (11). The dichloride **6** (2 g, 7.6 mmoles) in 20 ml of EtOH was added to 40 ml of 5% aqueous KOH and refluxed for 8 hr. The soln was extd several times with ether after cooling; ether exts were combined and evapd under reduced pressure. The sample was dried by azeotropic distn with C_6H_6. After cooling, white crystals (0.4 g) were collected by filtration. Addn of petr ether to the filtrate gave an addnl crop of crystals (0.2 g). These were combined and recrystd from C_6H_6 to give white crystals (0.5 g, 30%): mp 128–129°. *Anal.* ($C_{12}H_{18}O_4$) C, H.

3,6-Dimethoxy-4,5-dimethyl-1,2-bis(acetoxymethyl)benzene (7) was hydrolyzed under the same conditions and gave about 50% yield of the corresponding desired alcohol **11**.

3,6-Dimethoxy-4,5-dimethyl-1,2-bis(carbophenoxymethyl)benzene (12). Alcohol **11** (0.3 g, 1.3 mmoles) was dissolved in 6 ml of dry C_5H_5N and cooled in an ice bath. To the soln was added dropwise with stirring phenyl chloroformate (1 g). The soln was stirred at ice-cold temp for 2 hr and then allowed to stand at room temp overnight. Water (30 ml) was added to the reaction mixt and extd several times with 20 ml of $CHCl_3$. The $CHCl_3$ exts were combined and washed with cold dil HCl, dried, and evapd to dryness. The white powder was recrystd from EtOAc to give white crystals (0.6 g, 97%): mp 172–174°. *Anal.* ($C_{26}H_{26}O_8$) C, H.

2,3-Dimethyl-5,6-bis(carbophenoxymethyl)-1,4-benzoquinone (13). The diether **12** (0.2 g, 0.4 mmole) was dissolved in 5 ml of slightly warmed AcOH. To the soln was added dropwise 1.5 ml of fuming HNO_3 and the soln was stirred at room temp for 12 hr. The acid soln was dild with 30 ml of H_2O and extd with ether twice. The ether exts were combined, washed with aqueous $NaHCO_3$, dried, and evapd to dryness. The yellow crystals were recrystd from EtOAc and petr ether to give 0.12 g (67%) of yellow needles: mp 124–126°. *Anal.* ($C_{24}H_{20}O_8$) C, H.

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Synthesis and Antidepressant Activity of 5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and Derivatives

Cheuk-Man Lee,* Bruce W. Horrom, Raymond J. Michaels, Ronald M. Rasmussen, and Nicholas P. Plotnikoff

Division of Pharmacology and Medicinal Chemistry, Abbott Laboratories, North Chicago, Illinois 60064.
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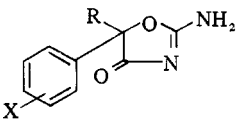
5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and derivatives were synthesized by heating 2-amino-5-phenyl-2-oxazolin-4-one and its derivatives with 2-propynylamine in ethanol. 2-[(1,1-Dialkyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-ones were obtained by cyclization of 1-(α-chlorophenylacetyl)-3-(1,1-dialkyl-2-propynyl)ureas with sodium ethoxide in ethanol. These compounds were evaluated for antidepressant activity by the dopa response potentiation test.

2-Amino-5-phenyl-2-oxazolin-4-one was synthesized by Traube and Ascher in 1913.[1] Because of its central stimulant property,[2] it has been used as a mild stimulant,[3] antidepressant,[4] and antifatigue agent.[5] Many of its derivatives and analogs had been synthesized. The 2-amino group was replaced by monoalkylamino,[6] dialkylamino,[7] allylamino,[7] cycloalkylamino,[8] phenylamino,[7] phenylalkylamino,[6] and 5,-6-membered nitrogen heterocycles such as pyrrolidine, piperidine, morpholine, and piperazine.[9,10] The pharmacologic spectrum of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (thozalinone) was found to lie between amphetamine and imipramine and is a central excitant with anorexigenic properties.[11] 2-Cyclopropylamino-5-phenyl-2-oxazolin-4-one is an antifatigue agent.[12] 2-Amino-5-phenyl-2-oxazolin-4-one (pemoline) with magnesium hydroxide was reported to be a unique type of stimulant.[13] Recently the spiral analogs of 2-amino-5-phenyl-2-oxazolin-4-one in which the carbon atom to which the phenyl group is attached is part of a spirane system were synthesized and were found to be less active in increasing spontaneous activity in mice than pemoline.[14]

Since the report of *N*-benzyl-*N*-methyl-2-propynylamine (pargyline) as a nonhydrazine MAO inhibitor,[15] used for treatment of hypertension and depression,[16] there have been several reports of incorporating the 2-propynylamino group in various structures to produce enhanced MAO inhibitors,[17,18] antidepressant activity,[19,20] and anticonvulsant activity.[21] The 2-propynylamino group appears to contribute its unique pharmacological properties to the molecules. Therefore, it seemed desirable to replace the amino group in 2-amino-5-phenyl-2-oxazolin-4-one by 2-propynylamino group and its homologs and to evaluate their antidepressant activity. Recently a review article of synthetic and natural acetylenic compounds as medicines appeared.[22]

Chemistry. Several new 2-amino-5-aryl-2-oxazolin-4-ones (Table I) were obtained by reaction of the appropriately substituted ethyl mandelates with guanidine in EtOH. 5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and derivatives **(3a-l)** (Table II) were prepared by refluxing 5-substituted 2-amino-2-oxazolin-4-ones **(1a-k)** with 2 equiv of 2-propynylamine **(2a)** or 1-methyl-2-propynylamine **(2b)** in EtOH (method A, Scheme I). Attempts to obtain 2-[(1,1-dimethyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-one **(7a)** by the above method were unsuccessful. 2-[(1,1-Dialkyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-ones **(7a-c)** (Table III) were prepared by method B, Scheme I. (1,-1-Dialkyl-2-propynyl)ureas **(5a-c)** were obtained by reaction of (1,1-dialkyl-2-propynyl)amines·HCl with aqueous KCNO. Treatment of **5a-c** with α-chlorophenylacetyl chloride in

Table I. 2-Amino-5-aryl-2-oxazolin-4-ones



Compd[a]	X	R	Mp, °C	Yield, %	Crystn solvent	Formula[b]
1d	3-CF_3	H	223-224	23	EtOH	$C_{10}H_7F_3N_2O_2$
1e	2-CH_3	H	212-222	44	EtOH	$C_{10}H_{10}N_2O_2$
1f	4-$CH(CH_3)_2$	H	227-229	52	EtOH	$C_{12}H_{14}N_2O_2$
1h	4-OC_5H_{11}	H	232-234	30	EtOH-H_2O	$C_{14}H_{18}N_2O_3$
1i	3,4,5-$(OCH_3)_3$	H	224-225	50	EtOH	$C_{12}H_{14}N_2O_5$

[a]Compd **1a** (X = H; R = H), mp 245-247°, lit.[7] mp 254-256°; **1b** (X = 4-Cl; R = H), mp 275-276°, lit.[7] mp 268-269°; **1c** (X = 2-F; R = H), mp 232-233°, lit.[7] mp 235-237°; **1g** (X = 4-OCH_3; R = H), mp 236-237°, lit.[25] mp 278-279°; **1j** (X = H; R = CH_3), mp 202-204°, lit[7] mp 206-207°; **1k** (X = H; R = C_6H_5), mp 253-255°, lit. [26] mp 250°. [b]All compds were analyzed for C, H, N.