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A Convenient Synthesis of 1*H*-Pyrrolo[3,2-*c*]quinoline-6,9-diones and 11*H*-Indolo[3,2-*c*]quinoline-1,4-diones Derivatives

PHILIPPE HELISSEY,^a HÉLÈNE PARROT-LOPEZ,^a JEAN RENAULT^{*.a}
and SUZANNE CROS^b

*Laboratoire de Recherche sur les Hétérocycles Azotés, Département de Chimie Organique,
Faculté des Sciences Pharmaceutiques et Biologiques de l'Université René
Descartes,^a 75270 Paris Cedex 06, France and Laboratoire de
Pharmacologie et de Toxicologie Fondamentales du
C.N.R.S.,^b Toulouse, France*

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8-Methoxy-2,3,4-trimethyl-1*H*-pyrrolo[3,2-*c*]quinoline-6,9-dione (**28**) and 2-methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (**31**) can be obtained from 4-hydrazino-6-methoxy-2-methyl-5-quinolinamine (**21**). The synthetic method consists in creating the pyrrole or indole nucleus by applying Fischer's indole synthesis to the hydrazones (**22** and **24**) to give the amines (**23** and **25**, respectively). The catalytic dehydrogenation of **25** leads to the quinolinamine (**26**). The oxidation of the amines (**23**, **25** and **26**) by Fremy's reagent (potassium nitrosodisulfonate) gives the quinones (**28**, **31** and **35**). The nucleophilic substitution of the methoxy group by aziridine leads to **29**, **33** and **36**, which have moderate cytotoxic activity on L 1210 cells.

Keywords—cytotoxicity; Fischer's indole synthesis; Fremy's salt; heterocyclic quinone; 11*H*-indolo[3,2-*c*]quinoline-1,4-dione; 1*H*-pyrrolo[3,2-*c*]quinoline-6,9-dione

A heterocyclic quinone system is present in various antitumor molecules such as streptonigrin¹⁾ (**1**) and it plays important roles in biological systems. The pyrrole nucleus is also found in some antitumor drugs: mitomycin,²⁾ netropsin³⁾ and distamycin.³⁾ An 11*H*-indolo[3,2-*c*]quinoline was found to possess antitumor activity.⁴⁾

Thus, it seemed interesting to study the synthesis of 8-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline-6,9-diones (**28**, **31**) and 2-methoxy-6-methyl-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (**35**), *i.e.*, those quinones derived from a heterocycle obtained by condensation of the quinoline nucleus with the pyrrole or indole nucleus and, like streptonigrin, possessing a methoxy group in the *p*-position relative to the nitrogen of the quinoline nucleus. The synthesis of derivatives of these quinones resulting from nucleophilic substitution of the methoxy group is also described. The cytotoxicity of these heterocycles was briefly examined on L 1210 cells.

Synthesis

The Graebe-Ullman method is the one most commonly used for the synthesis of 11*H*-indolo[3,2-*c*]quinoline. This consists of creating the pyrrole nucleus from 1-(4-quinolyl)-benzotriazole.⁵⁾

However, it was thought to be of greater interest to carry out Fischer's thermal cyclization of hydrazones derived from 4-hydrazinoquinoline. This method provides an easy access to the pyrrolo[3,2-*c*]quinolines⁶⁾ and we have extended it to the synthesis of 11*H*-indolo[3,2-*c*]quinolines. The fragility of the *o*-methoxy-*p*-quinone function makes it necessary to introduce this function at the end of the reaction by using a very mild process. To achieve this, two types of compound were chosen (Chart 1): a *p*-dibenzoyloxy-*o*-methoxyaryl com-

pound (2), which can be selectively hydrogenated to the *o*-methoxy-*p*-diphenol (3) and hence oxidized to the quinone (4), or an *o*-methoxyarylamine (15), which can be oxidized in neutral medium at 20 °C with potassium nitrosodisulfonate (Fremy's reaction)⁷⁾ into the *p*-quinone (4).

Chart 1

Chart 2

Attempted Preparation of 1*H*-Pyrrolo[3,2-*c*]quinoline-6,9-diones (28, 31) and 11*H*-Indolo[3,2-*c*]quinoline-1,4-dione (35) from a Type 2 Derivative

The attempted synthesis of the 4-quinolone (11) required for the preparation of the hydrazine (12), in turn required for use in the preparation of the corresponding quinone by reactions analogous to those shown in Charts 3 and 4, was unsuccessful.

The methoxyhydroquinone⁸⁾ (6) was treated with benzyl chloride in dimethyl sulfoxide⁹⁾ and sodium hydroxide to give the triether (7) (71%) (Chart 2). Nitration of 7 gave only the nitro derivative (8) (93%), the structure of which has been established by means of proton nuclear magnetic resonance (¹H-NMR) studies. Reduction with aluminum amalgam¹⁰⁾ gave the benzamine (9) (71%). Condensation of 9 with ethyl acetoacetate, under acid catalysis, gave the crotonate (10) (91%), identified from the ¹H-NMR spectrum (the methyl signal of the CO₂Et at δ 1.2) and infrared (IR) spectrum [bands at 1660 cm⁻¹ (C=O) and 3270 cm⁻¹ (NH)] (Table I). This crotonate (10) is unstable and cannot be cyclized thermally in diphenyl ether to form the 4-quinolone (11) (Conrad-Limpach reaction).¹¹⁾

Despite the risk of debenzoylation, attempts were made to cyclize 10 by using polyphosphoric acid or phosphorus oxychloride, but without success.

Syntheses of 1*H*-Pyrrolo[3,2-*c*]quinoline-6,9-diones (28, 31) and 11*H*-Indolo[3,2-*c*]quinoline-1,4-dione (35) from a Type 5 Derivative

It has already been shown¹²⁾ that 7-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline is destroyed by nitration. In addition, 3-methoxy-11*H*-indolo[3,2-*c*]quinoline yields the nitro derivative at C-8, *i.e.*, in the *p*-position relative to the nitrogen of the indole nucleus, and not in the *o*-position

Chart 3

TABLE I. Physicochemical Data for the Products

Compd.	mp (°C)	Yield (%)	IR (cm ⁻¹) ^{a)}	¹ H-NMR δ (J =Hz)	Formula	Analysis (%)		
						Calcd	Found	
						C	H	N
7 ^{a)}	76—77	71	1120 (OCH ₃)	3.75 (3H, s, OCH ₃), 4.85 (2H, s, OCH ₂ in 1), 4.95 (2H, s, OCH ₂ in 4), 6.3 (1H, dd, $J_{5-6} \approx 9$, H ₅), 6.5 (1H, d, $J_{3-5} \approx 2$, H ₃), 6.65 (1H, d, H ₆), 7.25 (10H, m, Ph-H)	C ₂₁ H ₂₀ O ₃	78.75 (78.43)	6.25 (6.47)	
8 ^{a)}	132—133	93	1530, 1260 (NO ₂), 1070 (OCH ₃)	3.80 (3H, s, OCH ₃), 5.0 (2H, s, OCH ₂ in 1), 5.1 (2H, s, OCH ₂ in 4), 6.5 (1H, s, H ₃), 7.3 (10H, m, Ph-H), 7.5 (1H, s, H ₆)	C ₂₁ H ₁₉ NO ₅	69.04 (69.14)	5.20 (5.28)	3.84 (4.01)
9 ^{a)}	88	71	3450, 3370 (NH ₂), 1120 (OCH ₃)	3.4 (2H, s, NH ₂), 3.65 (3H, s, OCH ₃), 4.9 and 4.95 (2H, s, OCH ₂), 6.3 and 6.45 (1H, s, H ₃ or H ₆), 7.25 (10H, m, Ph-H)	C ₂₁ H ₂₁ NO ₃	Not isolated in a pure state		
10 ^{a)}	≈ 90	91	3270 (NH), 1660 (C=O), 1060 (OCH ₃)	1.2 (3H, t, CH ₃), 1.6 (3H, s, CH ₃), 3.75 (3H, s, OCH ₃), 4.05 (2H, q, CH ₂), 4.55 (H, s, vinyl-H), 4.95 and 5.0 (2H, s, OCH ₂), 6.5 and 6.55 (1H, s, H ₃ or H ₆), 7.25 (10H, m, Ph-H), 9.9 (1H, s, NH)	C ₂₇ H ₂₉ NO ₅	Not isolated in a pure state		
14 ^{b)}	> 335	86	2750 (NH), 1595 (C=O), 1520, 1370 (NO ₂), 1065 (OCH ₃)	2.25 (3H, s, CH ₃), 3.8 (3H, s, OCH ₃), 5.8 (1H, s, H ₃), 7.6 (2H, s, H ₇ and H ₈), 11.8 (1H, s, NH)	C ₁₁ H ₁₀ N ₂ O ₄	56.41 (56.27)	4.27 (4.27)	11.97 (12.02)
16 ^{b)}	122—123	81	1535, 1375 (NO ₂), 1085 (OCH ₃)	2.6 (3H, s, CH ₃), 4.0 (3H, s, OCH ₃), 7.75 (1H, s, H ₃), 7.9 (1H, d, $J_{7-8} \approx 9$, H ₇), 8.2 (1H, d, H ₈)	C ₁₁ H ₉ ClN ₂ O ₃	52.28 (52.43)	3.56 (3.40)	11.09 (11.12)
18 ^{b)}	125—126	45	3450, 3360 (NH ₂), 1090 (OCH ₃)	2.5 (3H, s, CH ₃), 3.8 (3H, s, OCH ₃), 5.3 (2H, s, NH ₂), 7.1 and 7.15 and 7.35 (1H, d, $J \approx 9$, H ₃ or H ₇ or H ₈), 8.3 (1H, d, H ₄)	C ₁₁ H ₁₂ N ₂ O · H ₂ O	64.07 (63.91)	6.79 (6.76)	13.59 (13.69)
19 ^{b)}	154—155	82	1525, 1365 (NO ₂), 1060 (OCH ₃)	2.55 (3H, s, CH ₃), 3.85 (3H, s, OCH ₃ -e), 3.95 (3H, s, OCH ₃ -d), 7.0 (1H, s, H ₃), 7.75 (1H, d, $J_{7-8} \approx 9$, H ₇), 8.0 (1H, d, H ₈)	C ₁₂ H ₁₂ N ₂ O ₄	58.06 (57.99)	4.84 (4.73)	11.29 (11.26)
20 ^{b)}	148—149	96	3490, 3390 (NH ₂), 1110, 1080 (OCH ₃)	2.45 (3H, s, CH ₃), 3.8 (3H, s, OCH ₃ -e), 3.9 (3H, s, OCH ₃ -d), 5.55 (2H, s, NH ₂), 6.55 (1H, s, H ₃), 7.0 and 7.25 (1H, d, $J_{7-8} \approx 9$, H ₇ or H ₈)	C ₁₂ H ₁₄ N ₂ O ₂	66.05 (65.66)	6.42 (6.62)	12.84 (13.10)
21 ^{b)}	212—213	75	3400, 3310 (NH ₂), 3170 (NH), 1100 (OCH ₃)	1.95 (3H, s, CH ₃), 3.65 (3H, s, OCH ₃), 4.9 (2H, s, NH ₂), 5.4 (1H, s, H ₃), 6.05 and 6.55 (1H, d, $J_{7-8} \approx 9$, H ₇ or H ₈), 6.85 (2H, s, NH ₂), 9.3 (1H, s, NH)	C ₁₁ H ₁₄ N ₄ O	60.55 (60.26)	6.42 (6.42)	25.69 (25.85)

23^{b)}	252—253	60	3395, 3320 3250 1080	(NH ₂) (NH) (OCH ₃)	2.35 (6H, s, CH ₃₋₂ and CH ₃₋₃), 2.75 (3H, s, CH ₃₋₄), 3.85 (3H, s, OCH ₃), 4.85 (2H, s, NH ₂), 7.15 and 7.20 (1H, d, J ₆₋₇ ≈ 9, H ₆ or H ₇), 10.9 (1H, s, NH)	C ₁₅ H ₁₇ N ₃ O · H ₂ O	65.93 (66.01)	6.96 6.90	15.39 15.32)
25^{b)}	251—252	85	3380, 3310 3230 1075	(NH ₂) (NH) (OCH ₃)	1.8 (4H, m, 2CH ₂), 2.7 (3H, s, CH ₃), 2.75 (2H, m, CH ₂), 2.9 (2H, s, CH ₂), 3.85 (3H, s, OCH ₃), 4.9 (2H, s, NH ₂), 7.15 and 7.2 (1H, d, J ₃₋₄ ≈ 9, H ₃ or H ₄), 11.0 (1H, s, NH)	C ₁₇ H ₁₉ N ₃ O · H ₂ O	68.23 (67.88)	7.02 7.01	14.05 14.43)
26^{b)}	269—270	47	3400, 3100	(NH ₂)	2.95 (3H, s, CH ₃), 3.85 (3H, s, OCH ₃), 7.15 (2H, s, NH ₂), 7.2 (1H, t, J ₈₋₉ ≈ 8, H ₈), 7.3 (3H, m, H ₃ and H ₄ and H ₉), 7.7 (1H, d, J ₁₀₋₉ ≈ 8, H ₁₀), 8.05 (1H, d, J ₇₋₈ ≈ 8, H ₇), 12.2 (1H, s, NH)	C ₁₇ H ₁₅ N ₃ O · H ₂ O	69.15 (69.36)	5.76 5.73	14.24 14.35)
28^{b)}	297—298	79	3640, 3350 3180 1670, 1645 1050 3360 1650	(OH) (NH) (C=O) (OCH ₃) (NH) (C=O)	2.3 and 2.35 (3H, s, CH ₃₋₂ and CH ₃₋₃), 2.8 (3H, s, CH ₃₋₄), 3.8 (3H, s, OCH ₃), 6.15 (1H, s, H ₇), 11.75 (1H, s, NH)	C ₁₅ H ₁₄ N ₂ O ₃ · 1.5MeOH	62.26 (62.59)	6.29 5.96	8.81 9.07)
29^{b)}	218—219	38			2.2 (4H, m, N-CH ₂), 2.30 and 2.35 (3H, s, CH ₃₋₂ and CH ₃₋₃), 2.8 (3H, s, CH ₃₋₄), 6.15 (1H, s, H ₇), 11.75 (1H, s, NH)	C ₁₆ H ₁₅ N ₃ O · 0.5H ₂ O	67.25 (66.91)	5.43 5.32	14.71 14.55)
31^{b)}	256—257	70	3330 1650 1070	(NH) (C=O) (OCH ₃)	1.75 (4H, m, 2CH ₂), 2.75 (5H, m, CH ₃ and CH ₂), 2.85 (2H, m, CH ₂), 3.8 (3H, s, OCH ₃), 6.15 (1H, s, H ₃), 11.75 (1H, s, NH)	C ₁₇ H ₁₆ N ₂ O ₃	68.92 (69.20)	5.41 5.51	9.46 9.16)
32^{b)}	262—263	45	3200 1650	(NH) (C=O)	1.6 (6H, m, 3CH ₂), 1.75 (4H, m, 2CH ₂), 2.7 (5H, m, CH ₃ and CH ₂), 2.85 (2H, m, CH ₂), 3.4 (4H, m, 2CH ₂), 5.8 (1H, s, H ₃), 11.65 (1H, s, NH)	C ₂₁ H ₂₃ N ₃ O ₂	72.21 (72.36)	6.59 6.66	12.03 12.26)
33^{b)}	178—179	55	3340 1645	(NH) (C=O)	1.75 (4H, m, 2CH ₂), 2.2 (4H, m, N-CH ₂), 2.7 (5H, m, CH ₃ and CH ₂), 2.85 (2H, m, CH ₂), 6.15 (1H, s, H ₃), 11.75 (1H, s, NH)	C ₁₈ H ₁₇ N ₃ O ₂ · 1.25H ₂ O	65.55 (65.69)	5.91 5.84	12.74 12.50)
35^{b)}	310—311	19	3390 1650 1070	(NH) (C=O) (OCH ₃)	3.0 (3H, s, CH ₃), 3.85 (3H, s, OCH ₃), 6.25 (1H, s, H ₃), 7.3 (1H, t, J ₆₋₉ ≈ 8, H ₆), 7.5 (1H, t, J ₉₋₁₀ ≈ 8, H ₉), 7.8 (1H, d, H ₁₀), 8.15 (1H, d, J ₇₋₈ ≈ 8, H ₇), 12.35 (1H, s, NH)	C ₁₇ H ₁₂ N ₃ O ₃	67.77 (67.48)	4.32 4.34	9.30 9.54)
36^{b)}	208—209	45	3360 1650	(NH) (C=O)	2.25 (4H, m, N-CH ₂), 3.0 (3H, s, CH ₃), 6.25 (1H, s, H ₃), 7.3 (1H, t, J ₈₋₉ ≈ 8, H ₈), 7.5 (1H, t, J ₉₋₁₀ ≈ 8, H ₉), 7.75 (1H, d, H ₁₀), 8.15 (1H, d, J ₇₋₈ ≈ 8, H ₇), 12.4 (1H, s, NH)	C ₁₈ H ₁₃ N ₃ O ₂ · 0.5H ₂ O	69.23 (69.43)	4.49 4.22	13.46 13.11)

a) ¹H-NMR spectra were measured in CDCl₃. b) ¹H-NMR spectra were measured in DMSO-d₆. c) IR spectra were measured by the KBr disc method.

with respect to the methoxy group.¹²⁾ Consequently, an attempt was made to obtain the desired primary amines (**23**, **25** and **26**) directly from 4-hydrazino-6-methoxy-2-methyl-5-quinolinamine (**21**) (Chart 3).

This synthesis was initiated from 4-chloro-6-methoxy-2-methyl-5-nitroquinoline (**16**). This compound, which was described by Heindel *et al.*,¹³⁾ can be obtained in a yield of only 58% from the nitration of the corresponding 4-chloroquinoline, which can itself be prepared by chlorination of the 6-methoxy-2-methyl-4(1*H*)-quinolinone (**13**) (the yield was not specified), according to Basu and Chaudran.¹⁴⁾ We improved the method and brought the total yield to 69% from the 4-quinolinone (**13**) by reversing the order of the reactions (nitration of **13** followed by chlorination of **14**).

The sensitivity to nucleophilic substitutions of the methoxy group did not allow us to obtain the nitrated hydrazine (**17**), which is liable to form the aminohydrazine (**21**) by reduction. Thus, we tried to obtain it from 4-chloro-6-methoxy-2-methyl-5-quinolinamine (**15**) which can be prepared by the catalytic reduction of the nitro group of **16**. Catalytic reduction in the presence of Raney nickel in various solvents, chemical reduction with sodium borohydride in the presence of tin(II) chloride according to Satoh *et al.*¹⁵⁾ or reduction with iron in acetic medium according to Price *et al.*,¹⁶⁾ who selectively reduced the nitro group of 4-chloro-6-methoxy-8-nitroquinoline, led to complete hydrogenolysis of the C–Cl bond with the formation of 6-methoxy-2-methyl-5-quinolinamine (**18**).

We were able to solve this problem by substituting a methoxy group in place of the chlorine atom of **16** by the use of sodium methoxide. The nitro compound (**19**) thus obtained in a yield of 82% can then be easily reduced to an amino derivative (**20**).

Though Buchmann and Hamilton¹⁷⁾ showed that morpholine reacts with 2-chloro-4-ethoxyquinoline or 4-chloro-2-ethoxyquinoline without affecting the ethoxy group, we were hoping that the methoxy group at C₄ of **20** would be made labile by the –M effect of nitrogen, as noted in other hexagonal heterocyclic series containing methoxy groups located *ortho* or *para* to intracyclic nitrogen, *e.g.*, in 3-methoxy-1,2,4-triazine¹⁸⁾ and 2-chloro-4-ethoxyquinazoline.¹⁹⁾ The methoxy derivative (**20**) readily gave the hydrazine (**21**) in 75% yield when treated with hydrazine hydrate.

The hydrazones (**22** and **24**) can be synthesized from the reaction of hydrazine (**21**) with

Chart 4

butanone or cyclohexanone in an alcoholic medium (Chart 4). According to Fischer's indole synthesis, the amines (**23** and **25**) can be obtained through the thermal cyclization of **22** and **24**.

The aromatization of the amine (**25**) in the presence of palladium on carbon facilitates access to the 2-methoxy-6-methyl-11*H*-indolo[3,2-*c*]quinolin-1-amine (**26**).

The elemental analyses and IR and ^1H -NMR spectral data were consistent with the assigned structures (Table I).

Quinones were prepared as indicated in Chart 5 by oxidation of the corresponding amines (**23**, **25** and **26**) with potassium nitrosodisulfonate. The oxidation reaction leads to a quinonimine intermediate, which was not isolated in a pure state. For example, the oxidation of **23** exclusively gives the imine (**27**), characterized by ^1H -NMR spectroscopy. However, oxidation of **25** and **26** gave a 1 : 1 mixture of quinonimines (**30** and **34**) and quinones (**31** and **35**) (^1H -NMR quantitative analysis). The quinonimine (**30**) was purified through preparative chromatography and identified by ^1H -NMR spectroscopy, but, could not be completely separated from the quinone (**31**). These imines are rapidly hydrolyzed into quinones by acid

Chart 5

TABLE II. Cytotoxic Effects of 8-Substituted 1*H*-Pyrrolo[3,2-*c*]quinoline-6,9-diones (28, 29) and 2-Substituted 1*H*-Indolo[3,2-*c*]quinoline-1,4-diones (31 to 36) on Growth of L 1210 Cells *in Vitro*

Compound No.	IC ₅₀ ^{a)}	
	ng/ml	10 ⁻⁶ M
28	687	2.16
29	147	0.514
31	1336	4.51
32	3553	10.2
33	476	1.44
35	>1000	>33.2
36	238	0.762

a) Concentration that reduces the L 1210 cells growth *in vitro* by 50% after 48 h as compared to the control.

treatment.

The methoxy group *ortho* to the quinone is labile to nucleophilic reagents. It seemed to us that aziridine derivatives would be interesting because of their bioalkylating properties.²⁰⁾ The quinones (29, 33 and 36) were obtained from the corresponding quinones (28, 31 and 35) in the presence of an excess of amine. Thin-layer chromatography (TLC) showed the presence of a major compound, despite tar formation.

Pharmacology

***In Vitro* Cytotoxicity on L 1210 Leukemia Cells**—Cytotoxicity towards L 1210 leukemia cells was determined. Dose-effect relationships of the various compounds tested were determined from the regression line of percent cell growth inhibition plotted as a function of the logarithm of the dose. From these curves, the dose of drug which reduces the cell growth by 50% after 48 h as compared to the control was estimated. As shown in Table II, the compounds tested are cytotoxic to L 1210 cells.

Discussion

Replacement of the methyl groups at the C-2 and C-3 positions of 1*H*-pyrrolo[3,2-*c*]quinoline-6,9-diones (28 and 29) with a tetramethylene chain 31 and 33 had little effect on the cytotoxicity. Replacing the methyl groups of 28 by a divinyl chain 35 is extremely unfavorable, though in the aziridine (29), this modification is without effect. Substituting the methoxy group of 31 for piperidine (32) lowered the cytotoxicity. On the other hand, substituting a methoxy group for the 1-aziridinyl group leads to the quinones (29, 33 and 36), which are more cytotoxic. The increase of cytotoxicity is most probably due to the alkylating action of this 1-aziridinyl group.

Experimental

All melting points were determined on a Maquenne apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 157G spectrometer. NMR spectra were measured with a Bruker 270 MHz spectrometer with trimethylsilane (Me₃Si)₂ as an internal reference. TLC was carried out on Merck GF 254 silica gel plates.

Chemistry

1,4-Dibenzyloxy-2-methoxybenzene (7)—Benzyl chloride (23 ml, 200 mmol) was added to a solution of 7 g (50 mmol) of methoxyhydroquinol (6)⁹⁾ and 22.5 g (400 mmol) of potassium hydroxide in 50 ml of dimethyl sulfoxide (DMSO) at 20 °C. The mixture was stirred for 3 h, then H₂O (500 ml) was added and the whole was extracted with CH₂Cl₂. The solvent layer was washed with H₂O, dried, treated with charcoal and evaporated under reduced

pressure. The product was recrystallized from EtOH to give **7** (11.36 g).

1,4-Dibenzyloxy-2-methoxy-5-nitrobenzene (8)—Nitric acid (1.8 ml, 40 mmol, $d=1.42$) was added to a suspension of 3.2 g (10 mmol) of **7** in 25 ml of acetic acid at 20 °C. The mixture was stirred for 1 h, then H₂O (200 ml) was added. The solid that separated was filtered off, washed with H₂O and recrystallized from EtOH to give **8** (3.39 g).

2,5-Dibenzyloxy-4-methoxy-benzenamine (9)—A solution of 1.82 g (5 mmol) of **8** in 10 ml of tetrahydrofuran (THF) was added slowly to a suspension of 2 g aluminum amalgam shot in 10 ml EtOH–THF (1 : 1). The mixture was refluxed under N₂ for 3 h, then allowed to cool. The solid was filtered off, and washed with THF. The solvent was distilled off. The residue was unstable and could not be isolated in a pure state.

Ethyl 3-(2,5-Dibenzyloxy-4-methoxyphenylamino)crotonate (10)—Crude **9** (335 mg, 1 mmol) in 3 ml of benzene, 144 mg (1.1 mmol) of ethyl acetoacetate and a drop of 2 M ethanolic HCl solution were heated at 80 °C under N₂ for 3.5 h. The solvent was distilled off under reduced pressure and the residue was washed with petroleum ether. The precipitate was filtered but was not further purified.

6-Methoxy-2-methyl-5-nitro-4(1H)-quinolinone (14)—Potassium nitrate (5.3 g, 52.5 mmol) was added to a solution of 9.45 g (50 mmol) of 6-methoxy-2-methyl-4(1H)-quinolinone (**13**)¹¹ in 100 ml of sulfuric acid (d 1.84) at 0 °C. The mixture was stirred at 0 °C for 4 h before being poured on ice; ammonia (d 0.9) was added while cooling until pH 7 was reached. The solid was separated by filtration washed with H₂O, dried and recrystallized from EtOH to give **14** (10.06 g).

4-Chloro-6-methoxy-2-methyl-5-nitroquinoline (16)—Compound **14** (10.5 g, 45 mmol) was added to 55 ml of POCl₃ at 20 °C. The mixture was stirred at 105 °C for 4 h. The POCl₃ was evaporated off *in vacuo* and the residue was poured into a mixture of ice-ammonia (d 0.9) and extracted with CH₂Cl₂. The solvent layer was washed with water, dried, treated with charcoal and evaporated under reduced pressure. The product was recrystallized from EtOH–H₂O to give **16** (9.20 g).

6-Methoxy-2-methyl-5-quinolinamine (18)—A solution of 0.252 g (1 mmol) of **16** in 10 ml of MeOH was hydrogenated in the presence of 0.25 g of Raney nickel until the gas uptake ceased (4 mmol). After filtration to remove the catalyst under N₂, the mixture was treated with charcoal and evaporated. The residue was dissolved in 200 ml of boiling water, 1 M NaOH solution was added to give pH 8, and the mixture was extracted with CH₂Cl₂. The solvent layer was washed with water, dried, treated with charcoal and evaporated. This product was recrystallized from EtOH–H₂O to give **18** (0.085 g).

4,6-Dimethoxy-2-methyl-5-nitroquinoline (19)—A solution of 18.9 g (75 mmol) of **16** and 16.2 g (300 mmol) of sodium methoxide in 400 ml of dry MeOH was stirred for 24 h under reflux. The solvent was evaporated off under reduced pressure. The residue was dissolved in 100 ml of H₂O, HCl solution (d 1.19) was added to give pH 7, and the solution was extracted with CHCl₃. The combined solvent layers were washed with water, dried, treated with charcoal and evaporated to dryness. The residue was recrystallized from EtOH–H₂O to give **19** (15.25 g).

4,6-Dimethoxy-2-methyl-5-quinolinamine (20)—A solution of 4.96 g (20 mmol) of **19** in 200 ml of a 1 : 1 mixture of MeOH and dioxane was hydrogenated over 5 g of Raney nickel until the gas uptake ceased (68 mmol). After filtration to remove the catalyst under N₂, the mixture was treated with charcoal and evaporated to give 4.18 g of **20**. Recrystallized from EtOH–H₂O.

4-Hydrazino-6-methoxy-2-methyl-5-quinolinamine (21)—A suspension of 4.14 g (19 mmol) of **20** in 100 ml of hydrazine hydrate was heated at 120 °C under N₂ for 5 h. The precipitate was filtered off, washed with H₂O and dried to give 3.10 g of pure product.

8-Methoxy-2,3,4-trimethyl-1H-pyrrolo[3,2-*c*]quinolin-9-amine (23)—Compound **21** (1.09 g, 5 mmol) in 10 ml of EtOH and 1.08 g (15 mmol) of butanone were heated under reflux for 3 h. The solvent was evaporated off under reduced pressure, and the residue was washed with petroleum ether to give 1.08 g of the hydrazone (**22**) (yield, 80%). The hydrazone (1.36 g, 5 mmol), without purification, was taken up in 10 ml of diethylene glycol and heated at 250 °C under N₂ for 45 min. The reaction mixture was cooled and diluted with 35 ml of H₂O. The precipitate was filtered off, washed with H₂O and then crystallized from aqueous ethanol to give 0.76 g of **23**.

2-Methoxy-6-methyl-7,8,9,10-tetrahydro-11H-indolo[3,2-*c*]quinolin-1-amine (25)—Compound **21** (1.09 g, 5 mmol) in 10 ml of EtOH and 0.54 g (5.5 mmol) of cyclohexanone were heated under reflux for 2 h. The solvent was evaporated off under reduced pressure, and the residue was washed with petroleum ether to give 1.49 g of the hydrazone (**24**) (yield, 80%). The hydrazone (1.49 g, 5 mmol), without purification, was treated in the same manner as **22**. This product was recrystallized from aqueous ethanol to give 1.27 g of **25**.

2-Methoxy-6-methyl-11H-indolo[3,2-*c*]quinolin-1-amine (26)—A suspension of 1.82 g (6.5 mmol) of **25** and 2 g of 10% palladium on activated charcoal in 30 ml of decalin was refluxed under N₂ for 10 h, then allowed to cool. The solid was filtered off, extracted with CHCl₃–MeOH (1 : 1), dried, treated with charcoal and evaporated to give 0.91 g of **26**. Recrystallized from EtOH–H₂O.

General Procedure for Synthesis of 28, 31 and 35—A solution of 1.36 g (10 mmol) of monobasic potassium phosphate in x ml of H₂O was added to 2 mmol of amino compound (**23**, **25** or **26**) in y ml of acetone–MeOH (1 : 1). Potassium nitrosodisulfonate (2.15 g, 8 mmol) was added over 10 min. The mixture was stirred for m h, then 2 M HCl solution (5 ml) and 40 ml of MeOH were added and the whole was stirred for an additional n h. NaHCO₃ saturated solution was added to give pH 7. The organic solvent was removed under reduced pressure, and the residue was

extracted with CH_2Cl_2 . The organic layer was washed with H_2O , dried and evaporated to dryness to give a pyrroloquinoline-6,9-dione. The amine (**26**) gave a precipitate of indoloquinoline-1,4-dione. This precipitate was filtered off, and extracted with CHCl_3 -MeOH (1:1). The extract was treated with charcoal and evaporated.

8-Methoxy-2,3,4-trimethyl-1*H*-pyrrolo[3,2-*c*]quinoline-6,9-dione (**28**): $x=30$, $y=60$, $m=n=3$. The product was recrystallized from MeOH to give 0.502 g of **28**.

2-Methoxy-6-methyl-7,8,9,10-tetrahydro-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (**31**): $x=30$, $y=60$, $m=2$, $n=3$. The product was recrystallized from CH_3CN to give 0.414 g of **31**.

2-Methoxy-6-methyl-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (**35**): $x=40$, $y=70$, $m=24$, $n=5$. The product was recrystallized from MeOH to give 0.111 g of **35**.

Remarks—The imines (**27**, **30** and **34**) were prepared in the same manner as **28**, **31** and **35**. HCl solution was not added. These compounds were identified by ^1H -NMR analysis and not isolated in a pure state.

9-Imino-8-methoxy-6-oxo-2,3,4-trimethyl-6,9-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline (**27**): ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.3 and 2.35 (3H, s, Me-2 and Me-3), 2.8 (3H, s, Me-4), 3.9 (3H, s, CH_3O), 5.95 (1H, s, H_7), 11.2 and 11.45 (1H, s, NH).

1-Imino-2-methoxy-6-methyl-4-oxo-1,4,7,8,9,10-hexahydro-11*H*-indolo[3,2-*c*]quinoline (**30**): The precipitate was purified on preparative alumina plate (solvent: CHCl_3). ^1H -NMR ($\text{DMSO}-d_6$) δ : 1.75 (4H, m, 2CH_2), 2.75 (5H, m, CH_2 and CH_3), 2.85 (2H, m, CH_2), 3.9 (3H, s, CH_3O), 5.95 (1H, s, H_3), 11.3 and 11.45 (1H, s, NH).

1-Imino-2-methoxy-6-methyl-4-oxo-1,4-dihydro-11*H*-indolo[3,2-*c*]quinoline (**34**): ^1H -NMR ($\text{DMSO}-d_6$) δ : 3.0 (3H, s, CH_3), 3.9 (3H, s, CH_3O), 6.05 (1H, s, H_3), 7.3 (1H, t, $J_{8-9} \approx 8 \text{ Hz}$, H_8), 7.5 (1H, t, $J_{9-10} \approx 8 \text{ Hz}$, H_9), 7.9 (1H, d, H_{10}), 8.15 (1H, d, $J_{7-8} \approx 8 \text{ Hz}$, H_7), 11.65 and 12.0 (1H, s, NH).

General Procedure for Synthesis of 29, 33 and 36—Aziridine (2 ml, 40 mol) was added to a suspension of 0.5 mmol of the quinone (**28**, **31** or **35**) in 5 ml of dry MeOH. The mixture was stirred at 20°C for n h. The solid that separated was filtered off, and washed with petroleum ether.

8-(1-Aziridiny)-2,3,4-trimethyl-1*H*-pyrrolo[3,2-*c*]quinoline-6,9-dione (**29**): $n=4$. The product was recrystallized from MeOH to give 0.052 g of **29**.

2-(1-Aziridiny)-6-methyl-7,8,9,10-tetrahydro-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (**33**): $n=2$. The product was recrystallized from MeOH to give 0.091 g of **33**.

2-(1-Aziridiny)-6-methyl-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (**36**): $n=12$. The product was recrystallized from MeOH to give 0.070 g of **36**.

6-Methyl-2-piperidino-7,8,9,10-tetrahydro-11*H*-indolo[3,2-*c*]quinoline-1,4-dione (32**)**—Piperidine (5 ml, 50 mmol) was added to a suspension of 0.148 g (0.5 mmol) of **31** in 5 ml of dry MeOH. The mixture was stirred at 20°C for 1 h. The solvent was evaporated off under reduced pressure. The product was recrystallized from CH_3CN to give 0.078 g of **32**.

Pharmacology

Growth Inhibition of L 1210 Cells in Culture—The experimental protocol has been reported.²²⁾

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