Synthesis of Potential Antineoplastic Agents. XXIII. Compounds Related to Methyl 2-Cyano-1(2*H*)quinolinecarboxylate (1)

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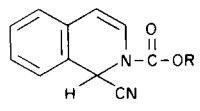
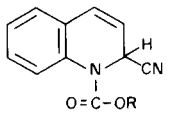
In connection with our studies of Reissert compounds (2) we had occasion to prepare (3) Reissert compound analogues of the type **1** and **2** by reaction os isoquinoline or quinoline with potassium cyanide and a variety of chloroformates. Most of these compounds were submitted to Drug Research and Development, Chemotherapy, National Cancer Institute for screening. Although all six isoquinoline compounds (**1**) submitted were inactive (T/C against L1210 leukemia was less than 111) as antineoplastic agents, the title compound (**2**, R = CH_3) was highly active as shown in Table I. Since only two other quinoline derivatives (**2**, R = C_2H_5 (3) and the analogue, R = C_2H_5, from benzo[*f*]quinoline (4)) were prepared in earlier work it was decided to prepare a series of compounds of the type **2** related to the title compound.

The compounds prepared by reaction of quinolines and chloroformates with potassium cyanide in methylene chloride-water are shown in Table II. In a few cases, compounds of the type **3** were obtained after recrystallization from ethanol. The isolation of compounds of this type has previously been reported (5) in studies of Reissert compounds. Despite the high order of activity of the title compound (**2**, R = CH_3) none of the compounds in Table II that were screened possessed any appreciable activity (T/C against L1210 leukemia was 113 at 400 mg./kg. for the most active analogue (**2**, R = C_6H_5)).



1



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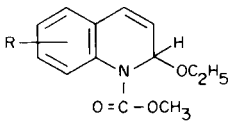

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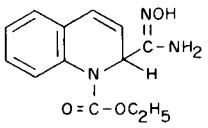

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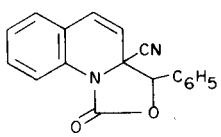

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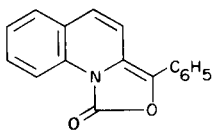

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Reaction of **2** (R = C_2H_5) with hydroxylamine gave **4** which was also inactive. The reaction of the anion of **2** with benzaldehyde proceeded in the same manner as **1** (3) to give **5** and **6**.

TABLE I

Summary of Screening Data of Methyl 2-Cyano-1(2*H*)quinolinecarboxylate Against L1210 Lymphoid Leukemia in BDF_1 Mice (a)

No. of Injections	Dose (mg/kg)	Animal Wt. Diff. (T-C) (b)	Percent T/C (c)
3	200	-2.6	155 (d)
3	100	-2.0	209
2	200	-3.7	156
2	100	-1.5	189
2	66	-1.8	173 (e)
2	44	-1.0	151

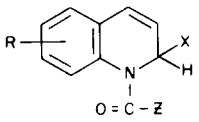
(a) Supplied by Drug Research and Development, Chemotherapy, National Cancer Institute. Intraperitoneal administration in Saline with Tween-80. First injection on day 1 with treatment every fourth day and evaluation on day 30 with 6/6 survivors. (b) Average weight change of test group minus average weight change of control animals in grams. (c) Ratio of survival time of treated to control animals expressed as %. (d) 5/6 Survivors. (e) 1 Cure.

EXPERIMENTAL (6)

Preparation of Analogues of the Title Compound (**2**, R = CH_3).

In a typical preparation, 0.064 mole of a chloroformate was added dropwise with stirring over a period of 30 to 60 minutes to a mixture of 0.032 mole of a quinoline in 40 ml. of methylene chloride and 0.096 mole of potassium cyanide in 15 ml. of water. The mixture was stirred for 3 hours and the layers separated. The organic layer was washed with water, 10% hydrochloric acid, 10% sodium hydroxide, and water and dried over magnesium sulfate. Evaporation of the methylene chloride and recrystallization from ethanol gave the products listed in Table II. The ir and nmr spectra were consistent with the structures assigned.

TABLE II



Z	X	R	Yield	M.p., °C	Formula	Analysis Calcd. / Found C	H	N
$OCH=CH_2$	CN	6-CH_3	80	141-142	$C_{14}H_{12}N_2O_2$	69.98 70.16	5.03 5.12	11.66 11.56
OCH_3	CN	5-$NHCO_2CH_3$ (a)	60	166-168	$C_{14}H_{13}N_3O_4$	58.53 58.71	4.56 4.63	14.62 14.59
OCH_3	CN	3-$NHCOCH_3$	40	166-167	$C_{14}H_{13}N_3O_3$	62.01 62.16	4.83 4.83	15.50 15.41
SC_2H_5	CN	6-CH_3	65	118-119	$C_{14}H_{14}N_2OS$	65.09 65.21	5.46 5.40	10.85 10.89
$OCH_2C_6H_5$	CN	6-CH_3	56	105-106	$C_{19}H_{16}N_2O_2$	74.98 75.23	5.30 5.47	9.21 9.07
SC_2H_5	CN	6-CH_3O	65	117-118	$C_{14}H_{14}N_2O_2S$	61.29 61.20	5.14 5.10	10.21 10.22
OCH_3	OC_2H_5	3-Br	22	99-100	$C_{13}H_{14}BrNO_3$	50.01 49.95	4.52 4.52	4.49 4.46
OCH_3	OC_2H_5	6-NO_2	63	112-114	$C_{13}H_{14}N_2O_5$	56.11 55.80	5.07 5.01	10.07 9.92
OC_2H_5	CN	6-Cl	25	121-122	$C_{13}H_{11}ClN_2O_2$	59.43 59.59	4.22 4.63	10.67 10.46
OCH_3	OC_2H_5	3-NH_2	64	232-233	$C_{13}H_{16}N_2O_3$			11.29 11.05
OCH_3	CN	6-CH_3	49	79-82	$C_{13}H_{12}N_2O_2$	68.45 68.56	5.30 5.27	
OCH_3	CN	4-Cl-6-CH_3O	22	153-154	$C_{13}H_{11}ClN_2O_3$	56.02 56.03	3.98 3.96	10.05 10.11
OCH_3	CN	6-CH_3O	49	102-104	$C_{13}H_{12}N_2O_3$	63.93 63.90	4.95 5.01	
OC_6H_5	CN	H	63	126-128	$C_{17}H_{12}N_2O_2$	73.90 73.71	4.38 4.37	

(a) Prepared from 5-aminoquinoline.

Reaction of **2** with Hydroxylamine, Preparation of **4**.

A solution of 3.93 g. (0.017 mole) of **2** (R = C_2H_5) in 140 ml. of methanol at -10° was added to a solution of 2.1 g. (0.03 mole) of hydroxylamine hydrochloride and 0.7 g. (0.03 g.-atom) of sodium in 40 ml. of methanol at -10°. The mixture was stirred at -10° for 1 hour, filtered and evaporated to give after recrystallization from ethanol 3.06 g. (68%) of **4**, m.p. 160-161°; nmr (DMSO-d_6): 1.3 (t, CH_3), 4.2 (q, CH_2), 3.3 (s, C_1H), 5.2 (NH_2), 5.7 (d, C_3H), 6.2 (OH), 6.7 (d, C_4H), 7.1-7.5 δ (4 ArH).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.09. Found: C, 59.74; H, 5.89; N, 16.05.

Reaction of **2** with Benzaldehyde, Preparation of **5** and **6**.

To a solution of 0.01 mole of **2** (R = C_2H_5) in 225 ml. of 2:1 anhydrous ether-dioxane at -20° under a nitrogen atmosphere was added sufficient *n*-butyllithium solution to cause a permanent red color. Benzaldehyde (6.0 ml.) was then added and the mixture stirred at -20° for 1 hour and allowed to come to room temperature. After washing with water, 10% hydrochloric acid, and water, the solution was dried over magnesium sulfate and evaporated to give an oil which was chromatographed on alumina with benzene to give two products. Compound **5**, m.p. 145-146° from ethanol, was obtained in 23% yield; ir (potassium bromide): 2350 and

1750 cm^{-1}; nmr (deuteriochloroform): 5.9 (d, C_3H), 6.7 (d, C_4H), 5.5 (s), 7.1-8.3 δ (9 ArH).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.22; H, 4.23; N, 9.34.

Compound **6**, m.p. 183-185° from ethanol, was obtained in 10% yield; ir (potassium bromide): 1740 cm^{-1}.

Anal. Calcd. for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.80; H, 4.46; N, 5.35.

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(6) All melting points are corrected. Analyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan and Gailbraith Laboratories, Knoxville, Tenn.