Synthetic Studies on Chemotherapeutics. III. (1) Synthesis of the 6,9-Dihydro-9-oxo-1*H*- and 2*H*-Pyrazolo[3,4-*f*]quinoline-8-carboxylic Acid Derivatives [Studies on the Syntheses of Heterocyclic Compounds. Part 718 (2)]

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1*H*- and 2*H*-Pyrazolo[3,4-*f*]quinolines were synthesized in order to get an antibacterial compound by two different methods from 6-nitro- and 6-aminoindazole.

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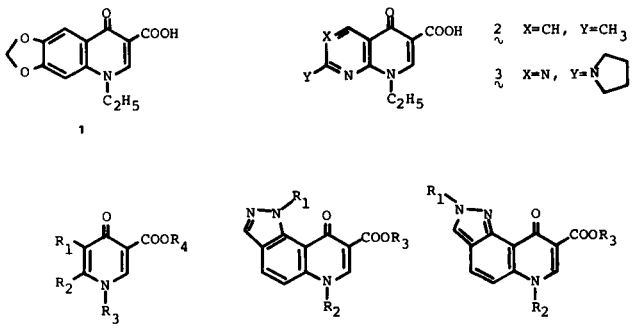
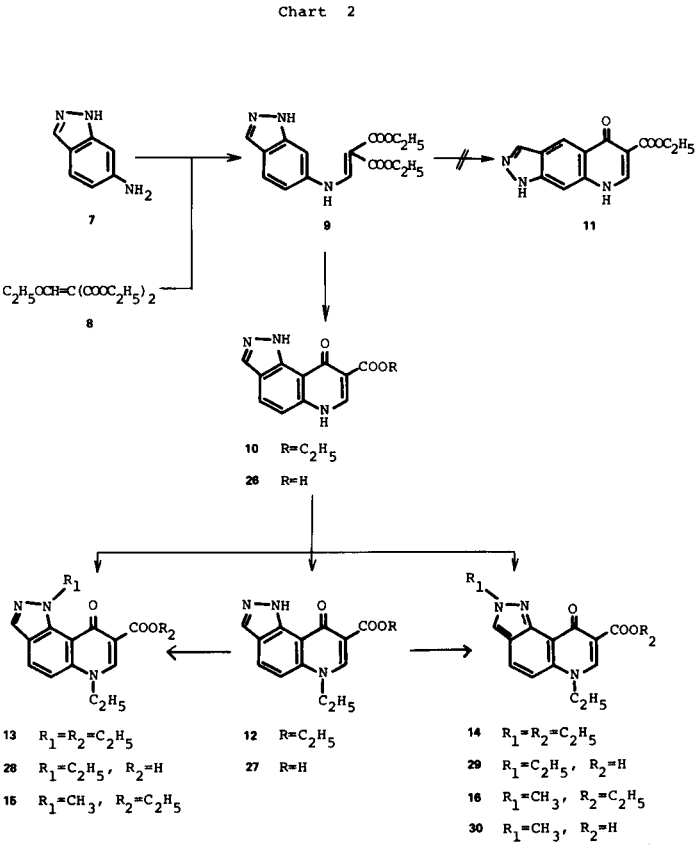
Since oxolinic acid (**1**), nalidixic acid (**2**) and pyromidic acid (**3**) have shown an antibacterial activity for Gram negative bacteria, many compounds having the similar structure with **1-3** have been synthesized in order to get more effective antibacterially active materials. We had also investigated a synthesis of the above type of compounds and reported previously a synthesis of 1,4-dihydro-4-oxonicotinic acid derivatives **4** which have the common partial structure of **1-3** (1-4). In this paper we wish to report a synthesis of 1*H*- and 2*H*-pyrazolo[3,4-*f*]quinoline-8-carboxylic acid derivatives (**5** and **6**) which would be expected to show an antibacterial activity, because these compounds have an α-acyl-β-aminoacrylic acid system as partial structure found in the compounds **1-3**.

Chart 1



Condensation of 6-aminoindazole (**7**), available commercially, with diethyl ethoxymethylenemalonate (**8**) gave the enamine type of compound **9**, which was cyclized under Gould-Jacobs reaction conditions or in the presence of Friedel-Crafts reaction catalyst such as polyphosphoric acid and phosphoryl chloride to afford ethyl pyrazolo-[3,4-*f*]quinoline-8-carboxylate (**10**). The structure of **10** [mass m/e 257 (M^+)] could be easily assigned by nmr spectrum revealing protons at C_4 and C_5 positions as AB type of doublet having J = 8 Hz. This fact ruled out that another possible product **11** has been formed during this cyclization.

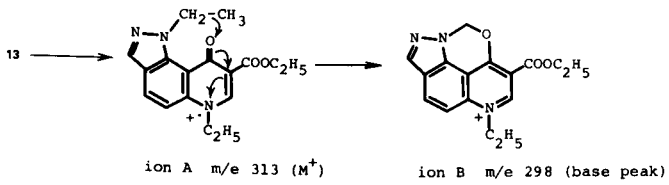
Chart 2



In order to introduce ethyl group on N_6 position the cyclization product **10** was treated with ethyl iodide in dimethylformamide in the presence of potassium carbonate. In this reaction, three types of ethylated pyrazolo[3,4-*f*]quinoline were formed, and the ratio of products depended upon the reaction time. The reaction for 1.5 hours gave **12**, **13** and **14** in 54.2, 0.6 and 10.9% yield, respectively, but three compounds **12**, **13** and **14** were formed in 28.8, 2.7 and 37.8% yield in the reaction during 2.5 hours. This phenomenon suggested that the products **13** and **14** would be formed from **10** *via* the compound **12**. In fact, ethylation of **12** under the same conditions was converted into **13** and **14** in 9.1 and 85.6% yield, respectively, and methylation of **12** gave two products **15** (3.8% yield) and **16** (65% yield).

Mass spectral analysis indicated that the first product **12** [m/e 285 (M^+)] was found to be monomethylated compound and the second **13** [m/e 313 (M^+)] and the third product **14** [m/e 313 (M^+)] were diethylated ones. In the nmr spectrum of **13** two types of methylene protons due to *N*-ethyl and *O*-ethyl functions were resonated at 4.32, 4.47 and 5.15 (q) ppm, but those of the other two products resonated at higher field (4.34 and 4.47 (q) in **12** and 4.25, 4.40 and 4.60 (q) in **14**) than the chemical shifts of **13**. Thus, the methylene protons on N_1 position in **13** were deshielded by the oxygen atom at the neighboring C_9 position. The same phenomena were observed in the chemical shift of *N*-methyl protons of the compound **15** (4.59 ppm) and **16** (4.30), in which the *N*-methyl group in **15** is located nearer at the C_9-oxygen than the case of **16**. The base peak of **13** in its mass spectrum was observed at m/e 298, which was assigned ion B derived from ion A as shown in Chart 3. This also supported the second product to have the structure **13**. Furthermore, the structure of **13** and **14** was proved by an alternative synthesis described later.

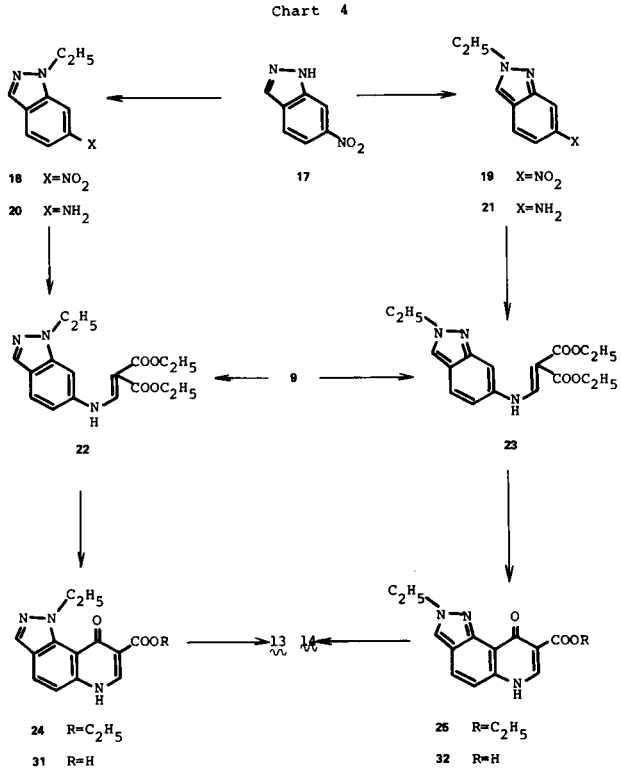
Chart 3



The above results indicated that *N*-alkylation of pyrazolo[3,4-*f*]quinoline would occur preferentially at the N_6 position under these conditions, the fact of which would be due to less hindered position at N_6 than N_1 and N_2 positions having steric repulsion between C_9 and these positions.

An alternative synthesis of **13** and **14** was carried out as follows: treatment of 6-nitroindazole **17** with ethyl iodide in the presence of potassium carbonate gave a mixture of **18** (26.5%) and **19** (64.8%), which was separated by crystallization (5). The reaction of **17** with ethyl iodide without base (6) proceeded in poor yield to give preferentially the product **19**. The structure of **18** and **19** was determined by pKa value and nmr and uv spectral data. The pKa value (7) of **18** and **19** was -0.894 and 0.328, respectively, whose values showed good agreement with the fact that the basicity of N_2-alkylindazoles was larger than that of the corresponding N_1-alkylated ones (8). In nmr spectral comparison of **18** and **19**, the shift at a lower field of C_3-proton in **19** (0.61 ppm) on changing from deuteriochloroform to deuteriodimethyl sulfoxide was larger than that of **18** (0.27 ppm) (9). Moreover, the uv spectrum of the starting material **17** was closely similar to that of the first product **18** but not the second one **19**

Chart 4



as shown in Figure 1, which was good agreement with the reported example (10). On the ground of the above consideration, the first product (**18**) could be assigned the N_1-ethylated structure having a benzenoid system and the second one to the N_2-ethylated *o*-quinonoid structure.

Reduction of the 6-nitroindazoles (**18** and **19**) with iron powder and dilute hydrochloric acid gave 1- and 2-ethyl-6-aminoindazole (**20** and **21**). The former product (**20**) formed the monohydrochloride (11) whose p*K*a value

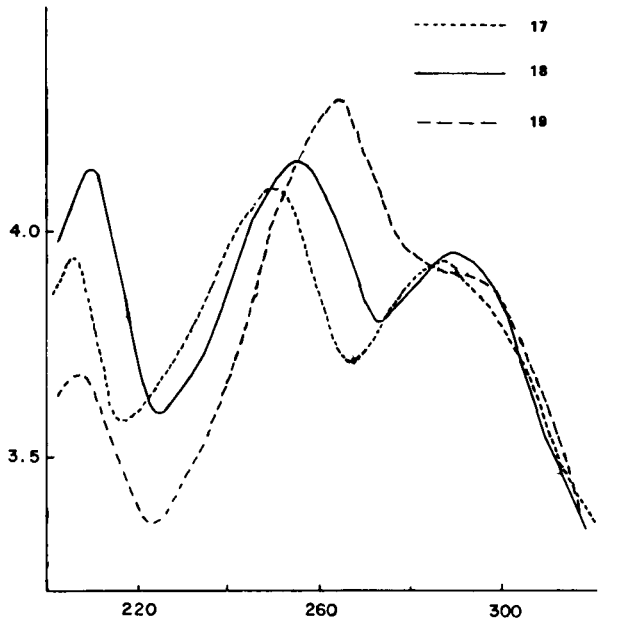


Figure 1. Uv spectra of the 6-nitro-1*H* and 2*H*-indazoles (**17**, **18**, and **19**) in ethanol

Table I

Diethyl *N*-(6-Indazolyl)aminomethylenemalonates

Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield % (method)	Formula	Analysis Calcd. (Found)	Ir (ν max cm^{-1})	Nmr (Deuteriochloroform)
9	168-169	colorless crystals (ethanol)	83.2 (method A)	$C_{15}H_{17}N_3O_4$	C, 59.39 (59.43) H, 5.65 (5.64) N, 13.86 (14.05)	3290, 1695, 1645, 1620 (potassium bromide)	1.37 (6H, t, J = 7 Hz, CH_2CH_3), 4.34 (2H, q, J = 7 Hz, CH_2CH_3), 6.99, 7.73 (each 1H, d, J = 8.5 Hz, C_4 & C_5-*H*), 7.27 (1H, s, C_7-*H*), 8.09 (1H, s, C_3-H), 8.61 (1H, d, J = 13 Hz, N-C*H*), 11.26 (1H, bd, J = 13 Hz, CH-N*H*)
22		colorless oil	95.9 (method A) 22.9 (method B)	$C_{17}H_{21}N_3O_4$	C, 61.62 (62.10) H, 6.39 (6.67) N, 12.68 (12.41)	3325, 1700, 1675, 1640 (liq.)	1.37, 1.42, 1.45 (each 3H, d, J = 7 Hz, CH_2CH_3), 4.31, 4.36, 4.43 (each 2H, q, J = 7 Hz, CH_2CH_3), 6.97 (1H, dd, J = 2 & 9 Hz, C_5-*H*), 7.14 (1H, d, J = 2 Hz, C_7-*H*), 7.77 (1H, d, J = 9 Hz, C_4-*H*), 7.98 (1H, s, C_3-*H*), 8.64 (1H, d, J = 13 Hz, >NC*H*=), 11.33 (1H, bd, J = 13 Hz, N*H*)
23	78-79	colorless needles (*n*-hexane)	90.0 (method A) 55.0 (method B)	$C_{17}H_{21}N_3O_4$	C, 61.62 (61.20) H, 6.39 (6.51) N, 12.68 (12.22)	3450, 1680, 1635, 1610 (potassium bromide)	1.33, 1.39, 1.63 (each 3H, d, J = 7 Hz, CH_2CH_3), 4.27, 4.34, 4.46 (each 2H, q, J = 7 Hz, CH_2CH_3), 6.92 (1H, dd, J = 2 & 9 Hz, C_5-*H*), 7.42 (1H, d, J = 2 Hz, C_7-*H*), 7.68 (1H, d, J = 9 Hz, C_4-*H*), 7.92 (1H, s, C_3-*H*), 8.62 (1H, d, J = 13 Hz, >NC*H*), 11.20 (1H, bd, J = 13 Hz, N*H*)

was -0.121, but the latter (**21**) gave the dihydrochloride (11), which showed 0.592 in p*K*a. These p*K*a values corresponded nicely to those of the nitro compounds (**16** and **17**). The condensation of the amino compounds (**20** and **21**) with diethyl ethoxymethylenemalonate (**8**) gave the corresponding enamines (**22** and **23**), which were identical with the products by the ethylation of **9**. The thermal cyclization of **22** and **23** afforded the 1- and 2-ethylpyrazolo[3,4-*f*]quinoline derivatives (**24** and **25**), respectively, which on ethylation were converted into the corresponding N_6-ethylated compounds (**13** and **14**). Both products were identical with the compounds (**13** and **14**) prepared by the route shown in Chart 1 in m.p. and ir and nmr spectral comparisons.

The ester (**10**, **11**, **12**, **13**, **14**, **16**, **19**, **20**, **21**, and **22**) (12) synthesized in Charts 2 and 4 were transformed into the corresponding 1*H*- and 2*H*-pyrazolo[3,4-*f*]quinoline-1-carboxylic acids (**26**, **27**, **28**, **29**, **30**, **31** and **32**) by treatment with sodium hydroxide in aqueous ethanol.

An antibacterial activity of the 1*H*- and 2*H*-pyrazolo-[3,4-*f*]quinolines prepared in this paper is now under examination.

EXPERIMENTAL

All melting points are uncorrected. The nuclear magnetic resonance (nmr) spectra were measured with a JEOL PMX-60 spectrometer (tetramethylsilane as an internal standard) and mass spectra with a Hitachi RMU-7 spectrometer.

Ethylation of 6-Nitroindazole (**17**) (5).

a) A mixture of 5 g. of 6-nitroindazole (**17**), 6 ml. of ethyl iodide, 5 g. of potassium carbonate, and 35 ml. of ethanol was heated for 4 hours at 75-80°, and then another 5 ml. of ethyl iodide and 3 g. of potassium carbonate was added to the reaction mixture. This was heated for further 4 hours at the same temperature. After removal of the solvent, the resultant mixture was extracted with chloroform and the extract was washed with water, dried over sodium sulfate and evaporated to give a reddish brown solid, a solution of which in 80% ethanol was treated with active carbon, and allowed to stand at room temperature overnight to afford 1.55 g. (26.5%) of **18** as pale orange needles, m.p. 98-99°; nmr δ (deuteriochloroform): 1.57 (3H, t, J = 7 Hz, CH_2CH_3), 4.51 (2H, q, J = 7 Hz, CH_2CH_3), 7.84 (1H, s, C_4-H), 7.88 (1H, d, J = 1 Hz, C_5-H), 8.06 (1H, s, C_3-H), 8.33 (1H, d, J = 1 Hz, C_7-H); (d_6-DMSO): 1.42 (3H, t, J = 7 Hz, CH_2CH_3), 4.60 (2H, q, J = 7 Hz, CH_2CH_3), 8.01 (1H, d, J = 1 Hz, C_5-H), 8.02 (1H, s, C_4-H), 8.33 (1H, s, C_3-H), 8.71 (1H, d, J = 1 Hz, C_7-H).

Anal. Calcd. for $C_9H_9N_3O_4$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.65; H, 4.65; N, 22.24.

Evaporation of the solvent from the above mother liquor afforded a solid, which was recrystallized from benzene-*n*-hexane to give 3.8 g. (64.8%) of **19** as pale orange prisms, m.p. 89-90°; nmr δ (deuteriochloroform): 1.68 (3H, t, J = 7 Hz, CH_2CH_3), 4.56 (2H, q, J = 7 Hz, CH_2CH_3), 7.78 (1H, d, J = 1 Hz, C_5-H), 7.80 (1H, s, C_4-H), 8.06 (1H, s, C_3-H), 8.62 (1H, s, C_7-H); (d_6-DMSO): 1.59 (3H, t, J = 7 Hz, CH_2CH_3), 4.62 (2H, q, J = 7 Hz, CH_2CH_3), 7.82 (1H, dd, J = 2 and 9 Hz, C_5-H), 8.01 (1H, d, J = 9 Hz, C_4-H), 8.65 (1H, d, J = 2 Hz, C_7-H), 8.67 (1H, s, C_3-H).

Table II

Ethyl 6,9-Dihydro-9-oxo-1*H*(and 2*H*)pyrazolo[3,4-*f*]quinoline-8-carboxylates

Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield % (method)	Formula	Analysis Calcd. (Found)	Ir (ν max cm^{-1}) (potassium bromide)	Nmr (deuteriochloroform) (a) ppm	Mass (m/e)
10	299-302 dec.	faintly brown crystals (acetic acid-dimethylformamide	73.2 (method A) 72.5 (method B)	$C_{13}H_{11}N_3O_3$	C, 60.69 (60.30) H, 4.31 (4.37) N, 16.34 (16.82)	1690, 1630 1615	1.63 (3H, t, J = 7 Hz, CH_2CH_3), 4.85 (2H, q, J = 7 Hz, CH_2CH_3), 8.23, 8.81 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 9.11, 9.60 (each 1H, s, C_3 & C_7-*H*) in trifluoro-acetic acid	257 (M^+), 211 (base peak, M^+-C_2H_5OH), 155, 141
12	238-239	colorless prisms (ethanol)	54.2 (method C) 28.8 (method D)	$C_{15}H_{15}N_3O_3$	C, 63.15 (63.17) H, 5.30 (5.41) N, 14.73 (14.93)	1675, 1635, 1600	1.45, 1.60 (each 3H, t, J = 7 Hz, CH_2CH_3), 4.34, 4.47 (each 2H, q, J = 7 Hz, CH_2CH_3), 7.16, 7.95 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.13, 8.46 (each 1H, s, C_3 & C_7-*H*)	285 (M^+) 240, 214, 213, (base peak, M^+-CO_2 & CH_2=CH_2), 141
13	127-127.5	colorless prisms (benzene-*n*-hexane)	0.6 (method C) 2.7 (method D) 9.1 (method E) 73.7 (method G)	$C_{17}H_{19}N_3O_3$	C, 65.16 (64.98) H, 6.11 (5.85) N, 13.41 (13.47)	1670, 1620	1.43 (6H, t, J = 7 Hz, CH_2CH_3), 1.55 (3H, t, J = 7 Hz, CH_2CH_3), 4.32, 4.47 (each 2H, q, J = 7 Hz, CH_2CH_3), 5.15 (2H, q, J = 7 Hz, N_1-CH_2CH_3), 7.20, 7.98 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.12, 8.42 (each 1H, s, C_3 & C_7-*H*)	131 (M^+), 298 (base peak, M^+-CH_3), 252, 155, 141
14	210-213	colorless prisms (acetone)	10.9 (method C) 37.8 (method D) 85.6 (method E) 86.4 (method G)	$C_{17}H_{19}N_3O_3$	C, 65.16 (64.82) H, 6.11 (6.07) N, 13.41 (13.32)	1700, 1620	1.41, 1.52, 1.60 (each 3H, t, J = 7 Hz, CH_2CH_3), 4.25, 4.40, 4.60 (each 2H, q, J = 7 Hz, CH_2CH_3), 7.08, 7.70 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.02, 8.30 (each 1H, s, C_3 & C_7-*H*)	313 (M^+), 242, 241 (base peak, M^+-CO_2, CH_2=CH_2 198, 141
15	215-216	colorless prisms (acetone)	3.8 (method F)	$C_{16}H_{17}N_3O_3$	C, 64.20 (64.01) H, 5.72 (5.85) N, 14.04 (13.68)	1710, 1620	1.41, 1.55 (each 3H, t, J = 7 Hz, CH_2CH_3 x 2), 4.28, 4.41 (each 2H, q, J = 7 Hz, CH_2CH_3 x 2), 4.59 (3H, s, $>NCH_3$), 7.12, 7.86 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 7.98, 8.38 (each 1H, s, C_3 & C_7-*H*)	

Table II (continued)

Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield % (method)	Formula	Analysis Calcd. (Found)	Ir (ν max cm^{-1}) (potassium bromide)	Nmr (deuteriochloroform) (a) ppm
16	228-229	colorless prisms (ethanol-acetone)	65.0 (method F)	$C_{16}H_{17}N_3O_3$	C, 64.20 (64.06) H, 5.72 (5.92) N, 14.04 (13.86)	1700, 1620	1.40, 1.47 (each 3H, t, J = 7 Hz, CH_2CH_3), 4.24, 4.37 (each 2H, q, J = 7 Hz, CH_2CH_3), 4.30 (3H, s, NCH_3), 7.05, 7.80 (each 1H, d, J = 9 Hz, C_4 & C_5-H), 7.97, 8.24 (each 1H, s, C_3 & C_7-H)
24	265-267	colorless leaflets (methanol)	58.1 (method A)	$C_{15}H_{15}N_3O_3$	C, 63.15 (62.90) H, 5.30 (5.30) N, 14.73 (14.79)	1700, 1630, 1610	1.38 (6H, t, J = 7 Hz, CH_2CH_3), 4.32 (2H, q, J = 7 Hz, OCH_2CH_3), 5.37 (2H, q, J = 7 Hz, N_1-CH_2CH_3), 7.28, 7.93 (each 1H, d, J = 9 Hz, C_4 & C_5-H), 8.09, 8.47 (each 1H, s, C_3 & C_7-H) in d_6-DMSO
25	236-238	colorless crystals (acetone)	41.3 (method A)	$C_{15}H_{15}N_3O_3$	C, 63.15 (62.66) H, 5.30 (5.23) N, 14.73 (14.56)	1700, 1625	1.47, 1.68 (each 3H, t, J = 7 Hz, CH_2CH_3), 4.51, 4.62 (each 2H, q, J = 7 Hz, CH_2CH_3), 7.63, 7.91 (each 1H, d, J = 9 Hz, C_4 & C_5-H), 8.03, 9.16 (each 1H, s, C_3 & C_7-H)

(a) The spectra were taken in deuteriochloroform unless otherwise stated.

Table III

6,9-Dihydro-9-oxo-1*H*(and 2*H*)pyrazolo[3,4-*f*]quinoline-8-carboxylic Acids

Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield %	Formula	Analysis Calcd. (Found)	Ir (ν max cm^{-1}) (potassium bromide)	Nmr (d_6-DMSO) ppm
26	>300	colorless crystals (methanol)	92.9	$C_{11}H_7N_3O_3 \cdot CH_3OH$	C, 55.17 (54.86) H, 4.24 (4.19) N, 16.09 (16.27)	1680-1670 1620	7.48, 8.20 (each 1H, d, J = 8 Hz, C_4 & C_5-*H*), 8.27, 8.87 (each 1H, s, C_3 & C_7-*H*)
27	>300	colorless leaflets (ethanol)	91.1	$C_{13}H_{11}N_3O_3$	C, 60.69 (60.61) H, 4.31 (4.16) N, 16.34 (16.24)	1710, 1625, 1605	1.48 (3H, t, J = 7 Hz, CH_2CH_3), 4.71 (2H, q, J = 7 Hz, CH_2CH_3), 7.70, 8.34 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.30, 9.08 (each 1H, s, C_3 & C_7-*H*)
28	259.5-261	colorless needles (ethanol)	91.6	$C_{15}H_{15}N_3O_3$	C, 63.15 (62.76) H, 5.30 (5.12) N, 14.73 (15.02)	1690, 1615 1590	1.37, 1.48 (each 3H, t, J = 7 Hz, CH_2CH_3), 4.70 (2H, q, J = 7 Hz, CH_2CH_3), 5.11 (2H, q, J = 7 Hz, N_1-CH_2CH_3), 7.71, 8.28 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.31, 9.07 (each 1H, s, C_3 & C_7-*H*)
29	274-275 dec.	colorless needles (ethanol)	86.1	$C_{15}H_{15}N_3O_3$	C, 63.15 (62.91) H, 5.30 (5.37) N, 14.73 (14.87)	1700, 1625, 1590	1.47, 1.54 (each 3H, t, J = 7 Hz, CH_2CH_3), 4.42, 4.67 (each 2H, q, J = 7 Hz, CH_2CH_3), 7.55, 8.22 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.63, 8.97 (each 1H, s, C_3 & C_7-*H*)
30	>300	colorless needles (ethanol)	76.4	$C_{14}H_{13}N_3O_3$	C, 61.98 (61.76) H, 4.83 (4.86) N, 15.49 (15.53)	1700, 1625, 1585	1.46 (3H, t, J = 7 Hz, CH_2CH_3), 4.63 (2H, q, J = 7 Hz, CH_2CH_3), 4.26 (3H, s, N-CH_3), 7.54, 8.18 (each 1H, d, J = 9 Hz, C_4 & C_5-*H*), 8.50, 8.90 (each 1H, s, C_3 & C_7-*H*)
31	285-286 dec.	colorless crystals (ethanol)	86.8	$C_{13}H_{11}N_3O_3$	C, 60.69 (60.33) H, 4.31 (4.34) N, 16.34 (16.00)	1685, 1620 1580	1.37 (3H, t, J = 7 Hz, CH_2CH_3), 5.28 (2H, q, J = 7 Hz, N_1-CH_2CH_3), 7.43, 8.12 (each 1H, d, J = 8 Hz, C_4 & C_5-*H*), 8.20, 8.82 (each 1H, s, C_3 & C_7-*H*)
32	>300	colorless crystals (methanol)	86.7	$C_{13}H_{11}N_3O_3 \cdot \frac{1}{2}CH_3OH$	C, 59.33 (59.67) H, 4.80 (5.03) N, 15.38 (15.44)	1710, 1630, 1590	1.54 (3H, t, J = 7 Hz, CH_2CH_3), 4.53 (2H, q, J = 7 Hz, CH_2CH_3), 7.38, 8.05 (each 1H, d, J = 8.5 Hz, C_4 & C_5-*H*), 8.51, 8.70 (each 1H, s, C_3 & C_7-*H*)

Anal. Calcd. for $C_9H_9N_3O_4$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.62; H, 4.62; N, 22.17.

b) (6) A mixture of 1 g. of 6-nitroindazole (**17**) and 6 ml. of ethyl iodide was heated at 100° under stirring in an autoclave for 4 hours. The reaction mixture was extracted with chloroform, and the extract was washed with water, dried over sodium sulfate, and evaporated to give a solid, which was recrystallized from benzene-*n*-hexane to afford 0.64 g. (54.7%) of **19** as pale orange prisms. This was identical with the sample obtained from the method (a). In this case, a small amount of **18** was detected on thin layer chromatography.

Reduction of 1- and 2-Ethyl-6-nitroindazole (**18** and **19**) with Iron-Hydrochloric Acid.

a) To a stirred solution of 2.3 g. of 1-ethyl-6-nitroindazole, 6 ml. of concentrated hydrochloric acid, 2 ml. of water, and 4 ml. of ethanol was added in small portions 2 g. of iron powder during 30 minutes at 65-70°. The stirring was continued for 30 minutes at the same temperature. After the reaction mixture had been diluted with water and filtered, the filtrate was basified with 10% sodium hydroxide solution. Benzene and an excess sodium sulfate was added to the above solution and the benzene layer was collected by decantation. This was dried over sodium sulfate and evaporated to give 1.4 g. (72.7%) of **20** as a reddish brown oil, which was crystallized from benzene-*n*-hexane to give pale yellow prisms, m.p. 118-119°; nmr δ (deuteriochloroform): 1.42 (3H, t, J = 7 Hz, CH_2CH_3), 3.89 (2H, broad s, NH_2), 4.19 (2H, q, J = 7 Hz, CH_2CH_3), 6.47 (1H, d, J = 2 Hz, C_7-H), 6.53 (1H, dd, J = 2 and 9 Hz, C_5-H), 7.47 (1H, d, J = 9 Hz, C_4-H), 7.82 (1H, s, C_3-H).

Recrystallization of the hydrochloride from ethanol-acetone gave colorless needles, m.p. 202-205°.

Anal. Calcd. for $C_9H_{11}N_3$·HCl: C, 54.68; H, 6.12; N, 21.26. Found: C, 54.94; H, 6.01; N, 21.66.

b) 2-Ethyl-6-nitroindazole (3.5 g.) was treated under the same procedure (a) using 7 ml. of concentrated hydrochloric acid, 3 ml. of water, 3 ml. of ethanol, and 4 g. of iron powder to give 2.0 g. (67.8%) of **21** as a reddish brown oil, nmr δ (deuteriochloroform): 1.56 (3H, t, J = 7.5 Hz, CH_2CH_3), 3.73 (2H, broad s, NH_2), 4.32 (2H, q, J = 7.5 Hz, CH_2CH_3), 6.55 (1H, dd, J = 2 and 8 Hz, C_5-H), 6.80 (1H, d, J = 2 Hz, C_7-H), 7.43 (1H, d, J = 8 Hz, C_4-H), 7.68 (1H, s, C_3-H).

Recrystallization of the hydrochloride from ethanol-acetone afforded colorless needles, m.p. 224-227° dec.

Anal. Calcd. for $C_7H_{11}N_3$·2HCl: C, 46.17; H, 5.60; N, 17.95. Found: C, 46.64; H, 5.61; N, 18.15.

Condensation of 6-Aminoindazoles (**7**, **20** and **21**) with Diethyl Ethoxymethylenemalonate (**8**) (Method A).

A solution of 2.8 g. of 6-aminoindazole (**7**), 5 g. of diethyl ethoxymethylenemalonate (**8**), and 5 ml. of benzene was heated under reflux for 1.5 hours. Evaporation of the solvent gave a solid, which was recrystallized from ethanol to give 5.05 g. (83.2%) of **9**. The reaction of 0.3 g. of 6-amino-1-ethylindazole (**20**) and 0.9 g. of 6-amino-2-ethylindazole (**21**) under the same conditions as above gave 0.69 g. (95.9%) of **22** and 1.28 g. (90.0%) of **23**, respectively (see Table I).

Ethylation of Diethyl *N*-(6-Indazolyl)aminomethylenemalonate (**9**) (Method B).

A mixture of 1 g. of diethyl *N*-(6-indazolyl)aminomethylenemalonate (**9**), 1.5 ml. of ethyl iodide, 1 g. of potassium carbonate, and 6 ml. of dimethylformamide was heated at 80-85° for 2 hours. After removal of the solvent under reduced pressure the resultant mixture was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give an oil, which was chromatographed on 40 g. of silica gel. The elution with benzene gave 0.25 g. (22.9%) of **22** as a colorless oil and further chloroform elution afforded 0.6 g. (55.0%) of **23** as a pale green solid. These ir and nmr spectra were identical with those obtained from method A.

Cyclization of Diethyl *N*-(6-Indazolyl)aminomethylenemalonates (**9**, **22** and **23**).

a) Thermal Cyclization (Method A).

A solution of 5 g. of diethyl *N*-(6-indazolyl)aminomethylenemalonate (**9**) in 120 ml. of diphenyl ether was heated at 250-270° under stirring for 30 minutes. Ethanol was added to the reaction mixture, by the result of which crystals were separated and recrystallized from dimethylformamide-acetic acid to give 1.8 g. (42.5%) of **10**. After removal of the ethanol from the mother liquor, the diphenyl ether layer was heated again at the same temperature to give an additional 1.3 g. (30.7%) of **10**. The same treatment of 170 mg. of **22** and 253 mg. of **23** gave 85 mg. (58.1%) of **24** and 90 mg. (41.3%) of **25**, respectively (see Table II).

b) Cyclization with PPA-Phosphorus Oxychloride. (Method B).

A mixture of 0.6 g. of **9**, 2.3 g. of polyphosphoric acid, and 8.2 g. of phosphoryl chloride was heated at ~100° for 4 hours. To the reaction mixture was added 20 ml. of ethanol to separate pale yellow crystals, which were washed with warm ethanol to give 0.37 g. (72.5%) of **10**. The ir and nmr spectra were identical with that obtained from method A.

Ethylation of Ethyl 6,9-Dihydro-9-oxo-1*H*-pyrazolo[3,4-*f*]quinoline-8-carboxylate (**10**).

a) Method C.

A mixture of 6 g. of ethyl 6,9-dihydro-9-oxo-1*H*-pyrazolo[3,4-*f*]quinoline-8-carboxylate (**10**), 6 ml. of ethyl iodide, 5 g. of potassium carbonate, and 50 ml. of dimethylformamide was heated at 80-90° for 1.5 hours. After removal of the solvent under reduced pressure, the resultant solid was recrystallized from ethanol to give 3.31 g. (49.7%) of **12**. Evaporation of the ethanol from the above mother liquor gave a solid, which was chromatographed on 150 g. of silica gel. Elution with chloroform gave a solid, which was recrystallized from benzene-*n*-hexane to give 40 mg. (0.6%) of **13**. The fraction from chloroform-methanol (100:1) afforded 320 mg. (4.5%) of **12**, and the elution with chloroform-methanol (100: 3-5) gave a pale brown solid, which was recrystallized from acetone to afford 0.8 g. (10.9%) of **14** (see Table II).

b) Method D.

A mixture of 0.5 g. of **10**, 0.7 ml. of ethyl iodide, 0.5 g. of potassium carbonate, and 5 ml. of dimethylformamide was heated at 80-90° for 2.5 hours. After evaporation of the solvent, the resultant mixture was chromatographed on 40 g. of silica gel under the same conditions as method C to give 15 mg. (2.7%) of **13**, 160 mg. (28.8%) of **12**, and 230 mg. (37.8%) of **14**.

Alkylation of Ethyl 6-Ethyl-6,9-dihydro-9-oxo-1*H*-pyrazolo[3,4-*f*]-quinoline-8-carboxylate (**12**).

a) Method E.

A mixture of 0.5 g. of ethyl 6-ethyl-6,9-dihydro-9-oxo-1*H*-pyrazolo[3,4-*f*]quinoline-8-carboxylate (**12**), 1.1 ml. of ethyl iodide, 1.7 g. of potassium carbonate, and 6 ml. of dimethylformamide was heated at 80-85° for 3 hours. After evaporation of the solvent, the resultant mixture was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give a brown solid, which was recrystallized from acetone to give 160 mg. (29.1%) of **14**. A solid obtained from the above mother liquor by evaporation of the solvent was chromatographed on 10 g. of silica gel. Elution with

chloroform gave 50 mg. (9.1%) of **13** and elution with chloroform-methanol (100:5) afforded 310 mg. (56.5%) of **14**.

b) Method F.

A mixture of 1.5 g. of **12**, 1.5 ml. of methyl iodide, 1.5 g. of potassium carbonate, and 8 ml. of dimethylformamide was heated at 70-80° for 2.25 hours. A solid obtained by the same treatment as above was recrystallized from ethanol-acetone to give 0.9 g. (57.2%) of **16**. After removal of the solvent from the above mother liquor, the resultant mixture was chromatographed on silica gel. Elution with chloroform gave 60 mg. (3.8%) of **15** and the fraction with chloroform-methanol (100: 2-5) afforded 0.12 g. (7.8%) of **16** (see Table II).

Ethylation of Ethyl 1-(and 2)-Ethyl-6,9-dihydro-9-oxo-1*H* (and 2*H*)-pyrazolo[3,4-*f*]quinoline-8-carboxylate (**24** and **25**) (Method G).

A mixture of 0.5 g. of ethyl 1-ethyl-6,9-dihydro-9-oxo-1*H*-pyrazolo[3,4-*f*]quinoline-8-carboxylate (**24**), 0.7 ml. of ethyl iodide, 0.5 g. of potassium carbonate, and 5 ml. of dimethylformamide was heated at 80-90° for 2.5 hours. After evaporation of the solvent, the resultant mixture was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave a solid, which was recrystallized from benzene-*n*-hexane to give 163 mg. (73.7%) of **13**.

The same treatment of 200 mg. of **25** gave 170 mg. (86.4%) of **14**.

Hydrolysis of Ethyl 6,9-Dihydro-9-oxo-1*H* (and 2*H*)-pyrazolo-[3,4-*f*]quinoline-8-carboxylates (**10**, **12**, **13**, **14**, **16**, **24** and **25**).

A solution of 1 g. of ethyl ester (**12**), 1 g. of sodium hydroxide, 10 ml. of water, and 10 ml. of ethanol was heated under reflux for 30 minutes. The aqueous layer obtained by removal of the ethanol was diluted with 20 ml. of water, whose solution was treated with active carbon under heating. The filtrate was adjusted to *p*H 4-5 with 10% hydrochloric acid and cooled to separate colorless crystals, which were recrystallized to afford 0.82 g. (91.1%) of **27**.

The same treatment as above gave the following results:

Starting material	Compound (mg.)	Product	(mg.)	Yield (%)
10	350	**26**	290	92.9
13	300	**28**	250	91.6
14	600	**29**	470	86.1
16	260	**30**	180	76.4 (a)
24	160	**31**	125	86.8
25	230	**32**	180	86.8

(a) In this case, sodium salt of **30** was precipitated during the reaction and this was collected by filtration. A suspension of precipitate in water was neutralized with acetic acid to give free carboxylic acid **30**.

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