Synthesis and Structure of Pyrazolo[5,1-*a*]isoindol-8-ones from Aromatic *Ortho* Diesters [1]

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The title compounds **2**, have now been shown to arise in certain cases from condensation of aromatic *ortho*-diesters with ketone, where formerly only indeno[1,2-*c*]pyrazol-4(1*H*)-ones **3** have been reported from such reaction. Heretofore **2** was obtained in a less direct fashion from phthalaldehydic acid esters. When hetero-aromatic diesters were employed, new heterocyclic ring systems as represented by **2a,b,c** were prepared for the first time. Structures of **2** have been verified from detailed ^1H and ^{13}C nmr studies, while representative intermediates **4-9** in the condensation of diesters to **2** have been isolated and identified.

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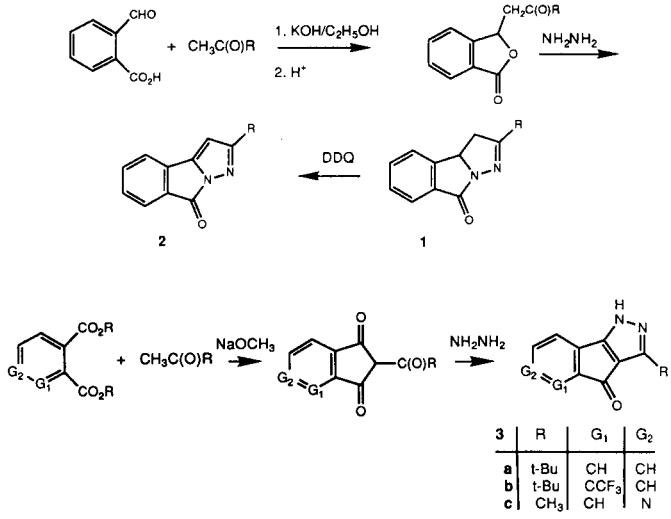
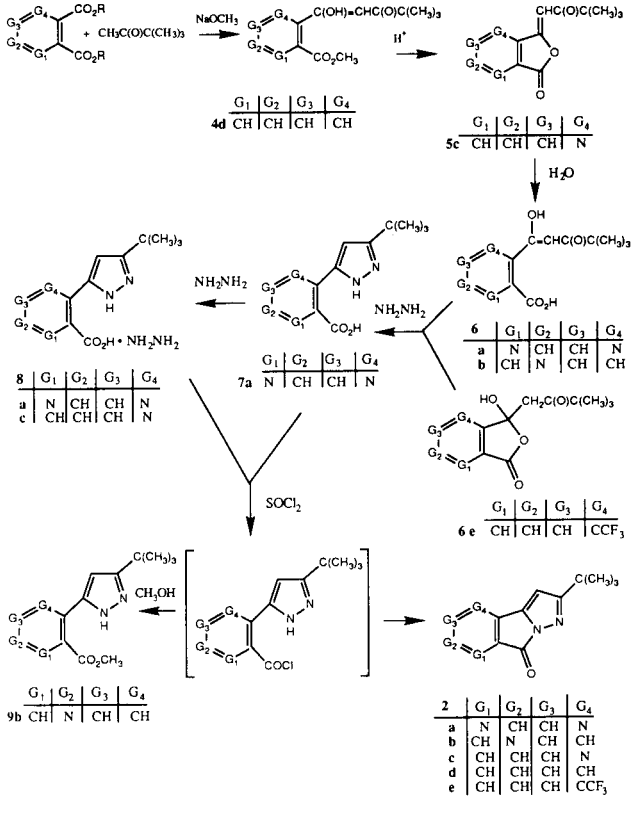
The title compounds (see note on nomenclature [3]) have previously been recorded as being made by a synthesis starting with phthalaldehydic acid ester, proceeding through the phthalide, which with hydrazine forms a 3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-one, **1**, which on oxidation yields 8*H*-pyrazolo[5,1-*a*]isoindol-8-ones, **2**, [4,5]. If **2** is desired directly, a seemingly obvious ploy would be to employ phthalic esters, having the next higher oxidation state, thus obviating formation of **1**. Curiously however the many literature references available report only the formation of indeno[1,2-*c*]pyrazol-4(1*H*)-ones, **3**, by using this sequence [6-16], with intermediate formation of 2-acylindanediones [17,18], even including several examples starting with pyridine *ortho* diacid derivatives [12,13]. This aforegoing status is summarized in Scheme 1.

Scheme 1



We wish to report here our results encountered when phthalic esters, and several nitrogen analogs thereof, were subjected to base promoted condensation with pinacalone. Although **3** (R = *t*-butyl), was formed easily, if care was taken in the condensation **4d** could be alternatively isolated. Saponification, followed by reaction with hydrazine then gave **2d**. When 3-(trifluoromethyl)phthalic acid was employed, both **2e** and **3b** could be separately identified. Finally, employment of several pyridine and pyrazine *ortho*-diacid esters gave a variety of intermediates **5-9**, but in all cases gave as end products only **2a-c**, but no **3**. these results are summarized in Scheme 2. Apparently as the aromatic diacid becomes more electron deficient it becomes easier to form **2** over **3**.

Scheme 2



Scheme 2 gives new materials not described in the literature. It was incumbent to verify the 8*H*-pyrazolo[5,1-*a*]iso-

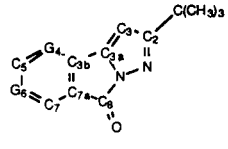
indol-8-one, **2**, rather than the alternative indeno[1,2-*c*]-pyrazol-4(1*H*)-one, **3**, structure. Moreover in the pyridine fused systems, it was necessary to confirm which of the two carboxyl groups condensed with pinacolone, thus determining the final regiochemistry of the carbonyl group. This was found definitively by examination of the ^{13}C as well as the ^{1}H nmr spectra of **2b,c**.

First, the isoindol-8-ones, **2**, and precursors were characterized by a consistent singlet in the ^{1}H nmr spectra in the δ 5.5-6.9 region, representing an olefinic proton. The sole exception to this is **6e**. This material clearly displays an AB quartet in the δ 3 region, best explained as representing a prochiral methylene adjacent to the asymmetric carbon of a lactone ring tautomer. Materials **6a,b** on the other hand are in the form of the chain tautomer and possess the =CH moiety. This last absorption was *absent* in authentic indenopyrazal-4-ones, **3**, and precursor triketones, including a pyridine-fused material from the literature, **3c** [12].

Secondly, a one dimensional INADEQUATE program was performed to generate connectivity tables of ^{13}C-^{13}C nmr coupling data for **2b** and **2c** (see below). These tables show conclusively that the carbonyl carbon (C_8 in **2**) is coupled to only one carbon nuclei rather than two, as would be the case in structure **3**. Likewise, the bridging carbon C_{3a} is connected to only two carbons; this atom would be coupled to three carbon nuclei in structure **3**. The tables also verify that the *more reactive* of the carboxyl groups (*i.e.* in *ortho* or *para* conjugation to the pyridine nitrogen) initially condensed with pinacalone, leaving the less reactive *meta* carboxyl free to ring close in subsequent steps, forming the 8-one moiety in **2c** and **2b** respectively. Using the same reasoning, the G_4 moiety in **2e** is assigned the CCF_3 function, since the *ortho* rather than *meta* carboxylate of the parent diester would be expected to be the more reactive.

Connectivity Table

^{13}C Chemical Shift and Coupling Constants for sp^2 Carbons



Material	Ring Carbon	δ (ppm)	J C-C, Hz
2b	2	173.3	$J_{C2\text{-}C3}$ 49.7
G_4= C_4	3	103.4	$J_{C3\text{-}C2}$ 49.7, $J_{C3\text{-}C3a}$ 75.1
G_6= N	3a	144.2	$J_{C3a\text{-}C3b}$ 63.4, $J_{C3a\text{-}C3}$ 75.2
	3b	139.2	$J_{C3b\text{-}C7a}$ 49.9, $J_{C3b\text{-}C3a}$ 63.1, $J_{C3b\text{-}C4}$ 63.2
	4	115.5	$J_{C4\text{-}C3b}$ 63.2, $J_{C4\text{-}C5}$ 53.5
	5	155.9	$J_{C5\text{-}C4}$ 53.5
	7	146.1	$J_{C7\text{-}C7a}$ 64.1
	7a	126.3	$J_{C7a\text{-}C3b}$ 50.0, $J_{C7a\text{-}C7}$ 64.1, $J_{C7a\text{-}C8}$ 70.2
	8	158.5	$J_{C8\text{-}C7a}$ 70.3
2c	2	173.3	$J_{C2\text{-}C3}$ 49.5
G_4= N	3	102.2	$J_{C3\text{-}C2}$ 49.8, $J_{C3\text{-}C3a}$ 74.8
G_6= C_6	3a	146.0	$J_{C3a\text{-}C3b}$ 72.8, $J_{C3a\text{-}C3}$ 74.8
	3b	153.4	$J_{C3b\text{-}C3a}$ 73.0, $J_{C3b\text{-}C7a}$ 53.2
	5	154.0	$J_{C5\text{-}C6}$ 56.6
	6	123.4	$J_{C6\text{-}C5}$ 55.8, $J_{C6\text{-}C7}$ 54.9
	7	133.0	$J_{C7\text{-}C6}$ 54.3, $J_{C7\text{-}C7a}$ 62.6
	7a	126.9	$J_{C7a\text{-}C3b}$ 53.2, $J_{C7a\text{-}C7}$ 62.9, $J_{C7a\text{-}C8}$ 71.1
	8	157.9	$J_{C8\text{-}C7a}$ 71.1

EXPERIMENTAL

Melting points were determined on a Haake Buchler apparatus and are uncorrected. The ^{1}H and ^{19}F nmr spectra were recorded on an XL300 (300 MHz), or XL400 (400 MHz) with instruments referenced to tetramethylsilane and fluorotrichloromethane respectively. Mass spectra were measured by a Varian CH7 mass spectrometer with *e.i.* or isobutane chemical ionization (c.i.) expressed as (m/e) and molecular weight respectively. Liquid chromatography purification was achieved on a Waters Prep LC, model 500A, with refractive index detector (hplc), or by Chromatotron™ (rotary tlc). Prior to use of one of these two methods, the reaction mixtures were developed on silica tlc plates. The solvent concentration of ethyl acetate in cyclohexane necessary to give Rf values between 0.05-0.2 (usually 0.5-50%) would then be used to effect macro-separation. Unless otherwise noted, boiling and sublimation points are recorded as oven temperatures during bulb-to-bulb (Kugelrohr) distillations. All microanalyses were performed by Atlantic Microlab Inc., P. O. Box 2288, Norcross, Georgia 30091.

The INADEQUATE (Incredible Natural Abundance Double Quantum Transfer Experiment) experiment [19] was run on the Varian XL-400. The free induction decays were collected for 1.21 seconds with a data size of 64K points. The sweepwidth included only the down field resonances in the 90 ppm region from approximately 95 to 185 ppm. This region included all carbon resonances except those from the *t*-butyl group. Approximately 10,000 scans were collected in blocks of 32, each block preceded by 2 dummy scans. A 20 second recycle delay was used between each scan. The refocussing delay was optimized for carbon-carbon couplings equal to 65 Hz. The carbon 90 degree pulse was 15 microseconds.

2-(1,1-Dimethylethyl)-8*H*-pyrazolo[1′,5′:1,2]pyrrolo[3,4-*b*]pyrazin-8-one (**2a**).

Material **7a** (0.45 g, 1.8 mmoles) was placed in 20 ml of thionyl chloride and refluxed 0.5 hour. After vacuum removal of solvent, including benzene evaporation to induce complete thionyl chloride elimination, the residue was treated with sodium bicarbonate, eluted through a Chromatotron™ with 25% ethyl acetate in cyclohexane, and product fractions recrystallized from methylcyclohexane and ethyl acetate to give 170 mg (41%) crystals, mp 175-176°; ^{1}H nmr (deuteriochloroform): δ 1.28 (s, 9H, $(CH_3)_3C$), 6.6 (s, 1H, =CH), 8.42 (s, 2H, ArH); ms: (glc) m/e 228.

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30. Found: C, 63.40; H, 5.47.

2-(1,1-Dimethylethyl)-8*H*-pyrazolo[1′,5′:1,5]pyrrolo[3,4-*c*]pyridin-8-one (**2b**).

Material **6b** (2.4 g, 10 mmoles) was reacted in 60 ml of ethanol with 0.6 g of anhydrous hydrazine. After 2 hours, the reaction mixture was evaporated under vacuum to give a soft tan tar, which crystallized eventually from ethyl acetate to give 1.6 g crystals. The carboxylic acid reaction product was treated with 15 ml thionyl chloride under reflux for 1 hour, followed by evaporation of excess reactant. The material was treated with benzene to give a gummy solid, not improved by potassium carbonate trituration. Chromatotron™ purification with 40% ethyl acetate in cyclohexane gave 260 mg product (11% from **6b**), eventually crystallizing, mp 134-137°; ^{1}H nmr (deuteriochloroform): δ 1.25 (s, 9H, $(CH_3)_3C$), 6.40 (s, 1H, =CH), 7.25 and 8.7 (2d, 2H, 7- and 8-H),

8.82 (s, 1H, 5-H); see Discussion for detailed ^{13}C nmr in Connectivity Table; ms: m/e 227.

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.48; H, 5.74; N, 18.36.

2-(1,1-Dimethylethyl)-8*H*-Pyrazolo[1',5':1,2]pyrrolo[3,4-*b*]pyridin-8-one (**2c**).

A preparation of **8c** (1.2 g, 4.3 mmoles), was charged to 15 ml of thionyl chloride and boiled for 2 hours. The clear solution was then vacuum treated to removed excess thionyl chloride (including several evaporations with benzene to remove traces of thionyl chloride), then the initially gummy residue triturated with aqueous potassium bicarbonate. Chromatotron™ purification of the resultant solid with 25% ethyl acetate in cyclohexane gave product in fractions 4-7 with 0.6 g (61%) recovered by recrystallization from ethyl acetate, mp 113-115°; ^1H nmr (deuteriochloroform): δ 1.31 (s, 9H, $(CH_3)_3C$), 6.51 (s, 1H, =CH), 7.20 (2d, 1H, *m*-ArH), 7.93 and 8.56 (2d, 2H, *o*- and *p*-ArH); see Discussion for detailed ^{13}C nmr in Connectivity Table; ms: (direct probe), m/e 227.

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.79; H, 5.82; N, 18.39.

2-(1,1-Dimethylethyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**2d**).

A mixture of **4d** (6.5 g, 24 mmoles), 1.4 g of hydrazine hydrate, and 150 ml of ethanol was heated and held at reflux for 3 hours. The mixture was treated on the rotovap, and half the residue treated with 75 ml of toluene and 4 ml (0.53 mmoles) of thionyl chloride, heating at reflux for 3 hours. The cooled mixture was poured into water, stirred for 1 hour at room temperature before separating, and the aqueous phase extracted with ether. The combined organic phases were washed with dilute sodium chloride solution, dried over magnesium sulfate, filtered, then the solvent vacuum removed. Separation of the residue by column chromatography using 5% ethyl acetate in cyclohexane gave 1.24 g (44% yield) yellow solid, mp 119-121°; ^1H nmr (deuteriochloroform): δ 1.4 (s, 9H, $(CH_3)_3C$), 6.3 (s, 1H, =CH), 7.3-7.8 (m, 4H, ArH); ms: (c.i.) mw 226.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.10; H, 6.23; N, 12.31.

2-(1,1-Dimethylethyl)-4-(trifluoromethyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (**2e**).

A mixture of **6e** (0.22 g, 0.69 mmole), 0.4 g of hydrazine hydrate, and 25 ml of ethanol was heated and held at reflux for 1 hour. The mixture was vacuum treated to remove solvent, then 5 ml of toluene added and the mixture vacuum treated once again. To the residue was added 15 ml of toluene and 3 ml of thionyl chloride. This reaction mixture was heated and held at reflux for 1 hour. The cooled mixture was poured into water followed by dichloromethane rinses, then stirred for 30 minutes at room temperature. The phases were separated, with the aqueous phase extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered and solvent removed under vacuum. Purification of the residue by Chromatotron™ using 5% ethyl acetate and 5% dichloromethane in cyclohexane afforded 0.18 g (88% yield) light yellow solid, mp 191-193°; ^1H nmr (deuteriochloroform): δ 1.2 (s, 9H, $(CH_3)_3C$), 6.3 (s, 1H, =CH), 7.5-7.6 (m, 3H, ArH); ^{19}F nmr: δ -63.0 (s); ms: (c.i.) mw 294.

Anal. Calcd. for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.45; N, 9.52. Found: C, 61.17; H, 4.46; N, 9.54.

3-(1,1-Dimethylethyl)indeno[1,2-*c*]pyrazol-4(1*H*)-one (**3a**).

The preparation of this material is detailed in reference [8], and is also available from Menai [20]; ^1H nmr (deuteriochloroform): δ 1.31 (s, 9H, $(CH_3)_3C$), 7.19-7.56 (m's, 4H, ArH), 11.88 (b, 1H, NH).

3-(1,1-Dimethylethyl)-5-(trifluoromethyl)indeno[1,2-*c*]pyrazol-4(1*H*)-one (**3b**).

A mixture of 90 mg (0.3 mmole) of the second product from preparation of **6e**, 0.15 g of hydrazine hydrate, and 20 ml of ethanol were heated and held at reflux for 2 hours. The mixture was vacuum treated to remove solvent, then the residue purified by Chromatotron™ using 10% ethyl acetate/5% dichloromethane in cyclohexane to give 0.20 mg (22% yield) white solid, mp 222-224°; ^1H nmr (deuteriochloroform): δ 1.5 (s, 9H, $(CH_3)_3C$), 7.4-7.9 (m, 3H, ArH); ^{19}F nmr: δ -64.9 (s); ms: (c.i.) mw 294.

Anal. Calcd. for $C_{15}H_{13}N_2F_3O \cdot 0.1H_2O$: C, 60.85; H, 4.49; N, 9.46. Found: C, 60.75; H, 4.59; N, 9.36.

3-Methylpyrazolo[3',4':3,4]cyclopenta[1,2-*c*]pyrindin-4(1*H*)-one (**3c**).

The preparation of 6-acetyl-5*H*-2-pyrindine-5,7(6*H*)-dione was similar to that recorded in the literature [12], although our material did not melt up to 300°. 3,4-Pyridinedicarboxylic anhydride (5.0 g, 33 mmoles) (Aldrich), freshly distilled, was mixed in a 100 ml flask with 3.4 g of acetylacetone, 6 ml of pyridine and 0.1 g of piperidine. After standing overnight, dark green-yellow crystals had formed; standing another 24 hours increased the amount. The mixture was triturated with 20 ml of ether, then filtered to give 4 g (64%). The material was easily vacuum sublimated on the Kugelrohr, after treatment with acid had failed to give mp up to 300°. The sublimed material also did not melt below 300°, although the literature [12] cited mp 245-246°; ^1H nmr (trifluoroacetic acid): δ 2.0 (s, 3H, CH_3), 7.7 and 8.4 (2d from AB quartet, 2H coupled, ArH), 8.55 (s, 1H, uncoupled ArH); ms: (direct probe) m/e 189.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.31; H, 3.74; N, 7.39.

6-Acetyl-5*H*-2-pyrindine-5,7(6*H*)-dione (1.65 g, 8.4 mmoles) as prepared above, was converted to the hydrazone by refluxing for 2 hours in 300 ml of ethanol containing 0.5 g of hydrazine hydrate. After cooling overnight the 1.0 g (58%) of crystals were filtered off, mp 241-243° (mp 239-241° [12]); ^1H nmr (methanol-d_4): δ 2.70 (s, 3H, CH_3), 7.57 and 8.80 (2d from AB quartet, 2H coupled, ArH), 8.72 (s, 1H, uncoupled ArH); ms: (direct probe) m/e 203. The 6-(1-hydrozonoethyl)-5*H*-2-pyrindine-5,7(6*H*)-dione so prepared, (0.4 g, 2 mmoles), was heated in 24 g of polyphosphoric acid using an oil bath at 90-95° for 20 minutes. The material appeared to dissolve. The material was poured into ice and stirred for 45 minutes to allow the thick syrup to dissolve. The solution was then neutralized to *p*H 6-7 with sodium hydroxide, and salt added causing a solid to precipitate. The material was filtered through a sintered glass filter, and the solid further washed with water on the filter, then thoroughly air dried. This gave 250 mg of brown crusty solid. A portion was sublimed 190-210° (1 mm), mp 264-267° (mp 255-257° [12]); ^1H nmr (methanol-d_4): δ 2.44 (s, 3H, CH_3), 7.55 and 8.65 (2d from AB quartet, 2H coupled, ArH), 8.62 (b, 1H, uncoupled ArH); ms: (direct probe and glc) m/e 185.

Methyl 2-(1-Hydroxy-4,4-dimethyl-3-oxo-1-pentenyl)benzoate (**4d**).

A mixture of 4.0 g (0.020 mole) of dimethyl phthalate, 2.0 g of pinacolone, 35 ml of anhydrous tetrahydrofuran, and 20 ml (0.020 mole) of 1.0 *M* lithium bis(trimethylsilyl)amide in tetrahydrofuran was heated and held at reflux for 4 hours. Another 25 ml of solution of lithium base was added to the cooled solution, and the mixture stirred at room temperature for 1 hour. The mixture was poured into dilute hydrochloric acid then extracted with ether. The ether extracts were dried over magnesium sulfate, filtered, and solvent removed by rotary vacuum evaporation. Separation by column chromatography using 2% ethyl acetate in cyclohexane and Kugelrohr distillation afforded 2.23 g (42% yield) yellow oil collected at 155-165° (1.4 mm); ^{1}H nmr (deuteriochloroform): δ 1.15 and 1.25 (ratio 1/10, 2s, 9H, $(CH_3)_3C$), 3.85 and 3.90 (ratio 10/1, 2s, 3H, OCH_3), 5.9 (s, 1H, =CH), 7.4-7.9 (m, 4H, ArH); ms: (c.i.) mw 262.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.75; H, 6.90.

7-(3,3-Dimethyl-2-oxobutylidene)furo[3,4-*b*]pyridin-5(7*H*)-one (**5c**).

Dimethyl 2,3-pyridinedicarboxylate (12.2 g, 62 mmoles) was dissolved in 250 of toluene with 6.3 g of pinacolone and 15 g of sodium methoxide. The mixture was refluxed for 11 hours, cooled, then the mixture treated with water, with the latter extract washed with fresh toluene. The aqueous extract then was acidified with hydrochloric acid, and the oil formed extracted 3x with ether. After drying over magnesium sulfate, the ether phase was evaporated to give 7.5 g oil. The material was Kugelrohr distilled to give 2.5 g. Chromatotron™ separation with 25% ethyl acetate in cyclohexane gave 1 g (7%) of solid as fraction 2; a portion was recrystallized from 2-propanol to give 120 mg light buff solid, mp 129-131°; ^{1}H nmr (deuteriochloroform): δ 1.2 (s, 9H, $(CH_3)_3C$), 6.8 (s, 1H, =CH), 7.5, 8.2 and 8.85 (3 m's, 3H, ArH); ms: m/e 231.

Anal. Calcd. for $C_{13}H_{13}NO_3 \cdot 0.1H_2O$: C, 67.00; H, 5.67; N, 6.00. Found: C, 66.85; H, 5.76; N, 5.83.

3-(1-Hydroxy-4,4-dimethyl-3-oxo-1-pentenyl)pyrazinecarboxylic Acid (**6a**).

Dimethyl 2,3-pyrazinedicarboxylate [21] (25 g, 0.128 mole) was dissolved in 400 ml of toluene with 13 g of pinacolone and 22 g of solid sodium methoxide. After stirring at room temperature for 1 hour, the material was refluxed 3 hours. The cooled contents were filtered, and the dark solid, *ca* 90 g, washed with ether. The resulting 45.7 g dissolved in water, neutralized with hydrochloric acid, then extracted several times with ether. The material was flash chromatographed to give 4.4 g (14%) granular brown solid, recrystallized from methylcyclohexane and ethyl acetate, mp 135-136°; ^{1}H nmr (deuteriochloroform): δ 1.20 (s, 9H, $(CH_3)_3C$), 6.57 (s, 1H, =CH), 8.70 (ABq, 2H, ArH), 15.42 (b, 1H, OH); ms: (glc) m/e 206 (decarboxylated **6a**); ms: (direct probe) m/e 250.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.63; H, 5.66; N, 11.01.

4-(1-Hydroxy-4,4-dimethyl-3-oxo-1-pentenyl)-3-pyridinecarboxylic Acid (**6b**).

Diethyl 3,4-pyridinedicarboxylate (Aldrich, 15.0 g, 0.067 mole) was dissolved in 250 ml of toluene with 7.0 g of pinacolone, and 12 g of sodium methoxide. After stirring for 1 hour at room temperature, the material was heated at reflux for 4 hours. The solution was cooled, the toluene carefully decanted from the crusty solid adhering to the flask wall, and washed with *ca* 200 ml water. This aqueous extract was then used to dissolve the crusty solid in the flask. The aqueous solution was extracted once with ether, then made acid to litmus with hydrochloric acid. A granular solid was thereby precipitated, weighing after air drying, 5.7 g (34%). Upon Chromatotron™ purification of a portion of this material with chloroform, 0.7 g material was isolated, with final recrystallization from chloroform to give white crystals, mp 153-156°; ^{1}H nmr (deuteriochloroform): δ 1.16 (s, 9H, $(CH_3)_3C$), 5.87 (s, 1H, =CH), 7.38, 8.80 and 9.13 (m's, 4H, ArH); ms: (glc) m/e 231 (mw of dehydrated **6b**).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.39; H, 6.13; N, 5.52.

2-(1-Hydroxy-4,4-dimethyl-3-oxo-1-pentenyl)-3-(trifluromethyl)-benzoic Acid (**6e**).

A mixture of 3.3 g (0.012 mole) of the dimethyl ester of 3-(trifluoromethyl)phthalic acid [22], 1.5 g of pinacolone, 1.0 g (0.018 mole) of sodium methoxide, and 90 ml of toluene was heated and held at reflux for 18 hours. The cooled mixture was poured into dilute caustic, and extracted with ether. The aqueous phase acidified with concentrated hydrochloric acid, then extracted with ether. The ether extracts were dried over magnesium sulfate, filtered and solvent evaporated. Purification by Chromatotron™ using 15% ethyl acetate/10% dichloromethane in cyclohexane followed by recrystallization afforded 0.34 g (8% yield) of **6e** as white solid, mp 120-122°; ^{1}H nmr (deuteriochloroform): δ 1.2 (s, 9H, $(CH_3)_3C$), 3.0, 3.25 (ABq, J = 18 Hz, 2H, prochiral CH_2), 7.4 (broad s, 1H), 7.7-8.0 (m, 3H, ArH); ^{19}F nmr: δ -60.6 (s); ms: (c.i.) mw 316.

Anal. Calcd. for $C_{15}H_{15}F_3O_4$: C, 56.96; H, 4.78. Found: C, 56.87; H, 4.75.

A second, less polar product was also obtained from the Chromatotron™ separation, representing the triketone (see Scheme 1, Discussion), 0.11 g yellow solid; ms: (c.i.) mw 298.

3-[3-(1,1-Dimethylethyl)-1*H*-pyrazol-5-yl]pyrazinecarboxylic Acid (**7a**).

Material **6a** (0.7 g, 5 mmoles) was mixed with 25 ml of ethanol and 0.16 g of hydrazine. The mixture was stirred for 15 minutes at room temperature, then refluxed for 1.25 hours. The material was then cooled in an ice bath and filtered to give 0.3 g of solid. The ethanol solution was evaporated to give 0.7 g (57%) of resinous solid, mp 110-113°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H, $(CH_3)_3C$), 6.92 (s, 1H, =CH), 8.57 and 8.67 (2d, 2H, ArH), 10.42 (b, 1H, OH); ms: (direct probe) m/e 246.

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.08; H, 5.95; N, 22.64.

3-[3-(1,1-Dimethylethyl)-1*H*-pyrazol-5-yl]pyrazinecarboxylic Acid, Salt with Hydrazine (1:1) (**8a**).

From the procedure describing the preparation of **7a**, 0.3 g (22%) of white precipitate was isolated after filtration, mp 216-217°; ^{1}H nmr (deuterio-water): δ 1.29 (s, 9H, $(CH_3)_3C$), 6.60 (s, 1H, =CH), 8.42 and 8.56 (2d, 2H, ArH); ms: (direct probe) m/e 245 (carboxylate anion).

Anal. Calcd. for $C_{12}H_{18}N_6O_2$: C, 51.53; H, 6.56; N, 30.03. Found: C, 51.79; H, 6.52; N, 30.20.

2-[3-(1,1-Dimethylethyl)-1*H*-pyrazol-5-yl]-3-pyridinecarboxylic Acid, Salt with Hydrazine (1:1) (**8c**).

Material **5c**, (0.9 g, 3.9 mmoles) was dissolved in 25 ml of eth-

anol and boiled 2 hours with 0.25 g of hydrazine. Some solid formed on cooling, but the bulk appeared upon evaporation under vacuum of most of the reaction solvent, yield 0.45 g (42%), mp 213-217°; ^{1}H nmr (deuterio-water): δ 1.32 (s, 9H, $(CH_3)_3C$), 4.78 (s, NH_2 and H_2O), 6.54 (s, 1H, =CH), 7.41 (2d, 1H, *m*-H), 7.78 and 8.49 (2d, 2H, *o* and *p*-ArH).

Anal. Calcd. for $C_{13}H_{19}N_5O_2$: C, 56.30; H, 6.91; N, 25.25. Found: C, 56.31; H, 6.91; N, 25.17.

Methyl 4-[3-(1,1-Dimethylethyl)-1*H*-pyrazol-5-yl]-3-pyridinecarboxylate (**9b**).

The carboxylic acid reaction product prepared as described above in the preparation of **2b** (0.8 g, 3.2 mmoles) was reacted in 10 ml of thionyl chloride at reflux for 1 hour. After thionyl chloride removal, the material was treated with excess methanol and potassium carbonate. The resulting material was eluted through the Chromatotron™ with 40% ethyl acetate in cyclohexane. Eventually 440 mg (53%) of product was isolated as yellow viscous oil; ^{1}H nmr (deuteriochloroform): δ 1.31 (s, 9H, $(CH_3)_3C$), 3.85 (s, 3H, OCH_3), 6.38 (s, 1H, =CH), 7.57, 8.63 (2d, 2H, 5- and 6-ArH), 8.82 (s, 1H, 2-ArH); ms: m/e 259.

Anal. Calcd. for $C_{14}H_{17}N_3O_2 \cdot 0.4H_2O$: C, 63.09; H, 6.73; N, 15.76. Found: C, 63.37; H, 6.73; N, 15.36.

REFERENCES AND NOTES

[1] Presented at the National ACS Meeting, Atlanta, Georgia, April, 1991, ORGN 170.

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[3] Although all of the materials, **2a-e** have the same general structure, and for convenience are collectively designated pyrazolo[5,1-*a*]isoindol-8-ones in the title of this article, after the original carbocyclic examples given in references [4] and [5], the correct CA/IUC nomenclature for them will differ, depending on the heterocycle fused to the pyrazole ring system. The correct CA name therefore for each of these materials is designated in the Experimental.

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