A New Method for the Preparation of 2-Carboalkoxypyrazolo-[5,1-*b*]quinazolin-9(1*H*)ones

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Anthranilic acid hydrazides were condensed with acetylene diesters, and the intermediate adducts were identified as acylhydrazones of oxalacetic diester. These anthranilic hydrazones could be thermally cyclized to 2-carboalkoxypyrazolo[5,1-*b*]quinazolin-9(1*H*)ones.

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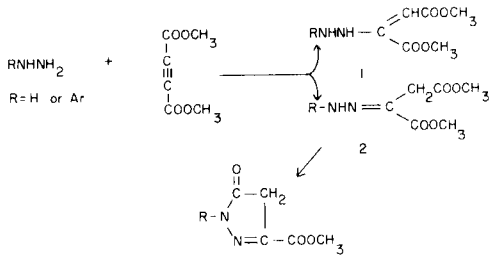
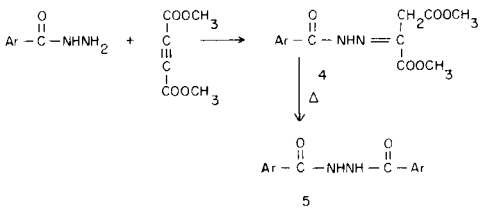
In a recent investigation (1), hydrazines and arylhydrazines were condensed with dimethyl acetylenedicarboxylate (DMAD) to yield mixtures of enehydrazines **1** and hydrazones **2**. The relative composition of these species was dependent upon reaction conditions. If the reaction was carried out at -40° in ethanol, a mixture of **1** and **2** was isolated; however, only **2** was obtained in ether at 0°. In these studies (1) and in related ones (2-4), it was demonstrated that these labile imine-enamine species could be versatile precursors of heterocyclic products; *e.g.*, the cyclization of **2** gives pyrazolone **3** (Scheme I).

George and co-workers (5) have reported that the condensation of DMAD with aroylhydrazines produced dimethyl oxalacetate aroylhydrazone **4** (imine form). Thermolysis of these intermediates at *ca.* 150° yielded diaroylhydrazones **5** (Scheme II) with no evidence of a heterocyclic product.

Scheme I



Scheme II



During the present investigation, isatoic anhydrides **6** were opened with hydrazine to give excellent yields of substituted anthranilic acid hydrazides **7**. When these hydrazides were condensed with dimethyl or diethyl acetylenedicarboxylate, they yielded the corresponding anthranilic acid hydrazones of oxaloacetic diester **8** (See Table I). Furthermore, these same hydrazones could be obtained, albeit in poorer yields, by treatment of the hydrazides with diethyl oxaloacetate (6). The structures of **8a-h** were established by absorption spectrometry, particularly ^{1}H nmr, and supported by combustion analysis. Some isochronous absorptions (Table I) were noted in several compounds for the methylene and ester methoxy signals at 3.80 ± 0.03 ppm. The absence of a vinyl proton resonance eliminated the possibility that these adducts are enehydrazines and confirms their assignment as hydrazones (5) (See Scheme III). Each anthranilic acid hydrazone **8a-h** was thermally cyclized in tetralin (*o*-dichlorobenzene and diphenyl ether could also be employed as cyclization

Scheme III

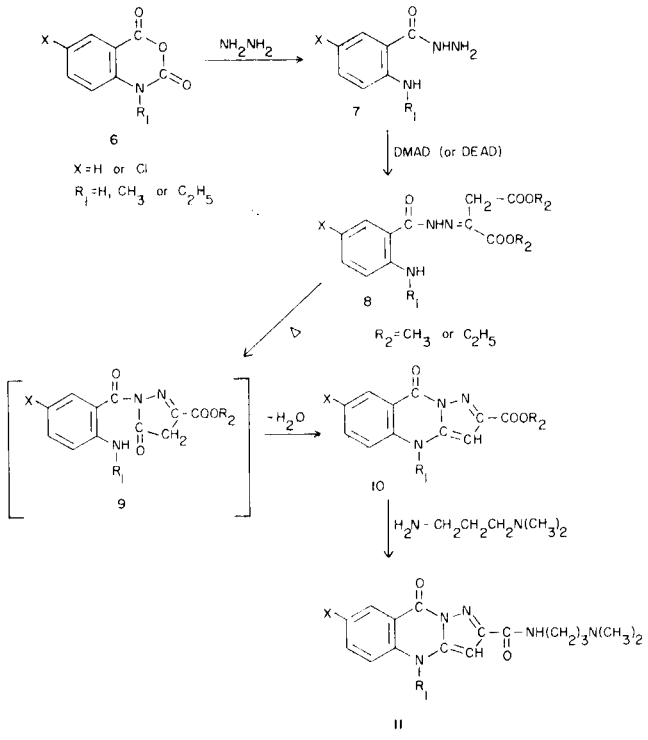


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Table I

Anthranilic Acid Hydrazones of Oxalacetic Diester

Compound Number	X	R_1	R_2	Empirical Formula	% Yield	M.p. (a) °C	Elemental Analysis Calcd. C	Calcd. H	Found N	Found C	Found H	Found N
8a (b)	H	H	CH_3	$C_{13}H_{15}N_3O_5$	92	159-161	53.24	5.16	14.33	53.48	5.30	14.27
8b (c)	Cl	H	CH_3	$C_{13}H_{14}ClN_3O_5$	98	168-169	47.64	4.30	12.82	47.92	4.44	12.59
8c (d)	H	CH_3	CH_3	$C_{14}H_{17}N_3O_5$	90	145-147	54.72	5.58	13.68	54.57	5.30	13.86
8d (e,f)	Cl	CH_3	CH_3	$C_{14}H_{16}ClN_3O_5$	91	185-187	61.98	4.83	15.49	62.09	4.90	15.78
8e (g)	H	CH_2CH_3	CH_3	$C_{15}H_{19}N_3O_5$	87	165-167	56.06	5.96	13.08	56.31	6.06	13.36
8f (h)	H	H	CH_2CH_3	$C_{15}H_{19}N_3O_5$	55	158-160	56.06	5.96	13.08	55.86	6.07	13.34
8g (i)	H	CH_3	CH_2CH_3	$C_{16}H_{21}N_3O_5$	78	134-135	57.30	6.31	12.53	57.31	6.21	12.29
8h (j)	Cl	CH_3	CH_2CH_3	$C_{16}H_{20}ClN_3O_5$	90	157-159	51.97	5.45	11.36	51.90	5.43	11.25

(a) Analytical samples of methyl and ethyl esters were prepared by recrystallization from methyl and ethyl alcohol, respectively. (b) Partial ^{1}H nmr for **8a**: δ 3.68 (s, OCH_3) and 3.82 (s, $-CH_2-$ and OCH_3). (c) ^{1}H nmr for **8b**: δ 3.67 (s, OCH_3), 3.78 (s, OCH_3) and 3.90 (s, OCH_3). (d) ^{1}H nmr for **8c**: δ 3.70 (s, OCH_3) and 3.83 (s, $-CH_2-$ and $-OCH_3$). (e) ^{1}H nmr for **8d**: δ 3.67 (s, OCH_3) and 3.83 (s, $-CH_2-$ and OCH_3). (f) Ms for **8d**: m/e 343/341 ($M^+ - Cl^{37}/M^+ - Cl^{35}$), P-32 ($-CH_3OH$), and P-59 ($-COOCH_3$). (g) ^{1}H nmr for **8e**: δ 3.70 (s, OCH_3) and 3.83 (s with shoulder, $-CH_2-$ and $-OCH_3$). (h) ^{1}H nmr for **8f**: 1.30 (m, $-CH_3$), 3.83 (s, $-CH_2CO$) and 4.2 (m, $-OCH_2-$). (i) ^{1}H nmr for **8g**: 1.30 (m, $-CH_3$), 3.78 (s, $-CH_2CO$) and 4.23 (m, $-OCH_2-$). (j) ^{1}H nmr for **8h**: δ 1.28 (m, $-CH_3$), 3.83 (s, $-OCH_2$) and 4.2 (m, $-CH_3$). Infrared spectra for **8a-h** contained two carbonyl absorptions 1715 ± 5 cm^{-1} and 1740 ± 5 cm^{-1}.

Table II

2-Carboalkoxypyrazolo[5,1-*b*]quinazolin-9(1*H*)ones

Compound Number	X	R_1	R_2	Empirical Formula (a)	% Yield	M.p. °C	Elemental Analysis Calcd. C	Calcd. H	Found N	Found C	Found H	Found N
10a	H	H	CH_3	$C_{12}H_9N_3O_3$	36	283-285	59.26	3.73	17.28	58.96	3.73	17.01
10b	Cl	H	CH_3	$C_{12}H_8N_3O_3$	42	313-314	51.91	2.90	15.13	52.06	2.92	15.43
10c	H	CH_3	CH_3	$C_{13}H_{11}N_3O_3$	64	285-287	60.69	4.31	16.34	60.47	4.32	16.56
10d	Cl	CH_3	CH_3	$C_{13}H_{10}ClN_3O_3$	48	313-315	53.34	3.79	14.36	53.25	3.42	14.25
10e	H	CH_2CH_3	CH_3	$C_{14}H_{13}N_3O_3$	58	217-219	61.98	4.83	15.49	62.24	4.93	15.62
10f	H	H	CH_2CH_3	$C_{13}H_{11}N_3O_3$ (b)	36	298-301	60.69	4.31	16.34	60.69	4.42	16.57
10g	H	CH_3	CH_2CH_3	$C_{14}H_{13}N_3O_3$	23	244-246	61.98	4.83	15.79	62.09	4.90	15.78
10h	Cl	CH_3	CH_2CH_3	$C_{14}H_{12}ClN_3O_3$	10	278-279	55.00	3.96	13.75	54.75	3.71	13.85
11a	H	H	$NH(CH_2)_3N(CH_3)_2$	$C_{16}H_{19}N_5O_2$ (c)	59	224-226	61.32	6.11	22.35	61.02	6.32	22.49
11b	Cl	H	$NH(CH_2)_3N(CH_3)_2$	$C_{16}H_{18}ClN_5O_2$	66	278-280	55.25	5.21	20.13	55.04	5.42	20.42

(a) Infrared spectra (Nujol) usually displayed two carbonyl absorptions at 1700 ± 5 cm^{-1} and 1735 ± 10 cm^{-1}. Compound **10f** displayed a single broad absorption, *ca* 1700 cm^{-1} with a shoulder. (b) Lit. m.p. 275-280° (see reference 6). (c) ms for **11a**: m/e 313 (M+).

media). The products, identified as pyrazoloquinazolinones **10a-h**, are listed in Table II. We were unable to isolate the plausible intermediate pyrazolin-5-one **9**. Presumably, once these intermediates **9** were formed (*ca* 150-160°), they spontaneously cyclodehydrated to give **10**, which was unlike the situation attained with the aroylhydrazones of oxalacetic diester, wherein thermolysis gave diaroylhydrazines **5**. No such products were formed from the anthranilic hydrazones. Heterocyclization to **10** is apparently preferred when an available *ortho*-amino group is present.

These pyrazoloquinazolinones, **10a-h**, were too insoluble for magnetic resonance studies but all displayed two characteristic carbonyl stretching bands *ca*. 1700 and 1735 cm^{-1}, and satisfactory combustion analyses (for C, H, and N). A mass spectrum of **10f** possessed the requisite parent ion (m/e, 257), and in addition major cleavage moieties were noted which corresponded to P-OC_2H_5 and P-$COOC_2H_5$.

A report has appeared in the patent literature for the preparation, in unspecified yields, of anthranilic acid hydrazones from diethyl oxaloacetate, and the subsequent cyclization of these to pyrazoloquinazolinones (6). While we have found the procedure to be reproducible after minor modification, as far as generation of the hydrazones **8**, it is considerably less convenient and results in lower conversions than the techniques reported herein (we obtain the same **8a** in 52% by the oxaloacetate method *vs*. 92% by the DMAD method). Furthermore, we have not been able to duplicate their ring-closure procedure for conversion of the hydrazone **8** to the heterocyclic product **10**.

In an attempt to prepare water soluble derivatives of these pyrazoloquinazolinones for medicinal studies, we condensed esters **10a** and **10b** with 3(*N*,*N*-dimethylamino)-propylamine. The corresponding amides, **11a** and **11b** were obtained, and they readily formed water-soluble hydrochlorides. The latter displayed no significant pharmacologic potential in animal studies.

EXPERIMENTAL

Acetylene esters and isatoic anhydrides were purchased from Aldrich Chemical Company and Columbia Organics. *N*-Ethyl isatoic anhydride was prepared by alkylation of isatoic anhydride with ethyl iodide (7). Nmr spectra (deuteriochloroform or deuteriochloroform + DMSO-d_6 solvent) were obtained from a Varian Associates EM-300X Nuclear Magnetic Resonance Spectrometer and chemical shifts are reported in δ ppm downfield from a tetramethylsilane (TMS) standard. Ir spectra were obtained from Perkin-Elmer 700 and 237 Spectrometers. Melting points were taken in a Thomas-Hoover melting point apparatus in open tubes and are uncorrected. Combustion analyses were supplied by Dr. Geroge I. Robertson's Microanalytical Laboratory, 73 West End Avenue, Florham Park, NJ 07932. Mass spectra for **8d** and **10f** were taken on an LKB 9000 Spectrometer at Vanderbilt University; **11a** was taken on a CED Model 21-110B double focusing spectrometer at the University of Delaware.

Anthranilic Acid Hydrazides.

A 0.1-mole sample of isatoic anhydride was suspended in 100-150 ml. of ethanol and treated with 10 ml. of hydrazine hydrate (85%). After evolution of carbon dioxide and heating under reflux for *ca*. 1 hour, the solution was filtered, the anthranilic hydrazides isolated in good yields, and recrystallized from ethanol. Anthranoyl, *N*-methylanthranoyl and 5-chloroanthranoyl hydrazides have been previously documented (8-10), and while *N*-methyl-5-chloroanthranoyl hydrazide (89% for this investigation), m.p. 150-152°, has been cited, its melting point and other properties are not readily available (11).

Anal. Calcd. for $C_8H_{10}ClN_3O$: C, 48.13; H, 5.05; N, 21.05. Found: C, 48.11; H, 5.15; N, 21.31.

N-Ethylanthranoyl hydrazide (71%), m.p. 98-100°, has not been previously described.

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.50; H, 7.47; N, 23.75.

General Preparation of Hydrazones of Dimethyl or Diethyl Oxalacetate.

The best yields were obtained when the anthranoyl hydrazide (0.05 mole) was added to 100 ml. of methanol (ethanol when ethyl ester used) and warmed on a stir plate until solution was complete. A 0.055-mole sample of dimethyl (or diethyl) acetylenedicarboxylate was added at a fast dropwise rate, and a yellow precipitate developed immediately. After addition was complete, the mixture (solid and solvent) was warmed and stirred an additional 20 minutes to complete the reaction. The heterogeneous mixture was cooled and filtered. The product was conveniently recrystallized from ethanol or methanol (see Table I).

The same materials (ethyl esters) were prepared in lower yield using another procedure (6). A 0.1-mole sample of sodium diethyl oxalacetate was dissolved in 100-200 ml. of methanol and neutralized with 0.1 mole of *p*-toluenesulfonic acid. Subsequently, 0.1 mole of anthranilic acid hydrazide was added, and the mixture stirred at room temperature for several hours. The precipitate that formed was filtered, dried, and recrystallized. Its properties were identical to the corresponding compound prepared from anthranilic acid hydrazide and diethyl acetylenedicarboxylate.

General Procedure for the Preparation of 2-Carboalkoxypyrazolo-[5,1-*b*]quinazolin-9(1*H*)ones (**10a-h**).

A 1.0-g. sample of **8a-h** was suspended in 100 ml. of tetralin contained in a 250 ml. Erlenmeyer flask. A stir bar was added, and the flask was placed on a stirring hot-plate. A thermometer could be placed in the solution, and the temperature was slowly raised to 185-190°. Complete solution usually resulted at 140-150°, and solid material (product) usually precipitated out at the higher temperature.

The mixture was heated and stirred at 185-190° for 1.5-2 hours, cooled and filtered. Each pyrazoloquinazolinone was recrystallized from xylene and dimethylformamide (DMF). The results are listed in Table II.

1,2-Dichlorobenzene could also be used as the solvent in a similar manner described for tetralin. If diphenyl ether was used, the resulting solution was poured into petroleum ether and filtered prior to recrystallization.

Preparation of Amides **11a** and **11b** from Pyrazoloquinazolinones **10a** and **10b**.

A 4.5-g. sample of pyrazoloquinazolinone was suspended in 25-35 ml. of dimethylformamide. Ten ml. of the diamine was

added, with modest evolution of heat as the reaction mixture became homogeneous. The mixture was allowed to stand at room temperature for 24 hours and then heated on a steam bath for 0.5 hour. It was cooled, poured into water, and the resulting precipitate was filtered, dried, and recrystallized from dimethylformamide and water (see Table II for results).

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REFERENCES AND NOTES

(1) N. D. Heindel, P. D. Kennewell and M. Pfau, *J. Org. Chem.*, 35, 80 (1970).

(2) N. D. Heindel, P. D. Kennewell and M. Pfau, *Chem. Commun.*, 757 (1969).

(3) N. D. Heindel, V. B. Fish and T. F. Lemke, *J. Org. Chem.*, 33, 3997 (1968).

(4) E. C. Taylor and N. D. Heindel, *ibid.*, 32 1666 (1967); *ibid.*, 32, 3339 (1967).

(5) M. N. Budi, J. G. Hiriyakkanauar and M. V. George, *Indian J. Chem.*, 9, 743 (1971).

(6a) K. H. Menzel, R. Puetter and G. Wolfrum, German Patent 1,120,455 (1961); *Chem. Abstr.*, 57, 4675 (1962). (b) K. H. Menzel, R. Puetter and G. Wolfrum, German Patent 1,111,505 (1960); *Chem. Abstr.*, 56, 4904g (1962). (c) R. Peutter, G. Wolfrum and K. H. Menzel, German Patent 1,139,123 (1962); *Chem. Abstr.*, 58, 9095g (1963).

(7) G. Palazzo and B. Silvestrini, U. S. Patent 3,409,668 (1968); *Chem. Abstr.*, 70, 37496m (1969).

(8) G. Heller and A. Siller, *J. Prakt. Chem.*, 116, 1 (1927).

(9) G. Heller, E. Goring, J. Kloss, and W. Kohler, *ibid.*, 111, 36 (1925).

(10) C. Casagrande, M. Canova and G. Ferrari, *Farmaco Ed. Sci.*, 20, 544 (1965).

(11) R. A. Rossi, R. Goeschke, G. Haas and A. Sallmann, German Patent 2,501,468 (1975); *Chem. Abstr.*, 84, 180047m (1976).