Synthesis of New 2-Aryl-3,3a-dihydro-4-oxo-5*H*-pyrazolo-[1,5-*d*][1,2,4]triazines and some of Their Derivatives

P. Coudert, S. Mavel, J. Couquelet* and P. Tronche

Laboratoire de Chimie Thérapeutique

C. Rubat and J. Bastide

Laboratoire de Pharmacologie et de Pharmacie Clinique,
Groupe de Recherches en Pharmacochimie, 28, Place Henri Dunant,
Cédex, France

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The preparation of new dihydropyrazolo[1,5-*d*][1,2,4]triazinones involved the formation of carboxylic acid hydrazides *via* the appropriate ethyl aroylacrylates, followed by condensation with an orthoester. The synthesis of some derivatives substituted on the nitrogen atom in the 5-position of the triazine ring was reported and their anticonvulsant activity was evaluated.

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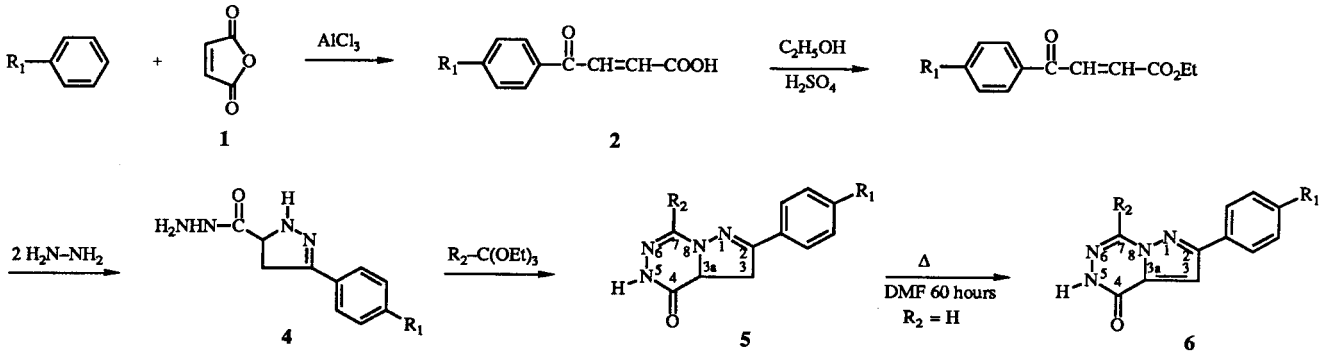
Fused heterocyclic systems containing a triazine ring were largely investigated because they were effective in many pharmacological areas. These derivatives presented a great number of biological properties especially antidepressant [1], antitumor [2], antiparasitic [3], antifungal [4], bactericidal [5], antiallergic [6] and antiinflammatory effects [7].

Many authors have proposed various procedures to obtain pyrazolo[1,5-*d*][1,2,4]triazines [8-15] but no pyrazolotriazin-4-ones hydrogenated in the 3 and 3a-positions and bearing an aryl substituent on the pyrazoline ring were described. We report in this paper a simple synthesis of this new bicyclic ring system by the methods shown in Scheme 1. 3-Aroylacrylic acids **2** were prepared by Friedel-

Scheme 1



Scheme 2

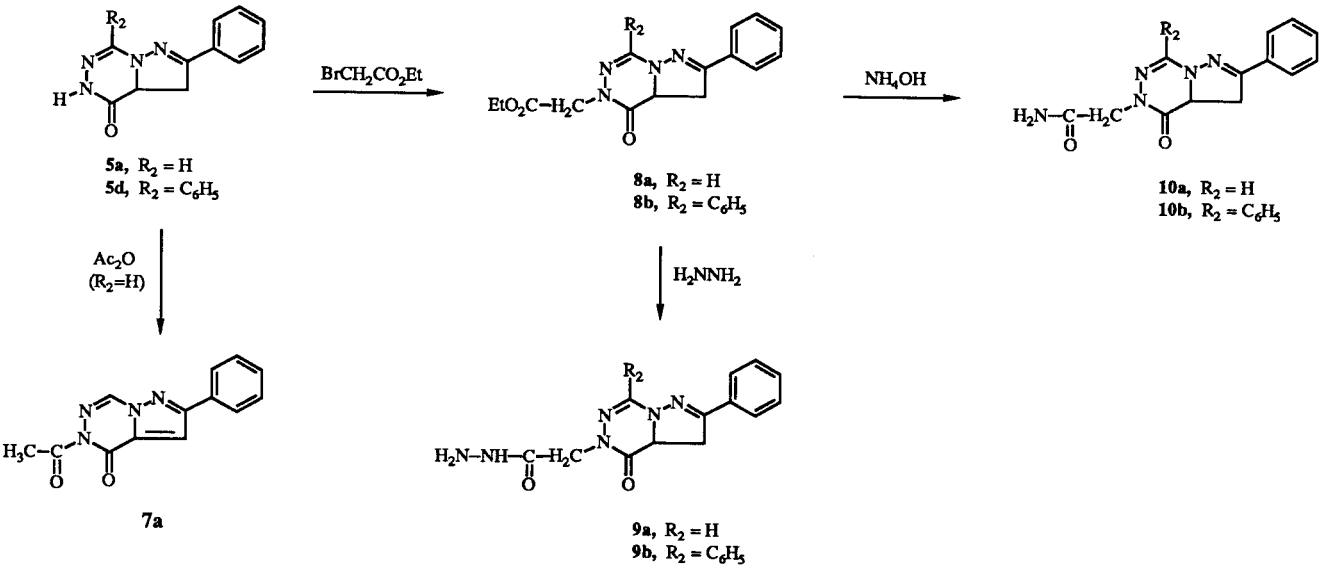


Table 1

Physical and analytical data for Compounds **5,6,7,8,9** and **10**

Compound No.	R_1	R_2	Mp (C°)	Yield %	Molecular Formula (MW)	Analysis Calcd./Found % C	H	N	Cl
5a	H	H	215	68	$C_{11}H_{10}N_4O$ (214)	61.68 61.64	4.67 4.53	26.17 26.28	
5b	H	CH_3	236	77	$C_{12}H_{12}N_4O$ (228)	63.16 62.95	5.26 5.33	24.56 24.41	
5c	H	C_2H_5	177	67	$C_{13}H_{14}N_4O$ (242)	64.46 64.53	5.79 5.63	23.14 23.02	
5d	H	C_6H_5	210	45	$C_{17}H_{14}N_4O$ (290)	70.34 70.35	4.83 4.90	19.31 19.23	
5e	OCH_3	H	220	67	$C_{12}H_{12}N_4O_2$ (244)	59.02 58.83	4.92 4.82	22.95 22.88	
5f	OCH_3	CH_3	204	88	$C_{13}H_{14}N_4O_2$ (258)	60.46 60.39	5.43 5.28	21.71 21.81	
5g	OCH_3	C_2H_5	214	66	$C_{14}H_{16}N_4O_2$ (272)	61.76 61.76	5.88 5.93	20.59 20.42	
5h	OCH_3	C_6H_5	190	47	$C_{18}H_{16}N_4O_2$ (320)	67.50 67.64	5.00 4.92	17.50 17.40	
5i	Cl	H	258	80	$C_{11}H_9N_4ClO$ (248.5)	53.12 53.14	3.62 3.69	22.54 22.75	14.28 14.10
5j	Cl	CH_3	228	45	$C_{12}H_{11}N_4ClO$ (262.5)	54.86 55.06	4.19 3.92	21.33 21.32	13.52 13.81
5k	Cl	C_2H_5	195	43	$C_{13}H_{13}N_4ClO$ (276.5)	56.42 56.33	4.70 4.72	20.25 19.94	12.84 13.02
5l	Cl	C_6H_5	225	15	$C_{17}H_{13}N_4ClO$ (324.5)	62.86 62.83	4.01 3.95	17.26 17.15	10.94 11.07
6a	H	H	263	78	$C_{11}H_8N_4O$ (212)	62.26 62.15	3.77 3.69	26.42 26.30	
6b	OCH_3	H	287	66	$C_{12}H_{10}N_4O_2$ (242)	59.50 59.40	4.13 4.04	23.14 23.29	
6c	Cl	H	255	60	$C_{11}H_7N_4ClO$ (246.5)	53.55 53.61	2.84 2.97	22.72 22.68	14.40 14.33
7a	H	H	262	27	$C_{13}H_{10}N_2N_4O_2$ (254)	61.42 61.31	3.93 3.86	22.05 21.91	
8a	H	H	108	56	$C_{15}N_{16}N_4O_3$ (300)	60.00 59.95	5.33 5.27	18.67 18.56	
8b	H	C_6H_5	176	97	$C_{21}H_{20}N_4O_3$ (376)	67.02 67.12	5.32 5.13	14.89 14.86	
9a	H	H	154	33	$C_{13}H_{14}N_6O_2$ (286)	54.55 54.68	4.89 4.80	29.37 29.32	
9b	H	C_6H_5	255	64	$C_{19}H_{18}N_6O_2$ (362)	62.98 62.80	4.97 4.98	23.21 23.34	
10a	H	H	150	76	$C_{13}H_{13}N_5O_2 \cdot 2H_2O$ (307)	50.81 50.75	5.54 5.68	22.80 22.87	
10b	H	C_6H_5	220	36	$C_{19}H_{17}N_5O_2$ (347)	65.71 65.62	4.90 4.85	20.17 20.29	

Crafts acylation using maleic anhydride [16]. After esterification of acrylic acids, the resulting derivatives **3** were treated with hydrazine hydrate to produce 4,5-dihydropyrazole carboxylic acid hydrazides **4**. Condensation of compounds **4** with orthoesters afforded the expected dihydropyrazolotriazinones **5**. On continued heating in DMF for 60 hours, compounds **5** were dehydrogenated in the 3 and 3a-positions and led to pyrazolotriazinones **6**.

The analogy of these compounds with *N*-substituted pyridazinones that exhibited anticonvulsant properties [17] prompted us to prepare some pyrazolotriazinone derivatives substituted in the 5-position by acetyl, hydrazide and amide chains (Scheme 2). Acetylation of compound **5a** was performed with acetic anhydride; simultaneous dehydrogenation of the pyrazoline nucleus occurred under reflux and acetyl derivative **7a** was obtained. Treatment of

Table 2

IR and ^{1}H-NMR for Compounds **5, 6, 7, 8, 9**and **10**

Compound No.	IR (KBr) ν (cm^{-1}) NH	C=O	C=N C=C	^{1}H-NMR (DMSO-d_6) δ (ppm)
5a	3200	1660	1640, 1610 1580, 1460	3.6 (m, 2H, CH_2), 4.8 (m, 1H, CH), 7.6 (m, 5H, C_6H_5), 7.8 (s, 1H, =CH), 10.7 (br s, 1H, NH)
5b	3240	1670	1610, 1580 1455	2.2 (s, 3H, CH_3), 3.5 (m, 2H, CH_2), 4.7 (m, 1H, CH), 7.7 (m, 5H, C_6H_5), 10.4 (br s, 1H, NH)
5c	3200	1660	1600, 1580 1450	1.3 (t, 3H, CH_3), 2.7 (q, 2H, CH_2), 3.6 (m, 2H, CH_2), 4.7 (m, 1H, CH), 7.7 (m, 5H, C_6H_5), 10.4 (br s, 1H, NH)
5d	3220	1660	1605, 1590 1500, 1450	3.8 (m, 2H, CH_2), 5.0 (m, 1H, CH), 7.7 (m, 10H, $2C_6H_5$), 11.2 (br s, 1H, NH)
5e	3220	1675	1610, 1580 1510, 1460	3.6 (m, 2H, CH_2), 3.8 (s, 3H, OCH_3), 4.7 (m, 1H, CH), 7.4 (m, 4H, C_6H_4), 7.8 (s, 1H, =CH), 10.6 (br s, 1H, NH)
5f	3260	1680	1600, 1510 1470	2.3 (s, 3H, CH_3), 3.5 (m, 2H, CH_2), (m, 2H, CH_2), 3.9 (s, 3H, OCH_3), 4.7 (m, 1H, CH), 7.5 (m, 4H, C_6H_4), 10.0 (br s, 1H, NH)
5g	3240	1670	1610, 1580 1510, 1460	1.3 (t, 3H, CH_3), 2.8 (q, 2H, CH_2), 3.6 (m, 2H, CH_2), 4.0 (s, 3H, OCH_3), 4.7 (m, 1H, CH), 7.5 (m, 4H, C_6H_4), 10.6 (br s, 1H, NH)
5h	3260	1670	1610, 1570 1440	3.8 (m, 2H, CH_2), 3.9 (s, 3H, OCH_3), 5.1 (m, 1H, CH), 7.5 (m, 9H, C_6H_5, C_6H_4), 11.1 (br s, 1H, NH)
5i	3200	1660	1620, 1580 1470	3.5 (m, 2H, CH_2), 4.8 (m, 1H, CH), 7.6 (m, 4H, C_6H_4), 7.8 (s, 1H, =CH), 10.7 (br s, 1H, NH)
5j	3220	1670	1610, 1580 1470	2.2 (s, 3H, CH_3), 3.5 (m, 2H, CH_2), 4.7 (m, 1H, CH), 7.6 (m, 4H, C_6H_4), 10.3 (br s, 1H, NH)
5k	3260	1680	1620, 1580 1450	1.2 (t, 3H, CH_3), 3.4 (q, 2H, CH_2), 3.5 (m, 2H, CH_2), 4.8 (m, 2H, CH_2), 7.7 (m, 4H, C_6H_4), 10.6 (br s, 1H, NH)
5l	3300	1660	1590, 1570 1480	3.6 (m, 2H, CH_2), 5.0 (m, 1H, CH), 7.6 (m, 9H, C_6H_5, C_6H_4), 11.2 (br s, 1H, NH)
6a	3200	1660	1610, 1550 1450	7.7 (m, 5H, C_6H_5), 7.8 (s, 1H, $=C_3H$), 9.1 (s, 1H, $=C_7H$), 12.6 (br s, 1H, NH)
6b	3200	1660	1600, 1560 1430	3.9 (s, 3H, OCH_3), 7.7 (m, 4H, C_6H_4), 7.9 (s, 1H, $=C_3H$), 9.2 (s, 1H, $=C_7H$), 12.3 (br s, 1H, NH)
6c	3200	1670	1600, 1500 1450	7.8 (m, 4H, C_6H_4), 8.2 (s, 1H, $=C_3H$), 9.1 (s, 1H, $=C_7H$), 13.1 (br s, 1H, NH)
7a	-	1765 1690	1630, 1550 1470	2.5 (s, 3H, CH_3), 7.9 (m, 5H, C_6H_5), 8.0 (s,1H, $=C_3H$), 9.2 (s, 1H, $=C_7H$)
8a	-	1740 1670	1615, 1600 1445	1.2 (t, 3H, CH_3), 3.4 (m, 2H, CH_2), 4.1 (q, 2H, OCH_2), 4.3 (s, 2H, NCH_2), 4.8 (m, 1H, CH), 7.5 (m, 5H, C_6H_5), 7.9 (s, 1H, =CH)
8b	-	1750 1670	1600, 1550 1450	1.3 (t, 3H, CH_3), 3.8 (m, 2H, CH_2), 4.2 (q, 2H, OCH_2), 4.7 (s, 2H, NCH_2), 5.1 (m, 1H, CH), 7.9 (m, 10H, $2C_6H_5$)
9a	3300	1660 1625	1590, 1500 1450	3.3 (m, 2H, CH_2), 3.9 (br s, 2H, NH_2), 4.2 (s, 2H, NCH_2), 4.3 (m, 1H, CH), 7.5 (m, 6H, C_6H_5, =CH), 9.3 (br s, 1H, NH)
9b	3310	1660 1625	1590, 1500 1450	3.9 (m, 2H, CH_2), 4.3 (br s, 2H, NH_2), 4.4 (s, 2H, NCH_2), 5.2 (m, 1H, CH), 7.7 (m, 10H, $2C_6H_5$), 9.4 (br s, 1H, NH)
10a	3300	1690 1660	1600, 1450	3.6 (m, 2H, CH_2), 3.9 (s, 2H, NCH_2), 4.2 (m, 1H, CH), 7.6 (m, 6H, C_6H_5, =CH), 8.0 (br s, 6H, NH_2, $2H_2O$)
10b	3410	1690 1650	1600, 1500 1450	3.9 (m, 2H, CH_2), 4.4 (s, 2H, NCH_2), 5.1 (m, 1H, CH), 6.9 (br s, 2H, NH_2), 7.9 (m, 10H, $2C_6H_5$)

5a and **5d** with ethyl bromoacetate gave the corresponding 5-substituted pyrazolotriazinones **8a** and **8b**, which were hydrolysed by hydrazine hydrate or aqueous ammonia to give hydrazides **9a-b** or amides **10a-b**, respectively.

The structure of compounds **5**, **6**, **7**, **8**, **9** and **10** was established from their analytical and spectral data (Tables 1, 2, 3). In Table 3 we only reported selected data of the ^{13}C nmr spectra.

Derivatives **7**, **9** and **10** were evaluated for anticonvulsant activity against electrically induced seizures. In the maximal electroshock test [18], the only pyrazolotriazinones which displayed any noteworthy anticonvulsant effects, were **9a** and **10b**. At 10 mg/kg orally, both com-

pounds protected against seizures in 42% of the animals.

Table 3

^{13}C-NMR for Compounds **5** and **6**

Compound No.	C_3	C_{3a}	C_7	C_2	C_4
5a	35.6	56.5	135.3	153.4	162.3
5b	35.4	56.6	143.1	152.5	162.6
5c	35.1	56.7	147.2	152.4	162.8
5d	36.0	56.3	144.3	151.7	163.8
5e	35.8	56.4	135.4	153.2	162.2
5f	35.5	56.6	144.1	154.1	162.3
5g	35.4	56.6	147.1	152.4	162.9
5h	36.1	56.1	144 4	151 6	163.7
5i	35.6	56.7	135.2	152.4	162.3
5j	35.3	56.7	143.1	151.7	162.7
5k	35.2	56.9	147.1	151.5	162.9
5l	36.0	56.5	144.2	150.8	163.7
6a	102.6	135.4	130.3	154.3	154.4
6b	102.0	135.4	130.2	154.3	154.4
6c	102.7	135.5	130.2	153.2	154.2

EXPERIMENTAL

All melting points were determined on a Reichert apparatus and are uncorrected. The infrared spectra were recorded on a Beckman 4240 spectrophotometer. The proton nmr spectra were recorded on a Varian EM 360 A in DMSO-d_6. Resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The nmr peaks were designated as follows: s, singlet; br s, broad singlet; t, triplet; q, quadruplet; m, multiplet. The ^{13}C nmr spectra were recorded on a Jeol FX 60 in DMSO-d_6. Elemental analysis were performed at the Service Central d'Analyses, Centre National de la Recherche Scientifique, 69390 Vernaison, France. Esters **3** were prepared from aroylacrylic acids using the method of Delaby [19].

3-Aryl-4,5-dihydropyrazole-5-carboxylic Acid Hydrazides **4**.

Pyrazolecarboxylic acid hydrazides **4** were synthesized using literature procedures [19,20].

2-Aryl-3,3a-dihydro-4-oxo-5*H*-pyrazolo[1,5-*d*][1,2,4]triazines and 7-substituted Derivatives **5a-l**.

A solution of 0.05 mole of compound **4** and 0.05 mole of the appropriate orthoester in 30 ml of DMF was refluxed for 4 hours. In most cases, the crude products precipitated after cooling and were filtered; otherwise the solvent was evaporated under reduced pressure and the residual mixture triturated with ethyl ether. Crude products were recrystallized from DMF (**5a-c**, **5e-g**, **5i**) or ethanol (**5d**, **5h**, **5j-l**).

2-Aryl-4-oxo-5*H*-pyrazolo[1,5-*d*][1,2,4]triazines **6a-c**.

A solution of 0.05 mole of the appropriate compound **5** in 30 ml of DMF was refluxed for 60 hours. After evaporation *in vacuo*, the crude product was washed with ethyl ether and recrystallized from methanol.

5-Acetyl-2-phenyl-4-oxopyrazolo[1,5-*d*][1,2,4]triazine **7a**.

A solution of 2.14 g (0.01 mole) of pyrazolo[1,5-*d*][1,2,4]triazin-4(5*H*)-one **5a** in 30 ml of acetic anhydride was heated under reflux for 1 hour. Then the solution was cooled and the crude product which separated was filtered off and recrystallized from ethanol.

2-Phenyl-3,3a-dihydro-4-oxopyrazolo[1,5-*d*][1,2,4]triazin-5-ylacetic Acid Ethyl Ester **8a** and 7-Phenyl Derivative **8b**.

A mixture of 0.01 mole of the compound **5a** or **5d**, 2.5 g (0.015 mole) of ethyl bromoacetate and 2.0 g (0.015 mole) of anhydrous potassium carbonate in acetone (100 ml) was refluxed under stirring for 24 hours in an oil-bath. The mixture was filtered hot, the filtrate was evaporated to dryness *in vacuo*, and the residue was triturated with diisopropyl ether. Compounds **8a** and **8b** were recrystallized from ethanol.

[2-Phenyl-3,3a-dihydro-4-oxopyrazolo[1,5-*d*][1,2,4]triazin-5-yl]-acetohydrazide **9a** and 7-Phenyl Derivative **9b**.

A mixture of the ester **8a** or **8b** (0.01 mole) in 20 ml of hydrazine hydrate and 20 ml of ethanol was refluxed for 4 hours. Then the mixture was cooled and the crude product which separated was filtered off and recrystallized from ethanol.

[2-Phenyl-3,3a-dihydro-4-oxopyrazolo[1,5-*d*][1,2,4]triazin-5-yl]-acetamide **10a** and 7-Phenyl Derivative **10b**.

A suspension of 0.005 mole of ester **8a** or **8b** in concentrated aqueous ammonia (15 ml) and ethanol (5 ml) was heated in a bomb apparatus at 100° for 24 hours. After cooling, the solvent was evaporated to dryness *in vacuo*. The solid residue was triturated with ethyl ether, until crystallization. Compounds **10a-b** were recrystallized from ethanol.

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