Indole Derivatives. 1. Synthesis of Tetracyclic Mesoionic Pyrimido[3,2:2′,3′]-*as*-triazino[5′,6′-*b*]indole-2,4-diones

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The synthesis of the title compounds **5** has been accomplished by the thermal cyclocondensation of bis(2,4,6-trichlorophenyl) malonates with the appropriately substituted alkyl or arylalkylaminotriazinoindole.

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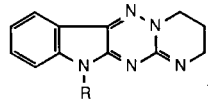
Introduction.

The pyrimido-*as*-triazinedione ring is of biological interest since it is an integral feature in the structure of a number of biochemically active compounds *e.g.* naturally occurring antibiotics fervenulin and related agents [1-5]. Certain tetracyclic heteroaromatic compounds of the type **1** which possess the pyrimido-*as*-triazine moiety fused to an indole nucleus were reported to exhibit significant antibacterial and antiviral activities [6]. We reasoned that structurally similar compounds **5** bearing a mesoionic pyrimidinedione moiety would show interesting biological properties [7]. As part of our on-going interest [8-12] in heteroaryl-fused mesoionic compounds as possible source of pharmacollogically active agents, we now report the synthesis and spectral properties of some novel mesoionic pyrimido-*as*-triazinoindole derivatives **5a-l**, which to our knowledge, have not yet been described in the literature.

Results and Discussion.

Compounds **5** were conveniently prepared in good yields by the thermal (160°) condensation of an alkyl or arylalkylaminotriazinoindole **3** [13] with an equimolar quantity of previously reported bis(2,4,6-trichlorophenyl) malonate **4a-d** [14]. Twelve mesoionic compounds **5a-l** were prepared as shown (Scheme 1). The currently accepted nomenclature for mesoionic indoles of type **5a-l** is anhydro(1-substituted-2-hydroxy-4-oxopyrimido[3,2:2′,3′]-*as*-triazino[5′,6′-*b*]indolium hydroxide). Reaction yields and some physical data for the compounds prepared are summarized in Tables 1 and 2.

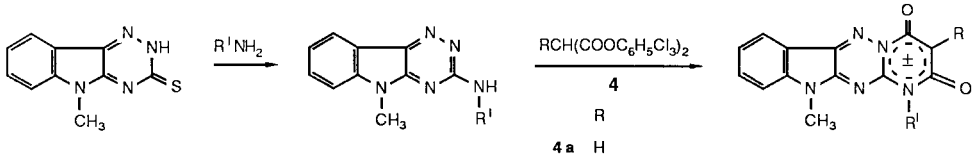


R = alkyl or arylalkyl

1

The mesoionic compounds are highly colored and are relatively soluble in most common organic solvents such as acetone, acetonitrile, chloroform and ethanol [15]. Structural assignments were based on spectral and elemental analysis. The infrared spectra of compounds **5** display two absorption bands in the carbonyl stretching region at 1690-1680 cm^{-1} and 1655-1630 cm^{-1}. The uv spectra of the mesoionic compounds **5** show two band absorption maxima at about 330 and 450 nm. The molecular ion peak in the mass spectra of the mesoionic analogs of this series are fully consistent with those expected for the assigned structures. In addition, the fragmentation observed appear to vary with substitution at N-1 and C-3. Furthermore, the usefulness of mass spectrometry for distinguishing between pairs of isomeric heterocycles *e.g.* **3h/3i, 5b/5c**

Scheme 1



2 **3** **5a - l**

	R′
3a	$C_6H_5CH_2$
3b	$C_6H_5CH_2CH_2$
3c	$CH_3(CH_2)_3$
3d	$CH_3(CH_2)_4$
3e	$CH_3(CH_2)_5$
3f	$CH_3(CH_2)_6$
3g	$CH_3(CH_2)_7$
3h	*o*-$FC_6H_4CH_2$
3i	*p*-$FC_6H_4CH_2$

4

	R
4a	H
4b	CH_3
4c	CH_3CH_2
4d	$C_6H_5CH_2$

Table 1

Properties of 3-Amino-*as*-triazino[5,6-*b*]indoles **3** and Mesoionic Pyrimido[3,2:2′,3′]-*as*-triazino[5′,6′-*b*]indoles **5**

	R	R′	Yield [a] (%)	Mp (°C)	Recrystallization Solvent [b]	Color	Formula	Analyses (%) Calcd./(Found) C	H	N
3h	*o*-$FC_6H_4CH_2$	–	79	199-200	AE	off white	$C_{17}H_{14}N_5F \cdot 1/3H_2O$	65.17 (65.13)	4.72 (4.65)	22.35 (22.31)
3i	*p*-$FC_6H_4CH_2$	–	54	188-189	AE	light yellow	$C_{17}H_{14}N_5F$	66.44 (66.58)	4.59 (4.64)	22.79 (22.70)
5a	$C_6H_5CH_2CH_2$	CH_3CH_2	92	278-280	TP	red-brown	$C_{23}H_{21}N_5O_2$	69.16 (68.92)	5.30 (5.34)	17.53 (17.46)
5b	$C_6H_5CH_2CH_2$	H	98	250-252	TP	rust	$C_{21}H_{17}N_5O_2 \cdot 1/2H_2O$	66.31 (66.21)	4.77 (4.75)	18.41 (18.26)
5c	$C_6H_5CH_2$	CH_3	94	315-316	TP	brick red	$C_{21}H_{17}N_5O_2$	67.91 (67.81)	4.62 (4.68)	18.86 (18.81)
5d	$C_6H_5CH_2$	CH_3CH_2	88	272-274	TP	rust	$C_{22}H_{19}N_5O_2 \cdot 15/8H_2O$	63.03 (63.09)	5.47 (5.29)	16.71 (16.76)
5e	$CH_3(CH_2)_3$	CH_3CH_2	98	237-238	TP	brick red	$C_{19}H_{21}H_5O_2$	64.94 (64.70)	6.02 (6.07)	19.93 (19.85)
5f	$CH_3(CH_2)_4$	CH_3CH_2	91	280-281	TP	shiny red	$C_{20}H_{23}N_5O_2 \cdot 1/2H_2O$	64.15 (64.01)	6.41 (6.23)	18.56 (18.69)
5g	$CH_3(CH_2)_5$	CH_3CH_2	85	241-242	TP	brick red	$C_{21}H_{25}N_5O_2 \cdot 2/3H_2O$	64.43 (64.60)	6.78 (6.54)	17.89 (17.84)
5h	$CH_3(CH_2)_6$	CH_3CH_2	94	153-155	TP	brick red	$C_{22}H_{27}N_5O_2 \cdot 5/4H_2O$	63.50 (63.55)	7.15 (6.98)	16.83 (16.78)
5i	$CH_3(CH_2)_7$	CH_3CH_2	75	150-151	TP	brick red	$C_{23}H_{29}N_5O_2 \cdot 3/4H_2O$	65.62 (65.53)	7.30 (7.12)	16.63 (16.53)
5j	*o*-$FC_6H_4CH_2$	CH_3CH_2	91	286	TP	dark red	$C_{22}H_{18}N_5O_2F \cdot 7/8H_2O$	63.04 (63.03)	4.75 (4.61)	16.71 (16.47)
5k	*p*-$FC_6H_4CH_2$	CH_3CH_2	76	274-275	TP	rust	$C_{22}H_{18}N_5O_2F \cdot H_2O$	62.70 (62.72)	4.78 (4.75)	16.61 (16.56)
5l	$C_6H_5CH_2$	$C_6H_5CH_2$	74	248-250	TP	red	$C_{26}H_{27}N_5O_2 \cdot 1/3H_2O$	69.80 (69.90)	6.17 (6.20)	15.65 (15.65)

[a] Yield refers to the final malonate condensation step. [b] Recrystallization solvents: absolute ethanol (AE), tetrahydrofuran-petroleum ether (TP).

Table 2

Spectral Data of Compounds **3** and **5**

Compound	^{1}H-NMR (δ ppm [a])	UV max (log e) [b]	IR (cm^{-1}) [c] ν NH	ν C=O	MS m/e (%)
3n	3.4 (s, 1H, NH exchanged with deuterium oxide) 3.7 (s, 3H, CH_3) 4.8 (d, 2H, NCH_2C, J = 4.5 Hz, collapses to a singlet at 4.8 upon deuteration) 7.0-8.4 (m, 8H, Ar-H) [A]		3250		307 (M^+, 100), 289 (5), 253 (4), 181 (5), 153 (4), 125 (10)
3i	3.5 (s, 1H, NH, exchanges with deuterium oxide) 3.8 (s, 3H, CH_3) 4.7 (d, 2H, NCH_2 C, J = 4.5 Hz, collapses to a singlet at 4.8 upon deuteration) 6.9-8.4 (m, 8H, ArH) [A]		3250		307 (M^+, 100), 267 (20), 223 (10), 159 (8), 132 (4)
5a	1.3 (t, CH_3, CCH_3, J = 6 Hz) 2.9 (q, 2H, ethyl-CH_2, J = 6 Hz) 3.3 (t, 2H, benzyl-CH_2 , J = 4 Hz) 4.1 (s, 3H, N-CH_3) 5.2 (t, 2H, α-CH_2, protons of $PhCH_2CH_2$, J = 4 Hz) 7.1-8.6 (m, 9H, ArH) [B]	325 (3.85) 450 (3.66)		1630 1700	399 (M^+, 60), 303 (100), 304 (50), 138 (20)
5b	3.3 (t, 2H, benzyl-CH, J = 4 Hz) 4.1 (s, 3H, CH_3) 5.1 (t, 2H, α-CH_2-protons of $PhCH_2CH_2$, J = 4 Hz) 6.5 [s, 1H, C(3)-H] 7.0-8.6 (m, 9H, ArH) [B]	343 (3.92) 450 (3.60)		1650 1700	371 (M^+, 4), 304 (10), 212 (100), 199 (95), 102 (5)

Table 2 (continued)

Compound	^{1}H-NMR (δ ppm [a])	UV max (log e) [b]	IR (cm^{-1}) [c] ν NH	ν C=O	MS m/e (%)
5c	2.5 (s, 3H, CCH_3) 4.2 (s, 3H, N-CH_3) 6.0 (s, 2H, benzyl-CH_2) 7.2-8.6 (m, 9H, ArH) [B]	325 (3.95) 450 (3.85)		1640 1700	371 (M^+, 5), 289 (10), 184 (8), 143 (7), 91 (100), 65 (30)
5d	1.3 (t, 3H, CCH_3, J = 4 Hz) 2.9 (q, 2H, ethyl CH_2, J = 4 Hz) 4.2 (s, 3H, NCH_3) 6.0 (s, 2H, benzyl CH_2) 7.2-8.6 (m, 9H, ArH) [B]	336 (3.89) 450 (3.64)		1640 1690	385 (M^+, 4), 289 (7), 211 (5), 185 (10), 91 (100), 65 (25)
5e	1.0-2.3 (m, 10 H, 2CCH_3 and $NCCH_2CH_2$) 2.9 (q, 2H, ethyl-CH_2, J = 4 Hz) 4.1 (s, 3H, NCH_3) 4.8 (t, 2H, NCH_2C, J = 4 Hz) 7.7-8.6 (m, 4H, ArH) [B]	323 (3.95) 450 (3.78)		1650 1690	351 (M^+, 5), 294 (15), 255 (100), 224 (22), 175 (40), 135 (20)
5f	0.9-2.3 [m, 12H, 2 x CCH_3 and $NC(CH_2)_3$] 2.9 (q, 2H, ethyl-CH_2, J = 6 Hz) 4.2 (s, 3H, N-CH_3) 4.8 (t, 2H, NCH_2C, J = 4 Hz) 7.7-8.6 (m, 4H, ArH) [B]	333 (4.18) 450 (4.08)		1645 1700	365 (M^+, 10), 300 (20), 269 (100), 218 (20), 167 (50), 133 (5)
5g	0.8-2.3 [m, 14H, 2 x CCH_3 and $NC(CH_2)_4$] 2.9 (q, 2H, ethyl-CH_2, J = 6 Hz) 4.1 (s, 3H, N-CH_3) 4.8 (t, 2H, NCH_2C, J = 4 Hz) 7.7-8.6 (m, 4H, ArH) [B]	325 (3.80) 450 (3.68)		1640 1690	379 (M^+, 30), 353 (50), 284 (30) 260 (48), 225 (58), 167 (100)
5h	0.7-2.2 [m, 16H, 2 x CCH_3 and $NC(CH_2)_5$] 2.9 (q, 2H, ethyl-CH_2, J = 6 Hz) 4.1 (s, 3H, NCH_3) 4.8 (t, 2H, NCH_2C, J = 4 Hz) 7.7-8.6 (m, 4H, ArH) [B]	323 (3.76) 450 (3.63)		1650 1690	393 (M^+, 10), 354 (95), 298 (50), 260 (70), 219 (90), 166 (100), 134 (40)
5i	0.7-2.3 [m, 18H, 2 x CCH_3 and $NC(CH_2)_6$] 2.9 (q, 2H, ethyl-CH_2, J = 6 Hz) 4.1 (s, 3H, NCH_3) 4.8 (t, 2H, NCH_2C, J = 4 Hz) 7.7-8.6 (m, 4H, ArH) [B]	321 (3.75) 450 (3.62)		1640 1700	407 (M^+ 80), 311 (100), 267 (30), 144 (20)
5j	1.4 (t, 3H, CCH_3, J = 4 Hz) 2.9 (q, 2H, CCH_2C, J = 4 Hz) 4.1 (s, 3H, NCH_3) 6.1 (s, 2H, NCH_2C) 7.0-8.6 (m, 8H, ArH) [B]	321 (3.69) 450 (3.53)		1650 1700	403 (M^+, 5), 353 (20), 307 (25), 237 (22), 212 (100), 165 (30)
5k	1.3 (t, 3H, CCH_3, J = 4 Hz) 2.9 (q, 2H, CCH_2C, J = 4 Hz) 4.1 (s, 3H, NCH_3) 6.1 (s, 2H, NCH_2C) 7.0-8.6 (m, 8H, ArH) [B]	325 (3.81) 450 (3.70)		1655 1700	403 (M^+, 70), 353 (50), 300 (30), 262 (30), 218 (50), 166 (100), 144 (55)
5l	0.7-2.2 [m, 1H, $C(CH_2)_4CH_3$] 4.1 (s, NCH_3) partially overlapped with 4.5 (s, benzyl-CH_2) (total area 5H) 4.8 (t, 2H, NCH_2C, J = 4 Hz) 7.1-8.6 (m, 8H, ArH) [B]	323 (3.45) 450 (3.50)		1600 1700	441 (M^+, 5), 400 (5), 358 (100), 283 (85), 189 (3), 160 (8)

[a] Measured solvents: [A] Deuteriodimethyl sulfoxide. [B] Deuteriotrifluoroacetic acid. [b] Measured solvent: Ethanol. [c] Recorded as potassium bromide disks.

and **5j/5k** was confirmed [16].

Studies on the biological activities of the mesoionic compounds described in this paper are in progress and will be reported elsewhere.

EXPERIMENTAL

Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. All compounds were prepared using starting materials obtained from either commercially available sources or made by standard literature procedures. Reagent grade solvents were used in all reactions and column chromatographic separations. The solvents were freshly distilled before use. Thin-layer chromatography (tlc) was performed on tlc plates precoated with silica gel 13181 (Eastman Kodak Co., Rochester, New York). The visualization of products in thin-layer chromatograms was accomplished by uv absorbance or iodine.

Infrared spectra (ir) were recorded as potassium bromide disks on a

Perkin-Elmer 283 spectrophotometer and an AEI MS-9 mass spectrometer was used for mass spectra. Proton magnetic resonance spectra (^{1}H nmr) were obtained with either a Varian T-60 or a JEOL FX900II spectrometer. The concentration of the samples was approximately 35 mg/0.5 ml of dimethyl-d_6 sulfoxide (DMSO-d_6) or deuteriotrifluoroacetic acid as specified. All ^{1}H nmr spectra were obtained using 5 mm spinning tubes and signals were referenced to internal tetramethylsilane (TMS). Coupling constants (J) are given in Hertz. The ^{1}H nmr signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad singlet. Ultraviolet spectra (uv) were recorded on a Beckman Acta MVII spectrophotometer using either spectrograde or purified solvents. Results are expressed as max in nanometers (nm).

Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia.

Preparation of 3-Aminotriazinoindoles **3**, General Procedure.

A solution of 5-methyl-5*H*-*as*-triazino[5,6-*b*]indole-3-thione **2** [17] and the appropriate primary amine (3 ml/g of thione) was heated at 160-180° until the evolution of hydrogen sulfide was complete (5-6 hours). The reaction mixture was cooled to room temperature and stirred with excess water. The solid product was filtered off, washed with water, dried and recrystallized from ethanol. Melting points for compounds **3a-g** were consistent with those reported [13]. Physical data for the new compounds (**3h** and **3i**) are summarized in Tables 1 and 2.

Preparation of Anhydro(2-hydroxy-4-oxopyrimido[3,2:2',3']-*as*-triazino-[5',6'-*b*]indolium Hydroxide) **5**, General Procedure.

An intimate mixture of bis(2,4,6-trichlorophenyl) malonate **4** [14] (10 mmole) and appropriate 3-aminotriazinoindole **3** (10 mmole) was heated neat at 160°, under an atmosphere of nitrogen, until a clear melt resulted (2 minutes). When cool, the resultant gum was triturated with anhydrous ether to afford a crude solid product. Recrystallization from tetrahydrofuran-petroleum ether mixture gave the mesoionic compound **5** (Table 1).

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[15a] For convenience, the ^{1}H NMR and UV spectra of **5** were obtained in deuteriotrifluoroacetic acid and 95% ethanol as solvents respectively; [b] This work has been reported, in part, at the 44th Joint Annual Meeting of the National Institutes of Science Beta Kappa Chi Scientific Honor Society and Brookhaven Semester Program in Dallas, Texas, April 1987.

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