Polyazasteroids II. (I). 1,2,4-Triazolo[3′,4′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)ones, Imidazo[2′,1′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)ones and 2,3-Dihydroimidazo[2′,1′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)ones

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Starting with 2-substituted quinoline-3,4-dicarboxylic acids, a series of substituted 1,2,3,4-tetrahydropyrimido[4,5-*c*]quinolinone-3-thiones were obtained. The latter compounds were converted to the three novel polyazasteroid series: 1,2,4-Triazolo[3′,4′:2,3]pyrimido[4,5-*c*]-quinolin-11(12*H*)ones, imidazo[2′,1′:2,3]pyrimido[4,5*c*]quinolin-11(12*H*)ones and 2,3-dihydro-imidazo[2′,1′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)ones. The intermediate 3-hydrazino-1,2-dihydropyrimido[4,5-*c*]quinolinones and nitrous acid gave the 3-azido derivatives rather than the tetrazolo compounds.

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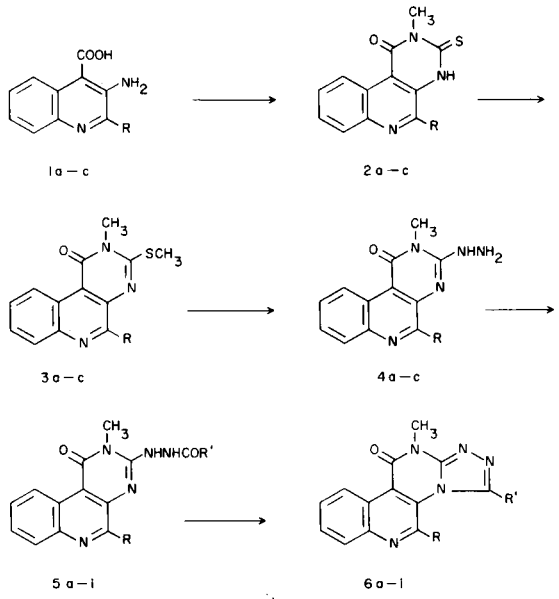
Increasing interest in azasteroidal compounds led us to initiate studies on the synthesis of several new types of polyazasteroids.

The synthesis of the first series of selenadiazasteroids was recently reported (2).

In the present work, the synthesis of three new series of polyazasteroids based on 1,2,3,4-tetrahydropyrimido-[4,5-*c*]quinolinone-3-thiones (**2a-c**) is reported. The intermediates, 2-substituted quinoline-3,4-dicarboxylic acids, were obtained through the reaction of isatin and the appropriate β-ketoesters in alkaline solutions (3). The imides of 2-substituted quinoline-3,4-dicarboxylic acids were prepared through heating the diacids with urea (4). Further treatment of the imides with potassium hypobromite gave the desired 2-substituted 3-aminoquinoline-4-carboxylic acids (**1a-c**) (4). The amino acids **1** and methyl isothiocyanate were allowed to react in the presence of triethylamine and led to the formation of 5-substituted 2-methyl-3-mercapto-1,2-dihydropyrimido[4,5*c*]quinolin-1-(2*H*)ones (**2a-c**). *S*-Methylation of compounds **2** in alkaline solutions gave the corresponding 3-methylthio derivatives **3a-c**. The latter compounds were hydrazinolyzed to give a series of 5-sustituted 2-methyl-hydrazino-1,2-dihydropyrimido[4,5-*c*]quinolin-1-(2*H*)ones (**4a-c**). *Ortho* esters and hydrazino compounds**4** failed to give the desired 1,2,4-triazolo[3′,4′:2,3]pyrimido[4,5-*c*]-quinolin-11(12*H*)ones (**5a-c**). Aliphatic acids and hydrazines **4** after several hours of refluxing gave the hydrazides **5a-i**. Ring closure of hydrazides **5** with polyphosphoric acid led to the formation of compounds **5**, which constitute a new series of polyazasteroids (see Schemes I and II).

The reaction of 2-methyl-3-hydrazino-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)ones (**4a-c**) with nitrous acid was of special interest. The "azido-tetrazole" equilibrium existing in similar reactions (5) had to be studied in this series. In each case, the solid which separated exhibited a strong

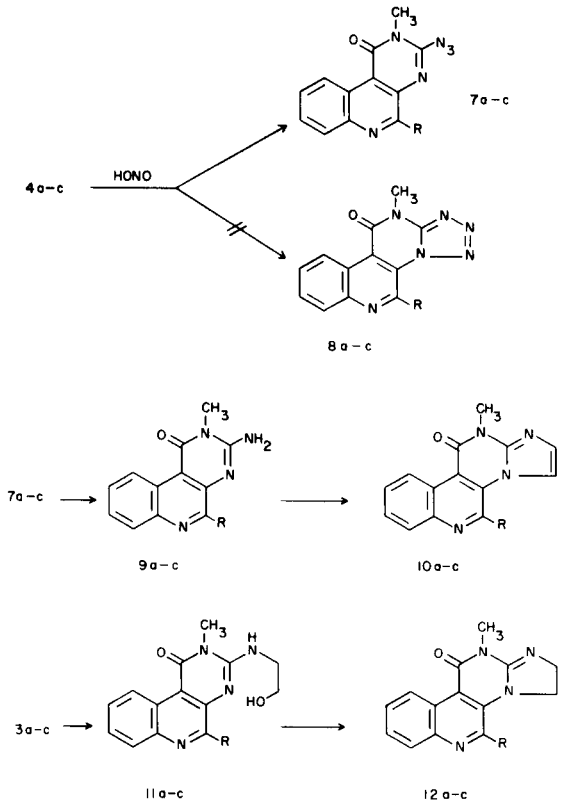
Scheme I



azide band at about 2150 cm^{-1} in potassium bromide disks as well as in different solvent systems. On the basis of previous results reported on "azido-tetrazole" equilibrium (5-7) it was concluded that the compounds obtained in this case were neither the 5-substituted 12-methyltetrazolo[5′,1′:2,3]pyrimido[4,5-*c*]quinolin-11-(12*H*)ones (**8a-c**), nor an equilibrium mixture of **8** and the corresponding 5-substituted-3-azido-1,2-dihydropyrimido-[4,5-*c*]quinolin-1(2*H*)ones (**7a-c**), but rather pure compounds **7**. This conclusion was in agreement with the nmr spectrum of compound **7a** in different solvents which exhibit sharp singlets for N-CH_3 and 2-CH_3. The azido structures assigned for compounds **7** were also supported by the fact that the predominance of the azido isomer correlates directly with the electron attracting characteristics of the adjacent heterocyclic ring B (the pyrimidone moiety) (5).

0022-152X/79/040707-04$02.25

Scheme 2

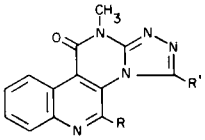


The azido compounds **7** were converted to 5-substituted 2-methyl-3-amino-1,2-dihydropyrimido[4,5-*c*]quinolin-11(12*H*)ones (**9a-c**) upon refluxing in tetralin. This finding can be attributed to the thermal decomposition of the corresponding azido compounds **7a-c** giving the intermediate nitrenes, which subsequently abstract hydrogen from tetralin to give the amino compounds **9**. The latter compounds were allowed to react with chloroacetaldehyde drate in ethanol to give 2-methyl-5-substituted imidazo[2′,1′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)ones (**10a-c**), which constitute another new class of polyazasteroids.

2-Methyl-3-methythio-1,2-dihydropyrimido-[4,5-*c*]quinolin-1(1*H*)ones (**4a-c**) were reacted with 2-aminoethanol to give 2-methyl-3-(2-hydroxyethanol-amino)-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)ones (**11a-c**). Cyclodehydration of the compounds **11a-c** with polyphosphoric acid gave 2,3-dihydroimidazo[2′,1′:2,3]-pyrimido[4,5-*c*]quinolin-11(12*H*)ones (**12a-c**), which constitute the third series of polyazasteroids reported in this work.

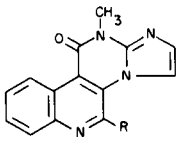
Structure elucidation of all polyazasteroids synthesized as well as their intermediates and the azido compounds **7a-c** were based on ir, nmr and mass spectroscopy and supported by elemental analysis. The nmr spectroscopy of all 1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)ones **2-5**, **7**, **9** and **11** as well as in steroids **6**, **10** and **12**, revealed that

Table I



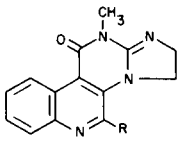
Compound	R	R′	M.p. °C	Yield	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
3a	Me	SMe	205-207	82	$C_{14}H_{13}N_3OS$	61.99	61.89	4.79	4.66	15.49	15.80
3b	Pr	SMe	130-135	95	$C_{16}H_{17}N_3OS$	64.21	64.27	5.68	5.60	14.04	14.11
3c	Ph	SMe	171-174	86	$C_{19}H_{15}N_3OS$	68.48	68.55	4.50	4.44	12.61	12.53
4a	Me	$NHNH_2$	265-270	95	$C_{13}H_{13}N_5O$	61.17	61.27	5.09	5.06	27.45	27.44
4b	Pr	$NHNH_2$	235-240	97	$C_{15}H_{17}N_5O$	63.60	63.63	6.00	5.95	24.73	24.20
4c	Ph	$NHNH_2$	248-252	93	$C_{18}H_{15}N_5O$	68.13	68.11	4.73	4.80	22.08	22.21
5a	Me	NHNHCOH	208-211	70	$C_{14}H_{13}N_5O_2$	59.36	59.40	4.59	4.61	24.73	24.79
5b	Me	NHNHCOMe	268-270	80	$C_{15}H_{15}N_5O_2$	60.60	60.66	5.05	5.10	23.56	23.73
5c	Me	NHNHCOEt	188-191	85	$C_{16}H_{17}N_5O_2$	61.73	61.86	5.46	5.44	22.50	22.66
5d	Pr	NHNHCOH	224-226	65	$C_{16}H_{17}N_5O_2$	61.73	61.77	5.46	5.60	22.50	22.39
5e	Pr	NHNHCOMe	260-262	71	$C_{17}H_{19}N_5O_2$	62.76	62.72	5.84	5.81	21.53	21.68
5f	Pr	NHNHCOEt	202-205	69	$C_{18}H_{21}N_5O_2$	63.71	63.63	6.19	6.17	20.64	20.69
5g	Ph	NHNHCOH	218-221	58	$C_{19}H_{15}N_5O_2$	66.08	66.11	4.37	4.41	20.28	20.40
5h	Ph	NHNHCOMe	290-293	63	$C_{20}H_{17}N_5O_2$	66.85	66.70	4.73	4.69	19.49	19.54
5i	Ph	NHNHCOEt	252-256	73	$C_{21}H_{19}N_5O_2$	67.56	67.80	5.09	4.99	18.76	18.80
7a	Me	N_3	235-237	85	$C_{13}H_{10}N_6O$	58.64	58.63	3.75	3.90	31.57	31.80
7b	Pr	N_3	142-146	78	$C_{15}H_{14}N_6O$	61.22	61.20	4.76	4.69	28.57	28.72
7c	Ph	N_3	193-196	81	$C_{18}H_{12}N_6O$	65.85	65.85	3.65	3.49	25.60	25.68
9a	Me	NH_2	285	60	$C_{13}H_{12}N_4O$	65.00	64.93	5.00	5.02	23.33	23.09
9b	Pr	NH_2	210	45	$C_{15}H_{16}N_4O$	67.16	67.25	5.97	5.90	20.89	21.03
9c	Ph	NH_2	> 300	56	$C_{18}H_{14}N_4O$	71.52	71.56	4.63	4.70	18.54	18.40
11a	Me	$NHCH_2CH_2OH$	238	75	$C_{15}H_{15}N_4O_2$	63.60	63.63	5.30	5.28	19.78	19.61
11b	Pr	$NHCH_2CH_2OH$	171-175	82	$C_{17}H_{20}N_4O_2$	65.38	65.36	6.41	6.50	17.94	17.84
11c	Ph	$NHCH_2CH_2OH$	185-190	73	$C_{20}H_{18}N_4O_2$	69.36	69.44	5.20	5.17	16.18	16.32

Table II



Compound	X	R	R′	M.p. °C	Yield	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
6a	N	Me	H	320	79	$C_{14}H_{11}N_5O$	63.39	63.44	4.15	4.20	26.41	26.66
6b	N	Me	Me	275	83	$C_{15}H_{13}N_5O$	60.45	60.40	4.65	4.53	25.08	25.19
6c	N	Me	Et	255-260	70	$C_{16}H_{15}N_5O$	65.52	65.73	5.11	5.06	23.89	24.11
6d	N	Pr	H	270	86	$C_{16}H_{15}N_5O$	65.52	65.44	5.11	5.13	23.89	23.59
6e	N	Pr	Me	285	79	$C_{17}H_{17}N_5O$	64.44	66.66	5.53	5.61	22.80	22.49
6f	N	Pr	Et	262	68	$C_{18}H_{19}N_5O$	67.28	67.27	5.91	6.02	21.80	21.59
6g	N	Ph	H	305	53	$C_{19}H_{13}N_5O$	69.72	69.49	3.97	4.00	21.40	21.56
6h	N	Ph	Me	285	64	$C_{20}H_{15}N_5O$	70.38	70.48	4.39	4.26	20.52	20.55
6i	N	Ph	Et	> 310	72	$C_{21}H_{17}N_5O$	70.98	70.77	4.78	4.65	19.71	19.19
10a	CH	Me	H	250	43	$C_{15}H_{12}N_4O$	68.18	68.15	4.54	4.61	21.21	21.41
10b	CH	Pr	Me	255	52	$C_{17}H_{16}N_4O$	69.86	62.79	5.47	5.55	19.17	19.26
10c	CH	Ph	Et	255-260	48	$C_{20}H_{14}N_4O$	73.61	73.74	4.29	4.11	17.17	17.40

Table III



Compound	R	M.p. °C	Yield	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
12a	Me	248-252	63	$C_{15}H_{14}N_4O$	67.66	67.50	5.26	5.30	21.05	20.92
12b	Pr	172-175	59	$C_{17}H_{18}N_4O$	69.38	69.22	6.12	6.19	19.04	19.19
12c	Ph	216-219	68	$C_{20}H_{16}N_4O$	73.18	73.28	4.87	4.68	17.07	17.15

the $C_{10}H$ proton absorption appeared at about 9.5 ppm. This down field shift is attributed to the influence of the carbonyl group at position 1 of these compounds.

The physical properties of all compounds which were prepared are reported in Tables I, II and III.

EXPERIMENTAL

Melting points were taken using a hot stage microscope and are uncorrected. The nmr spectra were recorded on a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The ir spectra were obtained using a Perkin-Elmer model 267 spectrograph. Mass spectra were run on a Varian Mat Ms-311 spectrometer at 70 eV.

2,5-Dimethyl-1,2,3,4-tetrahydropyrimido[4,5-*c*]quinolinone-3-thione (**2a**).

A mixture of 2.2 g. (0.01 mole) of 2-methyl-3-aminoquinolin-4-carboxylic acid (**1a**) (4) and 0.73 g. (0.01 mole) of methylisothiocyanate and 0.1 ml. of triethylamine was heated for one hour in an oil bath at 230°. After cooling, the solid was recrystallized from ethylene glycol monoethyl ether to give 2.50 g. (almost quantitative) of a pale yellow crystalline powder, m.p. 305-308°; ms: m/e 257 (M^+).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.49; H, 4.30; N, 16.66.

Compounds **2b** and **2c** were prepared similarly.

Compound **2b**.

This compound had m.p. 260-263° (69%); ms: m/e 285 (M^+).

Anal. Calcd. for $C_{15}H_{15}N_3OS$: C, 63.15; H, 5.26; N, 14.73. Found: C, 63.18; H, 5.12; N, 15.04.

Compound **2c**.

This compound had m.p. 310-314° (88%); ms: m/e 319 (M^+).

Anal. Calcd. for $C_{18}H_{13}N_3OS$: C, 67.71; H, 4.07; N, 13.16. Found: C, 67.67; H, 3.98; N, 12.91.

2,5-Dimethyl-3-methylthio-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)one (**3a**).

To a solution of 2.57 g. (0.01 mole) of **2a** in 25 ml. of 10% aqueous sodium hydroxide and 25 ml. of alcohol, 1.42 g. (0.01 mole) of methyl iodide was added. The mixture was stirred for one hour. The precipitate which formed was filtered and recrystallized from ethylene glycol monethyl ether to give 2.2 g. (82%) of a white crystallin powder, m.p. 205-207°; ms: m/e 271 (M^+); nmr (deuteriochloroform): 2.82 (s, 3H, CH_3). 3.26 (s, 3H, CH_3); 3.85 (s, 3H, NCH_3), 8-8.36 (m, 3H, aromatics) and 9.66-9.85 (m, 1H, $C_{10}H$).

Compounds **3b** and **3c** were prepared similarly. The physical properties of compounds **3** are reported in Table I.

2,5-Dimethyl-3-hydrazino-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)one (**4a**).

A solution of 2.71 g. (0.01 mole) of **3a** and 5 ml. of 98% hydrazine hydrate in 15 ml. of alcohol was refluxed for 10 hours. After cooling, the crystalline residue was separated and recrystallized from ethylene glycol dimethyl ether to give 2.4 g. (95%) of **4a**, m.p. 265-270°; ms: m/e 255 (M^+).

Compounds **4b** and **4c** were prepared similarly. The physical properties of compounds **4** are reported in Table I.

2,5-Dimethyl-3-formylhydrazido-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)one (**5a**).

The hydrazine **4a**, 2.55 g. (0.01 mole), in 10 ml. of 99% formic acid was refluxed for 4 hours. After cooling, 1.98 g. (70%) of a crystalline powder which was directly used for the preparation of steroid **6** was obtained, m.p. 210°; ms: m/e 283 (M^+). The analytical sample was recrystallized from ethylene glycol monoethyl ether.

Compounds **5b-i** were prepared similarly using the appropriate hydrazino compound and aliphatic acids. The physical properties of compounds **5** are reported in Table I.

2,5-dimethyl-3-azido-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)one (**7a**).

To an ice cold solution of 2.55 g. (0.01 mole) of hydrazine **4a** in 20 ml. of 2*N* hydrochloric acid, a solution of 1.03 g. (0.015 mole) of sodium nitrite in 3 ml. of water was added dropwise with stirring. After 6 hours of stirring at room temperature, the precipitate was filtered and recrystallized from ethylene glycol diethyl ether to give 2.26 g. (85%) of a yellowish crystalline powder, m.p. 235-237°; ms: m/e 266 (M^+); ir (potassium bromide): 3000, 2991, 2905, 2398, 1531, 1480, 1420, 1225, 1210, 1050, 1029, 929, 881, 856, 780 and 753 cm^{-1}. The 2398 band was not affected when the spectrum was run in nujol or other solvents.

Compounds **7b** and **7c** were prepared similarly. The physical properties of compounds **7** are reported in Table I.

2,5-Dimethyl-3-amino-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)one (**9a**).

A suspension of 2.66 g. (0.01 mole) of azide **7a** in 20 ml. of tetralin was refluxed for 8 hours. The resulting red solution was refrigerated to give a solid, 1.44 g. (60%), which was recrystallized from alcohol to afford the pure amine **9a**, m.p. 285°; ms: m/e 240 (M^+).

Compounds **9b** and **9c** were prepared similarly. The physical properties of compounds **9** are reported in Table I.

2,5-Dimethyl-3-(2-hydroxyethylamino)-1,2-dihydropyrimido[4,5-*c*]quinolin-1(2*H*)one (**11a**).

A suspension of 2.71 g. (0.01 mole) of the methylthio compound **3a** in 10 ml. of 2-aminoethanol was refluxed for 16 hours. After cooling, the solution was diluted with water to give a precipitate which was recrystallized from ethylene glycol monoethyl ether to give 2.12 g. (75%) of **11a**, m.p. 238°; ms: m/e 283; nmr (deuteriochloroform): 2.95 (s, 3H, CH_3), 3.76 (s, 3H, NCH_3), 3.97 (s, 4H, CH_2CH_2), 7.95 (m, 3H, aromatics) and 9.52-9.80 (m, 1H, $C_{10}H$).

Compounds **11b** and **11c** were prepared similarly. The physical properties of compounds **11** are reported in Table I.

3-Ethyl-5,12-dimethyl-1,2,4-triazolo[3′,4′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)one (**6c**).

A mixture of 3.11 g. (0.01 mole) of propionyl hydrazide **5c** and 25 g. of polyphosphoric acid was heated at 170° for 0.5 hour. After cooling, the mixture was diluted with water and basified with concentrated sodium hydroxide solution. The precipitate was recrystallized from ethylene glycol monoethyl ether to give 2.g (70%) of polyazasteroid **6c**, m.p. 255-260°; ms: 293 (M^+, 98%), 287 ($M-CH_3$, 100%), 251 (83%), 155 (95%), 127 (80%), and 97 (33%); nmr (DMSO-d_6): 1.42 (t, 3H, CH_3), 3.0 (s, 3H, CH_3), 3.16 (q, 2H, CH_2), 3.82 (s, 3H, NCH_3), 7.66-8.33 (m, 3H, aromatics) and 9.38-9.71 (m, 1H, $C_{10}H$).

All other compounds **6** were prepared similarly. The physical properties of compounds **6** are reported in Table II.

5,12-Dimethylimidazo[2′,1′:2,3]pyrimido[4,5-*c*]quinolin-11(12*H*)one (**10a**).

A solution of 2.40 g. of amine **9a** and 3 ml. of chloracetaldehyde hydrate in 5 ml. of ethanol was refluxed for 8 hours. After cooling, the reaction mixture was diluted with water and the precipitate was recrystallized from alcohol to give 1.13 g. (45%) of poly azasteroid **10a**, m.p. 250°; ms: 264; nmr (DMSO-d_6): 3.16 (s, 3H, CH_3), 3.83 (s, 3H, NCH_3), 7.15 (d, 1H, J = 8 Hz, C_2H), 7.61 (d, 1H, J = 8 Hz, C_3H), 7.68-8.12 (m, 3H, aromatics) and 9.8 (m, 1H, $C_{10}H$).

Compounds **10b** and **10c** were prepared similarly except that in the case of **10c**, ethylene glycol monoethyl ether was used as the reaction solvent. Physical properties of compounds **10** are reported in Table II.

5,12-Dimethyl-2,3-dihydroimidazo[2′,1′:2,3]pyrimido[4,5-*c*]quinolin-11-(12*H*)one (**12a**).

A mixture of 2.38 g. (0.01 mole) of compound **11a** in 25 g. of polyphosphoric acid was heated for 1 hour at 170°. Aftr cooling, the mass was worked up with water and basified with a concentratrated solution of sodium hydroxide. The resulting yellow precipitate was recrystallized from ethylene glycol monoethyl ether to give 1.67 g. (63%) of a yellow crystalin powder, m.p. 248-252°; ms: m/e 266; nmr (DMSO-d_6): 2.93 (s, 3H, CH_3), 3.33 (s, 3H, NCH_3), 3.98 (t, 2H, CH_2), 4.99 (t, 2H, CH_2), 7.50-7.97 (m, 3H, aromatics) and 9.50-9.85 (m, 1H, $C_{10}H$).

Compounds **12b** and **12c** were prepared similarly. The physical properties of compounds **12** are reported in Table III.

Acknowledgment.

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(1) This work was partly presented at the 6th International Congress of Heterocyclic Chemistry, July 9-13, 1977, Tehran, Iran. For part I see Reference (2).

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