Synthesis of Potential Antineoplastic Agents. XV. Some 1,4-Bisamides of 1,2,3,4-Tetrahydroquinoxaline[1,2]

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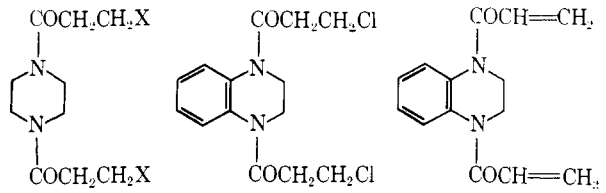
A number of chlorine-containing and unsaturated 1,4-bisamides have been prepared from 1,2,3,4-tetrahydroquinoxaline and from substituted 1,2,3,4-tetrahydroquinoxalines. Although many of these amides are active against KB cell culture, they are inactive against animal tumors. A number of related amides were also prepared from 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline.

In 1961 it was reported[4] that N,N′-bis(3-bromopropionyl)piperazine (I, X = Br) produced potent and reproducible antineoplastic activity in mice. It was also shown that the β-bromo substituent could be replaced by chloro or by methanesulfonyloxy and still have activity maintained. In view of the activity of I we reported[5] the preparation of a series of 3-chloropropionyl compounds from a variety of nitrogen heterocyclic systems. That paper[5] indicated that the 3-chloropropionylamides prepared were essentially inactive against the Dunning leukemia and against Adenocarcinoma 755. After the publication of that report, however, it was noted that the tetrahydroquinoxaline derivative II exhibited reproducible activity[6] against the KB cell culture system. The related tetrahydroquinoxaline derivative III[5] was also active in this system. In view of this activity it was decided to investigate additional analogs of II and III

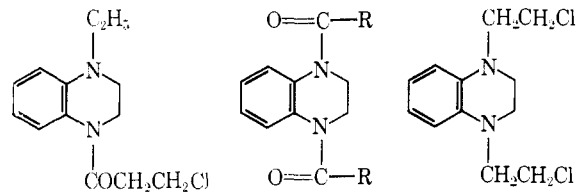


I II III

to see if the cell culture activity could be extended to animal systems. In some cases the corresponding N-substituted 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydroisoquinolines were also prepared as model compounds.

The substituted 1,2,3,4-tetrahydroquinoxalines were readily prepared by hydrogenation of the corresponding quinoxalines. These tetrahydroquinoxalines were treated with a number of acid chlorides to give the compounds in Table I and some of the compounds in Table II. The remaining compounds of the type III found in Table II were prepared by dehydrohalogenation on alumina of the corresponding 3-chloropropionyl compound.[5] 1-Ethyl-1,2,3,4-tetrahydroquinoxaline was treated with 3-chloropropionyl chloride to give IV. 1,2,3,4-Tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline were allowed to react with acid chlorides to give the compounds in Table III.

The two parent compounds (V, R = H, Cl) in the tetrahydroquinoxaline series were also prepared. The former (V, R = H) which had originally been prepared[7] by formylation of 1,2,3,4-tetrahydroquinoxaline was prepared in this work by a reductive formylation[8] of quinoxaline. The latter (V, R = Cl) was prepared by the addition of phosgene to 1,2,3,4-tetrahydroquinoxaline.



IV V VI

The monohydrochloride of the tetrahydroquinoxaline mustard VI was prepared in low yield by lithium aluminum hydride reduction of 1,4-bis(chloroacetyl)-1,2,3,4-tetrahydroquinoxaline. When diborane was used as the reducing agent, however, VI was obtained in an 80% yield.

The anticancer screening results for the various quinoxaline derivatives are included in Table IV. It can be noted that all of the compounds derived from chloroacetyl chloride and all of the compounds related to III were active[9] against KB cell culture. Only with quinoxaline itself, however, was the chloropropionyl compound (II) active. Extension of this chain to four carbons or introduction of substituents on the vinyl group of III caused loss of activity. All of the compounds tested failed to exhibit any significant activity against the animal tumors used. The reduction product VI, however, exhibited a T/C of 216% at a dose of 160 mg/kg against the Dunning leukemia.

The anticancer screening results for the quinolines and isoquinolines are included in Table V. No appreciable activity is noted for these compounds either against cell culture or animal tumors.

(1) Part XIV: W. Wasulko, A. C. Noble, and F. D. Popp, *J. Med. Chem.*, **9**, 599 (1966).

(2) Supported in part by research grants from the American Cancer Society (T-177D) and from the National Cancer Institute, U. S. Public Health Service (CA 06606-03). Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(3) A portion of this work was abstracted from the M.S. thesis of P. S.

(4) J. A. Carbon, S. M. Brehm, and J. D. Ratajczyk, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p 11-N.

(5) F. D. Popp, E. Cullen, R. B. Davis, and W. Kirsch, *J. Med. Pharm. Chem.*, **5**, 398 (1962).

(6) Screening results have been supplied by the Cancer Chemotherapy National Service Center (CCNSC).

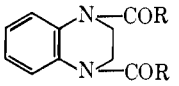
(7) H. König and R. Huisgen, *Chem. Ber.*, **92**, 429 (1959).

(8) I. Baxter, L. T. Allan, and G. A. Swan, *J. Chem. Soc.*, 3645 (1965).

(9) In this system the activity of the compound is considered to be statistically significant if the ED_{50} is 4×10^{0} μg/ml or less.

TABLE I

AMIDES OF 1,2,3,4-TETRAHYDROQUINOXALINE

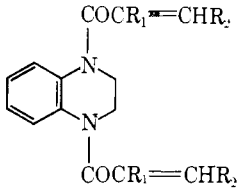


Ring substituent	R	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
None	C_2H_3	124–125	78	68.27	7.37	11.37	68.15	7.38	11.31
None[a]	CH_2Cl	175–176	57	50.20	4.17	9.75	49.89	4.12	9.71
None	$(CH_2)_2Cl$	121–122[b]	83						
None	$(CH_2)_3Cl$	Oil[c]	20	56.00	5.87	8.18	55.60	5.55	8.01
None[d]	$CHCl_2$	121–122	62	40.48	2.83	7.87	40.42	2.86	7.62
2-Methyl	CH_2Cl	119–120	44	51.80	4.69	9.32	51.55	4.74	9.45
2-Methyl	$(CH_2)_2Cl$	Oil[e]	39	54.80	5.50	8.53	54.38	5.51	8.32
6,7-Dimethyl[e]	CH_2Cl	136–137	77	53.40	5.08	8.89	53.69	5.36	8.69
6,7-Dimethyl[f]	$(CH_2)_2Cl$	128–129	70	56.10	5.83	8.17	56.05	6.16	7.93
2,3-Dimethyl	CH_2Cl	148–149	56	53.40	5.08	8.89	53.11	5.20	8.77
2,3-Dimethyl	$(CH_2)_2Cl$	124–125	78	56.10	5.83	8.17	55.82	5.87	8.00
5,6,7,8-Dibenzo	CH_2Cl	267–268	25	62.10	4.13	7.23	61.68	4.18	7.18
5,6,7,8-Dibenzo[g]	$(CH_2)_2Cl$	209–210	94	63.60	4.86	6.75	63.44	4.79	6.59

[a] *Anal.* Calcd: Cl, 24.69. Found: Cl, 24.39. [b] Lit.[5] mp 119–120°. [c] Purified by chromatography on acid-washed alumina. [d] *Anal.* Calcd: Cl, 39.83. Found: Cl, 39.65. [e] *Anal.* Calcd: Cl, 22.41. Found: Cl, 22.43. [f] *Anal.* Calcd: Cl, 20.65. Found: Cl, 20.60. [g] *Anal.* Calcd: Cl, 17.09. Found: Cl, 17.15.

TABLE II

UNSATURATED AMIDES OF 1,2,3,4-TETRAHYDROQUINOXALINE



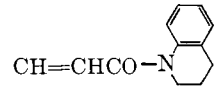
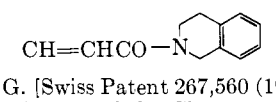
Ring substituent	R_1	R_2	Mp, °C	Yield, %	Method[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
None	H	H	171–172[b]	62	A						
None	H	CH_3	101–103	63	A	71.09	6.71	10.36	71.07	6.61	10.22
None	CH_3	H	164–165	88	A	71.09	6.71	10.36	71.02	6.69	10.32
None	H	C_6H_5	170–171	77	A	78.52	5.80	7.33	78.78	5.46	7.08
2-Methyl	H	H	58–60	68	B	70.30	6.28	10.93	70.67	6.51	10.34
6,7-Dimethyl	H	H	106–107	76	B	71.10	6.70	10.40	70.87	6.69	10.30
2,3-Dimethyl	H	H	130–131	97	B	71.10	6.70	10.40	70.85	6.56	10.40

[a] Method A by direct condensation of acid chloride and 1,2,3,4-tetrahydroquinoxaline. Method B by alumina chromatography of 1,4-bis(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxaline. [b] Lit.[5] mp 172–174° by method B.

TABLE III

N-ACYL-1,2,3,4-TETRAHYDROQUINOLINES AND -1,2,3,4-TETRAHYDROISOQUINOLINES

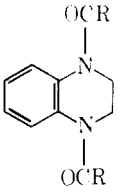
>NCOR

Tetrahydro base used	R	Bp (mm) or mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Quinoline	$CH{=}CHCH_3$	158–159 (2)[a]	73	77.56	7.51	6.96	77.55	7.39	6.87
Quinoline	$CCH_3{=}CH_2$	56–58[b]	70	77.56	7.51	6.96	77.30	7.45	7.00
Quinoline	$CH{=}CHC_6H_5$	98–99	96	82.10	6.51	5.32	81.92	6.47	5.41
Quinoline		196–198	84	76.28	6.40	8.09	76.28	6.40	7.98
Isoquinoline[c]	$CHCl_2$	87–88	78	54.12	4.54	5.74	54.20	4.52	5.84
Isoquinoline	$CCH_3{=}CH_2$	123–124 (0.2)	67	77.56	7.51	6.96	77.33	7.47	6.84
Isoquinoline	$CH{=}CHCH_3$	75–76[b]	71	77.56	7.51	6.96	77.51	7.43	6.82
Isoquinoline	$CH{=}CHC_6H_5$	109–110[d]	99	82.10	6.51	5.32	82.00	6.54	5.36
Isoquinoline		169–170	89	76.28	6.40	8.09	76.07	6.52	8.20

[a] J. R. Geigy, A. G. [Swiss Patent 267,560 (1950); *Chem. Abstr.*, **45**, 6219 (1951)] reported bp 143–147° (0.2 mm). [b] Recrystallized from ethyl ether. [c] *Anal.* Calcd: Cl, 29.05. Found: Cl, 29.10. [d] N. H. Cromwell and J. A. Caughlan [*J. Am. Chem. Soc.*, **67**, 903 (1945)] reported mp 101°.

TABLE IV

ANTINEOPLASTIC ACTION[a] OF

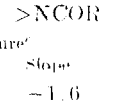


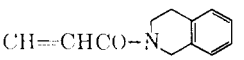
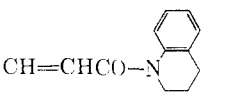
Ring substituent	R	KB cell culture[b] ED_{50}, μg/ml	KB cell culture[b] Slope	T/C (%)/dose (mg/kg) WA[c]	LE[d]	SA[e]	CA[f]	Other
None	CH_2Cl	1.3×10^0	−1.0	74/25				
None	$CHCl_2$	2.7×10^0	−2.6		100/90	51/125		59/100[g]
None	CH_2CH_2Cl	3.0×10^0	−0.8	107/50	103/500	105/500	91/500	90/100[h,i]
None	$CH_2CH_2CH_2Cl$	1.4×10^1	−0.5					
None	$CH{=}CH_2$	2.3×10^0	−1.1				109/100	
None	$CH{=}CHC_6H_5$	2.0×10^1	−0.9		93/400	89/500		
None	$CCH_3{=}CH_2$	7.0×10^1	−0.5		98/350	106/500		
2-Methyl	CH_2Cl	3.0×10^{-1}	−1.2	85/7	97/4	114/4		75/4[g]
2-Methyl	CH_2CH_2Cl	7.8×10^0	−0.5	113/200				
2-Methyl	$CH{=}CH_2$	4.1×10^0	−0.8		100/100	78/125	70/100	
2,3-Dimethyl	CH_2Cl	1.8×10^{-1}	−0.4	79/7				
2,3-Dimethyl	CH_2CH_2Cl	3.7×10^1	−1.1	84/200				
2,3-Dimethyl	$CH{=}CH_2$	2.8×10^0	−1.8		90/200	151/250	142/200	20/0.3[j]
6,7-Dimethyl	CH_2Cl	1.1×10^0	−1.3	93/7	100/20			88/32,[k] 65/8[l]
6,7-Dimethyl	CH_2CH_2Cl	9.8×10^0	−1.8	66/100				
6,7-Dimethyl	$CH{=}CH_2$	2.5×10^0	−1.3		113/50	97/250	67/200	
5,6,7,8-Dibenzo	CH_2Cl	3.2×10^0	−1.3	104/100				
5,6,7,8-Dibenzo	CH_2CH_2Cl	$M1.0 \times 10^0$		73/25				

[a] Data from CCNSC. [b] ED_{50} = dose that inhibits growth to 50% of control growth. Slope = difference in result for a tenfold difference in dose. [c] Walker carcinosarcoma 256 (sc). [d] L1210 lymphoid leukemia. [e] Sarcoma 180. [f] Adenocarcinoma 755. [g] Lewis lung carcinoma. [h] Dunning leukemia (solid). [i] Also inactive against spindle cell sarcoma, leiomyosarcoma of uterus, and Yoshida sarcoma (results kindly supplied by Dr. W. F. Dunning, University of Miami.). [j] HS1 human sarcoma (rat egg). [k] L5178Y lymphatic leukemia. [l] Walker carcinoma 256/cytoxan (sc).

TABLE V

ANTINEOPLASTIC ACTION[a] OF TETRAHYDROQUINOLINE AND TETRAHYDROISOQUINOLINE AMIDES



Base[b]	R	KB cell culture[c] ED_{50}, μg/ml	KB cell culture[c] Slope	T/C (%)/dose (mg/kg) LE[d]	SA[e]	LL[f]	Other
isoQ	$CHCl_2$	8.1×10^0	−1.6	96/90	118/125	103/90	71/25,[g] 100/250[h]
isoQ	CH_2CH_2Cl	$M1.0 \times 10^1$					
isoQ	$CH{=}CHCH_3$	2.5×10^1	−0.9	97/400			111/400,[i] 104/200[j]
isoQ	$CH{=}CHC_6H_5$	2.3×10^1	−1.1	92/200	79/250	107/200	
isoQ	$CCH_3{=}CH_2$	$M1.0 \times 10^2$		98/100			90/100,[i] 103/50[j]
isoQ	$CH{=}CHCO{-}$ 	5.0×10^1	−0.6	86/200	88/200	86/200	
Q	$CH{=}CHCH_3$	2.5×10^1	−1.0	94/125	57/125	94/40	
Q	$CH{=}CHC_6H_5$	4.7×10^1	−0.7	106/400	99/500		
Q	$CCH_3{=}CH_2$	$M1.0 \times 10^2$		96/500	89/500	49/200	
Q	$CH{=}CHCO{-}$ 	$M1.0 \times 10^2$		95/400	50/500	98/400	

[a] Data from CCNSC. [b] isoQ = 1,2,3,4-tetrahydroisoquinoline, Q = 1,2,3,4-tetrahydroquinoline. [c] ED_{50} = dose that inhibits growth to 50% of control growth. Slope = difference in result for a tenfold difference in dose. [d] L1210 lymphoid leukemia. [e] Sarcoma 180. [f] Lewis lung carcinoma. [g] Adenocarcinoma 755. [h] Dunning leukemia (solid). [i] P1798 lymphosarcoma. [j] Dunning leukemia (ascites).

Experimental Section[10]

1,2,3,4-Tetrahydroquinoxalines.—A mixture of 0.04 mole of the quinoxaline, 0.02 g of PtO_2, and 150 ml of 95% ethanol or glacial acetic acid was hydrogenated at 4.2 kg/cm². After the theoretical pressure drop, the mixture was warmed on a steam bath and filtered. The ethanol solution was concentrated or the acetic acid was made basic to give, after recrystallization from ethanol–water or petroleum ether (bp 60–90°), the 1,2,3,4-tetrahydroquinoxalines.

The following 1,2,3,4-tetrahydroquinoxalines have been prepared by this method: no substituent,[11] yield 93% in ethanol; 2-methyl,[12] yield 10% in ethanol and 93% in acetic acid; 6,7-dimethyl, yield 73% in ethanol, mp 143–144° (*Anal.* Calcd for $C_{10}H_{14}N_2$: C, 74.10; H, 8.65; N, 17.30. Found: C, 74.00; H, 8.65; N, 17.35.); 2,3-dimethyl,[13] yield 77% in ethanol; 5,6,7,8-dibenzo, yield 3% in ethanol and 60% in acetic acid, mp 188–191° (*Anal.* Calcd for $C_{18}H_{14}N_2$: C, 82.10; H, 5.99; N, 11.95. Found: C, 81.68; H, 5.67; N, 11.68.).

(10) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are taken in capillaries and are corrected.

(11) J. C. Cavagnol and F. T. Wiselogle, *J. Am. Chem. Soc.*, **69**, 795 (1947).

(12) M. Munk and H. P. Schultz, *ibid.*, **74**, 3433 (1952).

(13) S. Maffei and S. Pietra, *Gazz. Chim. Ital.*, **88**, 556 (1958).

1,4-Bisamides of 1,2,3,4-Tetrahydroquinoxaline.—To a solution of 0.05 mole of tetrahydroquinoxaline in 100 ml of anhydrous chloroform at 0° was added dropwise with constant stirring a solution of 0.11 mole of the acyl chloride in 50 ml of anhydrous $CHCl_3$. When the addition was complete, the mixture was refluxed until evolution of HCl had ceased. Filtration, followed by concentration *in vacuo*, and when necessary trituration with ether, gave solids that were purified by recrystallization from ethanol. The compounds prepared by this method are listed in Tables I and II (method A).

1-Ethyl-4-(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxaline (IV).—Reaction of 0.031 mole of 1-ethyl-1,2,3,4-tetrahydroquinoxaline[14] in 75 ml of chloroform with 0.031 mole of 3-chloropropionyl chloride in 25 ml of $CHCl_3$ by the general procedure described above gave an 84% yield of a thick oil. Treatment of this oil in ether with HCl gave the hydrochloride, mp 140–142° (from tetrahydrofuran).

Anal. Calcd for $C_{13}H_{17}ClN_2O \cdot HCl$: C, 54.05; H, 6.27; N, 9.69; Cl, 24.52. Found: C, 54.16; H, 6.51; N, 9.91; Cl, 24.25.

Amides of Tetrahydroquinoline and Tetrahydroisoquinoline.—Using the same general procedure as described above for the bisamides, 0.05 mole of amine and 0.06 mole of acyl chloride were allowed to react to give after recrystallization from ethanol the materials listed in Table III.

1,4-(Diacrylyl)-1,2,3,4-tetrahydroquinoxalines.—The 1,4-bis(3-chloropropionyl)-1,2,3,4-tetrahydroquinoxalines in benzene were chromatographed over Merck reagent grade aluminum oxide and eluted with benzene–ethanol (9:1) to give, as previously reported,[5] the compounds listed in Table II (method B).

(14) R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.*, **24**, 205 (1959).

1,4-Diformyl-1,2,3,4-Tetrahydroquinoxaline (V, R = H).—A solution of 0.036 mole of quinoxaline in 30 ml of formic acid and 100 ml of dimethylformamide was refluxed for 16 hr. The resulting solution was poured onto ice and the aqueous solution was extracted continuously with ether for 48 hr. The ethereal solution was dried and concentrated *in vacuo* to give an oil which crystallized on trituration with ethanol. Recrystallization from ethanol gave 3.0 g (44%), mp 125–126°, lit.[7] mp 119–122°.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.29; N, 14.72. Found: C, 63.12; H, 5.14; N, 14.69.

1,4-Bis(chlorocarbonyl)-1,2,3,4-tetrahydroquinoxaline (V, R = Cl).—A solution of 0.03 mole of 1,2,3,4-tetrahydroquinoxaline in 30 ml of benzene was added dropwise with stirring and cooling to a solution of 0.06 mole of phosgene in 50 ml of benzene. After addition the mixture was refluxed for several hours and concentrated *in vacuo* to give 5.9 g (76%) of a solid, mp 92–93° (from isopropyl ether).

Anal. Calcd for $C_{10}H_8Cl_2N_2O_2$: C, 46.35; H, 3.11; N, 10.81; Cl, 27.37. Found: C, 46.50; H, 3.22; N, 10.66; Cl, 27.16.

1,4-Bis(2-chloroethyl)-1,2,3,4-tetrahydroquinoxaline (VI).—A solution of 0.015 mole of 1,4-bis(chloroacetyl)-1,2,3,4-tetrahydroquinoxaline in 200 ml of tetrahydrofuran (THF) was added dropwise with stirring to 50 ml of a 1 *N* solution of borane under nitrogen at −10°. After the resulting mixture was refluxed for 1 hr, 8 ml of 6 *N* HCl was added followed by 75 ml of water. The THF was distilled and excess solid NaOH was added. The resulting mixture was extracted with ether, and the dried ether extract was concentrated to give 3.55 g (80%) of a yellow oil. The hydrochloride was prepared and recrystallized from THF, mp 149–152°.

Anal. Calcd for $C_{12}H_{16}Cl_2N_2 \cdot HCl$: C, 48.76; H, 5.80; N, 9.48; Cl, 35.98. Found: C, 49.00; H, 5.71; N, 9.47; Cl, 35.92.

Hypoglycemic Activity and Pharmacological Picture of 4-(1-Naphthyl)butylamine Derivatives

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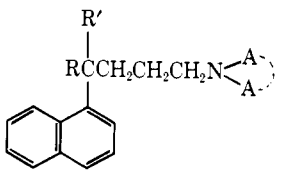
Forty-nine 4-(1-naphthyl)butylamine derivatives were prepared for hypoglycemic tests. They were also submitted to comprehensive screening, in order to obtain as complete as possible a pharmacological picture. The majority of the compounds examined revealed marked hypoglycemic activity, and of these the α-isopropyl-α-(3-dimethylaminopropyl)- (XXIII) and α,α-di(3-dimethylaminopropyl)-1-naphthylacetic acids (XXIV) were found to be the most active and comparable with chlorpropamide. None of the other actions investigated revealed anything of particular interest.

Our finding[1] that some α-aminoethyl-1-naphthylacetic acids possess hypoglycemic activity has led us to extend this investigation to compounds with related structures. Preliminary studies showed that substitution with an aminopropyl chain in the α position of 1-naphthylacetic acid was the most promising for reaching the highest activity, and an extensive series of 4-(1-naphthyl)butylamines of the following general structure was prepared. The methods used in obtaining the new compounds were quite similar to those reported in previous papers[1,2] and, in any case, are well illustrated in the Experimental Section.



R = H, alkyl, or aminopropyl
R′ = CN, $CONH_2$, CO_2H, CO_2R'', $CONHR''$, $CONPr_2$, CONHCONHPr, $CNHR''$, or COEt (R″ = alkyl, cyclohexyl, allyl, or phenyl)
NAA = tertiary amino group

The title compounds were submitted to a pharmacological investigation which included not only examination of the hypoglycemic action, but also studies of acute toxicity, behavioral effects, and antiinflammatory, analgesic, local anesthetic, antitussive, diuretic, antispasmodic, antipyretic, choleretic, and hypoten-

(1) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **9**, 603 (1966).

(2) (a) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 589 (1965); (b) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 594 (1965); (c) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *Farmaco (Pavia), Ed. Sci.*, **19**, 731 (1964); (d) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **19**, 933 (1964).