pended solid gradually dissolved as the addition progressed. If a clear solution was not attained, an additional 5 ml of AcOH was added to the reaction mixture. After about 20 min–1 hr the color of the reaction mixture gradually faded and the reaction mixture was stirred for a total of 2 hr. To the solution was then added, with ice-cooling, 80 ml of saturated aqueous AcONa and 160 ml of H_2O. The mixture was stirred for 10–15 min and allowed to stand for an equal time at 0°. The solid which formed was collected by either filtration or decantation and then was treated by stirring with a mixture of 150 ml of H_2O and 120 ml of Et_2O. The resulting mixture was allowed to settle for several hours (which facilitates the rate of filtration) and the white solid was collected (in some cases when a gel formation is noted, addition of saline water can usually ease the filtration difficulties). It was then washed successively with two 30-ml portions of H_2O (or dilute saline water), Et_2O, and petroleum ether, and dried at 110° over KOH *in vacuo*. The products obtained were usually of analytical purity. When necessary, these compounds can be purified by recrystallization from either EtOH–H_2O or DMF–H_2O.

For the crylation of the O analogs of cysteine, it was found that the optimum reaction conditions were 4 hr at room temperature. Higher reaction temperatures (*e.g.*, 50–60°) and or longer reaction times (*e.g.*, 24 hr) gave lower yields.

Acknowledgments.—The authors wish to thank Dr. Harry B. Wood, Jr., Dr. Florence R. White, and Dr. Robert E. Engle of CCNSC for their interest and encouragement. They also wish to express their appreciation to Mrs. Margaret L. Rounds and Mr. John Gravatt for their assistance in performing analytical and instrumental measurements.

Synthesis and Pharmacological Evaluation of α-Naphthylalkylamines

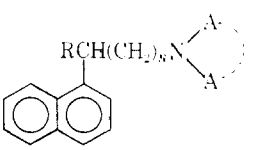
Silvano Casadio, Gianfranco Pala, Tiberio Bruzzese, Carla Turba, and Ernesta Marazzi-Uberti

Research Laboratories of Istituto De Angeli, Milan, Italy

Received December 23, 1969

Twenty-five α-naphthylalkylamines were prepared for extensive pharmacological screening. Some of the compounds revealed marked antiarrhythmic activity, and of these 1,5-dimorpholino-3-(α-naphthyl)pentane (**24**) was found to be the most promising and comparable with quinidine. None of the other actions investigated revealed anything of particular interest.

Continuing our investigation on the pharmacological properties of α-naphthylalkylamines,[1] we have prepared for pharmacological screening 25 compounds of the general structure I in which R was H, or alkyl, or aminoalkyl, and NAA was a tertiary amino group (n = 2 or 3).



I

Decyanation of the corresponding nitriles[2] by $NaNH_2$ in boiling xylene afforded α-naphthylalkylamines in which R was not H. As this procedure failed with monosubstituted α-naphthylacetonitriles, α-naphthylalkylamines with R = H were prepared by reduction with LAH in THF of tertiary 3-(α-naphthyl)propionamides.

Pharmacological screening included studies of acute toxicity, behavioral effects, and spontaneous motility, and analgetic, local anesthetic, antispasmodic, antihistaminic, antiinflammatory, hypotensive, coronary vasodilator, antiarrhythmic, antibacterial, and antifungal actions.

(1) S. Casadio, T. Bruzzese, G. Pala, G. Coppi, and C. Turba, *J. Med. Chem.*, **9**, 707 (1966).

(2) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 589 (1965).

Experimental Section[3]

The intermediate tertiary amides were prepared by treating 3-(α-naphthyl)propionyl chloride with the proper amines according to the following procedure.

***N,N*-Dimethyl-3-(α-naphthyl)propionamide.**—Me_2NH (21.6 g, 0.48 mol) in anhyd C_6H_6 (150 ml) was added with cooling to a solution of 3-(α-naphthyl)propionyl chloride (43.6 g, 0.2 mol) in anhyd C_6H_6 (150 ml). After addition, the solution was allowed to stand at room temperature for 2 hr, refluxed for an additional 2 hr, cooled to room temperature, washed with H_2O, and dried (Na_2SO_4). The solvent was evaporated and the residue was distilled at 157–160° (0.2 mm) to give a colorless oil (31.4 g, 69%). *Anal.* ($C_{15}H_{17}NO$) C, H, N.

The following amides were similarly obtained: ***N,N*-diethyl-3-(α-naphthyl)propionamide,** 79%, bp 150–152° (0.1 mm), *Anal.* ($C_{17}H_{21}NO$) C, H, N; ***N*-methyl-*N*-ethyl-3-(α-naphthyl)propionamide,** 63%, bp 155–158° (0.2 mm), *Anal.* ($C_{16}H_{19}NO$) C, H, N; ***N*-methyl-*N*-benzyl-3-(α-naphthyl)propionamide,** 75%, bp 190–192° (0.1 mm), *Anal.* ($C_{21}H_{21}NO$) C, H, N; ***N*-[3-(α-naphthyl)-propionyl]piperidine,** 72%, bp 194–196° (0.25 mm), *Anal.* ($C_{18}H_{21}NO$) C, H, N; ***N*-[3-(α-naphthyl)propionyl]morpholine,** 73%, bp 189–192° (0.3 mm), *Anal.* ($C_{17}H_{19}NO_2$) C, H, N.

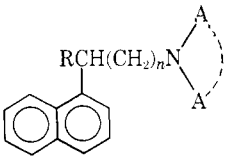
α-Naphthylalkylamines are listed in Table I, and their preparation is illustrated by the following methods.

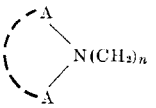
Method A. 1-Dimethylamino-3-(α-naphthyl)propane·HCl (1).—A solution of *N,N*-dimethyl-3-(α-naphthyl)propionamide (29.2 g, 0.128 mol) in THF (180 ml) was dropped into a stirred suspension of LAH (6.3 g, 0.166 mol) in THF (400 ml). The mixture was refluxed for 12 hr with stirring, cooled to room temperature, and then Et_2O (200 ml) was added. The reaction mixture was cautiously decomposed with H_2O and NaOH, and the organic layer was separated, washed with H_2O, and evaporated to complete removal of THF. The residue was taken up in Et_2O and HCl was bubbled into to yield a solid which, on recrystallization from *i*-PrOH, gave colorless crystals, mp 159–160°.

(3) Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

TABLE I

α-NAPHTHYLALKYLAMINES



Compd	R		Method	Yield, %[a]	Bp (mm) or mp, °C	Formula[b]
1	H	$(CH_3)_2N(CH_2)_2$	A	78	159–160	$C_{15}H_{19}N \cdot HCl$
2	CH_3	$(CH_3)_2N(CH_2)_2$	B	30	105–107 (0.2)	$C_{16}H_{21}N$
3	C_2H_5	$(CH_3)_2N(CH_2)_2$	B	76	115–118 (0.25)	$C_{17}H_{23}N$
4	*i*-C_3H_7	$(CH_3)_2N(CH_2)_2$	B	59	105–106 (0.12)	$C_{18}H_{25}N$
5	*sec*-C_4H_9	$(CH_3)_2N(CH_2)_2$	B	63	112–115 (0.15)	$C_{19}H_{27}N$
6	$(CH_3)_2N(CH_2)_2$	$(CH_3)_2N(CH_2)_2$	B	59	130–135 (0.1)	$C_{19}H_{28}N_2$
7	H	$CH_3(C_2H_5)N(CH_2)_2$	A	64	136–138	$C_{16}H_{21}N \cdot HCl$
8	*i*-C_3H_7	$CH_3(C_2H_5)N(CH_2)_2$	B	71	135–136 (0.4)	$C_{19}H_{27}N$
9	H	$(C_2H_5)_2N(CH_2)_2$	A	75	123–125	$C_{17}H_{23}N \cdot HCl$
10	*i*-C_3H_7	$(C_2H_5)_2N(CH_2)_2$	B	64	120–122 (0.2)	$C_{20}H_{29}N$
11	H	$CH_3(C_6H_5CH_2)N(CH_2)_2$	C	67	153–155 (0.1)	$C_{24}H_{29}N$
12	*i*-C_3H_7	$CH_3(C_6H_5CH_2)N(CH_2)_2$	B	42	170–172 (0.15)	$C_{24}H_{29}N$
13	H	*c*	A	86	222–223	$C_{18}H_{23}N \cdot HCl$
14	CH_3	*c*	B	49	125–128 (0.1)	$C_{19}H_{25}N$
15	C_2H_5	*c*	B	53	143–145 (0.2)	$C_{20}H_{27}N$
16	*i*-C_3H_7	*c*	B	43	140–143 (0.15)	$C_{21}H_{29}N$
17	*sec*-C_4H_9	*c*	B	55	150–152 (0.2)	$C_{22}H_{31}N$
18	*c*	*c*	B	70	180–182 (0.2)	$C_{25}H_{36}N_2$
19	H	*d*	A	83	175–176	$C_{17}H_{21}NO \cdot HCl$
20	CH_3	*d*	B	34	148–150 (0.2)	$C_{18}H_{23}NO$
21	C_2H_5	*d*	B	45	149–152 (0.2)	$C_{19}H_{25}NO$
22	*i*-C_3H_7	*d*	B	67	145–148 (0.1)	$C_{20}H_{27}NO$
23	*sec*-C_4H_9	*d*	B	63	147–149 (0.1)	$C_{21}H_{29}NO$
24	*d*	*d*	B	82	210–212 (0.15)	$C_{23}H_{32}N_2O_2$
					157–159	$C_{23}H_{32}N_2O_2 \cdot 2HCl$
25	*i*-C_3H_7	$(CH_3)_2N(CH_2)_3$	B	68	122–125 (0.15)	$C_{19}H_{27}N$

[a] Distilled or crystallized product. [b] All compounds were analyzed for C, H, N and the analytical results were within ±0.4% of the theoretical values. [c] 2-Piperidinoethyl. [d] 2-Morpholinoethyl.

Method B. 1,5-Dimorpholino-3-(α-naphthyl)pentane (24).—Finely powdered $NaNH_2$ (31.2 g, 0.8 mol) was added portionwise to a vigorously stirred solution of α,α-bis(2-morpholinoethyl)-1-naphthylacetonitrile (78.7 g, 0.2 mol) in dry xylene (600 ml). The mixture was refluxed for 30 hr with stirring and cooled to room temperature, and then H_2O was cautiously added. The organic layer was separated, washed with H_2O, and dried (Na_2SO_4). The solvent was removed and the residue was distilled to give a viscous and colorless oil, bp 210–212° (0.15 mm).

Method C.—The same as method A, except that the product was isolated as the base instead of the hydrochloride.

Results and Discussion

The most interesting results of the pharmacological screening are recorded in Table II. The methods used are referred to in the footnotes to the table. In addition, all the compounds were examined for CNS activity,[4] and some of them (**1**, **5**, **13**, **17**, **19**) for antibacterial and antifungal actions.[5]

Most of the substances induced behavioral excitement, but **6**, **17**, **22**, and **24** exerted instead a general CNS-depressant action. Some of the compounds inhibited the spontaneous motility, their activity being quite similar to that of meprobamate. As local anesthetics, **10**, **16**, and **25** were as active as lidocaine, but irritant. When tested on isolated guinea pig ileum, only **3**, **6**, and **15** inhibited spasms produced by histamine (activity not confirmed *in vivo*), while **15–17** exerted some antiacetylcholine activity. Only some of the compounds caused a fall of the arterial pressure in rats; the hypotensive action of **1**, **2**, **7**, **9**, **14**, and **18** was long-lasting whereas that of **6**, **13**, and **17** was less than 30 min. On the isolated rabbit heart, **5**, **16**, and **17** markedly increased the coronary flow but induced, at the same time, an evident reduction in the amplitude of contractions. Only the vasodilator action of **8**, which was quite similar to that of papaverine, was not accompanied by changes in amplitude of contractions and in cardiac frequency. Antiarrhythmic action was tested only for those compound which lacked overt cardiotoxicity; **18**, **19**, and **22–24** considerably reduced the maximal rate of stimulation of electrically driven isolated guinea pig auricles. This activity was comparable with that obtained with an equal dose of quinidine but, with the exception of **24**, all the compounds markedly inhibited the amplitude of contractions. None of the substances showed significant analgetic, antiinflammatory, antibacterial, and antifungal activities.

Due to the promising results shown in the preliminary antiarrhythmic testing of **24** [1,5-dimorpholino-3-(α-

(4) S. Irwin, Communication at the Gordon Research Conference on Medicinal Chemistry, New London, N. H., Aug 1959.

(5) G. Coppi, A. Maselli, and C. Ciani-Bonardi, *Farmaco Ed. Sci.*, **20**, 203 (1965).

TABLE II: PHARMACOLOGICAL SCREENING RESULTS

Compd	Approx LD_{50} (mouse), mg/kg ip	Act. on spontaneous motility (mouse) Decrease, %[a]	mg/kg ip	Analgesic act. (mouse) Increase of reaction time, %[b]	mg/kg ip	Surface local anesthetic act. (guinea pig), %[c]	Antispasmodic act. *in vitro* —% inhib of spasm produced by[d] Acetylcholine, 1×10^{-5} g/ml	Histamine, 1×10^{-6} g/ml	Nicotine, 2×10^{-6} g/ml	5-HT, δ 1×10^{-6} g/ml	Antibistaminic act. *in vitro* (guinea pig)[e] Protection, %	mg/kg ip	Antiinflammatory act. (rat) Inhib of edema, %[f]	mg/kg os	Hypotensive act. (rat), fall of blood pressure, mm of Hg[g]	Coronary vasodilator act. (isolated rabbit heart), increase of flow, %[h]	Anti-arrhythmic act. (electrically driven isolated guinea pig auricles) decrease, %[i]
1	150	38	50	54	50	30	Inact	Inact	39	Inact	Inact	50			35	Inact	
2	285	64	50	56	50	Inact	Inact	20	Inact	Inact	33	50			20	25	
3	100	38	25	Inact	25	28	Inact	86	Inact	Inact	Inact	25			Inact	Inact	
4	150	Inact	25	Inact	25	23	Inact	43	18	Inact	Inact	25	15	200	Inact	12	
5	71	47	25	45	25	25	Inact	56	Inact	Inact	Inact	25			Inact	65	
6	200	71	100	56	100	Inact	Inact	100	Inact	Inact	Inact	100	Inact	200	46	19	
7	150	Inact	25	Inact	25	20	Inact	53	29	Inact	Inact	25			40	Inact	
8	100	Inact	25	62	25	56	40	44	30	Inact	Inact	25			Inact	100	
9	150	50	25	Inact	25	61	32	30	37	34	Inact	25			50	Inact	
10	70	41	25	Inact	25	93	Inact	25	53	26	Inact	25			Inact	38	
11	82	63	50	40	25	27	32	Inact	Inact	19	Inact	25			Inact	32	
12	285	Inact	25	80	25	46	Inact	38	35	16	Inact	50	Inact	200	Inact	24	
13	150	52	25	70	25	44	30	Inact	Inact	Inact	Inact	25	Inact	50	35	35	
14	71	45	50	Inact	50	46	35	Inact	Inact	Inact	Inact	25			20	Inact	Inact
15	100	Inact	25	Inact	25	43	89	96	Inact	35	Inact	25			Inact	Inact	
16	140	Inact	12.5	Inact	12.5	94	87	18	42	34	Inact	12.5			Inact	68	
17	150	71	50	53	50	58	81	45	Inact	Inact	Inact	50			55	146	
18	100	38	25	Inact	25	22	Inact	25	Inact	Inact	Inact	25			47	Inact	75
19	285	32	25	43	25	24	Inact	40	Inact	Inact	Inact	25			Inact	Inact	86
20	280	57	100	49	100	24	Inact	62	Inact	Inact	33	100			Inact	Inact	
21	280	33	100	Inact	100	30	Inact	Inact	Inact	Inact	Inact	100	Inact	200	Inact	10	
22	150	59	100	48	100	30	Inact	Inact	Inact	Inact	Inact	100			Inact	Inact	91
23	200	31	50	46	50	23	Inact	Inact	Inact	Inact	Inact	50			Inact	28	81
24	452	51	200	43	200	Inact	20	Inact	Inact	Inact	Inact	200			Inact	Inact	52
25	86	41	12.5	Inact	12.5	79	40	31	69	47	Inact	12.5	Inact	50	Inact	39	
Meprobamate		50	200														
Morphine·HCl				67	5												
Lidocaine·HCl						64											
Diphenhydramine·HCl											100	25					
Phenylbutazone													59	200			
Guanethidine sulfate															78		
Papaverine·HCl																104	
Quinidine sulfate																	68

[a] Values referred to controls, 15 min after treatment [P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953)]. [b] Hot plate test, 1 hr after treatment [E. Adami and E. Marazzi, *Arch. Int. Pharmacodyn.*, **107**, 322 (1956)]. [c] The compounds were tested at a concentration of 1 mg/ml [M. B. A. Chance, and H. Lubstein, *J. Pharmacol. Exp. Ther.*, **82**, 203 (1944)]. [d] The compounds were tested at a concentration of 1 μg/ml [B. Magnus, *Arch. Gesamte Physiol. Menschen Tiere*, **102**, 123 (1904)]. The ED_{50} values for the standards are: atropine sulfate, 0.0035 μg/ml; diphenhydramine·HCl, 0.0074 μg/ml; hexamethonium bitartrate, 0.88 μg/ml; and chlorpromazine·HCl, 0.055 μg/ml. [e] Aerosol of histamine (0.25%), 15 min after treatment (H. Herxheimer, *J. Physiol.* (London), **117**, 251 (1952)]. [f] Carrageenin-induced edema, 5 hr after treatment [E. Marazzi-Uberti and C. Turba, *Arch. Intern. Pharmacodyn.*, **162**, 378 (1966)]. [g] The compounds were tested at 10 mg/kg iv; guanethidine sulfate was tested at 5 mg/kg iv; pressure was recorded at the carotid in urethan-narcotized rats. [h] The compounds were tested at a concentration of 1 μg/ml [C. Turba and E. Marazzi-Uberti, *Arzneim. Forsch.*, **16**, 386 (1966)]. [i] The compounds were tested at 10 μg/ml [C. Bianchi, G. P. Sanna, and C. Turba, *ibid.*, **18**, 845 (1968)].

naphthyl)pentane], this compound was submitted to a more detailed pharmacological and toxicological study,[6-9] as well as to a preliminary clinical trial.[10]

(6) C. Bianchi, T. Bruzzese, S. Casadio, G. Coppi, G. Pala, G. P. Sanna, and C. Turba, *Experientia*, **23**, 243 (1967).
(7) C. Bianchi, G. P. Sanna, and C. Turba, *Arzneim. Forsch.*, **18**, 845 (1968).
(8) G. Coppi, G. Bonardi, and R. Perego, *ibid.*, **18**, 1343 (1968).
(9) G. Coppi, G. Bonardi, E. Marazzi-Uberti, and C. Bianchi, *ibid.*, **19**, 156 (1969).
(10) V. Casadio, E. Baldoni, and P. Serenthà, *Curr. Ther. Res. Clin. Exp.*, **9**, 429 (1967).

An investigation of other substances chemically related to the title compounds is also in progress, in order to shed more light on the structure–antiarrhythmic activity relationships.

Acknowledgments.—The authors wish to thank Dr. G. Sekules for performing the microanalyses, Mr. O. Boniardi for assistance in preparing the compounds, and Mrs. L. Pozzi and Miss L. Tomasi for carrying out the pharmacological tests.

Anticancer Agents. IV.[1a,b] The Antitumor Activity of Some 1,4- and 1,5-(Bisthiosemicarbazones) and of Related Heterocycles

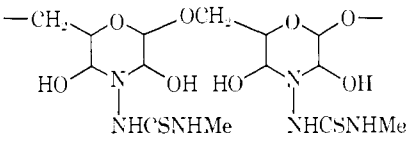
V. C. BARRY, M. L. CONALTY, JOAN E. MCCORMICK, R. S. MCELHINNEY,[1c] MARY R. MCINERNEY, AND J. F. O'SULLIVAN

Laboratories of the Medical Research Council of Ireland, Trinity College, Dublin 2, Ireland

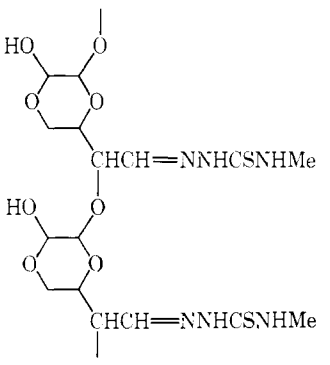
Received September 10, 1968

4-Alkylthiosemicarbazide derivatives of 1,4-diketones (2:1 and to a lesser extent 1:1), of succindialdehyde, of 3-heteraglutaraldehydes (2:1 and 1:1), and of 2,5-dihydroxy-1,4-dithian are in general active against Sarcoma 180 in mice, while the corresponding unsubstituted thiosemicarbazones have no activity. This parallels the striking difference previously observed between thiosemicarbazide (TSC) and its 4-alkyl counterparts when condensed with periodate-oxidized polysaccharides and with other dicarbonyl compounds. Where the effect of varying the 4-alkyl substituent of the TSC has been investigated, it seems that Pr derivatives of 3-heteraglutaraldehydes are more effective than Me or β-hydroxyethyl derivatives, whereas increasing the chain length of the TSC substituent in the diketone series is detrimental (as in the oxypolysaccharides). The vitamin B_6 antagonism characteristic of the polymeric derivatives has also been observed in some of the compounds now described. Many of them display activity against HeLa cells *in vitro*.

The polyaldehydes resulting from periodate oxidation of polysaccharides condense with substituted TSC's to give products which show activity against Sarcoma 180 in mice.[2] The composition of these N-containing polymers approximates 1 molecule of TSC per pair of aldehyde groups. Investigation of the structure[2,3] has revealed that some of the TSC residues are linked to the polymeric backbone by single bonds (C–N–C), the others by normal thiosemicarbazone bonds (C=N). The former are often incorporated into morpholine rings while the latter help to constitute a polythiosemicarbazone. Two consecutive morpholine units from an oxidized xylan are shown in I, and two such thiosemicarbazone units from oxidized starch in II. In the present work, we have prepared TSC derivatives of simple dicarbonyl compounds and tested them for antitumor activity, in order to compare them with the polymers.



I



II

Chemistry.—In the first attempt to prepare ring compounds modeled on I, acetonylacetone was chosen as the most readily available comparable dicarbonyl compound. When this reacts with 1 mol of 4-methyl-TSC, the intermediate dihydroxy compound (corresponding to the morpholine unit in I) is not isolable. It spontaneously loses H_2O to yield the pyrrole IIIa, an example of the well-known Paal–Knorr synthesis. Other pyrroles IIIb–d were prepared similarly.[4]

Reaction of 2 mol of 4-Me-TSC with the diketone gives the bisthiosemicarbazone IVb (*cf.* ref 5). 4-Monosubstituted TSC's in general react in this way to give IVa–g, but we have so far been unable to prepare bis derivatives from TSC's with other types of substitution.

(1) (a) Paper III: V. C. Barry, M. L. Conalty, C. N. O'Callaghan, and D. Twomey, *Proc. Roy. Irish Acad. Sect. B*, **65**, 309 (1967). (b) Part of this work was presented before the Ninth International Cancer Congress, Tokyo, Japan, Oct 1966 (Abstracts, p 318). (c) To whom correspondence should be addressed.
(2) V. C. Barry, M. L. Conalty, J. E. McCormick, R. S. McElhinney, and J. F. O'Sullivan, *Proc. Roy. Irish Acad. Sect. B*, **64**, 335 (1966).
(3) J. E. McCormick, *J. Chem. Soc. C*, 2121 (1966).
(4) R. S. McElhinney, to be published.
(5) H. Beyer, T. Pyl, and C.-E. Völcker, *Justus Liebigs Ann. Chem.*, **638**, 150 (1960).