Experimental Antileukemic Agents. Preparation and Structure–Activity Study of S-Tritylcysteine and Related Compounds[1]

KWANG-YUEN ZEE-CHENG AND C. C. CHENG

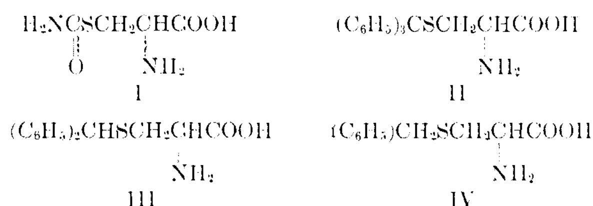
Midwest Research Institute, Kansas City, Missouri 64110

Received October 24, 1969

Structural modification of S-trityl-L-cysteine, which possesses confirmed antileukemic activity against leukemia L-1210, has been studied. This includes variation of (1) the aryl moiety and (2) the amino acid. Preliminary test results indicated that aryl-substituted S-trityl-L-cysteines containing moderate electron-withdrawing substituents usually retain or improve the antileukemic activity of the parent compound. The internal zwitterion form of the amino acid seems to be an important factor for antileukemic activity since substitution at either the amino or the carboxylic acid group decreased the activity. Of particular interest are the following facts: S-trityl-D-cysteine and O-trityl-L-serine possess low but definite antileukemic activity. Also, S-(2-naphthyldiphenylmethyl)-L-cysteine possesses better activity than the orginal compound but the corresponding 1-naphthyl isomer is totally inactive. Two possible mechanisms of action for compounds of this type are suggested.

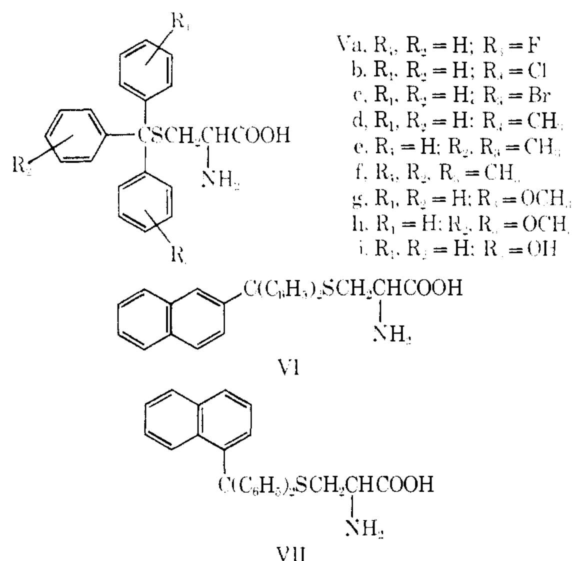
Among a number of amino acid antagonists synthesized, some S-substituted cysteines were found to exhibit growth-inhibitory activity against certain bacteria,[2,3] fungi, and algae.[4] S-Carbamyl-L-cysteine (I), for example, a noncompetitive antagonist of glutamine in bacteria,[3] has been shown to be cytotoxic against L-5178-Y L-asparaginase-sensitive and the L-1210 nonsensitive cells *in vitro*,[5] as well as having antitumor activity against a transplanted mouse adenocarcinoma,[6] P-1798, and L-asparaginase-sensitive lymphosarcoma[5] *in vivo*.

It was recently found that S-trityl-L-cysteine[7,8] (II), originally prepared as an S-protecting intermediate for peptide syntheses,[7–15] possessed confirmed antileukemic activity against leukemia L-1210.[16] This antileukemic property was not observed with the corresponding diphenylmethyl (III) or monophenylmethyl (IV) analogs, nor was it detected with triphenylmethanol, trityl chloride, or trityl mercaptan.[16]



Although it was reported that leukemic leukocytes have a high initial cysteine–cystine requirement,[17,18] the mode of antileukemic action of S-trityl-L-cysteine is not yet understood. Structural modification of this compound was therefore initiated in order to gain additional information with regard to the structure–activity relationships. Our preliminary study is focused in the following two areas.

Modification of the Aryl Moiety of S-Trityl-L-cysteine.—This includes preparation of substituted S-trityl-L-cysteines and study of the electronic and steric effects of various aryl substituents (V–VII) on the strength of the C–S bond. In addition, synthesis of tritylcysteine derivatives with hydrophilic group substituents (the parent compound is very insoluble in water) was also conducted.



There is a marked difference in chemical reactivity between S-trityl-L-cysteine (II) and the corresponding diphenylmethyl (III) analog. For example, S-trityl-L-cysteine is easily cleaved by agents such as HBr in AcOH or heavy metal salts (*e.g.*, $AgNO_3$) in pyridine, but less sensitive in cleavage in refluxing trifluoracetic acid.[14,19,20] On the other hand, III can be readily

(1) (a) This investigation was supported by Contract No. PH-43-65-94 with Chemotherapy, National Cancer Institute, of the National Institutes of Health, Public Health Service; (b) presented in part before the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969 (Medi 65).
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(16) Information provided by Dr. Harry B. Wood, Jr. of CCNSC.
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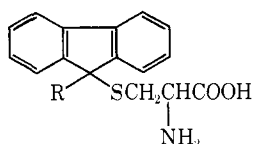
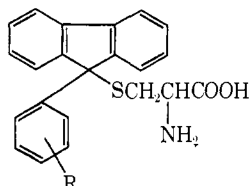
cleaved in refluxing trifluoroacetic acid but less readily by HBr, and is not affected by heavy metal salts (heavy metal salts can cleave the S–S bond on N-substituted cystine). Based on the results of König, *et al.*,[20] we postulate that the difference in sensitivity of II and III toward trifluoroacetic acid may be due to the presence of the benzylic H of III (and possibly of IV). It is probable that the rate and conditions of cleavage might be related to the inhibitory activity. Since practically no cleavage was observed for *S*-9-fluorenylcysteine (VIIIa) and *S*-9-(9-methyl)fluorenylcysteine (VIIIb), preparation and activity correlation study of various derivatives with aryl substitution (IX) were carried out.

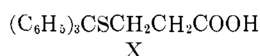


VIIIa, R = H
b, R = CH_3

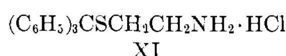


IXa, R = H
b, R = *p*-F
c, R = *p*-Cl
d, R = *p*-CH_3
e, R = *p*-CH_3O
f, R = 2,3-C_4H_4(α-naphthyl)

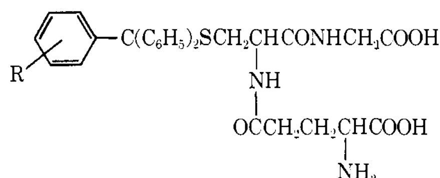
Modification of the Side Chain of *S*-Trityl-L-cysteine.—This includes preparation of possible catabolic (*e.g.*, X and XI) and anabolic products of *S*-trityl-L-cysteine—some of which might act as the actual inhibitor(s) *in vivo*—including certain polypeptides (detailed work of dipeptides will be treated in a separate part of our work) such as the glutathione derivatives[21] (XII). Other structural changes of the alanine moiety (XIII–XVI) of the parent compound, preparation of trityl derivatives of serine and lysine (XVII and XVIII), and preparation of *S*-trityl-D-cysteine (XIX) and *S*-trityl-DL-homocysteine (XX) were also carried out. Compound XX might interfere with the transmethylation reaction.[22]



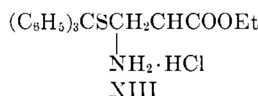
X



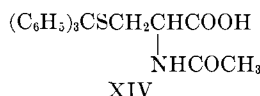
XI



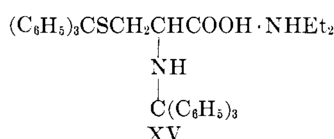
XIIa, R = H
b, R = *p*-F



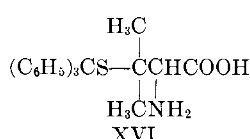
XIII



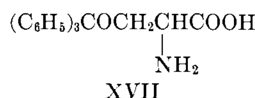
XIV



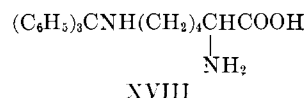
XV



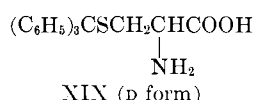
XVI



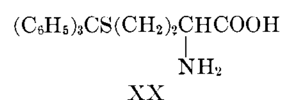
XVII



XVIII

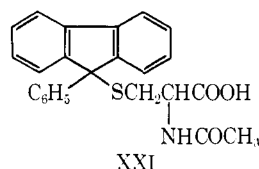


XIX (D form)

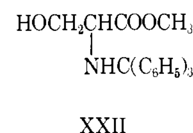


XX

In addition, for a comparison of biological activity, *N*-acetyl-*S*-9-(9-phenyl)fluorenylcysteine (XXI) and *N*-tritylserine Me ester (XXII) were also prepared.



XXI



XXII

Chemistry.—Among the known methods for the preparation of S-substituted cysteines[7,20,23–26] and S-tritylation reactions,[27–32] condensation of cysteine with the appropriate aryl-substituted carbinols with BF_3,[8,20] which involves initial carbonium ion formation of the carbinol followed by nucleophilic attack of the S atom of cysteine or related compounds, was adapted for the present preparation. The carbinols and fluorenols were obtained through conventional Grignard synthesis.

The BF_3–AcOH catalyzed condensation reactions between various carbinols with cysteines and related compounds can be generalized as follows. (1) Compounds containing primary SH groups (such as cysteine, β-mercaptopropionic acid, β-mercaptoethylamine, etc.) readily condense with tritanol or tri(substituted aryl)-carbinols in good (70–90%) yield and the products are usually of high purity; (2) electron-donating groups substituted on the aromatic rings favor the condensation, whereas electron-withdrawing groups retard the condensation; no reaction was noted between cysteine and *p*-nitrotritanol or diphenyl-4-pyridinylmethanol (the relative ease of carbonium ion formation of various triphenylmethanols in another medium has been reported[33] and is in accord with the present observation); (3) condensation of tertiary SH derivatives, such as penicillamine, and tritanols give fair (50–70%) yields of condensation products; (4) condensation of cysteine and secondary aralkyl alcohols, such as 9-fluorenol, gives poor (10–20%) yields, perhaps due to the relative instability of the carbonium ion; (5) in the case of O analogs of cysteine, condensation of tritanols with primary alcohols (*e.g.*, serine) give moderate (20–40%) yields; no reaction was observed between tritanols and secondary alcohols (*e.g.*, threonine) or between tritanols and phenolic derivatives (*e.g.*, tyrosine); (6) tritanols do not condense with the N analogs of cysteine (*e.g.*, lysine) because of protonation of the amino group by AcOH. N^{ϵ}-Tritylysine (XVIII) was prepared by the

(21) In general, higher glutathione content is found in tumor than in normal tissue. See, for example, V. I. Gorodyskii, I. V. Veselaya, and N. I. Uvarova, *Vop. Eksp. Onkol*, 147 (1965); *Chem. Abstr.*, **66**, 27172*g* (1967).

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TABLE I
S-TRITYL-L-CYSTEINE AND RELATED COMPOUNDS

Compd	Molecular formula[a]	Mp, °C	Yield[b] (%)	$[\alpha]^{25}_{D}$, deg (c = 1, 0.1 N NaOH)	Antileukemic activity against L-1210[c]: Dose, mg/kg	Survivors	Wt diff, T-C	T/C (%)
II	$C_{22}H_{21}NO_2S$	201–202	70	+19.2	100	12/12	−3.2	146
					50	12/12	−0.8	217
					25	12/12	−0.4	164
					12.5	12/12	−0.2	149
					6.25	12/12	−0.5	126
Va	$C_{22}H_{20}FNO_2S$	203–205	87	+12.8	100	6/6	−5.4	130
					50	6/6	−5.3	193
					25	6/6	−4.6	181
					12.5	6/6	−1.9	136
Vb	$C_{22}H_{20}ClNO_2S$[d]	193–195	84	+10.1	50	6/6	−4.8	203
					25	6/6	−2.7	212[e]
					12.5	6/6	−1.3	160
					6.25	6/6	−0.9	159
					3.13	6/6	−0.6	130
Vc	$C_{22}H_{20}BrNO_2S$	188–189	75	*f*	12.5	6/6	−2.6	142
					6.25	6/6	−0.8	151
					3.13	6/6	−2.5	124
Vd	$C_{23}H_{23}NO_2S$	198–200	72	+22.5	50	6/6	−3.2	147
					25	6/6	−1.7	144
					12.5	6/6	−2.6	144
					6.25	6/6	−0.5	141
					3.13	6/6	−0.4	133
Ve	$C_{24}H_{25}NO_2S$	196–198	90	*f*	50	6/6	−2.6	161
					25	6/6	−1.3	182[e]
					12.5	6/6	−0.4	137
					6.25	6/6	−1.3	136
Vf	$C_{25}H_{27}NO_2S$	209–210	73	+11.9	400	10/12	−4.6	160
					200	5/6	−5.1	210
					100	6/6	−5.6	175
					50	6/6	−4.4	148
					25	6/6	−4.0	125
Vg	$C_{23}H_{23}NO_3S$[d]	178–180	85	+19.5	50	6/6	−2.1	183
					25	6/6	−0.8	164
					12.5	6/6	−1.2	136
Vh	$C_{24}H_{25}NO_4S$	164–165	60	+4.0	25	18/18	−4.3	140
					12.5	6/6	−1.0	135
Vi	$C_{22}H_{21}NO_3S$	188–189	84	+38.8	25–50	Nontoxic, inact		
VI	$C_{26}H_{23}NO_2S$	172–174	92	*f*	25	6/6	−1.3	167
					12.5	6/6	−1.4	249[e]
					6.25	6/6	−0.5	147
					3.13	6/6	−1.4	137
VII	$C_{26}H_{23}NO_3S$	179–180	79	+26.3	25–400		Nontoxic, inact[h]	
VIIIa	$C_{16}H_{15}NO_2S$	201–203	48[i]	−22.6	25–400		Nontoxic, inact[h]	
IXa	$C_{22}H_{19}NO_2S$[j]	190–191	54	−28.7	25–400		Nontoxic, inact[h]	
IXb	$C_{22}H_{18}FNO_2S$	188–189	77	−33.2	200–400		Nontoxic, inact[h]	
IXc	$C_{22}H_{18}ClNO_2S$	194–195	76	−11.0	25–100		Nontoxic, inact[h]	
IXd	$C_{23}H_{21}NO_2S$	178–180	91	−36.0	25–200		Nontoxic, inact[h]	
IXe	$C_{23}H_{21}NO_3S$	171–172	95	−22.4	25–400		Nontoxic, inact[h]	
IXf	$C_{26}H_{21}NO_2S$[d]	178–180	83	*f*	25–400		Nontoxic, inact[h]	
X	$C_{22}H_{20}O_2S$	208–209[k]	100		25–400		Nontoxic, inact[h]	
XI	$C_{21}H_{21}NS \cdot HCl$[d,l]	128–130d	100		25–100		Nontoxic, inact[h]	
XIIa	$C_{29}H_{31}N_3O_6S$	200–201	72	+45.9	200	12/12	−2.0	124
XIIb	$C_{29}H_{30}FN_3O_6S$	208–210	65	+42.8	400	6/6	−1.9	140
					200	6/6	−3.2	150
					100	6/6	−2.2	136
					50	6/6	−1.2	128
XIII	$C_{24}H_{25}NO_2S \cdot HCl$	120 dec	47		100	12/12	−5.5	127
					50	12/12	−1.6	137
					25	10/12	−1.7	131
XIV	$C_{24}H_{23}NO_3S$[d]	108–110	83	+54.2	25–100		Nontoxic, inact	
XV	$C_{45}H_{46}N_2O_2S$[m]	205–207	65	*n*	25–75		Nontoxic, inact	
XVI	$C_{24}H_{25}NO_2S$[d]	180–182	64	*n*	50		Nontoxic, inact	
XVII	$C_{22}H_{21}NO_3$	208–209	38	+8.3	200	12/12	−2.4	150
					100	12/12	−1.7	133
XVIII	$C_{25}H_{28}N_2O_2$	230	78	*n*	6.25–100		Nontoxic, inact	
XIX	$C_{22}H_{21}NO_2S$	201–203	80	−19.5	50	12/12	−2.0	156
					25	18/18	−1.6	132

TABLE I (*Continued*)

Compd	Molecular formula[a]	Mp, °C	Yield[b] (%)	$[\alpha]^{24}D$, deg (c = 1, 0.1 N NaOH)	Antileukemic activity against L-1210[c]: Dose, mg/kg	Survivors	Wt. diff, T-C	T/C (%)
					12.5	6/6	−0.9	134
XX	$C_{23}H_{23}NO_2S$	215–217	75		50–200		Nontoxic, inact	
XXI	$C_{24}H_{21}NO_3S$	120–122	80	−17.9	25–200		Nontoxic, inact	
XXII	$C_{23}H_{23}NO_3$[p]	142–144	72	+44.8[q]	50–400		Nontoxic, inact	

[a] All compounds analyzed correctly for C, H, N. [b] Purified compounds. [c] Vehicle: saline (ip). [d] Hydrate. [e] 2 cures (see ref 35). [f] Formation of a gel was noted in 0.1 N NaOH during optical rotation determination. [g] Quarterhydrate. [h] 6/6 survived, T/C below 124. [i] Prepared by the method described in ref 7. [j] Hemihydrate. [k] Lit. [E. Billman, and N. V. Due, *Bull. Soc. Chim. Fr.*, **35**, 384 (1924)] mp 208–209°. [l] The hydrochloride salt of this compound was found to be identical with that prepared by a different method [F. I. Carroll, H. M. Dickson, and M. E. Wall, *J. Org. Chem.* **30**, 33 (1965)]. [m] Reference 10. [n] Immediate cloud formation was noted in 0.1 N NaOH. [o] Lit.[34] mp 230°. [p] Prepared by the method described in ref 9. [q] Measured in MeOH (c = 1).

method of Amiard and Goffinet[34] using the principle of selective detritylation.

Under the reaction conditions employed, tritylation of the Et ester of cysteine resulted in partial hydrolysis (to the extent of 10–20%) of the ester group. The products, which consist of a mixture of tritylated ester and tritylated acid, were readily separated since the acid is insoluble in either water or ether. The amide linkage, on the other hand, was found to be quite stable during the tritylation reaction. Consequently, the *S*-trityl and *S*-9-fluorenyl-9-phenyl derivatives of mercapturic acid were obtained in good yield. From the preceding study, it was found possible to selectively tritylate SH or primary OH groups in the presence of amino, secondary hydroxy, and/or amido groups. Thus compounds such as the *S*-tritylglutathione derivatives XIIa and XIIb can be readily prepared from glutathione in a single step.

Biological Activity and Discussion.—Preliminary test results[35] of derivatives of *S*-trityl-L-cysteine and related compounds in leukemia L-1210 (see Table I) are summarized as follows. (a) 3-Tritylthiopropionic acid (X) and the HCl salt of *S*-tritylcysteamine (XI), two possible metabolites of *S*-trityl-L-cysteine, are inactive against leukemia L-1210. Compound XI was found to be rather toxic. (b) All fluorenyl derivatives (VIII, IX, and XXI) are inactive. Toxicity was noted with *S*-9-(9-phenyl)fluorenylmercapturic acid (XXI). (c) Aryl-substituted *S*-trityl-L-cysteines (V) containing moderate electron-donating substituents retained or somewhat lowered the original activity; with moderate electron-withdrawing substituents the derivatives showed similar or slightly improved antileukemic activity when compared with that of *S*-trityl-L-cysteine. (d) *S*-(1-Napthyldiphenylmethyl)-L-cysteine (VII) possesses no antileukemic activity. The corresponding 2-naphthyl isomer VI, on the other hand, exhibits better activity than the original compound. (e) *S*-Tritylmercapturic acid (XIV) is totally inactive. *S*-Tritylglutathione (XIIa) possesses very low antileukemic activity, whereas the corresponding *p*-fluorotrityl analog (XIIb) shows slightly better activity. The Et ester of *S*-trityl-L-cysteine·HCl (XIII), which is more soluble in H_2O than the parent compound II, has only a trace of activity. The Et_2NH salt of *S*,*N*-ditrityl-L-cysteine (XV) is not active. These results indicate that substitution on the amino group of the original compound invalidates the activity. (f) The biological activity of *S*-trityl-D-cysteine (XIX) is somewhat reduced as compared to that of the corresponding L isomer. (g) *S*-Tritylpenicillamine (XVI) possesses no antileukemic activity. (h) *O*-Trityl-L-serine (XVII) shows low activity against leukemia L-1210; N^{ϵ}-trityl-L-lysine (XVIII) and the ester of *N*-tritylserine (XXII) are completely inactive. (i) *S*-Trityl-DL-homocysteine (XX) is nontoxic and inactive over a wide range of dose levels. (j) The Na salt of *S*-trityl-L-cysteine, which is readily soluble in H_2O, is only 50% as active as the original compound. This, together with the test results of amino-substituted derivatives (XII, XIV, XV, etc.), suggests that the internal zwitterion form might be important for biological activity.

Although the mode of antileukemic action of *S*-trityl-L-cysteine is not yet understood, two possible mechanisms for its action can perhaps be deduced based on the results of the present study.

Blocking Mechanism.—This amino acid may participate in certain peptide synthesis and subsequently block the S–S cross-linking of the peptide chains.

Carrier Mechanism.—The cysteine portion of this compound may act as an active carrier for the transport of the trityl radical for certain biological alkylating action.

The low but definite activity of *S*-trityl-D-cysteine as well as *O*-trityl-L-serine suggests that the second postulation is more probable.

Experimental Section

All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. Since the decomposition points of amino acids are usually irregular and depend on the rate of heating, the data reported were determined as follows. An approximate decomposition point of the amino acid was initially obtained by rapid heating. A second sample was heated rather rapidly to *ca.* 20° below the approximate decomposition point of the amino acid, at which point the temperature of the bath was then increased at the rate of 2°/min. The optical rotations were determined with a Hilger standard polarimeter. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

***S*-(Substituted trityl)-L-cysteines, *S*-[9-(9-Substituted phenyl)-fluorenyl]-L-cysteines and Related Compounds.**—To a stirred suspension of 0.03 mol of anhydrous L-cysteine·HCl or related compounds in 25 ml of AcOH was added 0.035 mol of the appropriate alcohol followed by 6.5 ml of purified BF_3-etherate.[36] The temperature of the reaction mixture throughout the addition was maintained at *ca.* 25°. An intense coloration (color varies from yellow to dark blue, depending on the nature of substituents on the ring system) usually developed immediately and the sus-

(34) G. Amiard and B. Goffinet, *Bull. Soc. Chim. Fr.*, 1133 (1958).

(35) Test results were provided by contract screeners of CCNSC. Detailed interpretations of test data are provided in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(36) *Cf.* L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 70.

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 tritylation 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

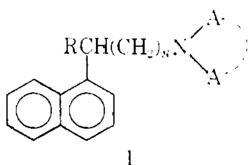
SILVANO CASADIO, GIANFRANCO PALA, TIBERIO BRUZZESE, CARLA TURBA, AND ERNESTA MARAZZI-UBERTI

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.

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°.

(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).

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