the solvent was removed under reduced pressure, and the products were recrystallized from the listed solvents.

1-Diphenylmethyl-4-sulfanilylpiperazine.—A mixture of 8.6 g (0.037 mole) of *p*-acetaminobenzenesulfonyl chloride, 10.7 g (0.037 mole) of 1-(diphenylmethyl)piperazine hydrochloride, 7.5 g (0.09 mole) of $NaHCO_3$, 250 ml of ether, 30 ml of $CHCl_3$, plus 80 ml of H_2O was vigorously agitated and refluxed for 1 hr. The mixture was chilled, and the precipitate was collected and hydrolyzed without further purification with 50 ml of concentrated HCl, 150 ml of H_2O, and 100 ml of EtOH by refluxing for 45 min. After chilling, a brownish precipitate was discarded. The filtrate, made alkaline and distilled under reduced pressure, yielded a light brown solid which was partially purified by dissolving it with heat in 250 ml of dilute HCl containing charcoal. The chilled filtrate, made alkaline, yielded a white precipitate. Table I gives additional data.

N,N-Diethyl-1-(2-N,N-diethylaminoethyl)-4-piperazinecarboxamide Sulfate.—The base corresponding to 7.0 g (0.041 mole) of 2-chlorotriethylamine hydrochloride was obtained by dissolving the latter in a minimum amount of H_2O, adding concentrated NaOH, extracting the solution several times with ether, and thoroughly drying the latter. To this filtered solution was added 13.8 g (0.074 mole) of N,N-diethylcarbamoylpiperazine and the mixture was heated on a water bath to remove the ether. The residue, dissolved in toluene, was then refluxed for 1 hr. The hydrochloride of N,N-diethylcarbamoylpiperazine (**10**) appeared on chilling. The residue obtained after removing the toluene under reduced pressure was dissolved in 100 ml of dry acetone and, while stirring, a chilled solution of H_2SO_4 in Me_2CO was added dropwise. The gummy product was subjected to preliminary purification by washing (Me_2CO, dry Et_2O). Table I gives additional information.

A New Class of Analgetic–Antiinflammatory Agents. 2-Substituted 4,5-Diphenyloxazoles

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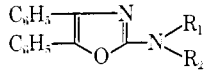
Received April 4, 1967

Recently, a number of five-membered heterocyclic amines, including oxadiazole,[2] indazole,[3] isoxazole,[4] and triazole[5] ring systems, have been shown to possess antiinflammatory and analgetic properties. We now wish to report the synthesis and some preliminary pharmacological results of a new series of substituted 2-aminooxazoles of general formula **1**, some of which show interesting analgetic and antiinflammatory properties associated with a low acute and chronic



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toxicity.

Chemistry.—The new aminooxazoles are listed in Table I, together with their analytical and physical data. All the compounds have been prepared in good yields by a conventional method, namely the reaction between the known 2-chloro-4,5-diphenyloxazole and the appropriate amine or amino alcohol; compound **7** has been synthetized also through the cyclization of the N-desyl-N-diethylurea, easily obtained by treating desyl bromide with N,N-diethylurea.

Pharmacological Results.—Some of the results have been summarized in Table I. Most of the new oxazole amines are characterized by a very low toxicity. Secondary amines are practically devoid of any antiinflammatory and analgetic activity, while most of the tertiary amines and amino alcohols possess such activities to a degree, which competes favorably with that of equal doses of phenylbutazone and aminopyrine, respectively. A noticeable exception is represented by the piperidine derivative **9**, which shows only a weak antiinflammatory activity and is practically devoid of analgetic properties.

Among tertiary amines maximum activity has been found with the pyrrolidine derivative (**8**), while in the amino alcohol series the diethanolamine (**18**) and the diisopropanolamine (**19**) derivatives, respectively, appear to be the most active compounds. It is interesting to note that among the diamino derivatives (**20–27**) some still retain the antiinflammatory activity, which is characteristic of the above tertiary amines, while they are all devoid of any analgetic properties.

The most interesting compound of the series appeared to be the diethanolamine derivative **18**, which has been selected for a more extensive pharmacological and toxicological evaluation. Its antiinflammatory activity was confirmed by the results obtained in the inhibition of edema induced by dextran, formalin, and serotonin; in the first test, 400 mg/kg *po* of **18** proved to be equipotent with an equal dose of aminopyrine, while in the two other tests 90 mg/kg *po* showed the same activity of an equal dose of phenylbutazone.

In addition, in the range between 30–90 mg/kg *po* **18** was equally active as phenylbutazone in inhibiting the cotton pellet induced granuloma. In the range between 300–400 mg/kg *po*, in the Randall and Selitto[6] and in the tail pinching tests,[7] the analgetic activity of **18** practically equalled the response obtained with the same dose of aminopyrine, while in the phenylquinone writhing test[8] **18** appeared to be less active than aminopyrine itself. In view of its interesting pharmacological activities, and low acute and chronic toxicity, **18** has been selected for clinical trial.

None of the compounds listed in Table I showed antipyretic activity.

Experimental Section

All melting points were taken on a W. Büchi melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Synthesis. General Method for the 2-Amino-4,5-diphenyloxazoles.—The reactions between 2-chloro-4,5-diphenyloxazoles[9] and the various amines were carried out in boiling C_6H_6 using a 3-mole excess of the basic compound. The reactions with low-boiling amines were carried out in a sealed tube; in the case of amino alcohols, EtOH was used as the solvent. The reaction time was usually 4–6 hr. The final reaction mixture was treated

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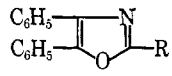
TABLE I



No.	R	Formula[e]	Mp, °C	Recrystn solvent[a]	Yield, %	Toxicity MLD (mice), mg/kg *po*[b]	Antiinflam act. (rat)[c]	Analgetic act. (mice)[d]
1	$NHCH_3$	$C_{16}H_{14}ON_2$	167–168	A	67	>3000	0.65	0
2	NHC_2H_5	$C_{17}H_{16}ON_2$	144–146	A	71	>3000	0	0
3	$NHCH(CH_3)_2$	$C_{18}H_{18}ON_2 \cdot H_2O$	135–137	C	78	>4000	0	0.50
4	$NH(CH_2)_3CH_3$	$C_{19}H_{20}ON_2$	91–93	A	81	4000	0	0
5	NH-cyclohexyl	$C_{21}H_{22}ON_2$	133–134	A	80	3000	0	0
6	$N(CH_3)_2$	$C_{17}H_{16}ON_2$	77–79	C	57	750	0.67	1.20
7	$N(C_2H_5)_2$	$C_{19}H_{20}ON_2 \cdot HCl$	117–118	A	55	>5000	0.80	0.39
8		$C_{19}H_{16}ON_2$	121–122	A	76	>4000	1	0.57
9		$C_{20}H_{20}ON_2$	140–141	A	86	2500	0.50	0
10		$C_{19}H_{18}O_2N_2$	122–124	A	75	2000	1.10	0.30
11	$NHCH_2CH_2OH$	$C_{17}H_{16}O_2N_2$	106–108	C	64	1000	0.70	0.71
12	$NHCH_2CH_2CH_2OH$	$C_{18}H_{18}O_2N_2$	132–134	A	66	>2000	0.60	0.80
13	$NHCH_2CHOHCH_3$	$C_{18}H_{10}O_2N_2 \cdot HCl$	174–175	D	61	800	0.50	0.60
14	NCH_2CH_2OH CH_3	$C_{18}H_{18}O_2N_2$	99–100	A	77	900	0.68	0
15	NCH_2CH_2OH C_2H_5	$C_{19}H_{20}O_2N_2$	55–57	A	53	1600	0.74	1.04
16	NCH_2CH_2OH $CH_2CH_2CH_2CH_3$	$C_{21}H_{24}O_2N_2$	76–77	C	78	>2000	0.70	0.80
17	NCH_2CH_2OH $C(CH_3)_3$	$C_{21}H_{24}O_2N_2$	70–72	C	57	>2000	0.80	1.10
18	$N(CH_2CH_2OH)_2$	$C_{19}H_{20}O_3N_2 \cdot H_2O$	96–98	A	70	2300	1.15	1.00
19	$N(CH_2CHOHCH_3)_2$	$C_{21}H_{24}O_3N_2$	139–140	A	64	2000	0.90	1.20
20	$NHCH_2CH_2N(CH_3)_2$	$C_{19}H_{21}ON_3$	84–85	B	62	400	0.70	...
21	$NHCH_2CH_2N(C_2H_5)_2$	$C_{21}H_{25}ON_3$	83–84	B	48	>3000	0	0
22	$NH(CH_2)_3N(CH_3)_2$	$C_{20}H_{23}ON_3$	92–93	B	81	1000	0.90	0
23	$NH(CH_2)_3N(C_2H_5)_2$	$C_{22}H_{27}ON_3$	100–101	B	70	400	0.80	...
24		$C_{19}H_{19}ON_3$	115–116	C	66	350	0.64	...
25		$C_2H_{21}ON_3$	85–86	B	67	850	1.10	0
26		$C_{22}H_{23}O_3N_3$	97–98	A	75	4000	0	0.20
27		$C_{21}H_{24}O_2N_3 \cdot HCl$	273–274	D	64	700	0.40	0.80

[a] A = EtOH 95%, B = hexane, C = ether–petroleum ether (bp 30–60°), D = absolute EtOH–ether. [b] Minimum lethal dose. [c] The figures represent the activity potency observed after administration of 100 mg/kg *po* of substance, the antiinflammatory activity of 100 mg/kg *po* of phenylbutazone being arbitrarily assumed as equal to 1. [d] The figures represent the activity potency observed after administration of 300 mg/kg *po* of substance, the analgetic activity of an equal dose of aminopyrine being arbitrarily assumed as equal to 1. [e] All compounds were analyzed for C, H, N.

with H_2O, the C_6H_6 layer was dried, and after elimination of the solvent a solid residue was usually obtained, which was directly crystallized from a suitable solvent (see Table I). When EtOH was used as the reaction solvent, crystalline materials could often be obtained simply by dilution with H_2O. When the products failed to crystallize, crystalline hydrochlorides were easily obtained. A few of the 2-substituted aminooxazoles gave crystals containing 1 mole of H_2O, which could be removed by heating *in vacuo*. Dry crystals of **18** rapidly acquired 1 mole of H_2O on standing.

2-Diethylamino-4,5-diphenyloxazole.—A solution of 41.3 g (0.15 mole) of desyl bromide and 70 g (0.6 mole) of N,N-diethylurea in 150 ml of DMF was heated on a water bath under stirring for 2 days. After removal of the solvent at reduced pressure, the residue was treated with 150 ml of 10% NaOH solution and repeatedly extracted with ether. The dried ethereal layers left an oily residue, which was taken into 70 ml of warm EtOH; by cooling, the alcoholic solution gave 22.4 g of the title compound, crystals with mp 74–75°.

Pharmacological Procedures.—The acute toxicity was determined in groups of five mice treated orally with increasing doses of each compound, suspended in 5% gum arabic. All the animals were observed for 5 days. Minimum lethal dose was recorded.

Antiinflammatory activity was tested primarily with the carrageenin test.[10] Groups of ten Wistar rats (150–170 g) were treated orally with the compounds to be tested, suspended in 5 ml of 5% gum arabic. One hour later the edema was produced by injection of 0.1 ml of 1% carrageenin in saline into the plantar surface of the hind paw of each rat. The foot volume was measured pletysmographically immediately after the injection and 3 hr later. The per cent volume was obtained from the formula: % edema = $(V_a - V_b)100/V_b$, where V_b is the mean volume of the hind paw before, and V_a after, the carrageenin injection. Antiinflammatory effect was expressed as % inhibition of edema = $(E_c - E_t)100/E_c$, where E_c is the per cent edema in the control animals and E_t in the treated animals. The compounds were tested at a dose of 100 mg/kg *po* in comparison with the same dose of phenylbutazone.

Analgetic activity was determined by the hot plate test,[11] using mice weighing 18–22 g. The analgetic activity was evaluated on the basis of the percentage of animals which showed an increase in the reaction time recorded before and after treatment. The compounds were administrated orally in 5% gum arabic to groups of ten mice and the activity was compared with that obtained with an equal dose of aminopyrine.

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