of the solvent and the H_2O formed], the appropriately substituted 2-aminophenol (2.03 moles), and either *n*-BuOH or *n*-AmOH (500 ml) were heated together. When the temperature reached approximately 100°, Cu powder (1.0 g) was added, and the reaction mixture was refluxed for 30 min. After cooling, $NaHCO_3$ (25 g) and a saturated solution of $NaHCO_3$ (250 ml) was added followed by steam distillation until all organic solvent was removed. The dark residual material was filtered and the filtrate was acidified with 6 *N* HCl. A dark precipitate was formed. This mixture was heated to approximately 60° and the dark solid was filtered from the hot aqueous acidic suspension, washed (H_2O), dissolved in EtOH, and passed through a charcoal column to remove most of the color. After removal of the EtOH and extracting with C_6H_6, the products (IIa-d) were of sufficient purity to be carried on to the lactonization step.

Dibenz[*b,e*][1,4]oxazepin-11(5H)-one (Ia).—N-(2-Hydroxyphenyl)anthranilic acid (0.009 mole, 2.0 g), *p*-tolnenesulfonic acid (0.5 g), and PhMe (200 ml) were refluxed together under N_2 with the H_2O formed being collected in a Dean–Stark receiver. After the theoretical amount of H_2O was collected, the cooled reaction mixture was extracted with saturated $NaHCO_3$, dried, filtered, and concentrated to dryness. The resulting solid was washed with cyclohexane yielding 1.0 g (53%) of Ia.

Dibenz[*b,e*][1,4]oxazepin-11(5H)-ones (I).—To a cooled solution of II (0.01 mole) in MeCN (300 ml), a solution of dicyclohexylcarbodiimide (0.012 mole) in MeCN (100 ml) was added slowly. After standing for 2 hr, the dicyclohexylurea formed was filtered off, and the filtrate was concentrated to dryness. The resultant yellow solids were recrystallized (C_6H_6) and analyzed for C, H, N: Ia ($C_{13}H_9NO_2$), yield 77%, mp 159–161°; Ib ($C_{13}H_8ClNO_2$), yield 47%, mp 236–238°; Ic ($C_{14}H_{11}NO_2$), yield 57%, mp 136–137°; Id ($C_{15}H_{13}NO_2$), yield 21%, mp 130–132.5°.

The Chemorelease of Norepinephrine from Mouse Hearts by Substituted Amphetamines[1]

F. BENINGTON AND R. D. MORIN

Department of Psychiatry, the University of Alabama in Birmingham, the Medical Center, Birmingham, Alabama 35233

Received January 16, 1968

The chemorelease of norepinephrine from mouse hearts by a large number of sympathomimetic and related amines has been studied extensively by Daly, *et al.*[2] Their results showed that chemorelease of cardiac norepinephrine was strongly influenced by the nature and position of both ring and side-chain substituents.

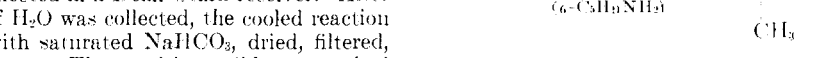
As part of a long-range study of the effects of ring substituents on the psychopharmacological activity of substituted amphetamines,[3] the relative ability of some 25 of these compounds to release cardiac norepinephrine has been determined. The chemorelease of norepinephrine by a few of these amphetamines has previously been reported,[2] and results obtained in our study were in agreement within experimental error as shown in Table I.

Substituted amphetamines which were not available commercially were synthesized from the corresponding substituted benzaldehydes by the following route

TABLE I

CHEMORELEASE OF NOREPINEPHRINE-^{3}H FROM MOUSE HEARTS BY SUBSTITUTED AMPHETAMINES PREVIOUSLY REPORTED

Substituent(s)	Dose, mg/kg	Norepinephrine-^{3}H in heart, % of control: This study	Previously reported[2]
None	10	58 (*dl*)	58 (*d*)
N-Methyl (*d* isomer)	10	57	62
3,4-Dihydroxy (*dl*)	5	45	39
4-Hydroxy (*dl*)	10	38	45
3,4-Dimethoxy (*dl*)	10	94	109
4-Chloro (*dl*)	10	77	71
3,4-Methylenedioxy (*dl*)	10	86	76



where R is substituted phenyl.

At a standard dose level of 10 mg/kg, the effectiveness of substituted amphetamines in chemorelease of cardiac norepinephrine divides these compounds into three groups: those with strong activity (release of 50% or more of the labeled norepinephrine), a group with moderate activity (release of 20 to 50% of the norepinephrine), and those with little or no activity (release of less than 20% of the norepinephrine). The norepinephrine releasing action of all amphetamines examined is summarized in Table II, tabulated in order of decreasing activity, and expressed in terms of per cent of labeled norepinephrine remaining in the heart compared with controls. The more active compounds were tried at lower dosages to obtain dose–response relationships.

The amphetamines with high activity include the 3-methyl, 4-hydroxy, 3-methoxy, 4-fluoro, 3,4-dihydroxy, and N-hydroxy derivatives as well as N-methylamphetamine and amphetamine itself. For all of these more active compounds, the effect of lower dosage was determined. In most cases, norepinephrine-releasing activity was negligible at a dose of 0.1 mg/kg, except for the 3-methoxy and 3,4-dihydroxy derivatives, which retained some activity even at a dose level of 0.1 mg/kg or less.

Methylation of the hydroxyl group in 4-hydroxyamphetamine to 4-methoxyamphetamine reduces the norepinephrine-releasing activity but does not abolish it as in the case of methylating the hydroxyl group in tyramine to 4-methoxyphenethylamine.[2] 3-Methoxyamphetamine exhibited an unexpectedly high activity for a methoxylated derivative.

Substituted amphetamines which retained moderate activity but were less active than unsubstituted amphetamine include 4-methoxy-, 3,4-dichloro-, 4-chloro-, and 3,5-dimethylamphetamines. Amphetamines with other indicated ring substituents failed to release norepinephrine from cardiac tissue.

Comparison of norepinephrine-releasing activity of amphetamines and β-phenethylamines with the same ring substituents shows that almost without exception the substituted amphetamines are more potent than the corresponding β-phenethylamines (Table III). However, substituents such as the hydroxyl group, which imparts greater activity to β-phenethylamine, do the same for amphetamine; this implies that in some instances the nature and position of the ring substit-

(1) This work was supported by Grant MH-11588 from the National Institute of Mental Health, U. S. Public Health Service.

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TABLE II

THE CHEMORELEASE OF NOREPINEPHRINE-^{3}H FROM MOUSE HEARTS BY *dl* RING-SUBSTITUTED AMPHETAMINES

Substituent(s)	Lit. Ref	Dose, mg/kg	Norepinephrine-^{3}H in heart, % of control
3-CH_3	*a*	10	40
		1	80
		0.1	103
4-OH	*b*	10	45
		1	78
		0.1	104
3-OCH_3	*c*	10	44
		5	47
		0.5	68
		0.05	87
4-F	*d*	10	50
		5	63
		2.5	73
		0.6	81
3,4-$(OH)_2$	*e*	5	45
		2.5	58
		1.0	62
		0.1	82
NOH	*f*	10	54
		5	65
		0.5	104
NCH_3 (*d* isomer)	*b*	10	57
None	*b*	10	58
4-OCH_3	*b*	10	61
		5	77
		0.5	94
3,4-Cl_2	*g*	10	77
4-Cl	*h*	10	77
3,5-$(CH_3)_2$	*i*	10	81
3,4-O_2CH_2	*b*	10	86
2,4,6-$(CH_3)_3$	*i*	10	88
2-CH_3	*j*	10	88
3,4,5-$(OCH_3)_3$	*k*	10	89
2-OCH_3	*c*	10	90
3,4-$(CH_3)_2$	*l*	10	90
4-CH_3	*m*	10	91
3,4-$(CH_3O)_2$	*n*	10	94
3,5-$(CH_3O)_2$	*o*	10	95
3,4,5-$(CH_3)_3$	*p*	10	96
N-$CH(CH_3)_2$	*q*	10	97
2,3-$(CH_3O)_2$	*o*	10	100
2,5-$(CH_3O)_2$	*r*	10	100
2,4,6-$(CH_3O)_3$	*s*	10	100

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uents may be more important than the aminoalkyl side chain structure for norepinephrine-releasing activity.

TABLE III

COMPARISON OF NOREPINEPHRINE RELEASE BY β-PHENETHYLAMINES AND THE CORRESPONDING AMPHETAMINES

Substituent(s)	Norepinephrine-^{3}H in heart, % of control: β-Phenethylamines	Norepinephrine-^{3}H in heart, % of control: Amphetamines
4-OH	50	45
3,4-$(OH)_2$	50	45
N-CH_3	80	57
None	65	58
4-OCH_3	102	61
4-Cl	101	77
2-CH_3	103	88
3,4,5-$(OCH_3)_3$	99	89
4-CH_3	94	91
2,3-$(OCH_3)_2$	87	100
2,5-$(OCH_3)_2$	98	100

Experimental Section

Materials.—All of the compounds were obtained in the *dl* form and were isolated and purified as their hydrochloride salts. The two substituted amphetamines not previously reported (2,4,6-trimethyl and 3,5-dimethyl) gave satisfactory analytical values for C, H, and N. *dl*-Norepinephrine-7-^{3}H was obtained from the New England Nuclear Corp. (specific activity, 5 mcuries/μmole).

Assay of Norepinephrine Release.—The assay procedure reported by Daly, *et al.*,[2] was used with slight modification. A 0.2-ml solution (isotonic NaCl (0.9%) containing 50 mg of heparin/l.) of 5 μcuries of norepinephrine-7-^{3}H was used for the tail vein injection of the mice (male Swiss white, random bred, 18–20 g). Drugs were administered subcutaneously after 1 hr, and the mice were sacrificed after 3 hr by neck fracture. The hearts (five mice/assay) were removed and treated as described.[2] After centrifugation, 0.5 ml of the supernatant solution was added to 10 ml of a modified Brays phosphor solution,[4] and the radioactivity was determined by liquid scintillation counting. Two sets of controls were run for each drug assay, which was also done in duplicate. Assays using tyramine at 5 mg/kg were included routinely as a standard to check on the experimental techniques. Injected norepinephrine-7-^{3}H retained by the heart tissue after drug treatment was calculated as per cent of the control value based on the average counts per minute for each set of samples.

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Some Compounds Active as Antirhinovirus in the Plaque Inhibition Test

CARLO RUNTI

Department of Pharmaceutical Chemistry, University of Trieste, Trieste, Italy

Received February 16, 1968

Few data concerning compounds active against rhinovirus have appeared in the literature.[1,2] In a previous paper we reported the antirhinovirus activity of some *p*-alkoxybenzensulfonylbiguanides,[3] and we now wish to report data concerning the activity against rhinoviruses 1059 and HGP shown by a different series

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