$NH_3$. After being kept at room temperature overnight, the solution was concentrated in vacuo to give the ammonium salt of **20** (2.0 g) which was heated on an oil bath (150–160 °C) under reduced pressure for 10 min. To the cooled residue was added AcOEt. The insoluble solid was collected and recrystallized from MeOH to give **21** (0.9 g, 53%), mp 189–194 °C. Anal. ($C_9H_9N_3O_4S$) C, H, N, S.

***N*-Acetyl-3-(sulfamoylmethyl)-1,2-benzisoxazole (22).** To 50 mL of AcCl was added **1a** (2.3 g). The mixture was refluxed for 48 h and then evaporated. The residue was washed with benzene, dried, and recrystallized from acetone to give **22** (2.5 g, 91%), mp 183–185 °C. Anal. ($C_{10}H_{10}N_2O_4S$) C, H, N, S.

**Biological Methods.** All experiments were carried out in male mice of STD-dd strain weighing 20–22 g. Diet and water were given ad libitum to animals until the time of experiment. All compounds were administered by gavage as a suspension of 5% tragacanth solution. In preliminary screenings, all compounds were tested for anticonvulsant activity at 100 mg/kg. For the determination of $ED_{50}$ and $NTD_{50}$, groups of ten mice were used per dosage level, using at least four dosage levels.

**Anticonvulsant Activity.** Drugs were evaluated for their ability to prevent the hind-limb extensor component of maximal electroshock seizure induced using a 60-Hz, 25-mA current for 0.2 s, delivered through corneal electrodes 2 h after dosing. $ED_{50}$ values were calculated by the method of Litchfield and Wilcoxon.[8]

**Neurotoxicity.** $NTD_{50}$ was determined employing the rotarod. The end point for minimal neurotoxicity was muscle incoordination and was based upon the inability of the mouse to retain on a horizontal rod (2.5-cm in diameter) rotating at 11 rpm 2 h after dosing. $NTD_{50}$ values were calculated by the method of Litchfield and Wilcoxon.[8]

**Acknowledgment.** The authors are grateful to Dr. M. Shimizu, the director of these laboratories, and Dr. S. Minami for their encouragement throughout the course of this work. Thanks are also due to Dr. T. Karasawa for his helpful discussion and members of the analytical section of these laboratories for elemental analyses and spectral measurements.

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# Azetidine Derivatives of Tricyclic Antidepressant Agents

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Tricyclic derivatives of azetidine were synthesized and screened for their potential antidepressant activity. The active series had the tricyclic rings attached to position 1 and a basic group in position 3 of the azetidine. The most interesting compounds were comparable to the reference standards for reserpine antagonism in mice, the most active being the dextrorotatory methylamino derivative **84**.[1] The pharmacological profile classifies it as a CNS stimulant devoid of peripheral anticholinergic activity.

One of the best represented classes in the field of psychoactive drugs with antidepressant effects is without doubt that of the tricyclic antidepressant agents. There has been a great deal of research on these structures in attempts to separate the documented therapeutic activity from the side effects, which are for the most part associated with their anticholinergic and cardiotoxic activities.[1-5] The novelty of the products synthesized is based on the association of the azetidine ring with the tricyclic structure. Some derivatives of this series were found in pharmacological screening to have potential antidepressant activity, the most encouraging results coming from products with two aliphatic amine groups, which is uncommon in the field of drugs with antidepressant activity.

**Chemistry.** The *tert*-butyl derivatives in Table I were obtained by alkylation of suitable substrates with 3-chloro-1-*tert*-butylazetidine, prepared by the method of Gaertner.[6] The other compounds were prepared according to Scheme I.

The alkylation was found to be difficult for $n = 1$ and A = $-CH_2CH_2-$. Compound **11** was so obtained by reductive dealkylation of the corresponding unsaturated derivative (A = $-CH{=}CH-$), which alkylates more easily. The yields of alkylation were 40–60%. Reductive dealkylation was, as expected, difficult for A = S, so that only the *tert*-butyl derivatives **2–4** and the unsubstituted azetidine **1** were prepared. To carry out the reductive amination,[8] it was necessary to carefully control times and temperatures for the compounds with A = $-CH_2O-$, in order to avoid cleavage of the benzyl ether.

The azetidines of Table V were synthesized from the corresponding mesylates prepared by the method of Anderson[7]. Tables II–IV list the intermediates, with their physical properties and yields. The general scheme (Scheme II) of synthesis is shown below. The methods

Scheme I[a]

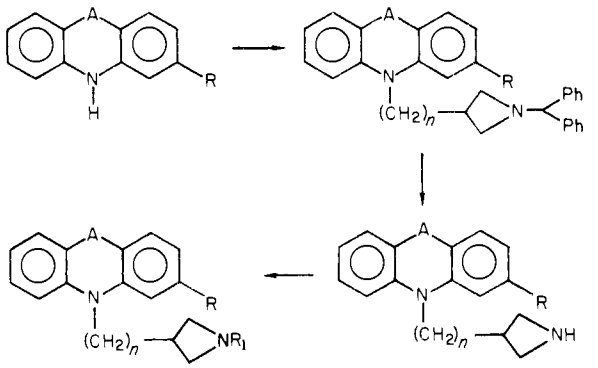
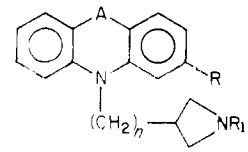



Table I

[a] For $n = 0$, the alkylating halide was a bromide;[7] for $n = 1$, a chloride.

Table I. 3-Tricyclic-Substituted Azetidines



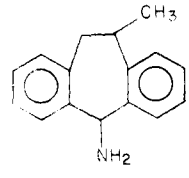
| no. | A | n | R | $R_1$ | mp, °C[a] | recrystn solvent | yield, % | formula[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | S | 0 | H | H | 263[c] | $MeOH/Et_2O$ | 35[d] | $C_{15}H_{14}N_2S$ |
| 2 | S | 0 | H | $C(CH_3)_3$ | 155-156 | hexane | 17[e] | $C_{19}H_{22}N_2S$ |
| 3 | S | 0 | Cl | $C(CH_3)_3$ | 190-193 | hexane | 28[e] | $C_{19}H_{21}ClN_2S$ |
| 4 | S | 0 | $CF_3$ | $C(CH_3)_3$ | 115-118 | hexane | 11[e] | $C_{20}H_{21}F_3N_2S$ |
| 5 | CH=CH | 0 | H | $C(CH_3)_3$ | 113-117 | $EtOH/H_2O$ | 12[e] | $C_{21}H_{24}N_2$ |
| 6 | $CH_2CH_2$ | 0 | H | H | 271-273[c] | $MeOH/Et_2O$ | 72[d] | $C_{17}H_{18}N_2$ |
| 7 | $CH_2CH_2$ | 0 | H | $CH_3$ | 115-116 | hexane | 62[f] | $C_{18}H_{20}N_2$ |
| 8 | $CH_2CH_2$ | 0 | H | $CH(CH_3)_2$ | 247-250[c] | $i$-PrOH/$Et_2O$ | 84[f] | $C_{20}H_{24}N_2$ |
| 9 | $CH_2CH_2$ | 0 | H | $C(CH_3)_3$ | 220-223[c] | AcOEt | 31[e] | $C_{21}H_{26}N_2$ |
| 10 | $CH_2CH_2$ | 0 | Cl | $C(CH_3)_3$ | 246-248[c] | $EtOH/Et_2O$ | 42[e] | $C_{21}H_{25}ClN_2$ |
| 11 | $CH_2CH_2$ | 1 | H | H | 144-148[c] | $MeOH/Et_2O$ | 86[d] | $C_{18}H_{21}ClN_2$ |
| 12 | $CH_2CH_2$ | 1 | H | $CH(CH_3)_2$ | 148-150[c] | $i$-PrOH/$Et_2O$ | 62[f] | $C_{21}H_{26}N_2$ |
| 13 | $CH_2O$ | 0 | H | H | 238-240[c] | $MeOH/Et_2O$ | 57[d] | $C_{17}H_{16}N_2O$ |
| 14 | $CH_2O$ | 0 | H | $CH(CH_3)_2$ | 231-233[c] | $i$-PrOH/$Et_2O$ | 46[f] | $C_{20}H_{22}N_2O$ |
| 15 | $CH_2O$ | 0 | H | $C(CH_3)_3$ | 108-109 | hexane | 18[e] | $C_{20}H_{24}N_2O$ |
| 16 | $CH_2O$ | 1 | H | H | 140-146[c] | $i$-PrOH | 70[d] | $C_{17}H_{16}N_2O$ |
| 17 | $CH_2O$ | 1 | H | $CH(CH_3)_2$ | oil | | 54[f] | $C_{20}H_{24}N_2O$ |

[a] Melting points are uncorrected. [b] The compounds were analyzed for all the elements except oxygen: the experimental values were within ±0.4 of the theoretical values. [c] Hydrochloride. [d] Reaction of reductive dealkylation of azetidine. [e] Alkylation of aromatic N. [f] Reductive alkylation of aliphatic N.

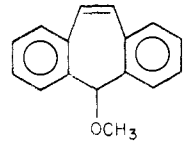
were those commonly used in organic chemistry, and some general examples are described in the Experimental Section. Some notes about the individual classes of compounds follow, to stress special features in their synthesis.

**Amines (Table II).** Nearly all the amines synthesized were already known. Nevertheless, we shall describe the general synthesis followed, which is based on the reduction of the corresponding oxime with $Zn/NH_4OH$ in $EtOH/H_2O$ according to J. K. Sugdan[9] because of the excellent yields and the selectivity.

In some cases, a cosolvent (DMF) was added to increase the solubility of the substrate and therefore have reductions which did not go satisfactorily with the "normal" procedure. For example, this was true for amines **25**–**27**. The yield of amine **22** was unusually low because it was not possible to avoid formation of the following side product coming from the opening of cyclopropyl ring.



**Azetidinols (Table III).** To synthesize compound **35**, the general method of V. R. Gaertner[10] of reacting the suitable amine with epichlorohydrin in methanol could not be used, because the following derivative was obtained instead, apparently through a cation of the tropylium type.



Therefore, the compound was prepared in two steps, avoiding the formation in position 5 of a good "leaving group", as the protonated amine proved to be. First, the amine was reacted with epichlorohydrin at room temperature, and this showed the complete selectivity of the amine toward the oxirane ring, since only traces of chloride ion were found. Ring closure was then carried out under basic conditions. Preparation of the azetidinols with $R_1 = CH_3$ and/or $R_2 = CH_3$ or Ph is described in the Experimental Section. We emphasize that 3-ketoazetidines, intermediates for the azetidinols with $R_2 = CH_3$ or Ph, were obtained by oxidizing the alcohols with the dimethyl sulfide–chlorosuccinimide adduct, according to Corey,[11] with excellent yields and with a better reproducibility than

Scheme II

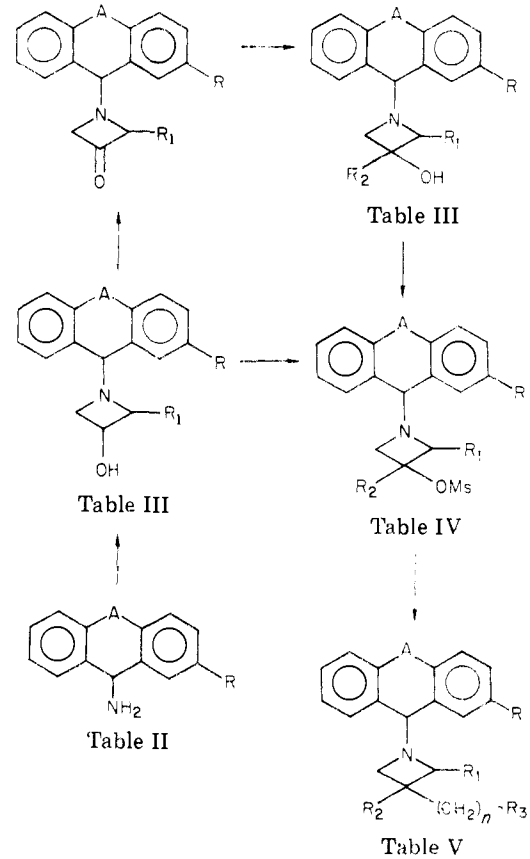
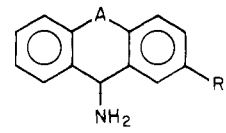


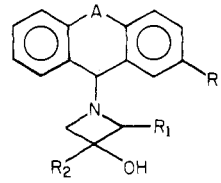
Table II. Tricyclic Amines



| no. | A | R | mp, °C[a] | recrystn solvent | yield, % | formula[b] |
|---|---|---|---|---|---|---|
| **18**[c] | $CH_2CH_2$ | H | 89-91 | hexane | 89 | $C_{15}H_{15}N$ |
| **19** | $CH_2CH_2$ | Cl | 71-75 | hexane | 85 | $C_{15}H_{14}ClN$ |
| **20** | $CH_2CH_2$ | $OCH_3$ | 104-105 | hexane | 80 | $C_{16}H_{17}NO$ |
| **21**[d] | CH=CH | H | 76-79 | hexane | 94 | $C_{15}H_{13}N$ |
| 22 | c-$C_3H_4$ | H | 147-150 | hexane | 35 | $C_{16}H_{15}N$ |
| **23**[e] | $CH_2O$ | H | 240-242[f] | | 92 | $C_{14}H_{13}NO$ |
| **24**[e] | $CH_2O$ | Cl | 57-59 | hexane | 78 | $C_{14}H_{12}ClNO$ |
| **25**[e] | $CH_2O$ | $OCH_3$ | 215-217[f] | | 95 | $C_{15}H_{15}NO_2$ |
| 26[g] | $CH_2S$ | H | 142-145 | hexane | 80 | $C_{14}H_{13}NS$ |
| 27 | $CH_2S$ | Cl | 143-146 | hexane | 65 | $C_{14}H_{12}ClNS$ |
| 28 | $CH_2S$ | $OCH_3$ | oil | | 95 | $C_{15}H_{15}NOS$ |

[a] Melting points are uncorrected. [b] The compounds were analyzed for all the elements except oxygen: the experimental values were within ±0.4 of the theoretical values. [c] A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, **6**, 255 (1963). [d] Netherlands patent 6 600 093 (1966); *Chem. Abstr.*, 66, 2426a (1967). [e] British patent 1 119 329 (1968); *Chem. Abstr.*, **70**, 11583p (1969). [f] Hydrochloride. [g] V. H. Seidlova, M. Rajsner, E. Adlezova, and M. Protiva, *Monatsh. Chem.*, 96, 650 (1965).

Table III. 3-Azetidinols



| no. | A | R | $R_1$ | $R_2$ | mp, °C,[a]·HCl | recrystn solvent | yield, % | formula[b] |
|---|---|---|---|---|---|---|---|---|
| 29 | $CH_2CH_2$ | H | H | H | 160-163 | $Me_2CO$ | 57 | $C_{18}H_{19}NO$ |
| **30** | $CH_2CH_2$ | H | $CH_3$ | H | 195-197[c] | $Me_2CO$ | 41 | $C_{19}H_{21}NO$ |
| **31** | $CH_2CH_2$ | H | H | $CH_3$ | 100-112[d] | | 75[e] | $C_{19}H_{21}NO$ |
| 32 | $CH_2CH_2$ | H | H | Ph | oil[d,f] | | 45[e,g] | $C_{24}H_{23}NO$[h] |
| 33 | $CH_2CH_2$ | Cl | H | H | 157-159 | $Me_2CO$ | 38 | $C_{18}H_{18}ClNO$ |
| 34 | $CH_2CH_2$ | $OCH_3$ | H | H | 184-186 | $Me_2CO$ | 54 | $C_{19}H_{21}NO_2$ |
| 35 | CH=CH | H | H | H | 105-109[d] | *i*-$Pr_2O$ | 38 | $C_{18}H_{17}NO$ |
| 36 | c-$C_3H_4$ | H | H | H | 195-197 | $Me_2CO$ | 57 | $C_{19}H_{19}NO$ |
| 37 | $CH_2O$ | H | H | H | 153-157 | $Me_2CO$ | 47 | $C_{17}H_{17}NO_2$ |
| 38 | $CH_2O$ | Cl | H | H | 152-157 | $Me_2CO$ | 37 | $C_{17}H_{16}ClNO_2$ |
| 39 | $CH_2O$ | $OCH_3$ | H | H | 135-145 | $Me_2CO$ | 33 | $C_{18}H_{19}NO_3$ |
| 40 | $CH_2S$ | H | H | H | 143-148 | $Me_2CO$ | 80[e] | $C_{17}H_{17}NOS$ |
| 41 | $CH_2S$ | Cl | H | H | 157-159 | $Me_2CO$ | 27 | $C_{17}H_{16}ClNOS$ |
| 42 | $CH_2S$ | $OCH_3$ | H | H | oil[d,f] | | 40 | $C_{18}H_{19}NO_2S$ |

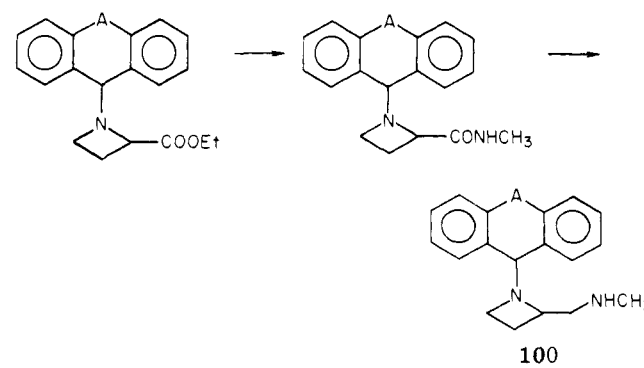
[a] Melting points are uncorrected. [b] The compounds were analyzed for all the elements except oxygen: the experimental values were within ±0.4 of the theoretical values, except for compound 31 (C: calcd, 81.68; found, 80.58). [c] Hydrobromide. [d] Free base. [e] Grignard on azetidin-3-one. [f] These products most probably solidify on standing. [g] Crude product. [h] Not microanalyzed.

described by S. S. Chatterjee.[12]

**Mesylates (Table IV).** High yields were obtained with the classical method in pyridine.[7] The reaction was more difficult as $R_2$ became larger. Thus, we succeeded in obtaining compound **45** ($R_2$ = $CH_3$), but compound **46** ($R_2$ = Ph) did not form at all. Therefore, the method of Crossland[13] was used, involving a sulfene intermediate, which is more reactive than methane–sulfonyl chloride.

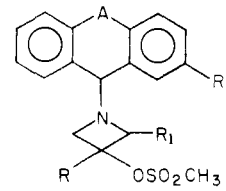
**Aminoazetidines (Table V).** The aminoazetidines were prepared by reacting the mesylates with a nucleophile (an amine for $n$ = 0) in DMF/$H_2O$.[14] For compounds **57**, **72**, and **73**, prepared by different synthetic procedures, and others, obtained by special methods, a description is given in the Experimental Section. Since some structure/activity theories[15] maintain that the terminal basic group should be near a phenyl for the product to have a good antidepressant activity, we synthesized a 2-methylaminomethyl derivative of azetidine (A = $CH_2CH_2$) according to Scheme III[16] to compare the activity with compound **58**. The compound was completely inactive, so we did not proceed with the synthesis of analogous derivatives.

Scheme III



100

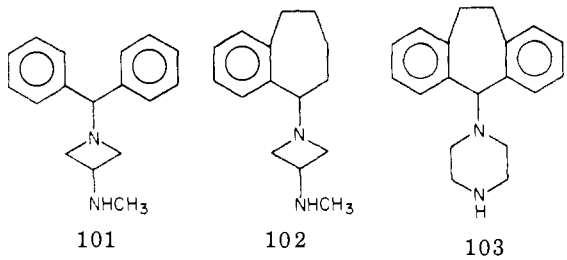
Table IV. 3-Mesyloxyazetidines



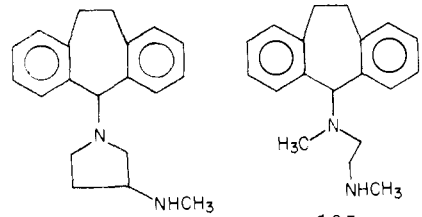
| no. | A | R | $R_1$ | $R_2$ | mp, °C[a] | recrystn solvent | yield, % | formula[b] |
|---|---|---|---|---|---|---|---|---|
| 43 | $CH_2CH_2$ | H | H | H | 102-104 | benzene/*i*-$Pr_2O$ | 68 | $C_{19}H_{21}NO_3S$ |
| 44 | $CH_2CH_2$ | H | $CH_3$ | H | 95-98 | *i*-$Pr_2O$ | 99 | $C_{20}H_{23}NO_3S$ |
| 45 | $CH_2CH_2$ | H | H | $CH_3$ | oil[c] | | 58 | $C_{20}H_{23}NO_3S$ |
| 46 | $CH_2CH_2$ | H | H | Ph | oil[c] | | 82 | $C_{25}H_{25}NO_3S$ |
| 47 | $CH_2CH_2$ | Cl | H | H | 114-118 | *i*-$Pr_2O$ | 80 | $C_{19}H_{20}ClNO_3S$ |
| 48 | $CH_2CH_2$ | $OCH_3$ | H | H | oil[c] | | 96 | $C_{20}H_{23}NO_4S$ |
| 49 | CH=CH | H | H | H | 96-98 | hexane | 52 | $C_{19}H_{19}NO_3S$ |
| 50 | c-$C_3H_4$ | H | H | H | 183-187 | *i*-$Pr_2O$ | 93 | $C_{20}H_{21}NO_3S$ |
| 51 | $CH_2O$ | H | H | H | 107-109 | hexane | 58 | $C_{18}H_{19}NO_4S$ |
| 52 | $CH_2O$ | Cl | H | H | 105-110 | | 94[d] | $C_{18}H_{18}ClNO_4S$ |
| 53 | $CH_2O$ | $OCH_3$ | H | H | oil[c] | | 87 | $C_{19}H_{21}NO_5S$ |
| 54 | $CH_2S$ | H | H | H | oil[c] | | 79 | $C_{18}H_{19}NO_3S_2$ |
| 55 | $CH_2S$ | Cl | H | H | 118-127 | | 90[d] | $C_{18}H_{18}ClNO_3S_2$ |
| 56 | $CH_2S$ | $OCH_3$ | H | H | oil[c] | | 94 | $C_{19}H_{21}NO_4S_2$ |

[a] Melting points are uncorrected. [b] The compounds were analyzed for all the elements except oxygen: the experimental values were within ±0.4 of the theoretical values, except for compound 54 (C: calcd, 59.81; found, 59.00). [c] These compounds most probably solidify on standing. [d] Crude product.

Chart I

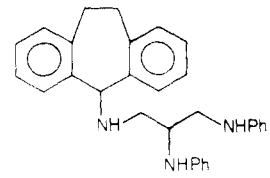


101 102 103



104 105

We also wished to see whether the pharmacological activity was specific for the azetidine–tricyclic ring coupling. Therefore, we synthesized the analogues listed in Chart I (compounds **101–105**) where one or other of the two factors was changed. The pharmacological results are given in Table VI. The preparation procedures are given in the Experimental Section. With regard to the reactivity of the sulfonates, if the amine was not sufficiently basic, there was the disadvantage of the azetidine ring opening[17] unless different reaction conditions were used. Thus, when compound **43** was reacted with an excess of aniline, derivative **106** was obtained. This is without doubt due to



106

the fact that the methanesulfonic acid formed during the reaction does not protonate the starting, less basic aniline but rather the azetidine nitrogen which causes the opening of the azetidine ring by an excess of the unprotonated aniline.

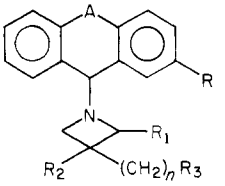
If there is no excess amine present, the nucleophile can be any other which happens to be present in the solution, the solvent itself, or even the "counterion" of the salt-forming acid.

The less basic the amine in position 3, the easier is attack. If, for example, the substituent is imidazole, it is enough to dissolve the compound in methanol with a few drops of HCl for it to be broken in a few hours at room temperature. In this way, the amido derivatives **98** and **99** were immediately broken under the same conditions at room temperature.

The opening of the ring is common to all the amine derivatives in Table V if they are protonated with a mineral acid and if $R_2$ = H. As the size of $R_2$ increases, the compounds become more resistant, so that the azetidine ring with $R_2$ = phenyl is stable. The poor stability of the salts of these amines with strong acids prompted us to prepare different organic salts of the two most interesting compounds (**58** and **83**); these salts are listed at the bottom of Table V and proved stable in aqueous solution. The racemate **83** was also resolved into its two optical isomers **84**.

**Pharmacological Results.** All the compounds listed in Tables I and V were evaluated for potential antidepressant activity, using as primary tests antagonism to reserpine-induced blepharospasm and hypothermia. Table VI includes only the compounds in Table V, those in Table I being devoid of activity. As suggested by the literature for tricyclic antidepressants,[5,18] we also determined the anticonvulsant activity by the pentylenetetrazole-antagonism test. Orientative acute toxicities, as observed from Irwin's test, are also reported. For antireserpine activity, the nature of the amino group in position 3 of the azetidine ring proved relevant. Activity reached its maximum with the methylamino substituent (**58**, **81**, **83**, **84**, and **92**), the activity being less but still present with the ethylamino (**59** and **85**), isopropylamino (**60** and **86**), and dimethylamino (**66**, **82**, and **87**). The other secondary (**61–65**) and tertiary (**67–71**) amines were far less active.

Table V. 3-Amino(alkyl)azetidines



| no. | A | *n* | R | $R_1$ | $R_2$ | $R_3$ | mp, °C,[a] ·2HCl | recrystn solvent | yield, % | formula[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| 57 | $CH_2CH_2$ | 0 | H | H | H | $NH_2$ | 165-170 | *i*-PrOH | 41[c] | $C_{18}H_{20}N_2$ |
| 58 | $CH_2CH_2$ | 0 | H | H | H | $NHCH_3$ | 83-86[d] | hexane | 68 | $C_{19}H_{22}N_2$[e] |
| 59 | $CH_2CH_2$ | 0 | H | H | H | $NHC_2H_5$ | 138-141 | *i*-PrOH | 61 | $C_{20}H_{24}N_2$ |
| 60 | $CH_2CH_2$ | 0 | H | H | H | $NHCH(CH_3)_2$ | 179-181 | *i*-PrOH | 40 | $C_{21}H_{26}N_2$ |
| 61 | $CH_2CH_2$ | 0 | H | H | H | $NHC(CH_3)_3$ | 177-179 | *i*-PrOH | 57 | $C_{22}H_{28}N_2$ |
| 62 | $CH_2CH_2$ | 0 | H | H | H | NH-c-$C_6H_{11}$ | 140-147 | *i*-PrOH/$Et_2O$ | 58 | $C_{24}H_{30}N_2$ |
| 63 | $CH_2CH_2$ | 0 | H | H | H | $NHCH_2Ph$ | 178-180 | *i*-PrOH/$Et_2O$ | 41 | $C_{25}H_{26}N_2$ |
| 64 | $CH_2CH_2$ | 0 | H | H | H | $NHC(CH_3)_2C{\equiv}CH$ | 108-110[d] | hexane | 47 | $C_{23}H_{26}N_2$ |
| 65 | $CH_2CH_2$ | 0 | H | H | H | $NHCH(CH_3)CH_2Ph$ | 168-182 | EtOH | 44 | $C_{28}H_{32}N_2$ |
| 66 | $CH_2CH_2$ | 0 | H | H | H | $N(CH_3)_2$ | →180 | benzene/hexane | 85 | $C_{20}H_{24}N_2$ |
| 67 | $CH_2CH_2$ | 0 | H | H | H | $N(CH_2C{\equiv}CH)_2$ | 170-172 | MeOH | 38 | $C_{24}H_{24}N_2$ |
| 68 | $CH_2CH_2$ | 0 | H | H | H | $N(CH_3)CH_2COPh$ | 120-125 | EtOH/$Et_2O$ | 80[f] | $C_{27}H_{28}N_2O$ |
| 69 | $CH_2CH_2$ | 0 | H | H | H | c-$N(CH_2CH_2)_2O$ | 114-117[d] | hexane | 71 | $C_{22}H_{26}N_2O$ |
| 70 | $CH_2CH_2$ | 0 | H | H | H | c-$N(CH_2CH_2)_2NCH_2CH_2OH$ | →130[g] | *i*-PrOH/$Et_2O$ | 71 | $C_{24}H_{31}N_3O$ |
| 71 | $CH_2CH_2$ | 0 | H | H | H |  | 109-118[d] | $Et_2O$/pentane | 40 | $C_{21}H_{21}N_3$ |
| 72 | $CH_2CH_2$ | 1 | H | H | H | $NH_2$ | 135-140 | *i*-PrOH/$Et_2O$ | 84[h] | $C_{19}H_{22}N_2$ |
| 73 | $CH_2CH_2$ | 1 | H | H | H | $NHCH_3$ | 90-120 | *i*-PrOH/$Et_2O$ | 63[i] | $C_{20}H_{24}N_2$ |
| 74 | $CH_2CH_2$ | 0 | H | $CH_3$ | H | $NHCH_3$ | oil[d] | | 68 | $C_{20}H_{24}N_2$ |
| 75 | $CH_2CH_2$ | 0 | H | H | $CH_3$ | $NHCH_3$ | oil[d] | | 57 | $C_{20}H_{24}N_2$ |
| 76 | $CH_2CH_2$ | 0 | H | H | Ph | $NHCH_3$ | oil[d] | | 45 | $C_{25}H_{26}N_2$ |
| 77 | $CH_2CH_2$ | 0 | Cl | H | H | $NHCH_3$ | →165 | *i*-PrOH/$Et_2O$ | 65 | $C_{19}H_{21}ClN_2$ |
| 78 | $CH_2CH_2$ | 0 | Cl | H | H | $N(CH_3)_2$ | 162-167 | *i*-PrOH/$Et_2O$ | 46 | $C_{20}H_{23}ClN_2$ |
| 79 | $CH_2CH_2$ | 0 | $OCH_3$ | H | H | $NHCH_3$ | oil[d] | | 40 | $C_{20}H_{24}N_2O$ |
| 80 | CH=CH | 0 | H | H | H | $NHCH_3$ | 156-159[j] | benzene | 38 | $C_{14}H_{20}N_2$ |
| 81 | c-$C_3H_4$ | 0 | H | H | H | $NHCH_3$ | 95-100[d] | pentane | 36 | $C_{20}H_{22}N_2$ |
| 82 | c-$C_3H_4$ | 0 | H | H | H | $N(CH_3)_2$ | 125-130[d] | hexane | 45 | $C_{21}H_{24}N_2$ |
| 83 | $CH_2O$ | 0 | H | H | H | $NHCH_3$ | 61-64[d] | hexane | 36 | $C_{18}H_{20}N_2O$[k] |
| 84 | $CH_2O$ | 0 | H | H | H | $NHCH_3$ | 179-182[l,m] | EtOH (99%) | | $C_{18}H_{20}N_2O$ |
| 85 | $CH_2O$ | 0 | H | H | H | $NHC_2H_5$ | 187-189[n] | MeOH/$Et_2O$ | 55 | $C_{19}H_{22}N_2O$ |
| 86 | $CH_2O$ | 0 | H | H | H | $NHCH(CH_3)_2$ | 205-207[n] | EtOH/$Et_2O$ | 50 | $C_{20}H_{24}N_2O$ |
| 87 | $CH_2O$ | 0 | H | H | H | $N(CH_3)_2$ | 120-125 | *i*-PrOH/$Et_2O$ | 57 | $C_{19}H_{22}N_2O$ |
| 88 | $CH_2O$ | 0 | Cl | H | H | $NHCH_3$ | 77-80[d] | hexane | 43 | $C_{18}H_{19}ClN_2O$ |
| 89 | $CH_2O$ | 0 | Cl | H | H | $N(CH_3)_2$ | 105-110[d] | hexane | 55 | $C_{19}H_{21}ClN_2O$ |
| 90 | $CH_2O$ | 0 | $OCH_3$ | H | H | $NHCH_3$ | oil[d] | | 81 | $C_{19}H_{22}N_2O_2$ |
| 91 | $CH_2O$ | 0 | $OCH_3$ | H | H | $N(CH_3)_2$ | oil[d] | | 63 | $C_{20}H_{24}N_2O_2$ |
| 92 | $CH_2S$ | 0 | H | H | H | $NHCH_3$ | oil[d] | | 86 | $C_{18}H_{20}N_2S$ |
| 93 | $CH_2S$ | 0 | H | H | H | $N(CH_3)_2$ | oil[d] | | 21 | $C_{19}H_{22}N_2S$ |
| 94 | $CH_2S$ | 0 | Cl | H | H | $NHCH_3$ | oil[d] | | 49 | $C_{18}H_{19}ClN_2S$ |
| 95 | $CH_2S$ | 0 | Cl | H | H | $N(CH_3)_2$ | oil[d] | | 55 | $C_{19}H_{21}ClN_2S$ |
| 96 | $CH_2S$ | 0 | $OCH_3$ | H | H | $NHCH_3$ | oil[d] | | 40 | $C_{19}H_{22}N_2OS$ |
| 97 | $CH_2S$ | 0 | $OCH_3$ | H | H | $N(CH_3)_2$ | oil[d] | | 52 | $C_{20}H_{24}N_2OS$ |
| 98 | $CH_2CH_2$ | 0 | H | H | H | $N(COCH_3)CH_3$ | oil[d] | | 91 | $C_{21}H_{24}N_2O$ |
| 99 | $CH_2CH_2$ | 0 | H | H | H | $N(CONH_2)CH_3$ | 105-109[d] | | 31 | $C_{20}H_{23}N_3O$ |

[a] Melting points are uncorrected. [b] The compounds were analyzed for all the elements except oxygen: the experimental values were within ±0.4 of the theoretical values except for compound 76 (N: calcd, 7.90; found, 7.28) and for compound 79 (N: calcd, 9.08; found, 8.60). [c] Hydrolysis of the corresponding pthalimido derivative. [d] Free base. [e] 58a hydrochloride, mp 170-184 °C; 58b nitrate, mp 168-172 °C; 58c acetate, mp 135-139 °C; 58d benzoate, mp 166-168 °C; 58e hemifumarate, mp 200-203 °C; 58f maleate, mp 164-166 °C. [f] By alkylation of compound 58. [g] Trihydrochloride. [h] By reduction of the corresponding cyano derivative. [i] By reduction of the NHCOOEt derivative. [j] Methanesulfonate in 2 N HCl turns immediately into 5*H*-5-hydroxydibenzo[*a,d*]cycloheptene. [k] 83a hemifumarate, mp 164-167 °C. [l] Hemifumarate, dextrorotatory isomer. [m] Hemifumarate, levorotatory isomer. [n] Fumarate.

Since the primary amine **57** was less active than the corresponding methylamino **58**, the only other synthesized was **72**, which served as intermediate for **73**. When R, $R_1$, and $R_3$ were changed from H to the substituents listed in Table V, the activity diminished or disappeared. This was also true when the basicity of the amino group in position 3 of the azetidine ring was suppressed, as in compounds **98** and **99**, or when *n* changed from 0 to 1. The coupling of tricyclic and azetidine rings appeared to be essential, as activity disappeared when one of the two factors was changed (**101**–**105**). These structure/activity findings are consistent with the results for pentylenetetrazole antagonism, except for the imidazole derivative **71**. It is a common experimental finding, in observational and behavioral laboratory tests, that standard tricyclic antidepressants show depressant (amitriptyline and doxepine) or mixed stimulant–depressant profiles (imipramine and derivatives). The original CNS stimulant profile, as shown by Irwin's test, the centrally shifted anticholinergic activity, and other pharmacological features, such as a low cardiac toxicity in the rabbit, appear to justify further research on this series. Detailed biological data for some of the

Table VI. Pharmacological Data

| compd no. | reserpine antag ($ED_{50}$, mg/kg po) blepharospasm | reserpine antag ($ED_{50}$, mg/kg po) hypothermia | pentylenetetrazole antag ($ED_{50}$, mg/kg po) | orientative acute toxicity ($LD_{50}$, mg/kg po) |
|---|---|---|---|---|
| 57 | 5.0 | 12.0 | 17.0 | >200 <400 |
| 58 | 2.9 | 7.3 | 13.4 | 400 |
| 59 | 10.0 | 12.5 | 16.7 | >200 <400 |
| 60 | 6.5 | 8.5 | 23.3 | >200 <400 |
| 61 | >25 | >25 | 28.7 | >400 <800 |
| 62 | >25 | >25 | >50 | >400 <800 |
| 63 | 12.0 | >25 | >50 | 800 |
| 64 | 9.0 | >25 | 19.6 | >800 |
| 65 | >25 | >25 | >50 | >800 |
| 66 | 7.0 | 12.5 | 21.5 | 400 |
| 67 | >25 | 21.0 | 38.0 | >800 |
| 68 | 15.0 | >25 | 46.8 | >800 |
| 69 | 17.0 | >25 | 46.9 | >800 |
| 70 | >25 | >25 | 31.0 | >400 <800 |
| 71 | >25 | >25 | 17.7 | 200 |
| 72 | >25 | >25 | >50 | 400 |
| 73 | >25 | >25 | >50 | >200 <400 |
| 74 | 9.0 | 10.5 | 25.0 | 400 |
| 75 | >25 | >25 | 44.6 | >200 <400 |
| 76 | >25 | >25 | >50 | >400[a] |
| 77 | >25 | >25 | 27.9 | >400 <800 |
| 78 | 12.5 | 8.6 | 29.9 | >400 <800 |
| 79 | 14.0 | >25 | >50 | >200 <400 |
| 80 | >25 | >25 | >50 | 200 |
| 81 | 4.4 | 11.4 | 18.5 | >200 <400 |
| 82 | 7.2 | 16.5 | 24.3 | >200 <400 |
| 83 | 2.6 | 15.0 | 21.5 | >200 <400 |
| 84[b] | 1.0 | 4.9 | 14.0 | 200 |
| 84[c] | 1.3 | 14.1 | >50 | 100 |
| 85 | 4.8 | 22.2 | 25.3 | >200 <400 |
| 86 | 3.9 | 24.5 | 27.0 | >200 <400 |
| 87 | 5.6 | 23.0 | 28.5 | >100 <200 |
| 88 | >25 | >25 | 15.4 | >100 <200 |
| 89 | >25 | >25 | >50 | >100 <200 |
| 90 | >25 | >25 | 45.8 | >200 <400 |
| 91 | >25 | >25 | >50 | >400 <800 |
| 92 | 12.0 | >25 | 14.7 | >200 <400 |
| 93 | >25 | >25 | 19.0 | >400 <800 |
| 94 | >25 | >25 | >50 | 400 |
| 95 | >25 | >25 | 50.0 | >400 <800 |
| 96 | 21.8 | >25 | >50 | >400 <800 |
| 97 | | | | |
| 98 | >25 | >25 | 28.0 | >400 <800 |
| 99 | >12.5 | >12.5 | >12.5 | >400 <800 |
| 100 | >25 | >25 | >50 | >800 |
| 101 | 3.5 | >25 | 9.6 | >200 <400 |
| 102 | >25 | >25 | 48.0 | >400 <800 |
| 103 | 24.0 | >25 | >50 | >50 <100 |
| 104 | >25 | >25 | 45.0 | >200 <400 |
| 105 | >25 | >25 | 18.0 | >200 <400 |
| Amipramine hydrochloride | 1.6 | 12.3 | 19.4 | >200 <400 |
| Amitriptiline hydrochloride | 1.3 | 6.6 | 8.0 | >100 <200 |

[a] Maximum tested dose. [b] Hemifumarate, dextrorotatory isomer. [c] Hemifumarate, levorotatory isomer.

compounds will be published in a separate paper.

## Experimental Section

Melting points were taken on a Büchi melting-point apparatus. Infrared spectra were obtained on a Perkin-Elmer 125 spectrophotometer and were in accordance with the proposed structures. Mass spectra were recorded on a CH-7 Varian-MAT spectrometer.

**Synthetic Procedures for the Derivatives of Table I. 1-*tert*-Butyl-3-[10-(2-chlorophenothiazinyl)]azetidine (3).** To 20 mL of anhydrous $Me_2SO$, 0.96 g of 55% NaH (22 mmol) was added and then, drop by drop, 4.66 g (20 mmol) of 2-chlorophenothiazine in about 50 mL of anhydrous $Me_2SO$. This was heated at 70 °C for 1 h and then cooled and added dropwise with 3.09 g (21 mmol) of 3-chloro-1-*tert*-butylazetidine in 20 mL of anhydrous $Me_2SO$. After 17 h at 110 °C and 5 h at 125–130 °C, 2–3 mL of ethanol was added to the cooled mixture, and the whole was poured into water and extracted with a mixture of ethyl ether/ethyl acetate. The extracts were washed with water, dried over $Na_2SO_4$, and evaporated to dryness. The residue was taken up in 250 mL of hot hexane, which was then cooled and filtered. The product crystallized from hexane to yield 1.95 g of a solid (28.3%), mp 190–193 °C.

**1-*tert*-Butyl-3-[5*H*-10,11-dihydro-3′-chloro-5-dibenzo-[*b*,*f*]azepinyl]azetidine (10).** In a round-bottomed flask, 0.65 g (2.8 mmol) of 3-(chloroimino)dibenzyl was dissolved under $N_2$ in a few milliliters of anhydrous xylene. To the solution at 80 °C was added 0.144 g (3.7 mmol) of $NaNH_2$ in a little xylene, and the mixture was heated at 100 °C for 2 h. After cooling to 45 °C, 0.544 g (3.7 mmol) of 3-chloro-1-*tert*-butylazetidine was added. The reaction mixture was heated at 100 °C overnight, the excess $NaNH_2$ was decomposed, the mixture was extracted twice with ethyl ether, and the extracts were washed with water, dried over $Na_2SO_4$, and evaporated to dryness. The residue was dissolved

in ethyl ether, alcoholic HCl was added, and the solution was evaporated to dryness again. The residue was taken up in 50 mL of ethyl acetate and filtered while warm. The solid crystallized out from 99% ethanol, to give 0.45 g (42%) of product melting at 247–248 °C (HCl).

**3-[5*H*-10,11-Dihydro-5-dibenzo[*b,f*]azepinyl]azetidine (11).** Four grams (9.3 mmol) of 3-(5-dibenzo[*a,d*]azepinylmethyl)-1-benzhydrylazetidine, obtained from 3-(chloromethyl)-1-benzhydrylazetidine by an alkylation procedure analogous to that described above, was dissolved in 250 mL of MeOH containing 9.4 mL of 1 N HCl and 3 g of 20% $Pd(OH)_2/C$, and the mixture was hydrogenated in a Parr bottle at 4–5 atm at room temperature. The reaction was stopped after 4 h, filtered, and evaporated to dryness, and the residue was crystallized from a mixture of $MeOH/Et_2O$ to obtain 2.4 g (86%) of product with mp 144–148 °C.

**1-Isopropyl-3-[(11-dibenzo[*b,e*]oxazepinyl)methyl]azetidine (17).** 3-(11-Dibenzo[*b,e*]oxazepinylmethyl)azetidine hydrochloride (1.05 g, 3.5 mmol), sodium acetate (0.29 g, 3.5 mmol), AcOH (0.4 mL), MeOH (50 mL), water (33 mL), 10% Pd/C (1 g), and acetone (0.31 mL) were placed in a Parr bottle and hydrogenated at 4–5 atm for 2.5 h. After filtration and evaporation to dryness, the residue was dissolved in water, made alkaline with 20% NaOH, and extracted with ethyl ether. The ether extracts were evaporated to dryness, and the residue was eluted on column chromatography with ethyl ether/petroleum ether/diethylamine (10:10:1) to obtain 0.58 g (54%) of an oil. When hydrogenation was prolonged, the reaction product obtained was 3-[*N*-(2-toluidyl)-*N*-[(2′-hydroxyphenyl)aminomethyl)]-1-isopropylazetidine, which melted at 189–191 °C.

**General Synthetic Procedure for the Amines of Table II.** To 1.0 mol of oxime in 1000 mL of EtOH, 40.18 g (0.52 mol) of ammonium acetate, 4900 mL of 32% $NH_4OH$, and 351 g (4.56 mol) of 85% Zn powder were added. The mixture was refluxed for 3 h, cooled, layered with ethyl ether, and made alkaline with 35% NaOH. It was extracted with ethyl ether; the extracts were washed with water, dried over $Na_2SO_4$, filtered, and evaporated to dryness; and the residue was crystallized. If the starting oxime was only slightly soluble, the alcohol could be mixed with up to three times as much DMF. It was then warmed to 80–90 °C (internal temperature) for 3.5 h and worked up by the usual procedures.

**General Synthetic Procedure for the Azetidinols of Table III.** To a solution of 0.4 mol of amine in 480 mL of $CH_3OH$, 31.6 mL (0.4 mol) of epichlorhydrin was added. After 3 days in the dark room temperature, the solution was refluxed for 3 days and evaporated to dryness, and the residue was taken up and completely dissolved in 2500 mL of acetone. On cooling, a solid separated, which was collected. The liquid phase was evaporated, and the residue was dissolved in methanol and refluxed overnight. It was then concentrated to dryness, taken up in acetone, and cooled, yielding a second batch of the substance.

**1-(5*H*-Dibenzo[*a,d*]cycloheptyl)-2-methyl-3-azetidinol (30).** The general procedure was followed starting from 1,2-epoxy-3-bromobutane:[19] yield 40.8%; mp 195–197 °C.

**1-(5*H*-Dibenzo[*a,d*]cycloheptyl)-3-methylazetidinol (31).** *N*-Chlorosuccinimide (1.99 g, 15 mmol) was dissolved in 90 mL of toluene, and 1.5 mL of dimethyl sulfide (20.5 mmol) was added drop by drop at 0 °C. Solid white crystals separated. The mixture was cooled to −25 °C, and 2.65 g (10 mmol) of azetidinol **29** in 10 mL of toluene and 10 mL of $CH_2Cl_2$ were added dropwise. After 2 h at −25 °C, 2.08 mL (15 mmol) of triethylamine in 2.5 mL of toluene was added. After standing overnight at room temperature, the mixture was poured into water and extracted with ethyl ether. The extracts were washed with water, dried, and evaporated to dryness. 1-(5*H*-Dibenzo[*a,d*]cycloheptyl)-3-oxoazetidine (2.1 g, 79.8%) was obtained, mp 96–105 °C. The ketone was dissolved in 50 mL of ethyl ether, cooled to 0 °C, and then added dropwise to a solution of Grignard reagent, prepared from 0.43 g (17.8 mmol) of Mg turnings and 0.87 mL (14 mmol) of methyl iodide. After stirring for 2 h at 0 °C and 1 day at room temperature, the mixture was decomposed with 80 mL of a saturated solution of $NH_4Cl$ and extracted with ethyl ether. The ether extracts were washed with saturated NaCl solution, dried, and evaporated to dryness. Product (1.69 g, 75%), mp 100–112 °C, was obtained.

**1-(5*H*-Dibenzo[*a,d*]cycloheptenyl)-3-azetidinol (35).** To 32 g of the amine **21** (0.155 mol) in 180 mL of $CH_3OH$, 13.35 mL of epichlorhydrin (0.17 mol) was added. After standing in the dark for 3 days at room temperature, the solution was evaporated to dryness and taken up again in 500 mL of hexane. The solid was filtered off and crystallized from $CCl_4$ to give 27.8 g of 1-(5-dibenzo[*a,d*]cycloheptenyl)amino-3-chloro-2-propanol, mp 94–102 °C. This product was dissolved in 280 mL of DMF, and 55 g (0.4 mol) of $K_2CO_3$ was added. It was stirred at room temperature for 24 h, then poured into ice water, and extracted with ethyl ether. The extracts were washed with water saturated with NaCl, dried over $Na_2SO_4$ and evaporated to dryness. The residue was crystallized from $i$-$Pr_2O$ to give 15.6 g (38.3%) of azetidinol, mp 105–109 °C.

**General Synthetic Procedure for the Mesylates of Table IV.** To a solution of 50 mmol of azetidinol in 100 mL of anhydrous pyridine, 5.88 mL of methanesulfonyl chloride (75 mmol) was added at −20 °C under vigorous stirring. After standing for 1 h at −20 °C and overnight at 0 °C, the solution was poured into ice water and extracted with ethyl ether, and the ether extracts were washed with water, dried, and evaporated to dryness.

**1-(5*H*-Dibenzo[*a,d*]cycloheptyl)-3-phenyl-3-azetidinol Mesylate (46).** Two grams of azetidinol **32** (5.8 mmol) was dissolved in 12 mL of benzene, and 0.815 mL (5.8 mmol) of triethylamine was added. The mixture was cooled to 0 °C, and 0.455 mL of methane sulfonyl chloride (5.8 mmol) was added dropwise. The mixture was stirred for 2 days at room temperature and then filtered and evaporated to dryness. Two grams (82%) of crude product was obtained and used for the preparation of amine **76** without further purification.

**General Synthetic Procedure for the Amines of Table V.** To a solution of 0.1 mol of sulfonate in 170 mL of DMF, a large excess of amine was added. After heating overnight in a 50–55 °C bath, in a stoppered flask, the reaction mixture was poured into water and extracted with ethyl acetate. The extracts were washed with water, dried over $Na_2SO_4$, evaporated to dryness, and crystallized.

**1-(6,11-Dihydrodibenzo[*b,e*]oxepinyl)-3-(methylamino)azetidine Hemifumarate (83c).** To 47.2 g (0.136 mol) of sulfonate **51** in 300 mL of DMF, 300 mL of 35% aqueous methylamine was added. The solution was heated overnight in a stoppered flask at 55 °C, then poured into a large amount of water, made basic with NaOH, and extracted with ethyl ether. The extracts were washed with water, dried over $Na_2SO_4$, and evaporated to dryness to give 36.5 g (96%) of a crude oil. The oil was extracted with 1500 mL of hot petroleum ether. The insoluble material was filtered out, and the solution was concentrated to dryness. The residue of 35 g of oil was dissolved in ethyl alcohol, and 0.068 mol of fumaric acid dissolved in the minimum amount of ethyl alcohol was added. After evaporation to dryness, the residue was taken up in ether and filtered. On crystallization from 99% EtOH, it gave 31.5 g (74%) of the hemifumarate, mp 180–182 °C.

**(+)-1-(6,11-Dihydrodibenzo[*b,e*]oxepinyl)-3-(methylamino)azetidine Hemifumarate (84).** **83** base (12.34 g, 44 mmol) was dissolved in 200 mL of ethyl ether, to which 6.09 g (40 mmol) of D-(−)-mandelic acid in 100 mL of ethyl ether was added; the salt precipitated. It was filtered and crystallized from 200 mL of 99% EtOH to give 8.5 g of mandelate, mp 160–165 °C, $[\alpha]^{20}_{589}$ +33.3°, $[\alpha]^{20}_{365}$ +120.9°, in 80% EtOH at a concentration of 2%. After three crystallizations from 99% EtOH, constant values were reached as follows: $[\alpha]^{20}_{589}$ +73.54°, $[\alpha]^{20}_{365}$ +272.23°. The free base was prepared by dissolving 4.9 g of the product in water, making the solution alkaline with 24 mL of 2 N NaOH, extracting with ethyl ether, and evaporating to dryness. There was obtained 2.8 g of oil, $[\alpha]^{20}_{589}$ +170.86°, $[\alpha]^{20}_{365}$ +633.88°, in 2% $CH_3OH$. The 2.8 g was dissolved in 50 mL of methanol and mixed with 0.58 g of fumaric acid in 30 mL of methanol. After evaporation to dryness, the residue was taken up in ethyl ether and filtered to give 3 g of the hemifumarate, mp 179–182 °C, $[\alpha]^{20}_{589}$ +140.45°, $[\alpha]^{20}_{365}$ +521.6°, in 80% EtOH at a concentration of 2%. By the same method, starting from L-(+)-mandelic acid the levorotatory isomer was prepared.

**1-(5*H*-Dibenzo[*a,d*]cycloheptyl)-3-aminoazetidine (57).** To 4 g (11.6 mmol) of sulfonate **43** in 30 mL of anhydrous DMF, 2.37 g (12.8 mmol) of potassium phthalimide was added. The

solution was stirred overnight at 70 °C and then for 8 h at 120 °C. It was poured into water and extracted with ethyl acetate, the extracts were washed with saturated NaCl, and the solution was dried over $Na_2SO_4$ and evaporated to dryness. The solid residue was ground to a fine powder in hexane/isopropyl ether and then partitioned between 1 N NaOH and ethyl ether to remove any phthalimide present. The aqueous solution was then further extracted with ether, and the extracts were washed with water until neutral, dried over $Na_2SO_4$, and evaporated to dryness. The 1-(5*H*-dibenzo[*a*,*d*]cycloheptyl)-3-pthalimidoazetidine weighed 2.8 g (60.8%), mp 111–114 °C. This 2.8 g was dissolved in 220 mL of methanol, and 0.84 mL (14.2 mmol) of 85% hydrazine hydrate was added. The mixture was refluxed for 1 h and then concentrated to dryness. The residue was partitioned between warm 20% NaOH and hexane, with long and vigorous stirring. The hexane was separated off, and the sodium hydroxide solution was extracted with ethyl ether. The mixed organic solutions were washed with saturated NaCl solution until neutral, dried over $Na_2SO_4$, and evaporated to dryness. The residue was dissolved in ethanol, 3 mL of 1 N HCl in alcohol was added, and the solution was evaporated to dryness. The residue was crystallized from a mixture of isopropyl alcohol, ethyl alcohol, and ethyl ether to give 1.59 g of product: mp 165–170 °C; overall yield 41%.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)-3-(aminomethyl)azetidine (72).** To a solution of 5.1 g (15 mmol) of sulfonate **43** in 30 mL of DMF, 2.21 g (45 mmol) of NaCN in 4 mL of water was added dropwise. The solution, after 24 h at 65 °C, was poured into ice water and filtered. There was obtained 3.8 g of 1-(5*H*-dibenzo[*a*,*d*]cycloheptyl)-3-cyanoazetidine: mp 152–163 °C. A solution of 3.5 g (13 mmol) of the nitrile in 40 mL of THF and 60 mL of ethyl ether was added to 0.74 g (19.5 mmol) of $LiAlH_4$ in approximately 40 mL of anhydrous ether. After stirring for 30 min at room temperature and refluxing overnight, the mixture was cooled to 0 °C and decomposed with 0.8 mL of water, 0.8 mL of 15% NaOH, and 2.4 mL of water. The solid material was filtered and washed thoroughly with ether, and the filtrates were concentrated to dryness to give 3.3 g of oil: overall yield 84.1%.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)-3-[(methylamino)-methyl]azetidine (73).** The amine **72** dihydrochloride (1.4 g, 4 mmol) was suspended in 16 mL of $CHCl_3$, and 7.2 mL (14.4 mmol) of 2 N NaOH was added. The mixture was cooled to 0 °C, and 0.61 mL (6.4 mmol) of ethyl chloroformate in 3 mL of $CHCl_3$ was added dropwise. After a 10-min stirring, the organic layer was separated, washed with water, dried over $Na_2SO_4$, and evaporated to dryness. The oily residue was solidified with isopropyl ether and filtered. One gram of 1-(5*H*-dibenzo[*a*,*d*]-cycloheptyl)-3-[[(ethoxycarbonyl)amino]methyl]azetidine, mp 103–108 °C, was obtained. The carbamate (28 mmol) was dissolved in 70 mL of anhydrous ether, and 0.336 g (84 mmol) of $LiAlH_4$ in 10 mL of ethyl ether was added. After refluxing overnight, the excess $LiAlH_4$ was decomposed with water, and the aqueous phase was extracted with ethyl ether. The extracts were washed with water until neutral and dried over $Na_2SO_4$, and the hydrochloride was precipitated with alcoholic HCl. The product (0.65 g, 63%) was hydroscopic and melted at 90–120 °C.

**Synthetic Procedures for Compounds 98–106. 1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)-3-[*N*-methyl-*N*-(acetylamino)]azetidine (98).** One gram (3.6 mmol) of amine **58** and 0.21 g (5.2 mmol) of NaOH were dissolved in 15 mL of $CH_2Cl_2$ and 8 mL of water. Acetyl chloride (0.392 g, 5 mmol) in a few milliliters of $CH_2Cl_2$ was added dropwise with stirring at −5 to 0 °C. The mixture was allowed to warm up to room temperature and kept at that temperature for 2 h. The organic layer was separated, and the aqueous layer was extracted twice with $CH_2Cl_2$. The combined organic solutions were washed with water, dried, and evaporated to dryness to obtain 1.05 g (91%) of a chromatographically pure oil.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)-3-[*N*-methyl-*N*-(carbamoylamino)]azetidine (99).** To 1.39 g (5 mmol) of amine **58** in 5 mL of 1 N HCl and 5 mL of glacial AcOH, 0.405 g (5 mmol) of KCNO was added. After 48 h at room temperature, the solution was poured into water, made alkaline with sodium hydroxide, and extracted with ethyl ether. The ether extracts were washed with water, dried over $Na_2SO_4$, and evaporated to dryness. The solid residue was ground with a little ether and filtered to yield 0.5 g (31%) of a product, mp 105–109 °C.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)-2-[(methylamino)-methyl]azetidine (100).** Amine **18** (34.9 g, 167 mmol), methyl 2,4-dibromobutyrate (14.45 g, 55 mmol), and acetonitrile (250 mL) were refluxed together for 24 h. After cooling, the solid was removed by filtration, and the filtrate was evaporated to dryness and redissolved in ethyl ether; then, the solid was removed, and the filtrate was evaporated to dryness again. The residue was purified by silica gel column chromatography, eluted with $CHCl_3$, to give 6 g (36%) of 1-(5*H*-dibenzo[*a*,*d*]cycloheptyl)-2-(methoxycarbonyl)azetidine as an oil. To 5.1 g (16.5 mmol) of this ester in 25 mL of DMF, 25 mL of 35% methylamine was added. It was heated overnight at 60 °C, then poured into water, and extracted with ethyl acetate. The extracts were washed with water, dried over $Na_2SO_4$, and evaporated to dryness, to obtain 5.0 g of 1-(5*H*-dibenzo[*a*,*d*]cycloheptyl)-2-(methylcarbamoyl)azetidine, mp 65–80 °C. This compound (16.3 mol) was dissolved in 50 mL of anhydrous THF and dropped into a suspension of 1.23 g (32 mol) of $LiAlH_4$ in 10 mL of anhydrous THF. The resulting mixture was refluxed for 10 h and worked up as usual to have an oil which was turned into its hydrochloride and crystallized from 99% ethyl alcohol: yield 1.75 g (30%); mp 125–150 °C.

**1-Benzhydryl-3-(methylamino)azetidine (101).** The general procedure was followed starting from benzhydrylamine.

**1-(1′-Benzocycloheptyl)-3-(methylamino)azetidine (102).** To 10.85 g (285 mmol) of $LiAlH_4$ in 130 mL of ethyl ether, 25 g (143 mmol) of benzocycloheptanone oxime in 200 mL of anhydrous benzene was added dropwise under $N_2$ and stirring at room temperature. After 24 h at 50 °C, the excess $LiAlH_4$ was decomposed with 11 mL of $H_2O$, 8.3 mL of 20% NaOH, and an additional 33 mL of $H_2O$, and the resulting mixture was filtered and thoroughly washed with boiling benzene. The organic solution was evaporated to dryness, and the residue was dissolved in an excess of 8% HCl ethanolic solution and evaporated to dryness again. The residue was ground with 350 mL of boiling isopropyl alcohol and filtered after cooling: yield 9.9 g (35.2%) of 1-benzocycloheptylamine hydrochloride; mp 280–282 °C. The yield is not very satisfactory because of the formation of another product isomer, not identified. Reduction of the oxime according to J. K. Sudgan[9] gives a dimer of the amine with loss of two hydrogen atoms. The aminoazetidine **102** was synthesized according to the general method.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)piperazine (103) and *N*-(5*H*-dibenzo[*a*,*d*]cycloheptyl)-*N*,*N*′-dimethylethylenediamine (105)** were prepared by reacting 5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptane with the suitable amines.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptyl)-3-(methylamino)-pyrrolidine (104).** To a solution of 2 g (9.5 mmol) of amine **18** in 12 mL of $CH_3OH$, 1.44 g (9.5 mmol) of 1,2-epoxy-4-bromobutane was added. After 3 days at room temperature in the dark and 3 days under reflux, the mixture was evaporated to dryness and ground with acetone to obtain 1.27 g (37%) of 1-(5*H*-dibenzo-[*a*,*d*]cycloheptyl)-3-pyrrolidinole hydrobromide, mp 185–188 °C. Starting from this compound, the product **104** was prepared with the general method.

**1-(5*H*-Dibenzo[*a*,*d*]cycloheptylamino-2,3-dianilinopropane (106).** To 4 g (11 mmol) of sulfonate **43** in 12 mL of DMF, 8 mL of aniline was added, and the solution was heated overnight at 70 °C. After pouring it into water, the organic layer was separated and the aqueous phase extracted with ethyl ether. The ether was dried over $Na_2SO_4$ and decolorized with charcoal, and a HCl ethanolic solution was added to form the hydrochloride. This was redissolved in ethanol at 99 °C and reprecipitated with ethyl ether. Three grams (51%) was obtained, mp 190–200 °C. The mass spectrum gave the molecular ion at 433 and the ions *m*/*e* 340 and 327 corresponding to the loss of NHPh and of $CH_2NHPh$. The base peak was at 193 and corresponds to the cycloheptadienyl fragment.

**Pharmacology.** All tests were conducted on male ICEM:CET (SPF Caw) male mice weighing 18–22 g. Four to ten animals were used at each dose level. All the compounds were administered orally by gavage, suspended or dissolved in 0.5% Methocel in a volume of 0.1 mL/10 g of body weight.

**Reserpine Antagonism.** Blepharospasm and hypothermia were the symptoms induced by reserpine that were evaluated in this test. Blepharospasm was observed by the scoring system

proposed by Rubin et al.[23] Body temperature was measured rectally by means of a thermocouple metal probe. Groups of ten mice were housed the evening before the experiment with a 9-h fasting period but free access to water until 2 h before testing sessions. All the compounds were tested at the screening dose of 25 mg/kg, and the active ones at this dose were subsequently tested at lower doses, in order to obtain an $ED_{50}$ by "eye-fit" linear plots on semilogarithmic paper. The compounds were administered 30 min before ip injection of 2.5 mg/kg of reserpine (dissolved in 0.5% acetic acid in a volume of 0.05 mL/10 g of body weight). The parameters considered were read blind 1 (blepharospasm) and 4 h (hypothermia) after reserpine treatment.

**Pentylenetetrazole Antagonism.** All the compounds were tested for their effect on the maximal extensor seizures induced by pentylenetetrazole given by ip injection at a dose of 130 mg/kg in a volume of 0.1 mL/10 g of body weight. This dose of pentylenetetrazole induces clonic and flexor–extensor tonic convulsions in 100% of the control animals. The test compounds were administered at different dosages 30 min before treatment with pentylenetetrazole, starting from the screening dose of 50 mg/kg, in order to obtain the dose–response curves. Groups of ten animals were used for each dose tested and for controls. From the dose-response curves obtained the dose was calculated, which prevents the onset of flexor–extensor tonic convulsions in 50% of the treated animals ($ED_{50}$).

**Orientative Acute Toxicity.** This information (ca. $LD_{50}$) was obtained in the course of the Irwin's test,[24] performed on all the tested compounds in order to have their symptomatologic profile. All the compounds were tested at least at six dose levels (25, 50, 100, 200, 400, and 800 mg/kg) on four animals for dose with careful observation for 60 min after treatment. Deaths occurring in 7 days after drug administration were registered.

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# Easily Hydrolyzable, Water-Soluble Derivatives of (±)-α-5-[1-(Indol-3-yl)ethyl]-2-methylamino-$\Delta^2$-thiazolin-4-one, a Novel Antiviral Compound


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The preparation of a series of indole *N*-acyl and *N*-carbamic esters of (±)-α-5-[1-(indol-3-yl)ethyl]-2-methylamino-$\Delta^2$-thiazolin-4-one (1) is reported. These derivatives were synthesized as potential water-soluble precursors of the antiviral thiazolinone 1, for evaluation by intranasal administration against influenza and other respiratory infections caused by viruses. Salts of the basic carbamic esters (16–19) possess the required water solubility, undergo rapid hydrolysis and decarboxylation at pH values greater than 6, and have high activity against influenza $A_2$ and Coxsackie $B_1$ viruses in vitro. In influenza $A_2$ infected ferrets a representative ester (16) reduced the severity and duration of disease symptoms and reduced nasal wash virus titres but caused local irritancy.


As a consequence of the intracellular replication of viruses and close integration of the biochemistry of virus replication and host cell metabolism, most compounds which have been shown to inhibit virus multiplication also interfere with some processes involved in the metabolism of uninfected cells. This anti-cell-activity can result in toxic effects in animals, such as immunosuppression and teratogenicity. However, when such compounds are administered systemically only a small proportion of the administered drug actually reaches the site of virus infection, which is often restricted to a particular tissue. Thus, for many viral diseases, significantly improved therapeutic ratios can be achieved by administration of the drug directly to the site of infection. This approach has, for example, been used successfully in the ocular treatment of herpes simplex keratitis with the nucleoside analogues 5-iodo-2′-deoxyuridine and 9-(β-D-arabinofuranosyl)adenine, which have activity against DNA viruses.

Infections with influenzas and rhinoviruses, which are RNA viruses, occur predominantly in the epithelium of the upper respiratory tract of man and should also be amenable to treatment with topically administered drugs. A major difficulty with intranasal administration is, however, that the mechanisms for clearance of both soluble and particulate foreign materials from the upper respiratory tract are extremely efficient. Only highly active compounds with high water solubility would therefore be expected to be sufficiently biologically available and even then many doses may be required daily. Provided that this

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