been recently postulated[8] to account for the ^{18}O-labeling pattern, kinetics, and substituent effects observed in the rearrangement of α,N-diphenylnitrone to *N*-phenylacetanilide under the influence of acetic anhydride. However, chemically induced nuclear polarization studies on the acetic anhydride affected conversion of 4-picoline *N*-oxide to 4-acetoxymethylpyridine have demonstrated the existence of free radicals in this reaction.[9] A free radical mechanism for the conversion of **3** to **4** cannot be excluded at this time.

These results establish that in the system examined an intramolecular migration of oxygen from nitrogen to carbon can be affected *via* the activated *N*-acetoxyimmonium intermediate **5**. Recently the intramolecular rearrangement of the *N*-1-desmethyl analog of **3** to the corresponding 3-hydroxybenzodiazapine was reported to occur in the presence of a Lewis acid in acetonitrile,[10] thus providing additional evidence as to the facile nature of nitrogen to carbon migration of oxygen in the nitrone system. An enzymatic process can be envisioned in which an electron-deficient "active oxygen"[11] combines with the nucleophilic imino nitrogen of compound **1** to form a high energy enzyme-substrate complex analogous to **5**. Spontaneous or enzymatically facilitated intramolecular rearrangement of this immonium intermediate followed by regeneration of enzyme would yield the observed metabolite **2**. The chemical model examined in this work is consistent with such a pathway.

Experimental Section

Reaction of 1-Methyl-5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-Oxide (3, Diazepam *N*-Oxide[11]) with ^{18}O-Enriched Acetic Anhydride. A solution of the *N*-oxide **3** (40 mg, 0.134 mmole) in acetic anhydride (0.2 ml, 95.52 atom % uniformly ^{18}O-enriched, Miles Lab.) was maintained at 80° for 1 hr under N_2. Upon cooling to 0° 1-methyl-3-[^{18}O]acetoxy-5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**4**, 3-acetoxydiazepam,‡ 35 mg, 0.102 mmole, 76%) separated as colorless crystals. The material was dried over P_2O_5 *in vacuo* (90°): mp 261–263° (lit.[6] mp 262–263°).

Mass Spectroscopy. Mass spectra were obtained on an AEI MS 902 using a direct insertion probe. The electron-ionizing voltage was 70 eV at an ionizing current of 485 mA. The source temp was 210°.

References

(1) W. Sadée, W. Garland, and N. Castagnoli, Jr., *J. Med. Chem.*, **14**, 643 (1971).
(2) J. R. Gillette, *Advan. Pharmacol.*, **4**, 219 (1966); R. E. McMahon, H. W. Culp, and J. C. Occolowtz, *J. Amer. Chem. Soc.*, **91**, 3389 (1969).
(3) M. H. Bickel, *Pharmacol. Rev.*, **21**, 325 (1969).
(4) M. H. Bickel, *Xenobiotica*, **1**, 313 (1971); A. H. Beckett, *ibid.*, **1**, 487 (1971); P. Jenner, J. W. Gorrod, and A. H. Beckett, *ibid.*, **1**, 497 (1971); M. H. Bickel, P. Willi, and P. L. Gigon, *ibid.*, **1**, 533 (1971).
(5) J. R. Baker and S. Chaykin, *J. Biol. Chem.*, **237**, 1309 (1962).
(6) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).
(7) W. Sadée, *J. Med. Chem.*, **13**, 475 (1970).
(8) S. Tamagaki, S. Kozuka, and S. Oae, *Tetrahedron*, **26**, 1795 (1970).
(9) H. Iwamura, M. Iwamura, T. Nichida, and S. Sato, *J. Amer. Chem. Soc.*, **92**, 7474 (1970).
(10) L. H. Schlager, *Tetrahedron Lett.*, **51**, 4519 (1970).
(11) J. R. Gillette, *Biochem. Aspects Antimetab. Drug Hydroxylation, Fed. Eur. Biochem. Soc., Meet., 5th*, **1968**, 109 (1969).

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2-Benzylaziridines. Cyclic Analogs of Amphetamines

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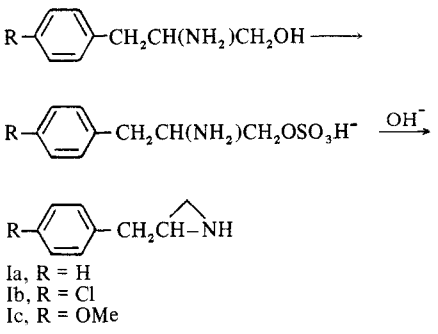
Aziridines exhibit a wide spectrum of biological properties and have found clinical application as antineoplastic agents.[1] In addition to interaction with cell constituents, the ability of aziridines to act as alkylating agents is reflected in drug-receptor interactions; for example, 2-haloalkylamines like dibenamine undergo cyclization *in vivo* to aziridinium ions prior to alkylation of the catecholamine α-receptor.[2] Our continuing interest in amphetamines and related compounds[3-5] prompted a study of the effects upon their biological activity of incorporation of part of the aminopropane side chain into an aziridine ring. 2-Benzylaziridine (Ia) has been described[6] but pharmacological data are not available. We now report the synthesis and pharmacology of this compound and its 4-chloro (Ib) and 4-methoxy (Ic) derivatives.

The classical Wenker synthesis of aziridines[1] (Scheme I) was satisfactory for Ia and Ib, but the sulfate ester of 4-methoxyphenylalaninol was obtained by dicyclohexylcarbodiimide coupling with H_2SO_4 in DMF[7] owing to the ease with which it underwent demethylation and subsequent decomposition under the very acidic conditions normally used. In our hands, a new synthesis of aziridines from vicinal amino alcohols using triphenylphosphine dibromide was singularly unsuccessful, though claimed yields are very poor for 1- and 3-unsubstituted aziridines.[8]

The three compounds had 0.1 the potency of amphetamine in reversing reserpine ptosis in mice,[4] but none of

Scheme I



Ia, R = H
Ib, R = Cl
Ic, R = OMe

them had any effect upon rabbit rectal temperature.[9] This relative lack of central stimulative actions is confirmed by their ineffectiveness in altering conditioned avoidance responses, in their inactivity in the Hall's open field test,[10] and in their lack of locomotor stimulation in mice;[5] indeed, Ia actually depressed spontaneous activity to a slight degree at 5 mg/kg. In the chloralosed cat, there were no effects *per se* at 5 mg/kg (iv) or upon the nictitating membrane contraction and responses to 5-hydroxytryptamine, noradrenaline, and isoprenaline.

It is likely that this lack of biological activity compared to amphetamine is due to the conformational restraint placed upon the molecule by incorporation of the amino function into the aziridine moiety, particularly since the analogous phenylcyclopropylamines exhibit considerable amphetamine-like activity.[11] However, it is possible that the aziridine ring

may open *in vivo* so that inactivity cannot be assigned to the aziridine *per se*, although the present compounds were unchanged by a 5-hr incubation at 37° in aqueous solution buffered at pH 7.3. The pK_a of Ia (7.2) is little different from that of aziridine itself (8.0) but is somewhat less than that of the more basic amphetamine (9.90[12]). It is possible that this leads to inefficient binding of the title compounds to a receptor because of the reduced availability of the nitrogen lone pair, a condition previously proposed for the reduced activity of the even less basic 2-amino-3-phenyl-1,1,1-trifluoropropanes[4] and 1-cyanophenethylamines.[5]

Experimental Section†

Phenylalaninyl Hydrogen Sulfates. A. To a cold suspension of 4-chlorophenylalaninol (18.3 g, 0.1 mole) in H_2O (30 ml) was added cold concd H_2SO_4 (10 g, 0.1 mole). The light yellow solution was heated at 120° to remove H_2O, the final traces being removed on the rotary evaporator. Recrystallization of the brown residue from 40% aqueous EtOH, with concentration of the mother liquors, gave 19 g (67%) of yellow needles, mp 277–279°. *Anal.* ($C_9H_{12}ClNO_4S \cdot H_2O$) C, H, N.

Phenylalaninyl hydrogen sulfate, obtained in 70% yield by the same procedure, had mp 253–255° (lit.[6] 265–270°). *Anal.* ($C_9H_{13}NO_4S \cdot H_2O$) C, H, N.

B. Dicyclohexylcarbodiimide (24.7 g, 0.12 mole) in DMF (50 ml) was added at 0° to a solution of 4-methoxyphenylalaninol (6.2 g, 0.033 mole) in DMF (60 ml). Concd H_2SO_4 (6 g, 0.0333 mole) in DMF (25 ml) was then added dropwise over 30 min at 0°. The mixture was stirred for 90 min at room temperature, the solid dicyclohexylurea was filtered off, and the filtrate was evaporated to dryness. The residue was washed well with cold water and recrystallized from aqueous EtOH, mp 255–256°, yield 4.4 g (55%). *Anal.* ($C_{10}H_{15}NO_5S$) C, H, N.

2-Benzylaziridine Hydrogen Maleates. A. 2-Benzylaziridine (Ia), bp 68–70° (0.5 mm), was prepared by continuous distillation from a mixture of aqueous NaOH and phenylalaninyl hydrogen sulfate.[6] **2-Benzylaziridine hydrogen maleate** had mp 93–94° (EtOH–Et_2O), yield 56%. *Anal.* ($C_9H_{11}N \cdot C_4H_4O_4$) C, H, N.

B. Typically, 6.5 g of 4-chlorophenylalaninyl hydrogen sulfate and 50 ml of 35% aqueous NaOH were refluxed together for 2 hr. The mixture was cooled, extracted with Et_2O, dried ($MgSO_4$), and distilled as a pale yellow oil, bp 97–98° (0.5 mm). Addition of a saturated ethereal solution of maleic acid gave the **hydrogen maleate (Ib)**, which was recrystallized from EtOH–Et_2O as colorless plates, mp 94–95°, yield 3.0 g (42%). *Anal.* ($C_9H_{10}ClN \cdot C_4H_4O_4 \cdot H_2O$) C, H, N. **2-(4-Methoxybenzyl)aziridine hydrogen maleate** (Ic) had mp 96–97° (EtOH–Et_2O), yield 36%. *Anal.* ($C_{10}H_{13}N \cdot C_4H_4O_4$) C, H, N.

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References

(1) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, London, 1969.
(2) N. B. Chapman and J. D. P. Graham, *Drugs Affecting Peripheral Nerv. Syst.*, **1**, 473 (1967).
(3) R. M. Pinder and A. Burger, *J. Pharm. Sci.*, **56**, 970 (1967).
(4) R. M. Pinder, R. W. Brimblecombe, and D. M. Green, *J. Med. Chem.*, **12**, 322 (1969).
(5) R. M. Pinder, A. Burger, and E. J. Ariens, *Arzneim.-Forsch.*, **20**, 245 (1970).
(6) D. V. Kashelikar and P. E. Fanta, *J. Amer. Chem. Soc.*, **82**, 4930 (1960).
(7) R. O. Mumma, *Lipids*, **1**, 221 (1966).
(8) K. Okada, K. Ichimura, and R. Sudo, *Bull. Chem. Soc., Jap.*, **43**, 1185 (1970).
(9) R. W. Brimblecombe, *Int. J. Neuropharmacol.*, **6**, 423 (1967).
(10) R. W. Brimblecombe, *Psychopharmacologia*, **4**, 139 (1963).
(11) A. Burger, *Fortschr. Arzneimittelforsch.*, **15**, 227 (1971).
(12) T. B. Vree and J. M. Van Rossum, *J. Pharm. Pharmacol.*, **21**, 774 (1969).

†Melting points are uncorrected and were measured in an Electrothermal capillary apparatus. Satisfactory analyses (within ±0.4% of the theoretical values) were obtained for all compounds, which were identified by ir and nmr spectroscopy. pK_a values were determined potentiometrically with a Radiometer Titrograph SBR 2c.

Central Nervous System Depressants. 10. 1-Carbamoylbenzodiazepines†,[1]

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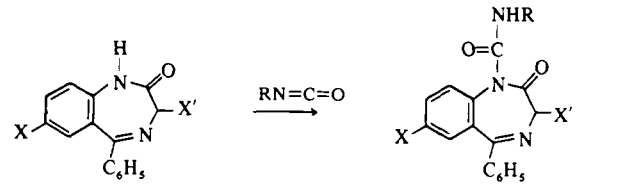
A considerable number of diazepam analogs have been reported in which other groups were substituted for the 1-methyl. In general, any such substituent containing more than 3 carbon atoms has been less active in tests thought to correlate with antianxiety activity.[2] In this work a series of 1-carbamoyl derivatives (I) is reported. These compounds



I

1, X = Cl; X' = H; R = $CH_2CH{=}CH_2$

were prepared by treatment of 1-unsubstituted benzodiazepin-2-one with the appropriate isocyanate. This procedure is exemplified in the Experimental Section by the preparation of 1, and the compounds are listed in Table I.

After the start of this work it came to our attention that Usui, *et al.*,[3] had prepared a similar series of benzodiazepine derivatives. However, our series overlapped theirs in only one compound, the methylcarbamoyl analog (**10**). Even though this was one of their more active compounds, our compound 1 proved to be more active in mice on all the parameters used (Table II).

Pharmacology. The pharmacologic results obtained with this series of 1-carbamoylbenzodiazepines are presented in Table II, and the results are compared to those obtained with diazepam in the same test systems. Compound 1, the allylcarbamoyl analog, was the most active compound in this series. It was equipotent or more active than diazepam on all end points except the antagonism of pentylenetetrazol-induced clonic convulsions and the potentiation of ethanol narcosis. The activity of the allyl derivative (1) in the traction and strychnine tests may indicate potent muscle relaxant activity.

Substitution of a cyano group for a chloro group in position 7 (2) markedly decreased the pharmacologic activity. Compound 2 was inactive in antagonizing strychnine lethality and pentylenetetrazol-induced clonic convulsions and on all other end points it was weakly active. Substitution of a cyano group (RO5-4528) for the chloro group in the diazepam series produced a compound more potent on almost all test systems except the simple reflex tests (chimney, dish, and pedestal) and antagonism of pentylenetetrazol-induced seizures. It appears therefore that the structure–activity relationships for the 1-carbamoylbenzodiazepines may be different from those established for the 1-methyl derivatives.

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