109–111.5° (lit.[1] mp 108–109°); $[\alpha]_D$ −6° (*c* 0.64, $CHCl_3$); ir (mull) and nmr (DMSO-d_6) spectra identical with those for authentic I. *Anal.* ($C_{11}H_{12}F_3NO_4$) C, H, F, N.

Characterization of the Glucuronide of I.—A crude glucuronide fraction was isolated from the combined 0- to 48-hr urine of one subject using the basic lead acetate procedure.[7] The glucuronide gum was methylated with CH_2N_2 in Et_2O, and the resulting ester was acetylated with pyridine–Ac_2O.[5] The crude product was purified by chromatog on a column (2.3 × 29 cm) contg 50 g of 100–200 mesh Florisil (Fisher Scientific Co., Fair Lawn, N. J.). Sample was introduced to the column in CH_2Cl_2 and elution accomplished with Me_2CO–isooctane mixtures of increasing polarity. A yield of 458 mg of crude crystals was obtained. This material was recrystd twice from C_6H_6–isooctane to give 285 mg of crystals: mp 168.5–169°; $[\alpha]_D$ −17 (*c* 0.78, $CHCl_3$); uv indistinguishable from that of I (λ_{max} and ϵ); ir very similar to the corresponding methyl tri-*O*-acetyl derivative of chlorphenesin carbamate *O*-glucuronide[5] and of the glucuronides of *p*-aminosalicylic acid,[10] *p*-hydroxybenzoic acid,[11] and 3-hydroxycarbazole;[12] nmr ($CDCl_3$) consistent with the structure methyl [3-(α,α,α-trifluoro-*m*-tolyloxy)-1,2-propanediol 1-carbamate 2-*O*-(tri-*O*-acetyl-β-D-gluosid)]uronate based on sharply defined acetate peaks at δ 1.83 and 2.03 (in the ratio of 1:2), a sharp peak at 3.75, broad multiplets attributed to carbinol and amide H between 3.5 and 5.5 and a typical meta-substituted aryl H pattern centered at 7.21 (all values in ppm, δ, downfield from Me_4Si); integration of the nmr spectrum accounted for 28 protons as 9 acetate, 3 Me, 4 Ar, and 12 carbinol and amide H. *Anal.* ($C_{12}H_{28}F_3NO_{13}$) C, H, N, Ac; F: calcd, 9.57; found, 10.06.

Chromatography.—Paper chromatog of the neutral fractions was carried out by the descending method on Whatman No. 2 paper (86 cm) in the Bush B-5 system (sheet equilibrated overnight at 34° in the vapor from a mixed solvent composed of C_6H_6–MeOH–H_2O, 2:1:1, and developed with the C_6H_6 phase)[13] and in the Mattox I system (sheet satd with MeOH–formamide, 1:1, dried 15 min at 37°, and developed with *n*-BuOAc–formamide–H_2O, 20:1:1).[14] Acidic metabolites were chromatographed on Whatman No. 1 paper with *i*-PrOH–NH_4OH–H_2O, 8:1:1 (IAW)[15] and with C_6H_6–AcOH–H_2O, 1:1:2 (BZAW). All chromatograms were viewed with a short-wavelength scanner[16] to detect zones absorbing uv light. Carbamate-contg metabolites were detected by spraying with *p*-dimethylaminobenzaldehyde or with NaOCl and *o*-tolidine.[4] Acidic metabolites were sprayed with 0.1% bromphenol blue (BPB) to detect acids and with diazotized sulfanilic acid (DZSA) for visualization of phenols.

Tlc of methyl tri-*O*-acetyl glucuronides was carried out on silica gel GF (Brinkmann Instrument Co., Great Neck, N. Y.) using 1.5% (v/v) MeOH in $CHCl_3$ or on alumina GF with 0.75% (v/v) MeOH in $CHCl_3$. Glucuronide esters were located by spraying the dried plates with 1% *p*-dimethylaminobenzaldehyde in 4 *N* HCl followed by 50% H_2SO_4 and subsequent heating to yield reddish zones.

Acknowledgments.—The authors thank Drs. S. S. Stubbs, E. W. Young, J. P. Webb, and H. L. Oster and Mr. M. J. White for assistance with the clinical portion of the study, Dr. G. A. Youngdale for synthesis of authentic compound IV, and Dr. G. Slomp for the nmr analyses.

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Synthesis and Analgetic Properties of Compounds Containing an Exocyclic Basic Center

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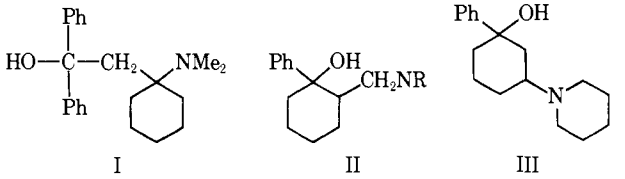
1-Dimethylamino-1-(2,2-diphenyl-2-hydroxyethyl)cyclohexane and 1-phenyl-3-piperidinocylohexan-1-ol have been prepared and tested for analgetic activity. In the latter case the two geometrical isomers were separated and esterified. Analgetic activity was present only in the trans (O/N) isomers. The conclusion is drawn that steric restrictions in the environment of the receptor site may be responsible for lack of activity in the cis isomers.

A very large number of pethidine reversed ester compounds have been prepared in the search for synthetic analgetics of high potency and low toxicity.[1] Potency equal to or greater than morphine has often been achieved, but toxic side effects have always accompanied an increase and no compd of real clinical importance has emerged since the original reversed esters of α- and β-prodine were prepared by Ziering and Lee[2] in 1947.

It is my belief that an improvement in therapeutic ratio is more likely to be achieved with compds which show a more dramatic change in parent structure. The bulk of the evidence so far accumulated seems to indicate that an analegtic must possess a basic center and an aromatic ring which are separated by a suitable distance.

With this in mind, 3 structures were first considered in which the piperidine nitrogen of the reversed ester compds was moved outside the ring. Of these, various



I II III

structures of type II had already been prepared and found to possess little or no activity.[3] Therefore, the syntheses of I and III were undertaken. During the course of this work, IV has been reported[4] with an

(1) For a review, see R. A. Hardy and M. G. Howell, *Med. Chem., Ser. Monogr.*, **5**, 179 (1965).
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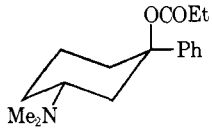
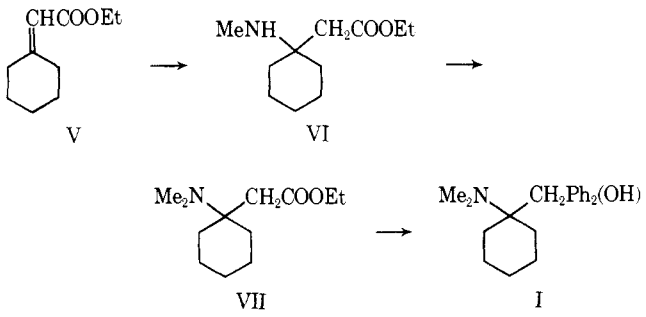


IV

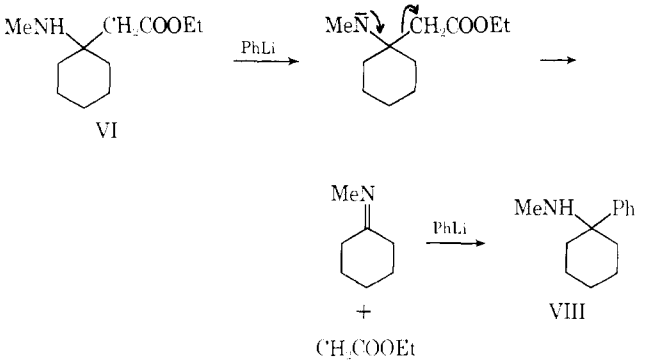
analgetic activity of 63 mg/kg (ED_{50}, hot plate). However the corresponding cis isomer was not obtained.

Chemical Syntheses.—The preparation of I is illustrated in Scheme I.

SCHEME I



It was hoped that Me_2NH would react with the α,β-unsaturated ester V[5] to give VII directly. Several attempts under various conditions failed to give any reaction, neither could piperidine be induced to add across the double bond. However, the addition of $MeNH_2$ took place in good yield at room temp to give the secondary amine VI which reacted with MeI in the presence of Na_2CO_3 to give the required tertiary amine VII. PhLi reacted to give the amino alcohol I. Attempts to carry out the reaction of the secondary amino ester VI with PhLi in order to obtain a secondary base for pharmacological testing led only to the isolation of *N*-methyl-1-phenylcyclohexylamine (VIII) presumably by the following route.

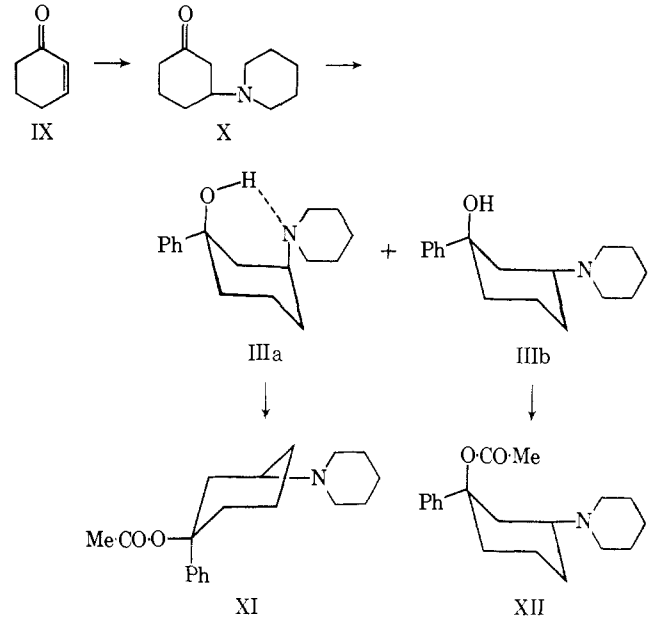


All attempts to convert I into its Ac ester by means of Ac_2O–pyridine or by reaction of Ac_2O on the Li salt lead to decomposition.

The preparation of III and its esters is illustrated in Scheme II.

The reaction of PhLi on the amino ketone X gave the required product III which was separated by fractional recrystallization into its cis (IIIa) and trans (IIIb) isomers. The structural assignments were made on the basis of the OH absorption in the ir spectra. The cis isomer showed a broad band due to OH vibration

SCHEME II



centered at 3150 cm^{-1} in CCl_4 which remained unchanged on high dilution, indicating the presence of conformer IIIa under these conditions. The trans isomer (IIIb) showed a broad band at 3350 cm^{-1} in concd soln which collapsed to a sharp singlet at 3600 cm^{-1} on dilution.

Each alcohol was treated with Ac_2O to give the cis (XI) and trans (XIII) esters.

Pharmacological Results and Discussion.—The results presented in Table I show that the trans isomers

TABLE I

ANALGETIC ACTIVITIES IN MICE[a]

Compd	ED_{50} (hot plate), mg/kg	ED_{50} (tail clip), mg/kg
I	>100	>100
IIIa	>100	>100
IIIb	85	90
XI	>100	>100
XII	48	48
Morphine	1.2	1.2

[a] P. A. J. Jansen and A. H. M. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957).

possess small but significant analgetic activity but the cis isomers are totally inactive even at 100 mg/kg dose level. This was surprising since the cis isomers appear to be a better fit on the analgetic receptor.[6] Molecular models indicate that C atoms 4, 5, and 6 of the cyclohexane ring occupy a volume which is not occupied by any part of the trans isomer molecule or of the morphine molecule. It may be that the inactivity of the cis isomer is due to a physical interaction between this trimethylene group and some structure attached to or close to the analgetic receptor. The large distance between the N and the center of the phenyl ring of the trans isomer (6.2 Å) compared to morphine (4.5 Å) is further evidence for the flexible receptor model suggested by Portoghese.[7]

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Experimental Section

3-Piperidinocyclohexanone (X).—A mixt of cyclohexen-2-one (40 g), piperidine (130 ml), and H_2O (10 ml) was refluxed 1 hr and distd to give X (35 g, 49%), bp 101–102° (0.6 mm). It gave a **hydrobromide**, mp 179° (from *i*-PrOH–Et_2O). *Anal.* ($C_{11}H_{20}BrNO$) C, H, Br, N.

***cis*-(IIIa) and *trans*-(IIIb) 1-Phenyl-3-piperidinocyclohexan-1-ol.**—A soln of X (40 g) in Et_2O (200 ml) was added to PhLi [from Li (4.9 g) and PhBr (55 g)] in Et_2O (200 ml) and refluxed 1 hr. The cooled product was poured into H_2O and acidified with AcOH. The aq soln was washed (Et_2O), basified (NH_4OH), and extd with Et_2O (3x). The combined exts were dried ($MgSO_4$) and evapd. Several recrystns of the residue from petr ether (bp 80–100°) gave IIIb, 20 g (35%), mp 111–112°. *Anal.* ($C_{17}H_{25}NO$) C, H, N. It gave a **hydrochloride**, mp 254–255° (from EtOH–Et_2O). *Anal.* $C_{17}H_{26}ClNO$) C, H, Cl, N. Evap of the mother liquors and recrystn from petr ether (bp 40–60°) gave IIIa (9 g, 16%), mp 80°. *Anal.* C, H, N. It gave a **hydrochloride**, mp 247.5° (from EtOH–Et_2O). *Anal.* C, H, Cl, N

***cis*-1-Acetoxy-1-phenyl-3-piperidinocyclohexane (XI).**—A soln of IIIa (0.5 g) in pyridine (1.5 ml) and Ac_2O (1.5 ml) was refluxed 0.75 hr, the solvents were evapd, and the residue was treated with HCl gas to give XI·HCl (0.4 g, 61%), mp 195° (from EtOH–Et_2O). *Anal.* ($C_{19}H_{28}ClNO_2$) C, H, Cl, N.

***trans*-1-Acetoxy-1-phenyl-3-piperidinocyclohexane (XII).**—A soln of IIIb (1 g) in Et_2O (5 ml) was added to PhLi [from Li (0.08 g) and PhBr (0.9 g)] in Et_2O (15 ml) and refluxed 15 min. Ac_2O (1.2 g) was added dropwise with ice cooling and the mixt was allowed to warm to room temp with stirring overnight. Acid–base extn and treatment of the crude product with HCl gas gave XII·HCl (1.3 g 99%), mp 184–185° (from EtOH–Et_2O). *Anal.* C, H, Cl, N.

Ethyl (1-Methylamino)cyclohexylacetate (VI).—A soln of $MeNH_2$ (2.5 g) and V (4.5 g) in EtOH (10 ml) was allowed to stand overnight. Evap of excess $MeNH_2$ and treatment of the residue with HCl gas gave VI·HCl (3 g, 48%), mp 114–115° (from EtOAc). *Anal.* ($C_{11}H_{22}ClNO_2$) C, H, Cl, N.

Ethyl (1-Dimethylamino)cyclohexylacetate (VII).—Na_2CO_3 (3.2 g) was added to a soln of VI (5 g) and MeI (6.3 g) in EtOH (50 ml). The mixt was refluxed 1.5 hr. After acid–base extn the residue was treated with HCl gas to give VII·HCl (4.5 g 72%), mp 117° (from EtOAc). *Anal.* ($C_{12}H_{24}ClNO_2$) C, H, Cl, N.

1-Dimethylamino-1-(2,2-diphenyl-2-hydroxyethyl)cyclohexane (I).—A soln of VII (9.5 g) in Et_2O (100 ml) was added to PhLi [from Li (1.7 g) and PhBr (17.6 g)] in Et_2O (200 ml) and refluxed 2 hr. Acid–base extn gave I (4 g, 35%), mp 152–153° (from petr ether, bp 80–100°). *Anal.* ($C_{22}H_{29}NO$) C, H, N. It gave a hydrochloride, mp 197° (from *i*-PrOH–Et_2O). *Anal.* ($C_{22}H_{30}ClNO$) C, H, Cl, N.

***N*-Methyl-1-phenylcyclohexylamine, (VIII).**—A soln of VI (10 g) in Et_2O (50 ml) was added to PhLi [from Li (2.8 g) and PhBr (31.4 g)] and refluxed 12 hr. After acid–base extn, the product was treated with HCl gas to give VIII·HCl (6 g, 53%), mp 190–191° (from EtOAc). *Anal.* ($C_{13}H_{20}ClN$) C, H, Cl, N. It gave a picrolonate, mp 227° dec (from MeOH). *Anal.* ($C_{23}H_{27}N_5O_5$) C, H, N.

Acknowledgment.—I am indebted to Dr. D. Jack of Allen and Hanburys Ltd., Ware, Hertfordshire, for the pharmacological results.

Antiinflammatory 3,4-Dihydro-2-alkyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxamide 1,1-Dioxides[1]

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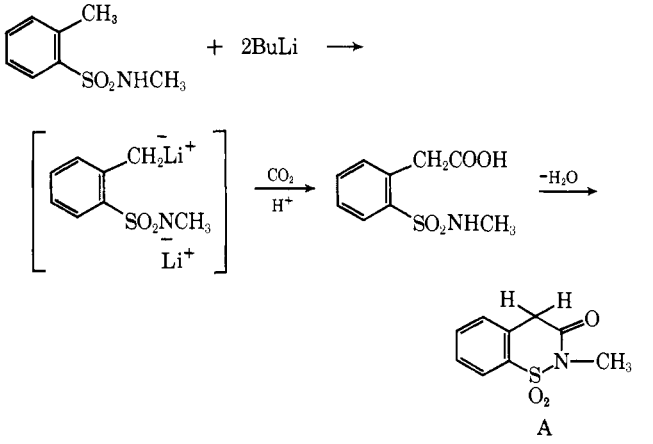
A general procedure for preparing 3,4-dihydro-2-alkyl-1,2-benzothiazine-3(2*H*)-one 1,1-dioxide has been found. A number of 4-carboxamides derived from this ring system are moderately acidic and exist as the diketo (nonenolized) form. These β-keto carboxamides exhibit potent antiinflammatory activity in the carrageenin-induced rat foot edema test. Such activity is also present in adrenalectomized rats. Activity as high as 1.5 times that of indomethacin was observed with some members of this family.

Previous publications have described the antiinflammatory activity of certain 2-methyl-1,3-dioxoisoquinoline-4-carboxanilides.[2] These results prompted the preparation of 3,4-dihydro-2-alkyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxamide 1,1-dioxides. Preparation of 3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide and the discovery of potent antiinflammatory activity for carboxamides derived from this heterocyclic system form the basis of this report.

Chemistry.—No examples of the 3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide ring system were known when this work was initiated. One possible approach to such compounds was visualized by applying the lithiation technique of Gay and Hauser[3] to *N*-methyl-*o*-toluenesulfonamide. When this was done, both the sulfonamide N and the *o*-Me group were apparently lithiated since treatment of the resultant dilithio salt with CO_2 followed by a cyclodehydration produced the desired 3,4-dihydro-2-methyl-1,2-benzothiazine-3(2*H*)-one 1,1-dioxide (A). (Intermediate compds will hereafter be given letter designations while all carboxamides will be numbered.) This technique proved to be quite



A

general since *N*-benzyl-*o*-toluenesulfonamide gave 2-benzyl-3,4-dihydro-3-oxo-2*H*-1,2-benzothiazine 1,1-

(1) Presented in part before the Medicinal Division at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971.

(2) (a) S. B. Kadin and E. H. Wiseman, *Nature (London)*, **222**, 275 (1969); (b) E. H. Wiseman, E. J. Gralla, J. Chiaini, J. R. Migliardi, and Y. H. Chang, *J. Pharm. Exp. Ther.*, **172**, 138 (1970).

(3) R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967).