5,11-Dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane, a Potent, Novel Analgesic

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5,11-Dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**2a**) has been found to be a potent narcotic analgesic of unusual structure. All of the analgesic activity was attributable to the levorotatory isomer **2b** which was approximately three times as potent as morphine in the rat. Removal of one *N*-methyl group from **2a** reduced, but did not abolish, the analgesic activity. However, *N*-allyl analogues were neither agonists nor antagonists. Replacement of one of the phenyls of **2a** with a cyclohexyl group yielded an analogue with considerable activity. Structural similarities with derivatives of ethenooripavine are noted.

Synthesis of 2,9-dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**1**) was recently accomplished in these laboratories.[1] This novel heterocycle is a substituted diazaditwistane[2] whose unique structure presents attractive opportunities for exploratory modification. Inspection of the molecule indicates identical nitrogens separated by four carbons through fused twist–boat rings. The bridgehead cyano substituents at 2,9 are also in a 1,4 arrangement to each other and are in the β position of one piperidine ring and in the γ position of another. Most interestingly, the molecule has a C_2 axis of symmetry as shown in Chart I. Thus, initial and 180°-rotated configurations about this axis are superimposable, making the 2,9 positions identical even in respect to absolute stereochemistry, although the molecule as a whole is resolvable. As a result, when symmetrically substituted, the diazaditwistane can make available two identical faces for binding to a receptor. When unsymmetrically substituted, specific interactions with more than one receptor can be considered.

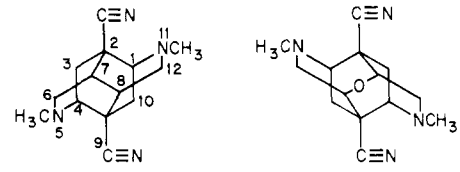
This paper reports studies which led to the discovery of the potent analgesic (−)-5,11-dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**2b**). Data on several close analogues illustrate some of the structural features which are associated with this activity.

Chemistry. Preparation of **2a** was achieved by treatment of **1** with an excess of benzylmagnesium chloride in THF. The optical antipodes (**2b** and **2c**) were similarly prepared after resolution of **1** via fractional crystallization of its dibenzoyl-*d*-tartaric acid salts from methanol.[1] The demethyl analogues of **2a** (**4** and **6**) were obtained by acid hydrolysis of urethanes **3** and **5**, which were synthesized by selective reaction of **2a** with excess or limited ethyl chloroformate, as described in the Experimental Section. Alkylations of **4** and **6** to afford **7** and **9** were achieved using ethyl iodide in DMF over K_2CO_3, whereas analogues **8** and **10** were prepared by direct reaction with allyl bromide.

Preparation of **11** and **12** was effected by reaction of **1** with cyclohexylmethylmagnesium bromide followed by chromatographic separation on silica. Reaction of **11** with benzylmagnesium chloride afforded **13** which was purified *via* its picrate salt. Formulas and numerical designations for these compounds are summarized in Table I.

Biological Results and Discussion. Pharmacological screening of *dl*-5,11-dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**2a**) uncovered its narcotic-like analgesic properties. Analgesia was measured on the basis of elevation of the pain reaction threshold to pressure applied to the untreated hind paw of rats as described by Winter and Flataker.[3,4] Compound **2a** (ED_{50} = 1.0 mg/kg sc) was on the order of 1.5 times more potent than morphine (ED_{50} = 1.5 mg/kg sc) as an analgesic in this procedure.

Chart I. 2,9-Dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**1**)[a]



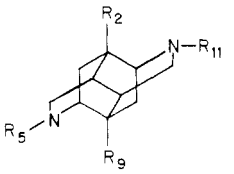
[a] The mirror image relationship and axis of symmetry (o) bisecting the 7,8 bond are shown.

The analgesic activity of **2a** was additionally demonstrated by its marked ability to prolong reaction times in rats in the tail-flick analgesia procedure[5] at a dose of 3.0 mg/kg sc. The analgesic activity of **2a** in the latter test was promptly and completely reversed by naloxone (10 mg/kg sc). Tolerance development to the action of compound **2a** was shown by complete abolition of its analgesic activity upon daily administration for 5 days.

In mice, compound **2a** (50 mg/kg sc) exhibited analgesia as determined in the Haffner clamp test.[6] Administration of naloxone (10 mg/kg ip) promptly elicited the jumping response which is characteristic of narcotic withdrawal and is a prime indicator of physical dependence liability.[7] Thus compound **2a** despite its unusual structure exhibits all the typical symptomatology of narcotic analgesics, namely, tolerance, naloxone antagonism, withdrawal, and physical dependence liability. In addition, compound **2a** produced catatonia, Straub tail, and exopthalmus in rats. These effects are also characteristic of narcotic agents.

Resolution of compound **2a** demonstrated that all of the analgesia was attributable to the levorotatory isomer **2b**. Potency of this enantiomer in the rat paw analgesia test (ED_{50} = 0.6 mg/kg sc) was about three times that of morphine. The bis-nor compound **4** was inactive at 81 mg/kg in the rat paw assay. Modest activity in the mono-nor-*N*-methyl analogue **6** is consistent with previous experience which requires only a single N-alkylated nitrogen for interaction with the morphine receptor site. It was surprising, however, that the bis(*N*-allyl) derivative **8** was neither an analgesic nor a narcotic antagonist either toward anileridine or toward the parent resolved analgesic **2b**. No evidence was obtained for mixed agonist–antagonist properties in the *N*-methyl-*N'*-allyl analogue **10**. Its ED_{50} was greater than 80 mg/kg as an analgesic and levels of 10 mg/kg iv were not effective in reversing the narcotic properties of **2b** in rats, in contrast to pentazocine which was effective at less than 5.0 mg/kg iv. Lower alkyls greater in size than methyl would appear to be inconsistent

Table I. Derivatives of 5,11-Diazaditwistane



Compd	R_2	R_9	R_5	R_{11}	Analgesic act.,[a,b] ED_{50}, mg/kg sc
2a [(±) isomer]	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	CH_3	1.0 (0.7-1.4)[d]
2b [(−) isomer]	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	CH_3	0.6 (0.3-0.9)
2c [(+) isomer]	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	CH_3	>80.0
3	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3CH_2OCO	CH_3CH_2OCO	NT[c]
4	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	H	H	>81.0
5	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	CH_3CH_2OCO	NT[c]
6	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	H	45.0 (31.3-56.7)
7	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3CH_2	CH_3CH_2	41.1 (23.6-54.0)
8	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	$CH_2=CHCH_2$	$CH_2=CHCH_2$	>81.0
9	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	CH_3CH_2	29.9 (23.1-37.7)
10	$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	CH_3	$CH_2=CHCH_2$	>80.0
11	$C_6H_{11}CH_2CO$	CN	CH_3	CH_3	NT[c]
12	$C_6H_{11}CH_2CO$	$C_6H_{11}CH_2CO$	CH_3	CH_3	>81.0
13	$C_6H_{11}CH_2CO$	$C_6H_5CH_2CO$	CH_3	CH_3	10.1 (6.7-12.9)

[a] Estimated dose to elevate the pain reaction threshold to pressure applied to the hind paw of rats to 50 mmHg. (See ref 3 and 4.) [b] Morphine as standard: ED_{50} = 1.5 (1.0-2.2) mg/kg sc. [c] Synthetic intermediate not tested. [d] Confidence limits (95%).

with good activity. The 5-methyl-11-ethyl analogue **9** and the 5,11-diethyl analogue **7** displayed ED_{50}'s of 29.9 and 41.1 mg/kg sc, respectively.

The requirement of only one phenyl for analgesia could be demonstrated. This was accomplished with the synthesis of the monophenylacetylmonocyclohexylacetyl analogue **13** whose activity was approximately one-tenth that of the *dl*-bis(phenylacetyl) compound **2a**. The related bis(cyclohexylacetyl) analogue **12** was inactive at dose levels up to 81.0 mg/kg as expected. These data are summarized in Table I.

At present the a priori assignments of absolute configurations to **2b** and **2c** are not possible. Inspection of CPK space-filling models suggests structural similarities of either isomer of **2a** to the conformations of morphine and its analogues.[8] In particular, comparison with the highly potent ethenooripavine derivatives prepared by Bentley's group offers a possible explanation for the observed supra morphine activity. Structure–activity studies of these oripavine derivatives demonstrate the existence of a hydrophobic binding site on the receptor which is not accessible to morphine itself.[9] Possible conformations of either antipode of **2a** indicate that one of the phenyl rings might derive binding energy from this site while the other aromatic ring occupies the site of the phenyl ring of morphine. These conformations are in accord with the proposal of Belleau et al.[10] in that the nitrogen lone pair projects away from the benzene ring in order to allow binding to the analgesic receptor. They are also in accord with the report of Boura and co-workers[11] that an unsubstituted methylene group next to the nitrogen is needed for optimum activity. Further extension of the structural analogies to the pentapeptide enkephalin[12] is possible if conformational suggestions such as those of Clark,[13] Bradbury et al.,[14] and Horn and Rogers[15] are shown to be valid. Our present efforts are directed toward further elaboration of the structure–activity relationships and toward the determination of the absolute configuration of the active antipode of **2a**.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. Microanalyses were performed by the laboratory's Developmental Research-Physical and Analytical Department and are within 0.4% of theory except where noted. IR, NMR, and mass spectra are consistent with presented structures. TLC was performed on silica gel plates (Kontes, Quantagram QLF) using the following systems: $CHCl_3$–CH_3OH (97:3) (I); CH_3OH (II); EtOAc (III). Spots were detected by fluorescence and I_2 absorption. We wish to acknowledge the assistance of Mr. R. N. Boos, Dr. A. W. Douglas, Mr. J. P. Gilbert, Mr. J. L. Smith, and Mr. R. C. Zerfing relative to the analytical and spectral data and Mr. D. G. Dortmund for technical assistance.

(±)-5,11-Dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (2a). This was prepared similarly to **2b**, except that the racemic **2a** tends to crystallize as a monohydrochloride at the interphase between benzene and the HCl solution during the removal of the neutral contaminants. It is expedient to separate the crystals and to work up the HCl solution separately. The overall yield is 98%, mp 84-91 °C. Anal. ($C_{28}H_{32}N_2O_2$) C, H, N.

(−)-5,11-Dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (2b). A slurry of the (−) enantiomer of **1** (1.00 g, 4.12 mmol) in dry THF (10 ml) was treated under N_2 with benzylmagnesium bromide (6.20 ml, 2.00 mol in THF, 12.4 mmol), refluxed for 2 h, cooled to −10 °C, and quenched with water (1 ml). After vigorous stirring for 0.5 h at ambient temperature, CH_2Cl_2 (10 ml) and $MgSO_4$ (~1 g) were added. The inorganics were filtered and washed well with CH_2Cl_2. The filtrate was evaporated to give the diimine of **2b**, which was hydrolyzed with HCl (10 ml of 1.25 N solution) for 1 h, while the neutral contaminants were removed by two extractions into benzene. The HCl layer was made alkaline with NaOH (5.0 ml, 2.5 N) to give an oil which was crystallized with ether, filtered, washed with water, and dried in vacuo to give 1.74 g (98.6%) of **2b**, mp 120–131 °C. A sample was recrystallized from ethanol (2.5 vol) to give pure product in 74% recovery: mp 133–135 °C; $[\alpha]_{578}$ −126.6° (*c* 0.55, CH_2Cl_2). Anal. ($C_{28}H_{32}N_2O_2$) C, H, N.

(+)-5,11-Dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (2c). **2c** was prepared as described for **2b**: 91% yield; mp 118–126 °C; $[\alpha]_{578}$ +127.0° (*c* 0.5, CH_2Cl_2).

5,11-Bis(carboethoxy)-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (3). A stirred mixture of **2a** (98.9 g, 0.231 mol) and ethyl chloroformate (625 ml) was heated slowly to reflux to allow for vigorous gas evolution, refluxed for 3 h, and cooled. The crystals (mainly quaternaries) were filtered and washed with benzene. The filtrate was concentrated and the resulting oily crystalline mass was triturated with 300 ml of ether, filtered, washed with ether (3 × 100 ml), and dried to yield 76.5 g (61%) of **3**. A second crop of 30.4 g (24%) was obtained by

concentration of the mother liquor and retreatment as above. This material was of sufficient purity for further use. A small sample was recrystallized from ethanol: mp 163–164 °C. Anal. ($C_{32}H_{36}N_2O_6$) C, H, N.

2,9-Bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (4). Hydrolysis of **3** (100 g, 184 mmol) was accomplished by treatment under pressure with concentrated HCl (600 ml) at 120 °C for 12 h. The resulting slurry was cooled to 5 °C, filtered, and washed with ice water (2 × 100 ml). The wet cake was treated with CH_2Cl_2 (1200 ml), water (500 ml), and slowly with NaOH (50 ml of 50% solution) and stirred at room temperature overnight. The CH_2Cl_2 layer was separated, combined with a CH_2Cl_2 (300 ml) wash, and evaporated in vacuo to yield 67.62 g (91.6%), mp 103–112 °C. Anal. ($C_{26}H_{28}N_2O_2$) C, H, N.

By TLC (systems I and II) no contamination with **2a** was detectable and a trace of **6** was present.

5-Carboethoxy-11-methyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (5). A mixture of **2a** (20.0 g, 46.4 mmol) and ethyl chloroformate (8.0 ml, 84 mmol) in benzene (400 ml) was refluxed for 2.5 h and concentrated in vacuo to an oil, which by TLC (system I) contained **2a**, **3**, and **5**. Preliminary separation was effected by partitioning the mixture between CH_2Cl_2 (100 ml) and 2.5 N HCl (100 ml). The **5**·HCl salt proved to be soluble in CH_2Cl_2 as was **3**, whereas unreacted **2a** was taken into the aqueous layer and partially crystallized as its HCl salt. Subsequent partitioning of the concentrated **3**–**5**·HCl mixture between H_2O and C_6H_6 followed by alkalinization of the aqueous layer, extraction into CH_2Cl_2, drying, and concentration afforded pure **5** as an oil (11.5 g, 21.8 mmol, 47%). Anal. ($C_{30}H_{34}N_2O_4$) C, H, N.

5-Methyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane Dihydrochloride Sesquihydrate (6). Compound **5** (11.35 g, 21.7 mmol) was heated at 120 °C in concentrated HCl (60 ml) under pressure for 12 h. The resulting solution was evaporated in vacuo to a crystal mass which was flushed with benzene (2 × 50 ml). The HCl salt was converted to the free base by basification with NaOH (30 ml, 2.5 N) and extraction with CH_2Cl_2 (100 ml). After drying ($MgSO_4$) and evaporation of the CH_2Cl_2 layer, the amorphous free base of **6** (9.12 g, 100.2%) was obtained essentially as a single spot by TLC (system II, R_f 0.45). All attempts to crystallize the free base failed. Chromatography of part (1.06 g) over Merck alumina (100 g) set up in acetone followed by displacement with benzene and gradient elution with benzene (500 ml), benzene (200 ml) mixed with $CHCl_3$ (50 ml), and benzene (150 ml) mixed with $CHCl_3$ (100 ml) gave purified base which was converted to the HCl salt by dissolving in ether, decanting from a small amount of insoluble gum, and introducing HCl gas. By TLC analysis no contamination of **2** was detectable. Anal. ($C_{27}H_{30}N_2O_2$·2HCl·1.5H_2O) C, H, N, Cl.

5,11-Diethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (7). A mixture of **4** (2.01 g, 5.0 mmol), EtI (1.72 g, 11 mmol), K_2CO_3 (1.5 g, 11 mmol), and DMF (25 ml) was stirred at ambient temperature for 70 h. Addition of water (100 ml) was followed by extraction with 2 × 60 ml of CH_2Cl_2. This was washed with H_2O (3 × 25 ml), dried ($MgSO_4$), and concentrated to an oil (1.9 g) which would not crystallize. Generation of the HCl salt (CH_2Cl_2, Et_2O, HCl), followed by washing (CH_2Cl_2, Et_2O), dissolution in 2.5 N aqueous HCl, washing (CH_2Cl_2) and regeneration (2.5 N NaOH), extraction (CH_2Cl_2), and evaporation, afforded the free base as an amorphous mass. Regeneration of the HCl salt (Et_2O, HCl) afforded 0.93 g of solvated dihydrochloride (single spot by TLC, system I, R_f 0.55) which was recrystallized from 3 ml of EtOH. Regeneration (2.5 N NaOH), extraction (CH_2Cl_2), and concentration afforded the free base (**7**): mp 105–112 °C. Anal. ($C_{30}H_{36}N_2O_2$) H, N; C: calcd, 78.91; found, 78.49.

5,11-Diallyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (8). Allyl bromide (40 ml) and **4** (10.0 g, 20.5 mmol) were stirred overnight at room temperature. The resulting hydrobromide was filtered, washed with CH_2Cl_2, and partitioned between 50 ml of 2.5 N NaOH and CH_2Cl_2 (50 ml). The CH_2Cl_2 layer was dried and concentrated to afford 8.14 g of crude **8**, mp 79–91 °C. This was recrystallized from CH_3OH (70 ml), redissolved in EtOAc (100 ml), filtered through a short silica gel bed (silica gel H, Stahl, 5 cm), and concentrated to afford pure **8**, mp 96–99 °C. Anal. ($C_{32}H_{36}N_2O_2$) C, H, N.

5-Ethyl-11-methyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane Dihydrochloride (Hydrated) (9). A mixture of the free base of **6** (2.50 g, 6.25 mmol), EtI (1.03 g, 6.6 mmol), K_2CO_3 (0.915 g, 6.6 mmol), and DMF (25 ml) was stirred at ambient temperature overnight. The reaction mixture was partitioned between H_2O (100 ml) and CH_2Cl_2 (100 ml) and the residue obtained by drying and concentrating the CH_2Cl_2 solution was chromatographed on silica gel (100 g, Baker 3405) using EtOAc–CH_3OH–HOAc (50:4:1). The product-containing fractions were concentrated, and the residue was dissolved in $CHCl_3$ and filtered. The oil resulting from the subsequent introduction of HCl gas was crystallized by addition of Et_2O, filtered, and recrystallized from ethanol (6 ml) to give 0.42 g (12.5%) of **9** hydrochloride. Anal. ($C_{29}H_{34}N_2O_2$·2HCl·1.2H_2O) C, H, Cl, N.

5-Allyl-11-methyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane Dihydrochloride Hydrate (10). Compound **10** was prepared in a manner similar to that used for the preparation of **8**. The basic reaction products were chromatographed over silica gel (Baker 3405) using a gradient from C_6H_6–$CHCl_3$ (1:1) to $CHCl_3$–CH_3OH (10:1). The crystalline salt was prepared from the combined product fractions in Et_2O with HCl gas. By TLC (systems I and III), no **2a** and only a trace of **8** were present. Anal. ($C_{30}H_{34}N_2O_2$·2HCl·H_2O) C, H, Cl, N.

2-Cyano-9-cyclohexylacetyl-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (11) and 2,9-Bis(cyclohexylacetyl)-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (12). A mixture of **1** (12.1 g, 50 mmol), cyclohexylmethylmagnesium bromide (1.0 M in THF, 225 ml, 22.5 mmol), and THF (125 ml) was refluxed under N_2 for 44 h, cooled, and quenched ($T \leq 20$ °C) with CH_3OH (25 ml), 50% NaOH (12 ml), and CH_3OH (25 ml). After stirring for 1 h the inorganics were filtered and washed with CH_2Cl_2 (200 ml). The filtrate was evaporated and the residue dissolved in 2.5 N HCl (100 ml). Neutral materials were extracted with C_6H_6 (3 × 30 ml) and CH_2Cl_2 (3 × 30 ml). After 1 h the HCl solution was treated with 2.5 N NaOH (40 ml) and extracted with CH_2Cl_2 (3 × 30 ml) which was evaporated to give 14.8 g of a mixture of **1**, **11**, and **12**. This was chromatographed on silica gel (Baker 3405, 1500 ml) using gradient elution from C_6H_6–CH_2Cl_2 (1:1) to CH_2Cl_2–CH_3OH (99:1). The combined fractions containing **11** were recrystallized from hexane (2 × 25 ml) to afford 1.65 g (9.7%) of **11**, mp 89–93 °C. Anal. ($C_{21}H_{31}N_3O$) C, H, N. The fractions containing **12** were recrystallized from methanol (2 × 12 ml) to afford 1.10 g (5.0%) of **12**, mp 108.5–112 °C. Anal. ($C_{28}H_{44}N_2O_2$) C, H, N.

2-Cyclohexylacetyl-5,11-dimethyl-9-phenylacetyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (13). The reaction was run using 3.41 g (10.0 mmol) of **11** in THF and an excess of benzylmagnesium chloride (33 mmol) at 25 °C for 2.5 h. After isolation of the basic reaction products, in a manner similar to that previously described, purification was achieved by forming a monopicrate salt (ethanol) and regeneration of the free base four times and final formation and isolation of 1.10 g (16.6%) of the pure picrate, mp 185–189 °C. Anal. ($C_{28}H_{38}N_2O_2$·$C_6H_3N_3O_7$) C, H, N. Use of excess picric acid affords a dipicrate, mp 215–219 °C. Anal. ($C_{28}H_{38}N_2O_2$·2$C_6H_3N_3O_7$) C, H, N. The sample could be converted to the HCl salt by standard means. Regeneration of the free base afforded **13** as an oil. Anal. ($C_{28}H_{38}N_2O_2$) C, H, N.

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Dibenz[*b*,*e*]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 1. 6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetic Acids

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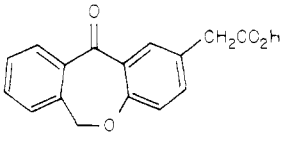
A series of 6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acids has been evaluated for both antiinflammatory and analgetic activity in the carrageenan paw edema and phenylquinone writhing assays. The requirements for optimal activity in this series appear rather specific: (a) an unsubstituted 6,11-dihydrodibenz[*b*,*e*]oxepin nucleus and (b) a carbonyl group in the 11 position. One derivative, 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetic acid (**11**), has been selected for further study.

Antiinflammatory research in the past several years has centered on the search for new substances which would not produce disturbing side effects, such as gastrointestinal irritation, bone marrow depression, and central nervous system symptoms. Many such substances have been reported in the literature, for example, ibuprofen,[1] naproxen,[2] ketoprofen,[3] and tolmetin,[4] which appear to be less toxic than indomethacin and phenylbutazone.

In this paper we wish to report on the syntheses and preliminary pharmacology of a number of 6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acids and derivatives [after this work had been completed, Belgian Patent Application No. 818055 (Daiichi Seiyaku) was published describing similar compounds], some of which have been highly active in animal models as antiinflammatory and analgesic agents. Based on these data, one of these, 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetic acid (**11**), appears to offer significant advantages over other reported nonsteroidal antiinflammatory agents and has been selected for further study.



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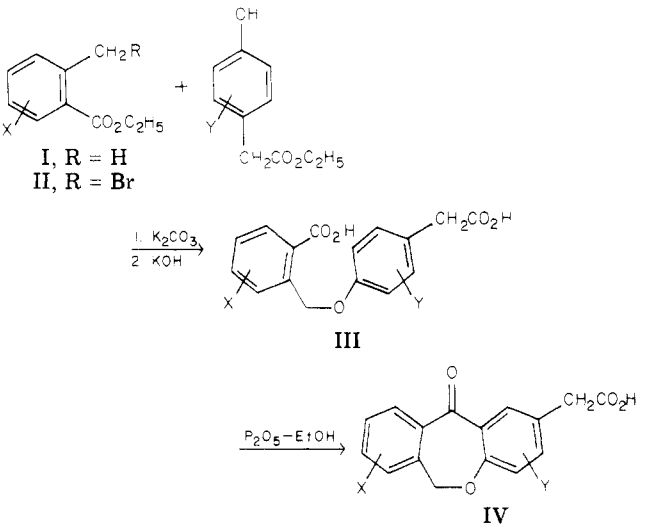
Chemistry. The synthetic sequence utilized in the preparation of the desired dibenz[*b*,*e*]oxepin-2-acetic acids (IV) is illustrated in Scheme I. A substituted ethyl *o*-toluate I was brominated with *N*-bromosuccinimide to provide an ethyl α-bromo-*o*-toluate II. This intermediate was then condensed with ethyl 4-hydroxyphenylacetate in butanone to afford the crude diester which was hydrolyzed to the diacid III. Initial attempts to cyclize the diacids with phosphorus pentoxide–ethanol according to the method of Stach and Spingler[5] gave poor yields. This was remedied by doubling the quantity of the prepared reagent and using sulfolane as a cosolvent. For compounds **11** and **27** a polyphosphoric acid–acetic acid mixture was superior.

Scheme I



Compound **28**, 6,11-dihydro-11-oxodibenz[*b*,*e*]thiepin-2-acetic acid, was prepared as shown in Scheme II. Thus, reaction of ethyl 4-hydroxyphenylacetate with dimethylthiocarbamoyl chloride provided the ethyl 4-(*O*-dimethylthiocarbamoyl)phenylacetate (**33**) which was thermally rearranged to the ethyl 4-(*S*-dimethylthiocarbamoyl)phenylacetate (**34**) according to Newman's[6] procedure. Hydrolysis of this intermediate followed by reesterification with ethanol gave the desired ethyl 4-mercaptophenylacetate (**36**). Condensation of this compound with ethyl α-bromo-*o*-toluate followed by alkaline hydrolysis yielded the diacid **10** which was cyclized with the polyphosphoric acid–acetic acid mixture (Table I).

The syntheses of several derivatives shown in Scheme III are worthy of special mention. The 11-hydroxy ester **30** was prepared by reduction of **12** with sodium borohydride but upon work-up was found to decompose; careful