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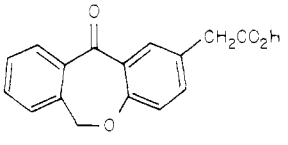
A series of 6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acids has been evaluated for both antiinflammatory and analgetic activity in the carrageenan paw edema and phenylquinone writhing assays. The requirements for optimal activity in this series appear rather specific: (a) an unsubstituted 6,11-dihydrodibenz[*b*,*e*]oxepin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

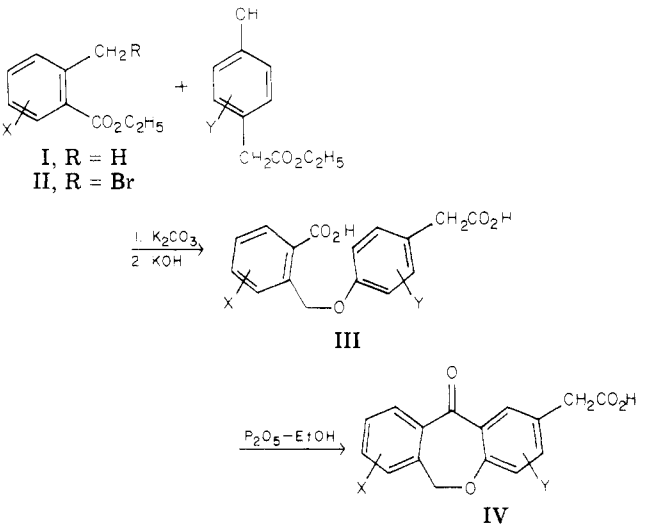
In this paper we wish to report on the syntheses and preliminary pharmacology of a number of 6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acids and derivatives [after this work had been completed, Belgian Patent Application No. 818055 (Daiichi Seiyaku) was published describing similar compounds], some 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.



**11**

**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 $\alpha$-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.

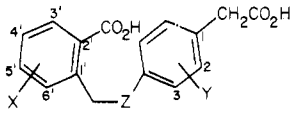
Scheme I



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 $\alpha$-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

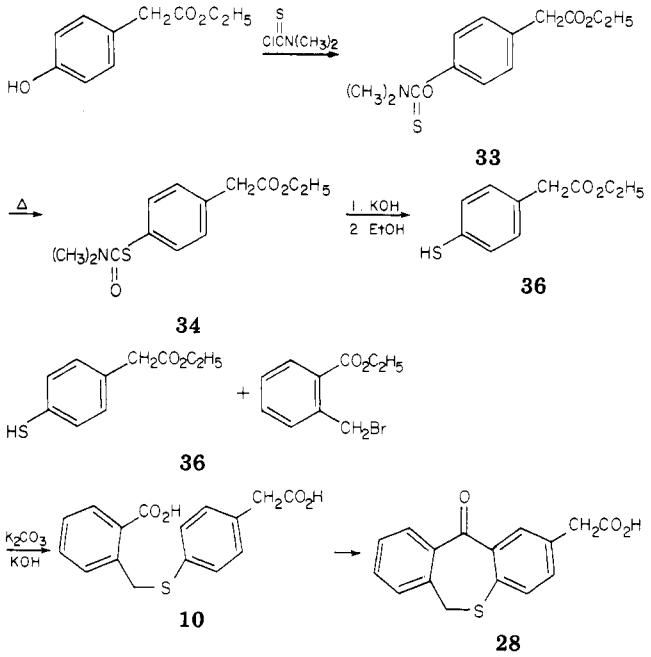
Table I. 2-Carboxybenzyloxyphenylacetic Acids



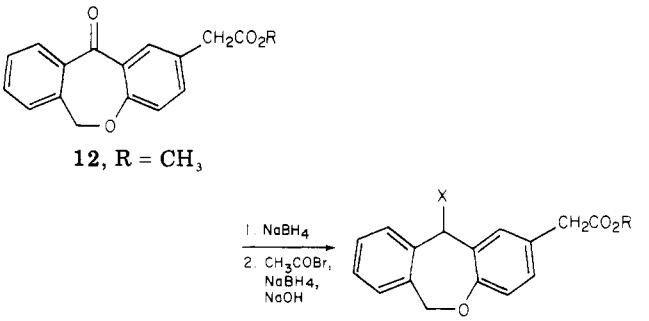
| No. | X | Y | Z | Mp, °C[a] | % yield[b,c] | Recrystn solvent[d] | Empirical formula | Analyses[e] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | O | 176-178 | 76 | AN | $C_{16}H_{14}O_5$ | C, H |
| 2 | 5'-Cl | H | O | 197-200 | 50 | I | $C_{16}H_{13}ClO_5$ | C, H, Cl |
| 3 | 5'-$OCH_3$ | H | O | 198-200 | 36 | I | $C_{17}H_{16}O_6$ | C, H |
| 4 | 4'-Cl | H | O | 205-208 | 70 | AN | $C_{16}H_{13}ClO_5$ | C, H, Cl |
| 5 | 4'-F | H | O | 195-197 | 50 | AN | $C_{16}H_{13}FO_5$ | C, H, F |
| 6 | H | 3-Cl | O | 211-212 | 38 | E-W | $C_{16}H_{13}ClO_5$ | C, H, Cl |
| 7 | 4'-$CF_3$ | H | O | 185-187 | 36 | D | $C_{17}H_{13}F_3O_5$ | C, H, F |
| 8 | 6'-Cl | H | O | 171-173 | 45 | AN | $C_{16}H_{13}ClO_5$ | C, H, Cl |
| 9 | 3'-$CH_3$ | H | O | 168-170 | 20 | M-W | $C_{17}H_{16}O_5$ | C, H |
| 10 | H | H | S | 153-155 | 32 | ER | $C_{16}H_{14}O_4S$ | H; C, S[f] |

[a] Uncorrected. [b] Yield of analytically pure material; no efforts were made to optimize yields. [c] Refer to Experimental Section, procedure A. [d] AA = HOAc; AN = MeCN; B = benzene; C = cyclohexane; D = diisopropyl ether; E = EtOH; ER = $Et_2O$; EA = ethyl acetate; I = 2-propanol; M = MeOH; W = $H_2O$. [e] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values. [f] S: calcd, 10.60; found, 9.57. C: calcd, 63.55; found, 61.39.

Scheme II



Scheme III



hydrolysis with acetic acid in tetrahydrofuran and controlled concentration in vacuo at 35 °C afforded the product.

The reduced oxepin derivative **31** was obtained by brominating the 11-hydroxy congener **30** with acetyl bromide and then reducing the intermediate with sodium borohydride in diglyme.

**Structure–Activity Relationships.** Representative dibenz[*b*,*e*]oxepin-2-acetic acids prepared by the aforementioned procedures are listed in Table II along with preliminary pharmacological data. In most cases these compounds were tested for both antiinflammatory (carrageenan paw edema) and analgesic (phenylquinone writhing) activity.

Structural requirements for good antiinflammatory activity in this series proved rather specific, with most alterations to the basic structure of parent compound **11** proving detrimental. For example, conversion of the acetic acid moiety to an amide **19** or an alcohol **29** greatly reduced activity. Ester derivatives of **11**, however, for the most part, exhibited a similar order of potency to the parent (e.g., **12**, **13**, **15**, and **16**) with several analogues (**14** and **17**) appearing somewhat more active; only the benzyl ester **18** was considerably less potent than **11**.

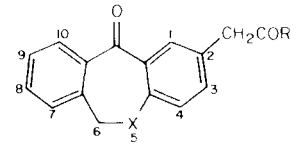
Nuclear substituted analogues of **11** also proved to have reduced antiinflammatory properties. This reduction in activity would seem for the most part to be independent of the nature or position of the substituent (e.g., **20**, **21**, and **23–27**). The eight position did, however, appear less sensitive to reduction in activity through substitution. In the case of this position, a chloro substituent (**22**) was more favorable than a methoxy substituent (**23**).

Variations in the center ring of the dibenz[*b*,*e*]oxepin nucleus also tended to reduce antiinflammatory activity in comparison with **11**. For example, reduction of the oxo group in the 11 position to a hydroxy (**30**) or to a methylene (**31**) group dramatically lowered activity as did conversion to a methyl ether (**32**). Replacement of the oxygen atom in the 5 position of **11** with the often bioisosteric[7] sulfur (**28**) surprisingly also led to a precipitous fall in antiinflammatory activity (Table III).

Structural requirements for analgesic activity in general seemed to parallel those for antiinflammatory activity, with the parent compound **11** being by far the best analgesic. The possible exceptions to this parallelism are the esters **12–17** which were less potent analgetics than one would have predicted based on their antiinflammatory activity.

Several of the more active compounds were evaluated against the adjuvant induced polyarthritis syndrome and for their ability to induce gastric irritation. Table IV shows the results obtained with **11** in comparison to indomethacin. Utilizing these data to calculate therapeutic ratios (e.g., $ID_{50}/ED_{50}$), it can be seen that the therapeutic

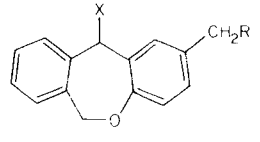
Table II. 6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetic Acids and Derivatives




| No. | Subst | X | R | Mp, °C[a] | % yield[b] | Method[c] | Recrystn solvent[d] | Empirical formula | Analyses[e] | $ED_{50}$, mg/kg[i] CPE | $ED_{50}$, mg/kg[i] PQW[f] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **11** | H | O | OH | 135-136 | 42 | D | AN | $C_{16}H_{12}O_3$ | C, H | 6.36 (5.19-8.26) | 7.57 (6.58-8.53) |
| **12** | H | O | $OCH_3$ | 74-76 | 78 | C | B-M | $C_{17}H_{14}O_3$ | C, H | 31.04 (25.05-41.09) | 26.61 (23.57-30.61) |
| **13** | H | O | $OCH_2CH_3$ | 89-91 | 91 | *c* | I | $C_{18}H_{16}O_3$ | C, H | 6.85 (5.87-8.23) | >50 |
| **14** | H | O | $O(CH_2)_2CH_3$ | 30-32 | 56 | C | | $C_{19}H_{18}O_3$ | C, H | 3 55 (3.30-3.83) | 16.7 (13.6-19.5) |
| **15** | H | O | $OCH(CH_3)_2$ | 67-68 | 84 | C | D | $C_{19}H_{18}O_3$ | C, H | 6.84 (5.87-8.23) | <50 |
| **16** | H | O | $O(CH_2)_3CH_3$ | 42-43 | 54 | C | C | $C_{20}H_{20}O_3$ | C, H | 14.69 (13.92-15.57) | 12.7 (8.1-16.3) |
| **17** | H | O | $O(CH_2)_4CH_3$ | - | 55 | C | | $C_{21}H_{22}O_3$ | C, H | 2.9 (2.7-3.1) | >50 |
| **18** | H | O | $OCH_2Ph$ | 81-83 | 39 | *c* | M | $C_{23}H_{18}O_3$ | C, H | >50 | |
| **19** | H | O | $NH_2$ | 156-157 | 20 | *c* | AN-EA | $C_{16}H_{13}NO_2$ | C, H, N | >100 | >100 |
| **20** | 4-Cl | O | OH | 197-198 | 25 | B | I | $C_{16}H_{11}ClO_3$ | C, H, Cl | ≈50 | - |
| **21** | 7-Cl | O | OH | 173-176 | 35 | B | AN | $C_{16}H_{11}ClO_3$ | H, C[g] | <50 | >50 |
| **22** | 8-Cl | O | OH | 188-190 | 64 | B | AN | $C_{16}H_{11}ClO_3$ | C, H, Cl | 26.5 (22.7-31.6) | 34.3 (28.1-44.3) |
| **23** | $8\text{-}OCH_3$ | O | OH | 163-165 | 34 | B | AA-I | $C_{17}H_{14}O_4$ | C, H | 58.6 (47.9-75.7) | >50 |
| **24** | 9-Cl | O | OH | 169-171 | 20 | B | I | $C_{16}H_{11}ClO_3$ | C, H, Cl | >50 | >50 |
| **25** | 9-F | O | OH | 173-175 | 43 | B | AN | $C_{16}H_{11}FO_3$ | C, H, F | 356 (225.0-837.0) | |
| **26** | $9\text{-}CF_3$ | O | OH | 152-155 | 36 | B | AN | $C_{17}H_{11}F_3O_3$ | C, H; F[h] | >50 | - |
| **27** | $10\text{-}CH_3$ | O | OH | 183-185 | 30 | D | AN | $C_{17}H_{14}O_3$ | C, H | >50 | |
| **28**[j] | H | S | OH | 161-163 | 10 | B | AN | $C_{16}H_{12}O_3S$ | C, H, S | 42.7% at 50 | |
| Indomethacin | | | | | | | | | | 4.35 (3.72-5.26) | 0.7 (0.4-1.4) |

[a] Uncorrected; a dash (-) means an oil. [b] Yields of analytically pure material; no efforts were made to optimize yields. [c] Refer to the Experimental Section. [d] See footnote *d*, Table I. [e] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values. [f] A dash (-) means no test results available. [g] C: calcd, 63.48; found, 62.93. [h] F: calcd, 16.95; found, 17.62. [i] CPE = carrageenan paw edema; PQW = phenylquinone writhing; values in parentheses are 95% confidence limits. [j] While this work was in progress, this compound was reported by the Yoshitomi Pharmaceutical Industries, Ltd., JA-7248389.

Table III. 11-Substituted 6,11-Dihydrodibenz[*b*,*e*]oxepins




| No. | X | R | Mp, °C[a] | % yield[b] | Recrystn solvent[c] | Empirical formula | Analyses[d] | $ED_{50}$, mg/kg, CPE[e] |
|---|---|---|---|---|---|---|---|---|
| **29** | OH | $CH_2OH$ | 135-136 | 60 | AN | $C_{16}H_{16}O_2$ | C, H | >200 |
| **30** | OH | $CO_2CH_3$ | 85-87 | 40 | ER | $C_{17}H_{16}O_3$ | C, H | >200 |
| **31** | H | $CO_2H$ | 155-157 | 53 | B | $C_{16}H_{14}O_2$ | C, H | 200 |
| **32** | $OCH_3$ | $CO_2CH_3$ | | 95 | | $C_{18}H_{18}O_3$ | C, H | >200 |

[a] Uncorrected. [b] Yields not optimized; yield of analytically pure material. [c] See footnote *d*, Table I. [d] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values. [e] CPE = carrageenan paw edema.

Table IV. Adjuvant-Induced Polyarthritis Syndrome

| Compd | Adj-treated paw, $ED_{50}$, mg/kg | Noninjected paw, $ED_{50}$, mg/kg | Gi $ID_{50}$,[b] mg/kg | $ID_{50}$ Adj $ED_{50}$ | $ID_{50}$ Noninjected paw $ED_{50}$ |
|---|---|---|---|---|---|
| 11 | 2.10 (2.02-2.19)[a] | 1.06 (1.05-1.06) | 82.47 (72.97-94.58) | 39 | 78 |
| Indomethacin | 0.47 (0.44-0.50) | 0.27 (0.24-0.30) | 1.8 (1.1-2.9) | 3.8 | 6.7 |

[a] 95% confidence limits. [b] $ID_{50}$ is defined as the dose required to cause irritation in 50% of the test animals.

ratio for 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid (11) is 10–12 times greater than that of indomethacin; in addition, the gastric irritating dose of 11 is 39–78 times greater than the dose needed to produce a good effect against the polyarthritis syndrome. These findings indicate that 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid may well represent a significant advance in the therapy of inflammation and should be a candidate for further study.

## Experimental Section

$ED_{50}$ values were determined according to the method of Litchfield and Wilcoxon.[8] Compounds were prepared as aqueous suspensions with 1 drop of "Tween 80"/10 ml and administered orally in a volume of 10 ml/kg body weight. Control animals received vehicle alone, orally (10 ml/kg).

**Carrageenan-Induced Rat Paw Edema (CPE).** Female Carworth Wistar rats weighing 120–150 g were arranged in groups of ten. The rats were starved 12–16 h (water ad libitum) prior to treatment. A modification of the carrageenan-induced rat paw edema method described by Winter et al.[9] was used. Paw edema was provoked by the subplantar injection of 0.1 ml of a 1% aqueous suspension of carrageenan into the left hind paw 1 h after the oral administration of test compounds. Paw volume measurements were taken prior to and 3 h after the carrageenan injection by means of mercury displacement. Drug activity is expressed as the percent difference between the test and control groups' edema.

**Phenylquinone-Induced Writhing (PQW).** The procedure employed was a modification of the method of Siegmund et al.[10] A 0.125% concentration of phenylquinone (phenyl-*p*-benzoquinone, Eastman) in a 5% aqueous ethanol solution was injected into male CD-1 Charles River mice weighing 18–24 g at 10 ml/kg ip. Animals received food and water ad libitum. Groups of five mice were treated with test drug orally at various time intervals prior to phenylquinone injection. Control mice were treated with an equal volume of vehicle. After phenylquinone injection the mice were placed individually in 1000-ml beakers and 5 min later the number of writhes was recorded for a 10-min period. The peak time of test drug activity was thereby determined. A dose–response study was performed in a similar manner except that ten animals per group were used at the peak time of activity. Animals were dosed and tested in a randomized manner using four drug doses and one control group. Drug activity is expressed as the percent inhibition of the control group per number of writhes.

**Adjuvant-Induced Polyarthritis (PA).** Female albino rats (Charles River–Lewis strain) weighing 150–170 g were arranged in groups of ten and housed individually. Heat-killed dry *Mycobacterium butyricum* (Difco) was suspended in white paraffin oil (0.5 mg/0.1 ml) and injected into the left hind paw of each rat. Body weights were recorded daily. Test compounds were administered orally the day prior to adjuvant injection and daily for 21 days. Paw volumes were recorded on the day of injection and on subsequent days thereafter using the same procedure as in CPE.

**Ulcerogenic Activity.** Groups of eight male Wistar rats weighing 150–175 g were fasted 48 h (water ad libitum) prior to administration of test drug orally (10 ml/kg). Control rats received vehicle only (10 ml/kg). For a time response, animals were treated with a highly active antiinflammatory dose of test drug and then sacrificed at 3, 5, and 7 h postdrug. Stomachs and intestines were removed and examined for the presence of lesions. The presence of single or multiple lesions (erosion, ulcer, or perforation) was considered an ulcerogenic effect. A dose–response was performed at the peak time using four doses of test drug.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Labs., Skokie, Ill. The symbols (ir, NMR) denote structures confirmed by spectral data alone. The structures of all compounds are supported by their ir (Perkin-Elmer 457) and NMR (Jeolco $C_{60}HL$) spectra.

The following known intermediates were prepared according to the cited literature references: ethyl α-bromo-*o*-toluate,[11] ethyl α-bromo-6-methyl-*o*-toluate,[11] ethyl α-bromo-4-chloro-*o*-toluate,[12] ethyl α-bromo-5-chloro-*o*-toluate,[12] ethyl α-bromo-6-chloro-*o*-toluate,[12] ethyl α-bromo-5-trifluoromethyl-*o*-toluate,[13] ethyl α-bromo-4-methoxy-*o*-toluate,[14] ethyl 5-fluoro-*o*-toluate.[15]

**Procedure A.** A mixture of 0.22 mol of a substituted ethyl 4-hydroxyphenylacetate, 0.22 mol of a substituted ethyl α-bromo-*o*-toluate, 0.88 mol of potassium carbonate, and 0.02 mol of potassium iodide in 900 ml of butanone was refluxed for 16 h, cooled, and filtered and the filtrate concentrated to one-third its original volume. After addition of water and ether the layers were separated and the aqueous phase was extracted with ether; the combined ether extracts were washed with 5% sodium hydroxide and water, dried ($Na_2SO_4$), filtered, and concentrated in vacuo to an oil which was refluxed with 3.60 mol of potassium hydroxide in 500 ml of ethanol for 12 h. The mixture was concentrated; the residue was dissolved in water and extracted with ether. Acidification of the aqueous layer provided a solid which was recrystallized from the appropriate solvent indicated in Table I.

**Procedure B.** To 4.0 ml of absolute ethanol was added 6.90 g (0.05 mol) of phosphorus pentoxide at such a rate that the temperature was kept below 80 °C. After stirring the white viscous mixture at 100–110 °C for 1 h, the temperature was adjusted to 85 °C and 30 ml of sulfolane was added followed by 0.008 mol of the diacid; the suspension was stirred at 88–90 °C for 4 h. After decanting into ice water, basifying, and extracting with toluene, the aqueous phase was ice cooled and acidified with concentrated HCl to provide a gum which crystallized upon standing overnight. The resulting solid was recrystallized from the appropriate solvent indicated in Table II.

**Procedure C.** The 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetates were prepared from the appropriate alcohols by the method of Fischer–Speier.[16]

**Procedure D.** A mixture of 0.005 mol of diacid, 9.0 g of polyphosphoric acid, and 7 ml of acetic acid was stirred at 80 °C for 6 h. After hydrolyzing the mixture with 75 ml of water, 10% sodium hydroxide was added until basic and the aqueous mixture extracted with ether. Acidification of the ice-cooled aqueous phase with concentrated hydrochloric acid provided a solid which was recrystallized from the appropriate solvent indicated in Table II.

**Ethyl 6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-acetate (13).** A mixture of 7.0 g (0.03 mol) of 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid, 50 ml of absolute ethanol, and 0.8 g of Amberlite IR-120 HC.P. was refluxed for 17 h, cooled, filtered, and concentrated to a solid. The crude product was dissolved in ether, washed with water, 5% sodium hydroxide, and water, dried ($Na_2SO_4$), filtered, and concentrated to a yellow solid which was recrystallized from 2-propanol to provide 6.0 g of off-white crystals, mp 89–91 °C.

**Benzyl 6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-acetate (18).** To 5.00 g (0.019 mol) of 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid in 70 ml of dry benzene was added with cooling 4.00 g (0.02 mol) of phosphorus pentachloride. The yellow solution was stirred at room temperature for 4 h, concentrated in vacuo, dissolved in 30 ml of dry chloroform, and added dropwise

to 2.16 g (0.02 mol) of benzyl alcohol and 2.00 g (0.02 mol) of triethylamine in 70 ml of chloroform at 10 °C. After stirring overnight at room temperature, the solution was refluxed for 1 h, cooled, and washed with 1 N HCl, water, 5% sodium hydroxide, and water. Drying ($Na_2SO_4$), filtration, and concentration in vacuo provided an oil which upon crystallization was washed with methanol to provide 2.6 g of colorless crystals, mp 82–84 °C.

**6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetamide (19).** A mixture of 5.4 g (0.02 mol) of 6,11-dihydro-11-oxodibenz[*b*,*e*]-oxepin-2-acetic acid, 2.4 g (0.02 mol) of thionyl chloride, 1 ml of dimethylformamide, and 10 ml of chloroform was refluxed for 1 h. The reaction mixture was concentrated to a red oil which was dissolved in 45 ml of chloroform and saturated with ammonia at 0 °C. Evaporation of the excess ammonia and filtration of the precipitate followed by concentration of the filtrate in vacuo yielded an orange residue which crystallized upon addition of benzene. Recrystallization from a mixture of acetonitrile–ethyl acetate (3:1) provided 0.6 g of light yellow crystals, mp 156–157 °C.

**6,11-Dihydro-11-hydroxydibenz[*b*,*e*]oxepin-2-ethanol (29).** A solution of 3.5 g (0.01 mol) of methyl 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetate in 150 ml of dry ether was added dropwise to a stirred suspension of 2.5 g (0.07 mol) of lithium aluminum hydride in 50 ml of dry ether. The mixture was refluxed for 3 h, chilled, hydrolyzed with saturated ammonium chloride solution, and extracted with ether. Drying ($Na_2SO_4$), filtration, and concentration in vacuo provided a solid which was recrystallized from acetonitrile to yield 2.5 g of colorless crystals, mp 135–136 °C.

**Methyl 6,11-Dihydro-11-hydroxydibenz[*b*,*e*]oxepin-2-acetate (30).** A mixture of 4.0 g (0.02 mol) of methyl 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetate (11), 1.4 g (0.04 mol) of sodium borohydride, and 200 ml of methanol was stirred at 5–10 °C for 4 h and then concentrated at 50 °C to provide a gum which was dissolved in chloroform, washed with water, dried ($Na_2SO_4$), and concentrated to a red oil. The oil was dissolved in 150 ml of 30% aqueous tetrahydrofuran, acidified with acetic acid, stirred for 2 h at room temperature, and concentrated to a gum. The crude product was dissolved in chloroform and then washed with a saturated sodium bicarbonate solution and water, dried ($Na_2SO_4$), filtered, and concentrated to an oil which crystallized upon addition of ether. Trituration with hot ether gave 1.6 g of colorless crystals, mp 85–87 °C.

**Methyl 11-Bromo-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetate.** A mixture of 5.68 g (0.02 mol) of methyl 6,11-dihydro-11-hydroxydibenz[*b*,*e*]oxepin-2-acetate, 2.50 g (0.02 mol) of acetyl bromide, and 120 ml of dry benzene was refluxed for 2 h and concentrated in vacuo to provide 6.0 g of green crystals, which upon trituration with petroleum ether (bp 30–60 °C) provided 5.68 g (85%) of a green solid, mp 90–94 °C (ir, NMR).

**6,11-Dihydrodibenz[*b*,*e*]oxepin-2-acetic Acid (31).** To a solution of 0.9 g (0.024 mol) of sodium borohydride, 0.25 g (0.006 mol) of sodium hydroxide, 8 ml of diglyme, and 4.2 ml of water was added at 50 °C 1.0 g (0.003 mol) of methyl 11-bromo-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetate in 8 ml of diglyme. The reaction mixture was stirred at 50 °C for 1 h, diluted with 50 ml of water, and extracted with ether, and the aqueous phase was acidified at 10 °C with HCl to provide a white precipitate. Recrystallization from benzene provided 0.4 g of colorless crystals, mp 155–157 °C.

**Methyl 6,11-Dihydro-11-methoxydibenz[*b*,*e*]oxepin-2-acetate (32).** A solution of 4.0 g (0.014 mol) of methyl 6,11-dihydro-11-hydroxydibenz[*b*,*e*]oxepin-2-acetate (**30**), 200 ml of methanol, and 8 ml of a saturated HCl ether solution was stirred at room temperature for 16 h, concentrated, and diluted with ether. The solution was washed with water and a saturated sodium bicarbonate solution, dried ($Na_2SO_4$), filtered, and concentrated to 4.0 g of a yellow oil (ir, NMR).

**Ethyl 4-(*O*-Dimethylthiocarbamoyl)phenylacetate (33).** This compound was prepared by applying a method devised by Newman and Karns.[6] A mixture of 8.80 g (0.05 mol) of ethyl 4-hydroxyphenylacetate, 18.2 g (0.15 mol) of dimethylthiocarbamoyl chloride, and 16.6 g (0.15 mol) of Dabco in 65 ml of dimethylformamide was stirred at 55 °C for 12 h. The solid was filtered, the filtrate was diluted with water and extracted with benzene, and the combined benzene extracts were washed with 3 N hydrochloric acid, 5% sodium hydroxide, and water. Drying ($Na_2SO_4$), filtration, and concentration in vacuo gave yellow crystals which upon trituration with 2-propanol provided 7.0 g (59%) of colorless crystals, mp 48–50 °C.

**Ethyl 4-(*S*-Dimethylthiocarbamoyl)phenylacetate (34).** Ethyl 4-[*O*-dimethylthiocarbamoyl]phenylacetate (31.1 g, 0.12 mol) was heated over a temperature range of 210–240 °C under a nitrogen atmosphere for a period of 70 h, then cooled, washed with cold cyclohexane, and dried. Recrystallization from cyclohexane provided 24.9 g (80%) of colorless crystals, mp 73–74 °C.

**4-Mercaptophenylacetic Acid (35).** A mixture of 5.0 g (0.02 mol) of ethyl 4-[*S*-dimethylthiocarbamoyl]phenylacetate, 5.2 g (0.09 mol) of potassium hydroxide, 81 ml of methanol, and 20 ml of water was refluxed for 2 h. Concentration in vacuo gave a light brown oil which was dissolved in a minimum amount of water and filtered; the filtrate was cooled and acidified to pH 2 with concentrated hydrochloric acid and the precipitate collected by filtration. Recrystallization from ethanol provided colorless crystals, mp 97.5–100 °C.

**Ethyl 4-Mercaptophenylacetate (36).** This compound was prepared according to procedure C.

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