of the induced spasm. For further details of this method, see J. Lulling, F. El Sayed, and P. Lievens, *Med. Pharmacol. Exp.*, 16, 481 (1967); J. Lulling, P. Lievens, F. El Sayed, and J. Prignot, *Arzneim.-Forsch.*, 18, 995 (1968).

(27) For a more detailed discussion of these results, see F. Dessy, unpublished results.

(28) L. I. Kleinman and E. P. Radford, *J. Appl. Physiol.*, 19, 360 (1964).

Dibenztroponeacetic and -propionic Acids. Potent New Antiinflammatory Agents[1]

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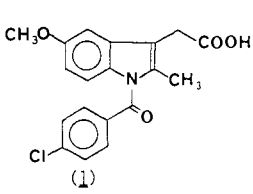
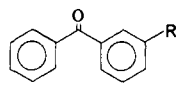
The syntheses and antiinflammatory assays of some dibenztroponeacetic and -propionic acids and derivatives are described. The most potent compound, *d*-2-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)propionic acid, has a potency of ca. 70 times phenylbutazone in the rat carrageenan paw assay and two to three times indomethacin in long-term animal assays. Some β-dialkylaminoethyl esters of this compound also show high antiinflammatory activity.

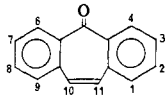
In recent years a number of arylacetic and arylpropionic acids have been reported to possess useful antiinflammatory activity. The aryl moieties in these agents show considerable structural diversity, examples of mono-,[2a] bi-,[2b] and tricyclic[3] types having been reported, including both carbocyclic and heterocyclic rings. It has also been shown that the acetic acid group can be replaced by other acidic functions such as tetrazole,[4] trifluoromethylsulfonamide,[5] or acylhydroxamic acid.[6] Using the results of conformational studies on indomethacin (1), Shen[7]



(1)



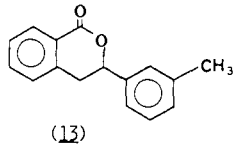
(2)
(a) R=CH_2COOH
(b) R=$NHSO_2CF_3$



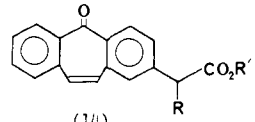
(3)

proposed an antiinflammatory receptor site for this molecule, a feature of which was the presence of a cavity to accommodate the *p*-chlorobenzoyl substituent, which had been shown to be twisted out of plane and out of conjugation with the indole nucleus. Subsequently a number of benzophenones substituted (usually in the meta position) with an acidic group (e.g., **2a**[8] and **2b**[5]) have been reported to show antiinflammatory activity. It is evident that these molecules and indomethacin have common structural features and that, if the unsubstituted phenyl ring in **2a** and **2b** is rotated out of coplanarity with the ring bearing the acidic group, these compounds can be accommodated by the hypothetical indomethacin receptor site. We report here the synthesis and biological activity of arylacetic acids containing the 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (dibenztropone) moiety (**3**), in which the two benzene rings are held in a noncoplanar orientation by the two-carbon bridge. However, these compounds differ from those described above in that the acidic function is para, rather than meta, to the carbonyl group. Nevertheless, as will be seen, these compounds show considerable antiinflammatory activity.

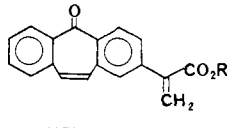
Chemistry. Attempted Friedel–Crafts acylation of the commercially available dibenztropone and the 10,11-dihydro derivative, dibenzsuberone, gave no reaction. Rather than pursue this approach, which would in any case be expected to lead predominantly to 3-substituted products, and not to the desired 2-compounds, an efficient synthesis of 2-methyldibenztropone (**4**) was developed, as shown in Scheme I. Attempts were made to cyclize the Wittig product **17**, obtained as a ca. 1:1 cis–trans mixture, directly to **4**; however, the lactone **13** was the only isolable product. The double bond was therefore removed by catalytic hydrogenation, and the product, **6**, was cyclized cleanly to **7** using polyphosphoric acid (the alternative cyclization product, 4-methyldibenzsuberone, was not formed in appreciable amounts). After introduction of the double bond by *N*-bromosuccinimide bromination followed by dehydrobromination, the benzylic bromide **8a** was produced by treatment of **4** with *N*-bromosuccinimide. Conversion of **8a** to the nitrile **8b** proceeded in only moderate yield and was accompanied by many side reactions which complicated isolation of the product. After extensive experimentation it was found that the highest yield was obtained by using sodium cyanide in acetone cyanohydrin. However, the process was far from ideal, and methods were sought for protection of the 5-ketone in **8a**, to the presence of which were ascribed the side reactions in the formation of **8b**. Ketalization of dibenztropones is difficult,[9] and since the labile bromide in **8a** would not survive the forcing conditions necessary, an alternative, milder method was required. Treatment of **8a** with 1 mol of phosphorus pentachloride in benzene at room temperature gave a solution presumed to contain the equilibrium mixture of **9a** and **9b**[10] (the solution was colorless in benzene, but pink in acetonitrile, indicating a greater proportion of the ionized form **9a** in the more polar solvent). The solution of **9** was then added to a mixture of ethylene glycol, triethylamine, and acetonitrile to give a high yield of the ketal **10**, from which the bromide could be cleanly displaced with cyanide ion to give **11**; acid hydrolysis then afforded the acetic acid **12**. Alkylation of the lithio anion of the methyl ester of **12** with methyl iodide or, respectively, ethyl iodide gave after base hydrolysis the propionic acid **14a** and the butyric acid **14b**. Treatment of the anion with formaldehyde vapor gave a low yield of the acrylic ester **15a**; larger quantities were produced by treatment of the ester **14c** with *N*-bromosuccinimide to give **16a** which on treatment with silver



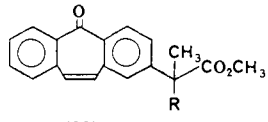
(13)



(14)
(a) R=CH_3 R'=H
(b) C_2H_5 H
(c) CH_3 CH_3



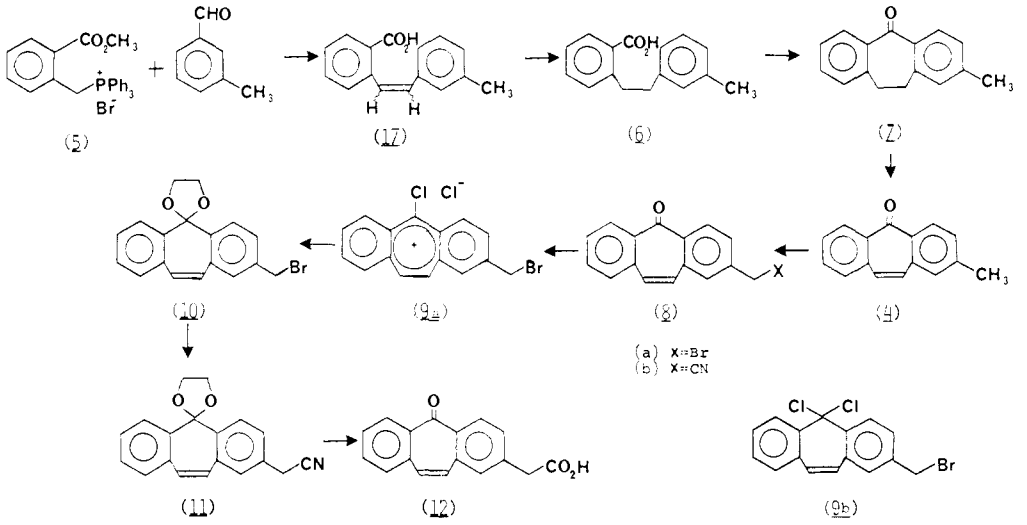
(15)
(a) R=CH_3
(b) H



(16)
(a) R=Br
(b) OH

perchlorate in aqueous acetone gave approximately equal

Scheme I



amounts of **15a** and the α-hydroxy ester **16b**. Attempts to dehydrobrominate **16a** or to dehydrate **16b** under conventional conditions were unsuccessful. After screening a number of optically active bases as resolving agents, it was found that the propionic acid **14a** could be resolved using *l*-amphetamine to afford *d*-**14a**; use of *d*-amphetamine gave the *l* isomer. The progress of the resolution and the enantiomeric purity of the resolved products were determined by acid-catalyzed esterification of the acid with *d*-2-octanol, followed by gas–liquid chromatographic determination of the diastereomeric ratio of the resultant esters.[11] The biologically active esters of *d*-**14a** were obtained by reaction of the derived acid chloride of **14a** with the appropriate alcohol in the presence of pyridine. (Use of triethylamine resulted in racemization.)

Biological Section

(a) Methods. Inhibition of Carrageenan-Induced Rat Paw Edema. The method used was basically that described by Winter et al.[12a] The test materials were given po by gavage in 1 mL of aqueous vehicle to 80–90-g female rats.[20] One hour later, 0.05 mL of a 1% solution (in 0.9% NaCl) of the irritant carrageenan was injected into the pad of the right hind paw. The rats were sacrificed 4 h after drug administration, at which time both hind paws were removed and weighed separately. The percent increase in weight of the inflamed paw was determined. Six rats were used in each treatment group. Three doses (3.6, 11, and 33 mg/kg) of the standard, phenylbutazone, were used in most of the tests.

Inhibition of Cotton Pellet Granuloma. A modification of the procedure initially described by Meier et al.[16] was used. Two 50-mg cotton pellets, which had been immersed for 24 h in a 1% solution of carrageenan and then dried, were dipped into a solution containing 1% penicillin G and 1% streptomycin. These were then inserted sc in the dorso-lumbar area of 180–200-g rats of either sex (same sex within each test). Beginning on the same day, and continuing daily for 7 days, the test materials were administered po. The rats were sacrificed on the day after the last treatment, at which time they were weighed, and the cotton pellets with adhering granulomas were removed, dried for 24 h at 100 °C, and weighed. Each treatment group usually contained nine rats. Four doses (0.5, 1, 2, and 4 mg/kg/day) of the standard, indomethacin, were used in each test.

Inhibition of Adjuvant-Induced Arthritis. A modification of the procedure initially described by Pearson[17] was used. Female rats weighing 160–180 g received 0.1 mL of a suspension in paraffin oil of heat-killed *M. butyricum* (10 mg/mL) by means of an intradermal injection into the proximal quarter of the tail on day 1. Beginning on day 1, the test materials were administered po in an aqueous vehicle (0.5 mL per dose) twice each day for 17 days. On day 18 the intensity of the swelling of the four foot pads and tail was determined utilizing a scoring system in which the swelling in the four paws was scored 0–4 for each paw and the tail swelling was scored 0–3. The total maximum score was 19. The body weights and the weights of both hind foot pads were also obtained. Each treatment group usually contained 15 rats.

Scheme II

$$\underset{l\text{ isomer}}{\text{RCH(CH}_3\text{)COOH}} \rightarrow \text{RC(=CH}_2\text{)COOH} \rightarrow \underset{d\text{ isomer}}{\text{RCH(CH}_3\text{)COOH}}$$

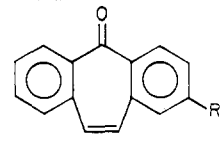
R = *p*-$(CH_3)_2CHCH_2C_6H_4$

Inhibition of Phenylquinone-Induced Writhing. A modification of the method of Hendershot and Forsaith[13] was used. The test materials were administered po in an aqueous vehicle at time zero to male mice weighing 18–20 g. Twenty minutes later, 0.25 mL of a 0.02% solution of phenylquinone was injected ip to induce writhing. The animals were then observed during the next 10 min for writhing. Each treatment group usually contained eight to ten mice. Three doses (16.5, 50, and 150 mg/kg) of the standard, aspirin, were usually used in each test. The relative potencies were either determined graphically or computed using methods described by Finney.[21]

(b) Results. The compounds were initially tested by oral administration in the carrageenan-induced rat paw edema antiinflammatory[12] assay and mouse writhing analgetic[13] assay. The results are shown in Table I.

The modest activity exhibited by the acetic acid **12** is approximately sevenfold enhanced by the introduction of the α-methyl substituent. Resolution of the *dl*-propionic acid **14a** indicated that activity resided entirely in the *d* isomer; the small activity exhibited by the *l* isomer can be attributed to the presence of ca. 2% of the *d* isomer in the sample tested. The enantiomers of α-methyl-*p*-isobutylphenylacetic acid have been reported to have comparable antiinflammatory potencies in animals and in man. The in vivo conversion of the biologically inactive *l* isomer, via oxidation to 2-(*p*-isobutylphenyl)acrylic acid and stereospecific reduction to the *d*-propionic acid (Scheme II), has been demonstrated.[14] In the majority of analogous cases, however, only one propionic acid enantiomer shows

Table I. Antiinflammatory and Analgesic Activities



Compd no.	R	*d*, *l*, or *dl*	Rat paw assay × phenylbutazone	Mouse writhing assay × aspirin
12	CH_2COOH		6 (84)[a]	2 (70)[b]
30	CH_2COOCH_3		~3 (41)	<1 (20)
14a	$CH(CH_3)COOH$	*dl*	44 (144)	12 (90)
14a	$CH(CH_3)COOH$	*d*	68 (143)	20 (30)
14a	$CH(CH_3)COOH$	*l*	1.5 (18)	1.5 (30)
18	$CH(CH_3)COONa$	*l*[c]	62 (72)	NT[d]
19	$C(CH_3)_2COOH$		0.5 (18)	NT
14b	$CH(C_2H_5)COOH$	*dl*	7 (18)	2 (24)
15b	$C(=CH_2)COOH$		~4 (12)	1 (8)
14c	$CH(CH_3)COOCH_3$	*dl*	11 (44)	2 (30)
14c	$CH(CH_3)COOCH_3$	*d*	~15 (24)	NT
20	$CH(CH_3)COO(CH_2)_2CH(CH_3)_2$	*dl*	6 (24)	1.7 (24)
21	$CH(CH_3)COO(CH_2)_{11}CH_3$	*dl*	~15 (18)	<0.5 (32)
22	$CH(CH_3)COO(CH_2)_{19}CH_3$	*dl*	≤1 (18)	<0.5 (8)
23	$CH(CH_3)COO(CH_2)_2N(CH_3)_2$	*dl*[c]	~30 (18)	~7 (16)
23	$CH(CH_3)COO(CH_2)_2N(CH_3)_2$	*d*[c]	45 (36)	NT
24	$CH(CH_3)COO(CH_2)_2N(CH_3)(C_2H_5)$	*dl*	20 (30)	<2 (24)
25	$CH(CH_3)COO(CH_2)_2N(C_2H_5)_2$	*dl*[e]	14 (18)	~10 (16)
26	$CH(CH_3)COO(CH_2)_2N(CH_2)_5$	*dl*	~15 (37)	<2 (16)
27	$CH(CH_3)COO(CH_2)_2N(CH_2)_2O(CH_2)_2$	*dl*[e]	9 (36)	<1 (16)
28	$CH(CH_3)COO(CH_2)_4N(CH_3)_2$	*dl*	7 (18)	<3 (24)
29	$C(OH)(CH_3)COOH$	*dl*	<0.5 (12)	1.5 (32)

[a] Number of rats. [b] Number of mice. [c] *d* acid affords *l* salt. [d] NT = not tested. [e] Tested as the hydrochloride salt.

activity. The apparent absence, at least in mice and rats, of such an interconversion via the acrylic acid **15b** is also indicated by the low activity of the latter compound. Since only one enantiomer is active, it would be expected that the *d* isomer would show twice the potency of the *dl*, whereas the observed potency ratio is ca. 1:1.5 in both the acids **14a** and the *dl* and *d* esters **14c** and **23**. The α-ethyl acid **14b** also showed significant activity; the isomeric α,α-dimethyl acid **19** was almost inactive, a finding which has been reported in several other series.[15] The alkyl esters of the propionic acid show moderate antiinflammatory activity. Significant activity was shown even by the C_{20} ester **22**. A series of dialkylaminoethyl esters showed higher activity than the alkyl esters; the dimethylamino ester **23** was the most potent; the morpholinoethyl ester **27** was less active. It is not clear whether the high activity of some of these esters is due to a preferential transport process to the active site or to facile enzymic hydrolysis to the parent acids. The dimethylaminobutyl ester **28** was considerably less active. The analgesic activities of these esters were erratic and did not follow the approximate parallel with the antiinflammatory activities which are shown by the free carboxylic acids. Some of the compounds in this series were also examined in longer term antiinflammatory assays: the cotton pellet granuloma[16] and adjuvant arthritis[17] assays. The question as to which antiinflammatory assay is most predictive of future potency in man has been discussed by many authors; a priori, it might be expected that the longer duration of the cotton pellet and adjuvant assays (7 and 17 days, respectively) would better simulate the chronic rheumatoid arthritis condition. However, a good correlation between activity (mg/kg) in the rat paw assay and human studies has recently been established for a number of antiarthritic agents which are used clinically.[18] The activities of three of the dibenztropone compounds in the long-term assays are shown in Table II.

The acetic acid can be seen to be poorly active in both assays; the propionic acid is approximately 30 times as potent—much more potent than would be predicted from the short-term (rat paw) assay. The methyl ester, on the other hand, is of comparable potency to the free acid in the long-term assay but much less potent in the short-term assay, apparently indicating that a greater degree of in vivo hydrolysis to the acid can occur more easily in the longer term assay.

Table II. Long-Term Antiinflammatory Assays

	12	14a (*d* isomer)	14c (*d* isomer)
Cotton pellet assay × indomethacin	0.1 (78)[a]	3.5 (225)	
Adjuvant arthritis assay × indomethacin	0.1 (105)	2-3 (233)	2 (75)

[a] Number of rats.

The propionic acid **14a** is thus seen to be one of the more potent antiinflammatory agents so far reported. The activity resides entirely in the *d* isomer; this conclusion is reached as a result of the accurate measurement of optical purities of the resolved enantiomers. Without this measurement, reliance would have to be placed on the possession by the enantiomers of equal and opposite specific rotations. This criterion can, however, give equivocal results in some cases.[19] The more potent of the dialkylaminoethyl esters of **14a** are almost equal in activity to the parent acid.

Experimental Section

Melting points are uncorrected. NMR spectra were obtained in $CDCl_3$ solution unless otherwise stated, at 60 or 100 MHz using Me_4Si as internal standard: d = doublet, q = quartet. Microanalyses were within ±0.4% of theory unless otherwise stated. All temperatures are in °C.

2-(Carbomethoxy)benzyltriphenylphosphonium Bromide (5). Methyl *o*-toluate (97 g, 0.645 mol) and *N*-bromosuccinimide (NBS) (115 g, 0.645 mol) were refluxed in CCl_4 (1 L) while irradiating with a 100-W lamp for 1.5 h. The cooled mixture was diluted with hexane (1 L), filtered, and evaporated. The residual oil was diluted with acetonitrile (500 mL) and reevaporated.

Acetonitrile (800 mL) and triphenylphosphine (186 g, 0.71 mol) were added and the mixture was refluxed for 30 min, then cooled, and diluted with Et_2O (1 L). The separated solid was filtered, washed with Et_2O, and dried to yield **5** (188 g, 59%); mp 239–242 °C. Anal. ($C_{29}H_{24}BrPO_2$) C, H.

2-[β-(3-Methylphenyl)ethyl]benzoic Acid (6). 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) (116.5 g, 0.94 mol) was added to a mixture of **5** (400 g, 0.81 mol) and *m*-tolualdehyde (107.5 g, 0.91 mol) in acetonitrile (1 L). The mixture was heated briefly to reflux and cooled, and the solvent was removed under vacuum. The residual oil was dissolved in $CHCl_3$ (1.5 L) and washed (dilute HCl), dried, and evaporated. The residue was refluxed for 8 h in water (1 L) and MeOH (150 mL) containing KOH (112 g, 2 mol), then cooled, diluted with water (1 L), and extracted with $CHCl_3$ (3 × 1 L). The aqueous solution was acidified (concentrated HCl) and extracted with $CHCl_3$. The extract was washed, dried, and evaporated to afford 2-carboxy-3′-methylstilbene (**17**) (177.5 g, 91%) as a cis–trans mixture. This material was hydrogenated in four equal portions in a 500-mL Parr shaker at 51 psi for 1.5 h, using DMF (230 mL) as solvent and 5% Pd on C (2.0 g) as catalyst. The combined DMF solutions were filtered and evaporated. The residue was dissolved in Et_2O (1.5 L), washed, dried, and evaporated, and the residue was recrystallized (Et_2O–hexane) to give **6** (158.2 g, 90%): mp 82–84 °C. Anal. ($C_{16}H_{16}O_2$) C, H.

2-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (7). A solution of **6** (75 g, 0.31 mol) in sulfolane (400 mL) was heated to 110 °C and PPA (300 mL) was added with stirring. After 90 min at 110 °C the liquid was poured into water (2 L), the mixture extracted with hexane (3 × 750 mL), and the extract washed, dried, diluted with Et_2O (300 mL), and percolated through silica gel (500 g). The eluate was evaporated to afford **7** as an oil (64 g, 89%): NMR 2.35 (CH_3), 3.17 ppm [$(CH_2)_2$].

2-Methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (4). Compound **7** (60.5 g, 0.26 mol) and NBS (58.2 g, 0.314 mol) were refluxed for 5 h in CCl_4 (600 mL). The solution was cooled, filtered, and evaporated, the residue was dissolved in DMF (200 mL), and DBN (44 g, 0.32 mol) was added, with cooling in ice. The mixture was heated to 80 °C for 20 min, then poured into water (750 mL), and extracted with Et_2O (3 × 600 mL). The extract was washed (2 × dilute HCl, 5 × water), dried, and evaporated. The residue was crystallized from Me_2CO–hexane to give **4** (39.7 g, 69%): mp 78–80 °C. Anal. ($C_{16}H_{12}O$) C, H.

2-Bromomethyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (8a). Compound **4** (39.7 g, 0.172 mol) and NBS (32.2 g, 0.18 mol) were refluxed for 14 h in CCl_4 (1200 mL) while irradiating with a 100-W incandescent lamp. The solution was cooled, filtered, and evaporated, and the residue was recrystallized from CH_2Cl_2–hexane to afford **8a** (24.1 g, 45%): mp 128–132 °C; NMR 2.43 (CH_2), 6.98 ppm (CH=CH). Anal. ($C_{16}H_{11}BrO$) C, H. The mother liquors yielded, after charcoal treatment, an additional 3.2 g (6%) of **8a**.

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-ylacetonitrile (8b). This compound was formed, in varying but generally low yields, by reaction of **8a** with a cyanide (CuCN, KCN, or NaCN, preferably the latter) in polar solvents (DMF, Me_2CO–water, EtOH, MeCN, and Me_2SO). The highest yield was obtained using acetone cyanohydrin; **8a** (6.0 g, 0.019 mol) and NaCN (12.0 g, 0.25 mol) were stirred at 80 °C in freshly distilled acetone cyanohydrin (150 mL) for 40 min. *Caution*: hydrogen cyanide is evolved. The mixture was cooled, poured into water (500 mL), and extracted with Et_2O (2 × 200 mL). The extract was washed (6 × 200 mL of water), dried, and evaporated. The residue was chromatographed on silica gel (700 g) eluting with 3:2 hexane–EtOAc so as to isolate **8b** which was recrystallized from EtOAc–hexane: yield 3.45 g (56%); mp 119–121 °C; NMR 3.84 (CH_2), 6.87, 6.99, 7.01, 7.13 ppm (CH=CH). Anal. ($C_{17}H_{11}NO$) C, H, N.

5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-ylacetic Acid (12). (a) **By Acid Hydrolysis of 8b.** The nitrile **8b** (0.3 g, 0.0125 mol) was refluxed for 16 h in constant boiling HCl (10 mL). The cooled solution was extracted with EtOAc, and the organic solution was extracted with aqueous Na_2CO_3. The aqueous extract was acidified with dilute HCl and extracted with EtOAc. The EtOAc solution was dried and evaporated to afford **12** (0.297 g, 86%): mp 148–150 °C (Me_2CO–hexane); NMR 3.69 (CH_2), 6.96 ppm (CH=CH). Anal. ($C_{17}H_{12}O_2$) C, H.

(b) **Via Ketal-Protected Dibenztropones 10 and 11.** The bromide **8a** (31.9 g, 0.1 mol) and PCl_5 (26.6 g, 0.128 mol) were stirred in dry C_6H_6 (160 mL) until a clear solution was obtained (ca. 1 h). This solution was added to an ice-cooled mixture of ethylene glycol (73 mL, 1 mol), Et_3N (76 mL, 0.5 mol), MeCN (380 mL), and 4A molecular sieve (40 g). The mixture was stirred for 1 h and then water and Et_2O were added. The organic layer was washed (5 × 100 mL of water), dried, and evaporated to yield **10** (28.2 g, 78%) as a gum: NMR 3.4–4.3 [m, $(CH_2)_2$], 4.45 (CH_2Br), 7.08 ppm (CH=CH).

The product, **10** (26.9 g, 0.074 mol), and NaCN (4.62 g, 0.089 mol) were stirred in DMF (135 mL) for 24 h. Water and EtOAc were added and the organic layer was washed, dried, and evaporated to yield **11** (22.4 g, 98%) as an oil: IR (film) 2250 cm^{-1} (CN); NMR 3.63 (CH_2CN), 3.88 [$(CH_2)_2$], 7.07 ppm (CH=CH).

Compound **11** (0.497 g, 0.0016 mol) was refluxed for 4 h in AcOH (2 mL) and concentrated HCl (3 mL). The mixture was cooled, diluted with water, and extracted with Et_2O, and the extract was dried and evaporated. The residue was recrystallized from Me_2CO–hexane to afford **12** (0.263 g, 58%).

***dl*-2-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)propionic Acid (14a).** (a) **Methyl 2-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)acetate (30).** The acid **12** (3.0 g, 0.0114 mol) was refluxed for 4 h in C_6H_6 (100 mL), MeOH (8 mL), and H_2SO_4 (2 mL), then cooled, poured into water, and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$, dried, and evaporated. The residue was recrystallized from Me_2CO–hexane to afford **30** (2.5 g, 79%): mp 79–81 °C. Anal. ($C_{18}H_{14}O_3$) C, H.

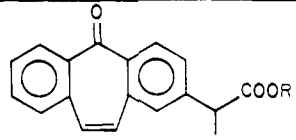
(b) ***dl*-Methyl 2-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)propionate (14c).** *n*-BuLi (1.58 M) in hexane (5.3 mL, 0.008 mol) was added to a solution of isopropylcyclohexylamine (1.18 g, 0.008 mol) in THF (80 mL) at 25 °C. After 5 min the solution was cooled to −78 °C and **30** (2.2 g, 0.008 mol) in THF (20 mL) was added. A deep red color formed. After 3 min MeI (1.130 g, 0.008 mol) was added and the cooling bath was removed. Water and Et_2O were added after 1 h and the organic layer was washed (dilute HCl, water), dried, and evaporated. The residue was chromatographed on silica gel (150 g) eluting with 7:3 hexane–Et_2O to afford **14c** (1.12 g, 50%): mp 35–37 °C. Anal. ($C_{19}H_{16}O_3$) C, H. The chromatography also yielded 0.22 g (8%) of methyl 2-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)-2-methylpropionate as an oil, slightly less polar than **30**.

(c) **Hydrolysis of 14c.** The ester **14c** (1.12 g) was refluxed for 2 h in MeOH (5 mL) and water (25 mL) containing KOH (1 g). The solution was cooled, washed with Et_2O, then acidified (dilute HCl), and extracted with EtOAc. The extract was dried and evaporated, and the residue was recrystallized from Me_2CO–hexane to afford *dl*-**14a** (0.85 g, 80%): mp 113–115 °C. Anal. ($C_{18}H_{14}O_3$) C, H.

Resolution of 14a. The racemic acid *dl*-**14a** (3.6 g, 0.013 mol) and *l*-amphetamine (1.75 g, 0.013 mol) were mixed in hot *i*-PrOH (150 mL). The solution was cooled slowly and then filtered, and the residue was recrystallized four times from *i*-PrOH. The melting points of successive crops of the salt showed no systematic variation. The isolated salt (1.87 g, 35%) was shaken with dilute HCl–Et_2O, the Et_2O solution was dried and evaporated, and the residue was recrystallized from $CHCl_3$–hexane to afford *d*-**14a** (1.1 g, 30%): mp 104–107 °C; $[\alpha]_D$ +46° (10 mg/mL, $CHCl_3$). Anal. ($C_{18}H_{14}O_3$) C, H. This material was shown to contain 99% *d* and 1% *l* isomers as follows.[11] About 0.5 mg was dissolved in C_6H_6 (0.5 mL), and *d*-2-octanol (50 μL) and H_2SO_4 (5 μL) were added. The mixture was heated to 80 °C for 2 h, then cooled, and washed with aqueous $NaHCO_3$. The dried solution was then injected onto a GLC column (1.75 m, 10% OV 101, 260 °C) and the ratio of the areas of the peaks due to the diastereomeric 2-octyl esters was determined by integration. After correcting for the optical purity of the 2-octanol, the optical purity of *d*-**14a** was calculated. Resolution of *dl*-**14a**, as described above, using *d*-amphetamine, gave *l*-**14a**: mp 105–107 °C; $[\alpha]_D$ −47° (1 mg/mL, $CHCl_3$). Anal. ($C_{18}H_{14}O_3$) C, H. GLC analysis as described above indicated 98% *l* and 2% *d* isomers.

2-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)acrylic Acid (15b). (a) **From 30.** *n*-BuLi (1.6 M) in hexane (1.25 mL, 0.002 mol) was added to a solution of diisopropylamine (0.28 mL, 0.002 mol) in THF (30 mL) at −80 °C, and **30** (0.556 g, 0.002 mol) was added. A red color developed. After 10 min the cooling bath was

Table III. Esters



Compd no.	R	*dl* or *d*	Salt	Mp, °C	Emp formula	Analyses
14c	CH_3[a]	*d*		44-45[b]	$C_{19}H_{16}O_3$	C, H
20	$(CH_2)_2CH(CH_3)_2$	*dl*		Oil	$C_{23}H_{24}O_3$	*c*
21	$(CH_2)_{11}CH_3$	*dl*		Oil	$C_{30}H_{38}O_3$	H; C[d]
22	$(CH_2)_{19}CH_3$	*dl*		63-64[b]	$C_{38}H_{54}O_3$	C, H
23	$(CH_2)_2N(CH_3)_2$	*dl*	HCl	136-137[e]	$C_{22}H_{24}ClNO_3$	C, H
23	$(CH_2)_2N(CH_3)_2$	*d*	HCl	138-140[e]	$C_{22}H_{24}ClNO_3$	C, H
24	$(CH_2)_2N(CH_3)(C_2H_5)$	*dl*		Oil	$C_{23}H_{25}NO_3$	*f*
25	$(CH_2)_2N(C_2H_5)_2$	*dl*	HCl	117-123[e]	$C_{24}H_{28}ClNO_3$	C, H
26	$(CH_2)_2N(CH_2)_5$	*dl*		Oil	$C_{25}H_{27}NO_3$	*g*
27	$(CH_2)_2N(CH_2)_2O(CH_2)_2$	*dl*	HCl	146-150[e]	$C_{22}H_{26}ClNO_4$	H, N; C[h]
28	$(CH_2)_4N(CH_3)_2$	*dl*		Oil	$C_{24}H_{27}NO_3$	*i*

[a] Made by treating *d*-14a with excess diazomethane. [b] Hexane. [c] MS M$^+$ 348. [d] C: calcd, 80.68; found, 81.77. [e] *i*-PrOH-Et_2O. [f] MS M$^+$ 313. [g] MS M$^+$ 389. [h] C: calcd, 67.36; found, 63.83. [i] MS M$^+$ 327.

removed and formaldehyde vapor, produced by 150 °C pyrolysis of paraformaldehyde, was passed in. The color faded rapidly. The organic layer was washed (dilute HCl, water), dried, and evaporated. TLC examination showed many products. The crude product was chromatographed (preparative TLC, 0.25 mm thick, 3:1 hexane–EtOAc) so as to isolate methyl 2-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)acrylate (**15a**) (40 mg, 6%): mp 153–156 °C (EtOAc–hexane); NMR 3.80 (MeO), 5.99, 6.46 (CH_2), 7.01 ppm (CH=CH). Anal. ($C_{19}H_{14}O_3$) C, H. This material (20 mg) was refluxed in water (5 mL), EtOH (5 mL), and saturated aqueous Na_2CO_3 (0.5 mL) for 4 h, then cooled, acidified (dilute HCl), and extracted with EtOAc. The extract was dried and evaporated to afford **15b** (17 mg, 90%): mp 232–235 °C (EtOAc–hexane). Anal. ($C_{18}H_{12}O_3$) C, H.

(b) **From 14c.** **14c** (2.0 g, 0.007 mol) and NBS (1.22 g, 0.007 mol) were refluxed in CCl_4 (150 mL) for 24 h, irradiating with a 100-W incandescent lamp. The cooled solution was filtered and evaporated, and the residue was chromatographed on silica gel (50 g) (C_6H_6). The main fraction was recrystallized from Et_2O–hexane to afford **16a** (1.13 g, 45%): mp 84–87 °C; NMR 2.33 (CH_3), 3.80 (OCH_3), 7.08 ppm (CH=CH). Anal. ($C_{19}H_{15}BrO_3$) C, H. This material (1.87 g, 0.005 mol) was refluxed for 24 h in water (7 mL) and Me_2CO (70 mL) containing $AgClO_4$ (1.59 g, 0.0075 mol). The cooled solution was diluted with water and extracted with EtOAc. The extract was washed, dried, and evaporated, and the residue was chromatographed on silica gel (50 g C_6H_6) so as to obtain **15a** (0.35 g, 24%) and then methyl 2-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)-2-hydroxypropionate (**16b**) (0.75 g, 48%): mp 105–107 °C (EtOAc–hexane). Anal. ($C_{19}H_{16}O_4$) C, H. Base hydrolysis of **15a** as described above gave additional **15b**.

2-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)-2-hydroxypropionic Acid (29). The ester **16b** (0.4 g) was refluxed for 3 h in water (45 mL) and MeOH (5 mL) containing KOH (0.4 g). The cooled solution was washed with EtOAc, acidified (dilute HCl), and extracted (EtOAc). The extract was dried and evaporated, and the residue was recrystallized from 1:1 aqueous MeOH to afford **29** (0.33 g, 87%: mp 180–182 °C. Anal. ($C_{18}H_{14}O_4$) C, H.

***dl*-2-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)butyric Acid (14b).** *n*-BuLi (1.6 M) in hexane (1.08 mL, 0.0017 mol) was added to a solution of diisopropylamine (0.24 mL, 0.0017 mol) in THF (15 mL). HMPA (0.3 mL, 0.0017 mol) was added and the mixture cooled to −60 °C. **30** (0.465 g, 0.0016 mol) in THF (10 mL) was added. A deep red color formed. After 15 min EtI (0.24 mL, 0.0027 mol) was added, and the cooling bath was removed. The mixture was diluted with water and extracted with Et_2O. The extract was washed (dilute HCl), dried, and evaporated. The residue was chromatographed on silica gel (40 g) (5:1 hexane–Et_2O) so as to isolate the methyl ester of **14b** as an oil (0.326 g, 64%) which was refluxed for 4 h in MeOH (10 mL) and water (20 mL) containing KOH (0.5 g). The cooled solution was washed with Et_2O, acidified (dilute HCl), and extracted (EtOAc). The extract was dried and evaporated, and the residue was recrystallized from Me_2CO–hexane to afford **14b** (0.20 g, 58%): mp 147–148 °C. Anal. ($C_{19}H_{16}O_3$) C, H.

Sodium Salt of *d*-14a. The acid *d*-**14a** (0.556 g, 0.002 mol) and $NaHCO_3$ (0.164 g, 0.002 mol) were mixed in MeOH (3 mL) and water (2 mL) and warmed to give a clear solution. This was evaporated to dryness and the residue was azeotropically distilled four times with C_6H_6. The residue was crystallized from MeOH–Et_2O to give 18 (0.61 g, 100%): mp 200–240 °C; $[\alpha]_D$ −34° (10 mg/mL, H_2O); NMR (D_2O) 1.47 (d, J = 7 Hz, CH_3), 3.70 (q, J = 7 Hz, CH), 6.20 ppm (CH=CH).

Esters of 14a. The acid (*dl* or *d*) was converted to the acid chloride by stirring in $CHCl_3$ containing excess $SOCl_2$ and a trace of DMF for 6 h. The solution was evaporated under high vacuum to give the acid chloride. This was treated with a slight excess of the appropriate alcohol, in THF or MeCN containing 1 equiv of pyridine. The ester was isolated and purified by silica gel chromatography if necessary. Some esters containing a basic nitrogen were converted into salts as shown in Table III.

Attempted Cyclization of 17 to 4. (a) Compound **17** (1.0 g, 0.0042 mol) was stirred in H_2SO_4 (10 mL) for 5 min. The mixture was added to H_2O and extracted with EtOAc. The extract was washed, dried, and evaporated, and the residue was recrystallized from EtOAc–hexane to afford **13** (0.25 g, 25%): mp 66–67 °C; NMR 3.05 (dd, J = 17, 4 Hz), 3.29 (dd, J = 17, 10 Hz), 5.45 ppm (dd, J = 10, 4 Hz). Anal. ($C_{16}H_{12}O_2$) C, H.

(b) Compound **17** (1.0 g, 0.0042 mol) was dissolved in sulfolane (15 mL) at 90 °C and polyphosphoric acid (15 mL) was added. The mixture was stirred for 25 min, then poured into water, and extracted with EtOAc. The crude product, which contained a large number of compounds, was chromatographed so as to obtain 10% of **13**; no other products were identified. **4** was not formed in either this reaction or in reaction (a) above.

References and Notes

(1) Contribution No. 485 from the Syntex Institute of Organic Chemistry.

(2) (a) See, for example, S. S. Adams, P. Hebborn, and J. S. Nicholson, *J. Pharm. Pharmacol.*, **20**, 305 (1968); S. S. Adams, K. F. McCullough, and J. S. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, 178, 115 (1969); Boots Pure Drug Company Limited, South African Patent 62/294 (1962); G. Lambelin, J. Roba, C. Gillet, and N. P. Buu-Hoi, *Arzneim.-Forsch.*, **20**, 610 (1970); (b) I. T. Harrison, B. Lewis, P. Nelson, W. Rooks. A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, 13, 203 (1970); see also J. W. Buckler and S. S. Adams, *Med. Proc.*, 14, 574 (1968); J. Redel, H. Brouilhet, F. Delbarn, N. Bazely, and M. Jouanneau, *C. R. Hebd. Seances Acad. Sci., Ser. D*, 273, 911 (1971).

(3) (a) T. Y. Shen, T. B. Windholz, A. Rosegay, B. E. Witzel, A. N. Wilson, J. D. Willett, J. D. Holtz, R. L. Ellis, A. R. Matzuk, S. L. Lewis, C. H. Stammer, F. W. Holly, L. H. Sarett, E. A. Risley, G. W. Nuss, and C. A. Winter, *J. Am. Chem. Soc.*, 85, 488 (1963); (b) H. B. Lassman, R. E. Kirby,

J. C. Wilker, and W. J. Novick, *Pharmacologist*, 17, 226 (1975); M. Messer, D. Farge, J. C. Guyonnet, C. Jeanmart, and L. Julou, *Arzneim.-Forsch.*, 19, 1193 (1969); A. W. Pircio, M. E. Bierwagen, W. E. Strofe, and W. D. Nicolosi, *Arch. Int. Pharmacodyn. Ther.*, **199**, 151 (1972); E. T. Steller, P. A. Diassi, D. Gerschutz, D. Meikle, J. Moetz, P. A. Principe, and S. D. Levine, *J. Med. Chem.*, 15, 1029 (1972).
(4) Bristol Myers Co., Netherlands Patent Application 66-09235 [*Chem. Abstr.*, 67, 82215u (1967)].
(5) J. K. Harrington, J. E. Robertson, D. C. Kvam, R. R. Hamilton, K. T. McGurran, R. J. Trancik, K. F. Swingle, G. G. Moore, and J. F. Gerster, *J. Med. Chem.*, 13, 137 (1970).
(6) G. Lambelin, N. P. Buu-Hoi, H. Brouilhet, M. Gautier, C. Gillet, J. Roba, and J. Thiriaux, *Arzneim.-Forsch.*, 18, 1404 (1968).
(7) T. Y. Shen in "Non-Steroidal Antiinflammatory Drugs", S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1965, p 13.
(8) (a) L. Julou, G. Guyonnet, R. Ducrot, C. Garret, M. Bardone, G. Maignan, and J. Pasquet, *J. Pharmacol.*, 2, 259 (1971); (b) A. Allais, G. Rousseau, J. Meier, R. Deraedt, J. Benzoni, and L. Chifflot, *Eur. J. Med. Chem.-Chim. Ther.*, 9, 381 (1974).
(9) W. Tochtermann, G. Schnabel, and A. Mannschreck, *Justus Liebigs Ann. Chem.*, 705, 169 (1967); W. Tochtermann, U. Walter, and A. Mannschreck, *Tetrahedron Lett.*, 2981 (1964).
(10) See H. L. Slates and N. L. Wendler, *J. Med. Chem.*, 8, 886 (1965), for an alternative formulation of the dibenztropylium compound obtained by reacting dibenzsuberone with phosphorus pentachloride.
(11) G. Thompson and J. Collins, Syntex Institute of Pharmaceutical Sciences, unpublished results.
(12) (a) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962), modified as described in ref 12b; (b) A. P. Roszkowski, W. H. Rooks II, A. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, 179, 114 (1971).
(13) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, 125, 237 (1959), modified as described in ref 12b.
(14) D. G. Kaiser, G. J. Vangeissen, R. J. Reischer, and W. J. Wechter, *J. Pharm. Sci.*, 65, 269 (1976).
(15) G. Nannini, P. N. Giraldi, G. Molgora, G. Biasoli, F. Spinelli, W. Logemann, E. Dradi, G. Zanni, A. Buttinoni, and R. Tomassini, *Arzneim.-Forsch.*, 23, 1090 (1973); H. Miyamatsu, S. Ueno, M. Shimizu, J. Hosono, M. Tomari, K. Seida, T. Suzuki, and J. Wada, *J. Med. Chem.*, 17, 491 (1974).
(16) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, 6, 469 (1950).
(17) C. M. Pearson, *Proc. Soc. Exp. Biol. Med.*, 91, 95 (1956).
(18) J. G. Lombardino, I. G. Otterness, and E. H. Wiseman, *Arzneim.-Forsch.*, 25, 1629 (1975).
(19) See, for example, K. Ueno, S. Kubo, H. Tagawa, T. Yoshioka, W. Tsukada, M. Tsubokawa, H. Kojima, and A. Kasahara, *J. Med. Chem.*, 19, 941 (1976).
(20) All animals were obtained from Simonsen Laboratories, Inc., Gilroy, Calif. Rats were designated as "Sprague–Dawley derived". Mice were designated as "Swiss–Webster".
(21) D. J. Finney, "Statistical Methods in Biological Assay", Hafner Publishing Co., New York, N.Y., 1964.

Pyrazolodiazepines. 2. 4-Aryl-1,3-dialkyl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones as Antianxiety and Anticonvulsant Agents

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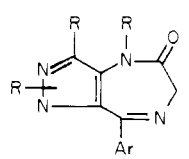
A series of 4-aryl-1,3-dialkyl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones was synthesized and screened for psychotropic activity. In animals, a number of these pyrazolodiazepinones had strong CNS effects similar to diazepam. One compound, 4-(2-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-one (**54**), is being studied in the clinic as a component of a new animal anesthetic, Tilazol.

A number of years ago, we became interested in preparing 1,4-diazepines fused to a heterocylic system instead of a benzene system, a type of compound that was relatively unexplored at that time. An earlier paper[1] described the initial results of that work, a series of 8-arylpyrazolo[4,3-*e*][1,4]diazepin-5(1*H*)-ones (I) which were active CNS agents. An isomeric series, the 4-aryl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazepin-7(1*H*)-ones (II), was developed concurrently and is the subject of this paper.[2] 1,4-Diazepines fused to thiophenes,[3a] imidazoles,[3b] pyrazines,[3c] pyrroles,[3d] and isoxazoles[3e] have been discussed. However, of all these systems, the pyrazolodiazepines appear to be most accessible and amenable to the transformations that have been performed on the 1,4-benzodiazepines.



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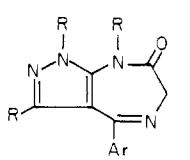

II

Key intermediates to II were the amino ketones V which were generally prepared by treatment of (1,3-dialkyl-5-chloro-1*H*-pyrazol-4-yl)arylmethanones[4] (III) with amines or by a Friedel–Crafts aroylation of 1,3-dialkyl-1*H*-pyrazol-5-amines IV (Scheme I). The preparation and physical properties of many of the amino ketones V used as intermediates were described in the patent literature[5] and are the subject of a manuscript in preparation. The detailed procedures for several amino ketones not described[5] have been included in the Experimental Section to illustrate approaches used for the synthesis of special compounds in this series. Two of these procedures are shown in Scheme II to prepare amino ketones **5** and **8**.

Elaboration of the pyrazolodiazepinones from the amino ketones V was accomplished by acylation with a potential glycyl radical and conversion to the uncharacterized aminoacetamide by processes of aminolysis, hydrazinolysis, or hydrogenation. The uncharacterized 2-aminoacetamides cyclized under the conditions of the reaction. These methods have been used previously for benzodiazepines. Acylation of the weakly nucleophilic 1*H*-pyrazol-5-amine system was accomplished only with the use of stable acid chlorides, haloacetyl halides, phthalimidoacetyl chloride, and azidoacetyl chloride. Acylation with esters, anhydrides, or activated glycyl intermediates useful in peptide synthesis failed. Alkylation of the amide nitrogen (method