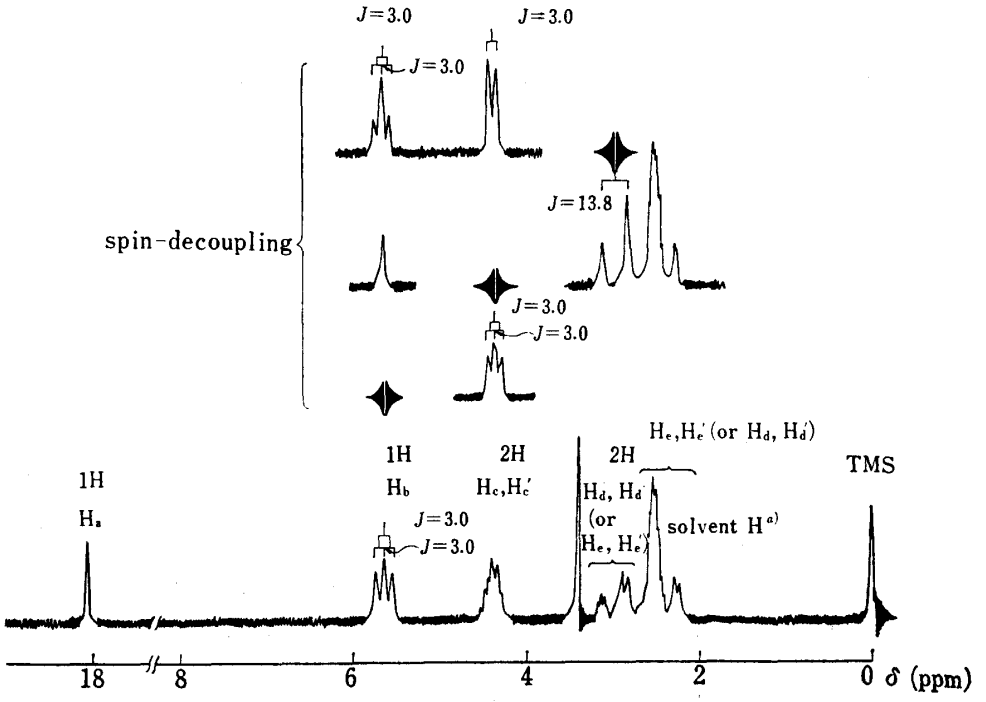

Fig. 1. The NMR Spectrum of Ib and the Results of Spin-Decoupling (Dimethylsulfoxide-d_6)

a) This signal might veil a part of the signals due to He and He' (or Hd and Hd'). *b*) *J* is expressed in cps.

at *Rf* value of 0.52, and identified with Ib by the overlapping method in the development. Furthermore, the water extract of the spot showed an identical absorption spectrum to Ib. These evidences clearly explained that Ib was produced as a main coloring matter in the reaction. It is important to note that such bicyclic compound as I is formed even in the aqueous Janovsky reaction.

Details of the study on I will be published in the near future, and the investigations of role of I in the reaction of acetone with a large amount of picric acid are now going on.

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6-Chloro-5-cyclohexylindan-1-carboxylic Acid (TAI-284), a New Antiinflammatory Agent

In the present communication we wish to report the synthesis and biological activity of a new antiinflammatory agent, 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) (I), which has a simplified steroidal structure and reserves an interesting steric requirement for the activity.

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The structure of indan-1-carboxylic acid bears a certain similarity to that of antiinflammatory corticosteroids, if the carboxyl group at C-1 is considered to represent the cortical dihydroxyacetone side chain and other functional groups at C-3 and C-11 of the steroids are disregarded. In addition, Robinson, *et al.*[1] synthesized 11β-chlorocorticosteroids including dichlorisone (9α,11β-dichloro-17α,21-dihydroxypregna-1,4-diene-3,20-dione) (II) and interestingly it was found that introduction of 11β-chlorine resulted in good separation of the antiinflammatory from glucocorticoid activity.[2] These led us to speculate that 6-chloroindan-1-carboxylic acid derivatives, C-6 of which corresponds to C-11 of the steroid nucleus, might show the antiinflammatory activity. Thus, some 6-chloroindan-1-carboxylic acids were prepared to evaluate the biological activity. Among them, I, which closely resembles the structure of II as shown in Fig. 1, showed the most potent activity.

The synthesis of I was accomplished by the procedures as shown in Chart 1, starting with 4-cyclohexylphenylacetonitrile (III). III was chlorinated directly with chlorine in carbon tetrachloride using ferric chloride as a catalyst. The resulting 3-chloro-derivative (IV), $C_{14}H_{16}NCl$, bp 136—140° (4 mmHg), was condensed successively with diethyl carbonate and ethyl bromoacetate, and subsequent hydrolysis gave 3-chloro-4-cyclohexylphenylsuccinic acid (VI), $C_{16}H_{19}O_4Cl$, mp 175—177°. VI was converted to the anhydride (VII), $C_{16}H_{17}O_3Cl$, mp 119—121°, by heating with acetic anhydride. Cyclization of VII with aluminum chloride in methylene chloride afforded 6-chloro-5-cyclohexyl-3-oxoindan-1-carboxylic acid (VIII), $C_{16}H_{17}O_3Cl$, mp 184—186°. In addition to VIII, the isomeric 4-chloro-5-cyclohexyl-3-oxoindan-1-carboxylic acid (IX), $C_{16}H_{17}O_3Cl$, mp 188—191°, was obtained as a minor product. Clemmensen reduction of VIII gave I, $C_{16}H_{19}O_2Cl$, mp 151—152°. I showed remarkable antiinflammatory, analgetic and antipyretic activities comparable or even superior to those of indomethacin in various animal assays.[3]

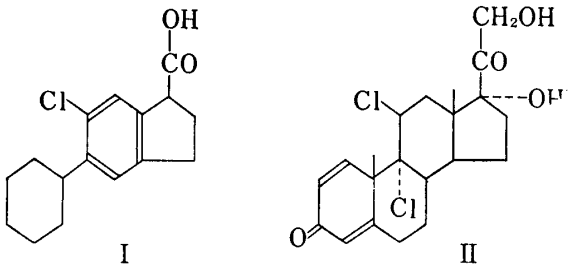
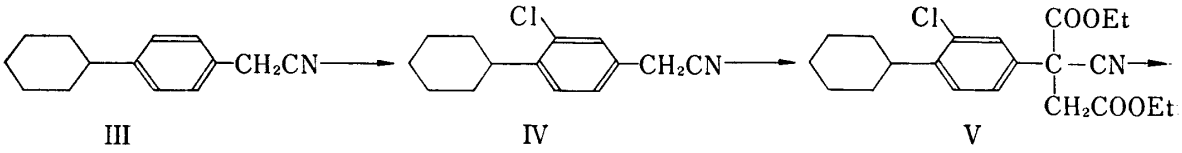


Fig. 1



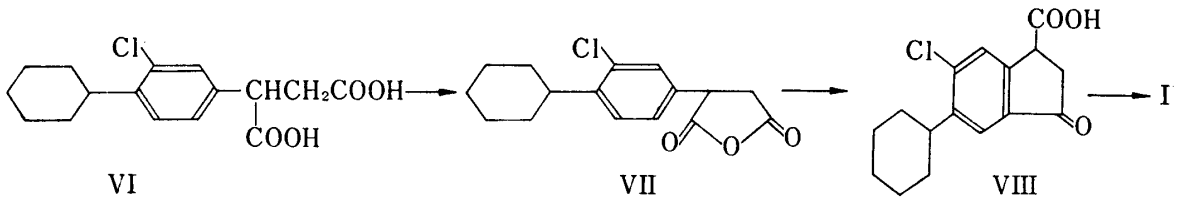


Chart 1

For the study of the structure-activity relationship, some structural homologs have been prepared. Thus, replacement of the cyclohexyl group by other alkyl groups, like isobutyl and

1) C.H. Robinson, L. Finckenor, E.P. Oliveto and D. Gould, *J. Am. Chem. Soc.*, **81**, 2191 (1959).
2) S. Tolksdorf, F. Warren and P.L. Perlman, *Federation Proc.*, **19**, 158 (1960).
3) Detailed pharmacological results will be published elsewhere by Dr. K. Kawai, *et al.*, biologists of our laboratories.

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isopropyl, resulted in a considerable loss of the activity. The position of the chlorine substituent seemed to be particularly important: 4-chloro-5-cyclohexylindan-1-carboxylic acid, the 4-chloro isomer of I, $C_{16}H_{19}O_2Cl$, mp 120—123°, which was prepared from IX by the Clemmensen reduction, was devoid of the activity. Furthermore, the dechlorinated derivative,5-cyclohexylindan-1-carboxylic acid, $C_{16}H_{20}O_2$,mp 140—144°, which was prepared by similar procedures, was only slightly active.

I possesses an asymmetric center at C-1, the position bearing the carboxyl group. The resolution of I was effected with quinine and it was found that the antiinflammatory activity virtually resided in the dextro isomer, mp 130—135°, $[\alpha]_D^{25}$ +28.1° (MeOH). The absolute configuration of the dextro isomer was assigned the sinister series by the optical rotatory dispersion (ORD) spectrum[4] and X-ray crystallography. This is in good accord with other observations that the antiinflammatory activity of α-methylarylacetic acids, such as α-methylated indomethacin analogs[5] or 3-chloro-4-cyclohexyl-α-methylphenylacetic acid,[6] is associated with the dextro rotatory isomer having the sinister configuration at the α-carbon.[7] Interestingly, corticosteroids also have the same configuration at C-17. These facts will indicate that the configuration of the carboxyl group of I may play an important role like the dihydroxyacetone side chain of corticosteroids.

While the mode of action of antiinflammatory agents is still unclear, the structural analogy between I and corticosteroids observed in the present study is greatly suggestive for the mechanistic consideration of the antiinflammatory action.

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4) J.H. Brewster and J.G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966); B. Sjöberg, *Acta Chem. Scand.*, **14**, 273 (1960).
5) Brit. Patent 957990 (1964) [*Chem. Abstr.*, **61**, 4319 (1964)].
6) T.Y. Shen, *et al.*, 2nd Mid-Atlantic Regional Meeting of American Chemical Society, New York, Feb. 6—7, 1967; *Chem. Eng. News*, 45, 10 (Feb. 13, 1967); T.Y. Shen, *Chim. Ther.*, **1967**, 459.
7) The only exception was observed in ibuprofen (4-isobutyl-α-methylphenylacetic acid). The two enantiomorphs have indicated no difference in the antiinflammatory potency in the guinea pig ultraviolet erythema test [S.S. Adams, E.E. Cliffe, B. Lessel and J.S. Nicholson, *J. Pharm. Sci.*, **56**, 1686 (1967)].

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