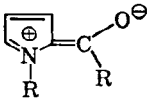
is observed. This decrease in the transition energy may be associated with the difference in the steric strain of the two ring systems. The highly strained five-membered ring system should make the allowable electronic transition more difficult relative to the strainless six-membered ring system. The slight decrease in the ϵ_{max} is probably due to a decrease in the number of molecules in which the carbonyl group is coplanar with the pyrrole ring. Models show that in the strainless six-membered ring molecule the carbonyl group is slightly skewed with respect to the pyrrole ring.

In the spectrum of 6-ketocycloheptano[*a*]pyrrole the primary band is not displaced from that observed in the six-membered ring system, but there is a large decrease in the intensity of the band. Braude[7] suggests that changes of this type are due to relatively weak steric inhibitions. Models show that if the carbonyl group is to assume a coplanar conformation with the pyrrole ring, strain is introduced into the system because of C-H oppositions in the seven-membered ring. Fewer molecules, then, would be capable of undergoing the allowable electronic transition.

The use of the less polar cyclohexane solvent resulted in a constant shift of λ_{max} to shorter wave lengths, in an increase in the ϵ_{max} and in the appearance of fine structure in the curves. Such solvent effects have been attributed[8] to a hindrance in molecular rotation and a perturbation of the electrical forces in the solute molecule by the polar solvent. The increase in the ϵ_{max} suggests that the ethanol solvent may have reacted with the carbonyl group to a certain extent.

Eisner and Erskine[1d] have suggested that the low carbonyl stretching frequencies observed in the acylpyrrole series are due to significant contributions of the polar structure to the resonance



hybrid. The carbonyl frequencies of the ketocycloalkano[*a*]pyrroles fall within this range and are found to decrease with increasing size of the cycloalkano ring system. Similar decreases in carbonyl frequencies have been reported in the benzocyclanone series[9] and in the cyclanone series.[9,10]

The higher carbonyl stretching frequencies in the five-membered ring compounds compared to the six-membered ring compounds is due, according to Ingraham,[11] to the increased *s* character of the carbonyl carbon resulting from a rehybridization in the carbonyl orbitals caused by the angular strain associated with the five-membered ring.

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EXPERIMENTAL

The infrared spectra were measured with a Perkin-Elmer Model 21 recording spectrophotometer using a sodium chloride prism. Chloroform solutions of 1 to 2% concentration were used. The ultraviolet spectra were measured with a Beckman Model DK-2 ratio recording spectrophotometer. Concentrations of the solutions were 10^{-4} to 10^{-5} *M*. The wave length maxima and the carbonyl absorption frequencies are given in Table I.

The ketocycloalkano[*a*]pyrroles (Ia–Ic) were synthesized by a modification and extension of the procedure described by Clemo *et al.*[12] Details of the synthesis will be described in a future report.

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Some 3,5-Disubstituted Benzotrichlorides as Possible Insecticides

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The structure and insecticidal activity of DDT is well known. Various explanations have been advanced to explain its activity.[1-6] It has been suggested[6] that the effect of the trichloromethyl group is to give the required steric orientation to the rest of the molecule, and that this orientation produces a maximum toxicity when the chlorine atoms on the aromatic nucleus are in the *para* positions. An alternate way to generalize the structural features required is to employ a unique spatial arrangement of the active substituents

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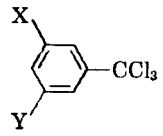
rather than by specifying the *para* position as emphasized by Prill, Synerholm, and Hartzell.[1] Based on this generalized point of view, the structural feature necessary for insecticidal activity is suggested to be a Y-shaped skeleton with active constituents occupying the three ends. The present study was carried out in order to prepare compounds which might be used to test this idea. To this end we have prepared compounds of the general formula



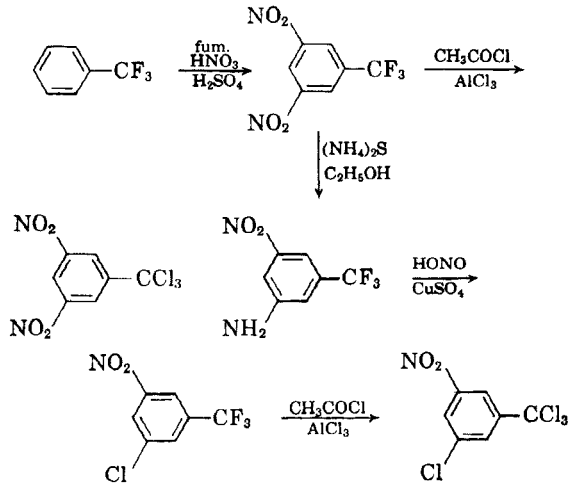
where X = Y = Cl
X = Y = NO_2
X = Cl, Y = Cl

No variation was made in the trichloromethyl group in order to maintain some similarity to DDT derivatives.

The obvious method of synthesis involving direct substitution on a ring compound having a trichloromethyl group is, in fact, not very practical. Mononitration of benzotrichloride with fuming nitric acid and concentrated sulfuric acid at room temperature is reported[7] to give an 85% yield of *m*-nitrobenzoic acid. It is possible that the hydrolysis precedes the nitration, since benzotrichloride on nitration with nitrogen pentoxide in cold carbon tetrachloride gives an oily mixture of nitrobenzotrichlorides which are more stable to hydrolysis than the original compound. On hydrolysis with alkali or concentrated sulfuric acid a mixture of nitrobenzoic acids containing 70% of *m*-nitrobenzoic acid is obtained.

As the direct substitution approach is not adequate for preparing the 3,5-disubstituted benzotrichlorides, a second approach was studied. This method involved the introduction of substituents into the *meta* position of toluene prior to conversion of the methyl group to a trichloromethyl group. Thus it is possible to prepare 3,5-dichlorotoluene[8,9] and 3-chloro-5-nitrotoluene[10] from *o*- or *p*-acetaminotoluene by nitration and/or chlorination followed by removal of the acetamino group by hydrolysis, diazotization, and reduction.

α,α,α-Trichloro-3,5-dichlorotoluene was prepared by direct side-chain chlorination of 3,5-dichlorotoluene. The side-chain chlorination of 3,5-dinitrotoluene and of 3-chloro-5-nitrotoluene was not successful. Similarly, Kharasch and Brown[11] reported that the nitrotoluenes do not undergo peroxide-catalyzed reaction with sulfuryl chloride and that the inactivity is probably due to inhibitory (chain-breaking) properties of the nitro group. Accordingly, the following scheme was devised and adopted for the preparation of α,α,α-trichloro-3,5-dinitrotoluene and α,α,α-trichloro-3-chloro-5-nitrotoluene.



The major point of this synthesis is that α,α,α-trifluorotoluene, unlike α,α,α-trichlorotoluene, can undergo nitration without destruction of the trihalomethyl group, and that subsequently the trifluoromethyl group can be converted to a trichloromethyl group by treatment with acetyl chloride and aluminum chloride. α,α,α-Trifluorotoluene was converted to α,α,α-trifluoro-3,5-dinitrotoluene by the method of Benkeser and Buting[12] and to α,α,α-trifluoro-3-chloro-5-nitrotoluene by the method of Finger and Reed.[13] The conversion of these 3,5-disubstituted benzotrifluorides to the corresponding trichlorides was accomplished by an extension of the procedure of Henne and Newman.[14]

EXPERIMENTAL

α,α,α-Trichloro-3,5-dichlorotoluene. A vigorous stream of chlorine gas was passed through 3,5-dichlorotoluene (10 g., 0.062 mole) at 240° under illumination of a sunlamp for 8 hr. The increase in weight was 6 g. (calcd., 6.2 g.). Distillation gave 14.5 g. (91%), b.p. 124–126° (3 mm.).

Anal. Calcd. for $C_7H_3Cl_5$: Cl, 67.04. Found: Cl, 67.11.

α,α,α-Trichloro-3,5-dinitrotoluene. A mixture of α,α,α-trifluoro-3,5-dinitrotoluene (20 g., 0.084 mole) and acetyl chloride (9.5 g., 0.12 mole) was stirred while anhydrous aluminum chloride (11.2 g., 0.084 mole) was added slowly in small portions. The mixture was then heated to 70° and stirring was continued until the mixture nearly solidified. Treatment of the mixture with water and extraction with ether, followed by evaporation of the ether and steam distillation of the residue gave 9 g. of recovered α,α,α-

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trifluoro-3,5-dinitrotoluene in the distillate. The deep yellow residue from the steam distillation was recrystallized from methanol to give 12 g. (50%) of α,α,α-trichloro-3,5-dinitrotoluene, m.p. 76.5–77.5°.

Anal. Calcd. for $C_7H_3Cl_3N_2O_4$: Cl, 37.26. Found: Cl, 37.08.

α,α,α-Trichloro-3-chloro-5-nitrotoluene. A mixture of α,α,α-trifluoro-3-chloro-5-nitrotoluene (7.5 g., 0.033 mole) and acetyl chloride (10 g., 0.128 mole) was stirred gently while anhydrous aluminum chloride (5 g., 0.038 mole) was added slowly in small portions. The mixture was heated to 70° and stirring was continued until the mixture became a viscous mass. The mixture was treated with water and extracted with ether. Evaporation of the dried ether gave a residue which was distilled through a 6-in. helices-packed column to give 2 g. of unchanged starting material, b.p. 96–97° (10 mm.) and 4.5 g. (50%) of α,α,α-trichloro-3-chloro-5-nitrotoluene, b.p. 150–154° (3 mm.).

Anal. Calcd. for $C_7H_3Cl_4NO_2$: Cl, 51.58. Found: Cl, 51.55.

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Fluorosulfanilanilides

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Although 4′-fluorosulfanilanilide[1] is not a useful therapeutic agent, it was of interest to determine the effect on antibacterial activity of further substitution of fluorine. An increase in activity[2] due to increased amide acidity was expected. Condensation of 4-nitrobenzenesulfonyl chloride with eight fluoroanilines[3] in pyridine-acetone solution produced the fluorinated 4-nitrobenzenesulfonanilides listed in Table I; catalytic reduction of these intermediates gave the corresponding sulfanilanilides, Table II, in good yield.

Greater activity[4] against Gram-positive organisms *in vitro* was shown by 2′,4′- and 3′,5′-difluorosulfanilanilide than by the monofluoro analogs or sulfanilanilide itself. This increase in activity compared with the parent anilide or the monofluoro compounds is accompanied by an increase in acidity. Thus, 2′,4′- and 3′,5′-difluorosulfanilanilides in 30% aqueous acetone have pK_a values of 8.5 and 8.1, respectively, compared with 9.6 for sulfanilanilide (*cf.* 2-sulfanilamidopyridine, 8.4, and 2-sulfanilamidopyrimidine, 6.6, under the same conditions). However, no promising activity[5] *in vivo* was observed: the 2′, 4′- and 3′,5′-difluoro derivatives were only about one sixty-fourth as active as 2-sulfanilamidopyrimidine[6] against a lethal infection with *staphylococcus aureus*, strain Smith, in mice. The remaining compounds in Tables I and II were less active.

TABLE I

4-NITROBENZENESULFONANILIDES[a]

Compound	Yield, %	M.P. Corr.	Calcd., % / Found, % C	H	N	F
2′-F	78	163–165	48.7	3.1	—	6.4
			48.3	3.3	—	6.1
3′-F	65	131–132	48.6	3.1	9.5	6.4
			48.7	3.2	9.4	6.4
4′-F	97	182–183	48.6	3.1	—	6.4
			48.3	3.1	—	6.7
2′-CH_3-5′-F	26	147–148	50.3	3.5	—	6.1
			50.4	3.6	—	6.1
2′,4′-F_2	87	151–152	45.9	2.6	—	12.1
			46.2	2.5	—	12.6
2′,5′-F_2	98	139–140	45.9	2.6	8.9	12.1
			46.1	2.8	9.0	12.1
3′,5′-F_2	87	149–150	45.9	2.6	8.9	12.1
			46.1	2.9	9.0	12.0
3′-CF_3	58	148–149	45.1	2.6	—	16.5
			45.3	2.8	—	16.2

[a] The 4-nitrobenzenesulfonanilides were prepared by the condensation of *p*-nitrobenzenesulfonyl chloride with the corresponding fluoroaniline in pyridine-acetone solution by the procedure given for the preparation of 3′,5′-difluoro-4-nitrobenzenesulfonanilide. The 4-nitrobenzenesulfonanilides were dissolved as their sodium salts and precipitated with dilute acid; no further purification was necessary.

EXPERIMENTAL

3′,5′-Difluoro-4-nitrobenzenesulfonanilide. An exothermic reaction was observed on the addition of 48.7 g. (0.220 mole) of 4-nitrobenzenesulfonyl chloride to a solution of 25.8 g. (0.200 mole) of 3,5-difluoroaniline in 160 ml. of acetone and 32 ml. (0.40 mole) of reagent grade pyridine. After 10 min. the reaction was complete as indicated by arylamine analysis (Bratton-Marshall).[7] The solution was poured into 400 ml. of 0.6*N* hydrochloric acid, and a white precipitate was isolated. This material was dissolved in 200 ml. of 10% potassium hydroxide, and the orange solution then added to 400 ml. of 10% hydrochloric acid resulting in the isolation of 54.8 g. (87%) of white 3′,5′-difluoro-4-nitrobenzenesulfonanilide, m.p. 149–150° corr.

3′,5′-Difluorosulfanilanilide. A solution of 38.9 g. (0.124 mole) of 3′,5′-difluoro-4-nitrobenzenesulfonanilide in 150 ml. of acetone and 14.0 g. of Raney nickel in ethanol was shaken in a Parr hydrogenation apparatus under a pressure

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