required about 5 hr. Excess chlorine was swept out with nitrogen, the mixture was filtered, and the filtrate concentrated *in vacuo* on the steam bath. The residual oil was extracted with 500 ml. of toluene, the extract was treated with Darco, filtered, dried, and concentrated to give 434 g. (81% yield) of crude sulfonyl chloride as a dark oil. This was used without further purification.

Potassium 2-nitro-α,α,α-trifluoro-p-toluenesulfonate. A suspension of 5.8 g. (0.02 mole) of 2-nitro-α,α,α-trifluoro-p-toluenesulfonyl chloride, 3 g. (0.02 mole) of anhydrous potassium carbonate, and 24 ml. of water was stirred and refluxed for 1 hr., filtered, and cooled to give 6.1 g. (98% yield) of the potassium salt, as broad yellow plates. An analytical sample was recrystallized from 90% ethanol; when heated in an open flame, the compound decomposed without melting.

Anal. Calcd. for $C_7H_3F_3KNO_5S$: K, 12.64. Found K, 12.39.

2-Amino-α,α,α-trifluoro-p-toluenesulfonic acid. The solution of the potassium salt obtained as in the previous example by the treatment of 428 g. (1.48 moles) of 2-nitro-α,α,α-trifluoro-p-toluenesulfonyl chloride with 225 g. (1.64 moles) of anhydrous potassium carbonate and 1750 ml. of water, was reduced by the procedure of Wertheim.[9] The yield of air-dried amino derivative was 286.4 g. (80%). An analytical sample was obtained from dimethylformamide-ether; this material decomposed in an open flame without melting.

Anal. Calcd. for $C_7H_6F_3NO_3S$: C, 34.85; H, 2.51. Found: C, 34.78; H, 2.62.

Sodium α,α,α-trifluoro-p-toluenesulfonate.[10] To the diazonium compound obtained from 270 g. (1.12 moles) of the amino compound[7] was added dropwise 582 ml. (5.6 moles) of 50% hypophosphorous acid, maintaining the temperature at 0 to 5°; the reaction mixture was kept for 48 hr. at 5°, filtered, and the filtrate concentrated to about one fourth its original volume and cooled. The precipitated solid was filtered and extracted with 3 l. of boiling methanol. The methanol extract was made strongly alkaline with 50% aqueous sodium hydroxide, concentrated, and cooled to give 182.4 g. (65% yield) of the sodium sulfonate.

α,α,α-Trifluoro-p-toluenesulfonyl chloride. To 116.5 g. (1.0 mole) of chlorosulfonic acid was added in small portions a total of 49.6 g. (0.2 mole) of the sodium sulfonate. Subsequently, the mixture was heated for 1 hr. on the steam bath, cooled somewhat, and poured on about 1 kg. of ice. The crystalline sulfonyl chloride which separated was filtered, washed well with water, and used directly in the next step.

α,α,α-Trifluoro-p-toluenesulfonamide. The sulfonyl chloride obtained in the previous step was added rapidly, with stirring, to 600 ml. of cold concd. aqueous ammonia, the mixture was slowly warmed by means of a steam bath to 75–80° and kept at this temperature for 1 hr. The mixture was cooled, the solid filtered and recrystallized from aqueous alcohol to give 30.6 g. (68% yield over-all for the last two steps) of sulfonamide, m.p. 176–177°.

Ethyl α,α,α-trifluoro-p-tolylsulfonylcarbamate. Employing the procedure described above, 30.6 g. (0.14 mole) of the sulfonamide, 49 g. (0.35 mole) of anhydrous potassium carbonate, and 19.6 g. (0.18 mole) of ethyl chloroformate afforded 28.6 g. (71% yield) of the crude ethyl carbamate, m.p. 85–87°. An analytical sample recrystallized from benzene-hexane (1:1), melted at 93–95°.

1-Butyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea. From 8.9 g. (0.03 mole) of the ethyl carbamate and 11.5 g. (0.1 mole) of *n*-butylamine, by the procedure above, there was obtained 6.0 g. (62% yield) of product, m.p. 127–128° after recrystallization from aqueous ethanol.

Alternate procedure to ethyl α,α,α-trifluoro-p-tolylsulfonylcarbamate. Chart II, B. α,α,α-Trifluoro-*m*-toluidine and chlorosulfonic acid according to the procedure of Kracker and Herrlein[3a] gave a 95% yield of an amino-α,α,α-trifluorosulfonic acid whose infrared spectrum was identical with that obtained above. This acid, 241 g. (1.0 mole), when diazotized and the diazonium group reductively eliminated, gave 146 g. (59% yield) of sodium *α,α,α-trifluoro-p-toluenesulfonate.*

Anal. Calcd. for $C_7H_4F_3NaO_3S$: S, 12.92. Found: S, 12.97.

The sodium salt, 17.4 g. (0.07 mole) and 46.5 g. (0.39 mole) of chlorosulfonic acid gave the *sulfonyl chloride,* and this without purification was treated with 200 ml. of concd. aqueous ammonia to give 9.8 g. (62% yield in two steps) of *α,α,α-trifluoro-p-toluenesulfonamide,* m.p. 176–177°; a mixture melting point with the product obtained above was 176–177°, and the infrared spectra of both products were identical. The sulfonamide, 9.8 g., gave an 81% yield of ethyl *α,α,α-trifluoro-p-tolylsulfonylcarbamate,* m.p. 93–94°; a mixture melting point with the product obtained above was 93–94°, and the infrared spectra of both products were identical.

Isolation of the cyclohexylamine salt of 1-cyclohexyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea and 1,3-dicyclohexylurea from the reaction of cyclohexylamine with α,α,α-trifluoro-p-tolylsulfonylcarbamate. A solution of 20.8 g. (0.07 mole) of ethyl α,α,α-trifluoro-*p*-tolylsulfonylcarbamate and 50 g. (0.5 mole) of cyclohexylamine was treated as above. The pyrolysis product crystallized spontaneously and was recrystallized from aqueous ethanol to give the pure salt, m.p. 177–179°.

Anal. Calcd. for $C_{14}H_{17}F_3N_2O_3S \cdot C_6H_{13}N$: C, 53.44; H, 6.73; N, 9.35. Found: C, 53.25; H, 6.29; N, 9.43.

The salt was dissolved in 300 ml. of warm 0.5*N* aqueous sodium hydroxide and filtered from 0.9 g. of 1,3-dicyclohexylurea, m.p. 226–227°.[11] The warm filtrate was acidified with aqueous hydrochloric acid. The precipitated solid was filtered and recrystallized from 95% ethanol to give 10.5 g. (43% yield) of 1-cyclohexyl-3-(α,α,α-trifluoro-*p*-tolylsulfonyl)urea, m.p. 177–178°.

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(9) E. Wertheim, *Org. Syntheses,* Coll. Vol. II, 471 (1943).

(10) This compound was screened for ascaricidal activity but no description of its synthesis is reported; *cf. J. Am. Pharm. Assoc.,* **38,** 570 (1949).

(11) A. Skita and H. Rolfes, *Ber.,* **53,** 1242 (1920) have reported the melting point for 1,3-dicyclohexylurea as 229–230°.

Indole-3-alkanamides

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Since the first implication of indole-3-acetic acid in the growth of plants,[1] the series of indole-3-alkanoic acids has received a great deal of attention from both chemists and biologists. Although the acetic acid was first prepared by Ellinger in 1904,[2] it was not until twenty-one years later that its amide was reported[3] and still another twenty-

(1) F. Kögl, A. J. Haagen-Smit, and H. Erxleben, *Z. physiol. Chem.,* **228,** 90(1934).

(2) A. Ellinger, *Ber.,* **37,** 1801 (1904).

(3) R. Majima and T. Hoshino, *Ber.,* **58,** 2046 (1925).

TABLE I

INDOLE-3-ALKANAMIDES

Compound	M.p.	Yield, %	% N		Growth Stimulation[a]		
			Calcd.	Found	$10^{-4}M$	$10^{-5}M$	$10^{-6}M$
Indole-3-acetamide	149–151°	70	16.1	—	400	90	0
Indole-3-propionamide	131.5–133°	80	14.9[b]	14.8	70	0	0
Indole-3-butyramide	117–118°	40	13.9	13.8	100	120	0
Indole-3-valeramide	127–128°	87	13.0	12.9	50	0	0
Indole-3-caproamide	134.5–136°	99	12.2	11.9	350	400	300

[a] Per cent of control elongation. Indole-3-acetic acid at 10^{-6} M = 400. Values greater than 40 are statistically-significant at the 1% level. [b] *Anal.* calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.43. Found: C, 70.4; H, 6.70.

seven years before the biological activity of this amide was described.[4] Despite the wide variety of derivatives of other indole acids which have been examined, and the importance ascribed to their effect on plant growth, no data have been available on the preparation and biological properties of other simple amides of this series.

Early attempts to prepare indole amides through the intermediate acid chlorides were unsuccessful,[5] although Shaw and co-workers later were able to obtain indole-3-acetamide by this method.[6] In the present work, amides were prepared by reaction of an ethereal solution of the acid chloride, prepared from the acid and phosphorus pentachloride, with excess concentrated ammonium hydroxide followed by isolation and recrystallization. Their properties are shown in Table I.

Ammonolysis of methyl indole-3-propionate has been mentioned in the literature.[7] However, the melting point of the product was 205°, 72° higher than that of our preparation. Upon repetition of the ammonolysis of the ester, we obtained a compound which exhibited a melting point, mixed melting point, and infrared spectrum identical with those of indole-3-propionamide obtained through the acid chloride. In addition, hydrolysis of both amide samples to indole-3-propionic acid was demonstrated through the use of paper chromatography.

The purified amides were bioassayed by the method of Nitsch and Nitsch,[8] in which elongation of sections of oat first-internodes was measured. The results presented in Table I are distinctly different from those obtained with the corresponding acids.[9] In general, the amides exhibit a lower order of activity than the acids; the possibility that the high value for indole-3-acetamide at 10^{-4} M could be due to the presence of a small amount of indole-3-acetic acid present as an impurity is unlikely because of the chromatographic homogeneity of the sample. The high degree of stimulation observed with the caproamide is unusual and does not coincide with the lowered activity of the corresponding indole-3-caproic acid relative to the acetic acid or with the decreasing activity of the other amides as chain length increases.

EXPERIMENTAL[10]

General preparation of amides. The indole-3-alkanoic acid was dissolved or suspended in anhydrous ether in a flask equipped for the exclusion of moisture. The mixture was stirred magnetically and chilled while a 10% molar excess of phosphorus pentachloride was added, and stirring was continued for 1 hr. The resulting solution was then added dropwise to a large excess of concd. ammonium hydroxide which was stirred and chilled in ice during the addition. After 30 min., the ether was removed in a stream of air or nitrogen, the aqueous layer filtered, and the solid remaining on the filter washed with cold water and air dried. Chloroform, ethyl acetate, and benzene were found to be suitable solvents for recrystallization of the crude amides.

Bioassay. Sections of first internodes of dark-grown oat seedlings (*Avena sativa* L., Var. Brighton), 4.0 mm. in length, were rotated at 1 r.p.m. in citrate-phosphate buffer (*p*H 5.0) which contained 2% sucrose. The indole amides were incorporated in the buffer at concentrations of 10^{-4} to $10^{-7}M$, and at the end of about 20 hr. the final length of each section was measured with the aid of a photographic enlarger. Results were expressed as the average increase in length of eight sections compared with that of the controls.

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NOTE ADDED IN PROOF. In May, 1960, C. H. Fawcett, R. L. Wain, and F. Wightman [*Proc. Royal Soc. Series B*, **152**, 231 (1960)] reported synthesis of several of these indole-3-alkanamides by ester ammonolysis.

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(4) J. A. Bentley and S. Housley, *J. Exptl. Botany*, **3**, 393 (1952).

(5) J. W. Baker and F. C. Happold, *Biochem. J.*, **34**, 657 (1940).

(6) K. N. F. Shaw, Armand McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).

(7) H. T. Huang and C. Niemann, *J. Am. Chem. Soc.*, **74**, 5963 (1952).

(8) J. P. Nitsch and Colette Nitsch, *Plant Physiol.*, **31**, 94 (1956).

(9) C. H. Fawcett, R. L. Wain, and F. Wightman, *Nature*, **181**, 1387 (1958).

(10) All melting points were measured in a Vanderkamp block and are corrected.