Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.70; H, 9.81; N, 6.84.

1-Methyl-2-phenyl-5-propylpyrrolidine (IV).—A solution of 10.4 g. of the above pyrrolidine in 200 ml. of absolute ethanol was hydrogenated in the presence of 200 mg. of Adams platinum oxide catalyst. One mole of hydrogen was consumed in 5 minutes. The mixture was worked up as usual to furnish 8.5 g. of the dihydro base, b.p. 111–113° (4 mm.), $n^{25}D$ 1.5090.

Anal. Calcd. for $C_{14}H_{21}N$: N, 6.86. Found: N, 6.90.

4-Dimethylamino-1-phenyl-1-heptene (VI).—The above dihydro base IV (13.3 g.) was covered with 50 ml. of methyl iodide. The solution warmed spontaneously and then deposited a yellow gum. The methyl iodide was allowed to evaporate and the residue was treated with enough fresh methyl iodide to just cover it. The mixture was warmed and after all the methyl iodide had evaporated the gum was dissolved in warm acetone. On cooling a white solid, m.p. 126–130°, deposited; wt. 14.7 g.[19]

Silver oxide was freshly prepared from 12.6 g. of silver nitrate and washed thoroughly with distilled water. The mixture of methiodides (m.p. 126–130°, wt. 12.0 g.) was dissolved in 100 ml. of water and heated on the steam-bath with the silver oxide for one hour. The solids were collected on a filter and digested for 15 minutes with 50 ml. of hot water. The united aqueous extracts were evaporated at 45° (1 mm.). The residue was dissolved in methanol, freed of a small amount of insoluble material and distilled at a pressure of 0.3 mm. A liquid distilled at 83–100°; wt. 5.0 g.

On redistillation there was obtained a fraction, b.p. 125–128° (4.0 mm.), $n^{25}D$ 1.5200. The ultraviolet absorption spectrum showed ϵ_{253} 11,650.

Anal. Calcd. for $C_{15}H_{23}N$: N, 6.46. Found: N, 6.44.

4-Dimethylamino-1-phenylheptane (VII).—The above styrene (2.3 g.) was reduced in 200 ml. of 95% ethanol in the presence of 100 mg. of Adams platinum oxide. When the reduction was over, an aliquot was removed for ultraviolet spectral analysis (ϵ_{253} 219).

The remainder of the solution was concentrated to dryness and the residue was treated with alcoholic picric acid. After three recrystallizations from ethanol the salt melted at 92.5–94° and did not depress the m.p. of the authentic specimen described below.

Anal. Calcd. for $C_{21}H_{28}N_4O_7$: N, 12.49. Found: N, 12.23.

1-Phenyl-4-heptanone (VIII).—N-Propylmagnesium iodide was prepared in 400 ml. of ether from 68 g. of propyl iodide and 10.2 g. of magnesium turnings. A solution of 43.5 g. of γ-phenylbutyronitrile in 100 ml. of ether was added dropwise. The ether was replaced by dry benzene and the mixture was refluxed for three hours. The mixture was treated with 200 ml. of 6 *N* hydrochloric acid and refluxed for 5 hours. The layers were separated and the benzene solution was washed with water, dried and distilled to give 23 g. of the desired ketone, b.p. 95–108° (0.3–0.5 mm.). Redistillation gave a pure product, b.p. 96–98° (0.1 mm.), $n^{25}D$ 1.5022.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.07; H, 9.43.

The 2,4-dinitrophenylhydrazone melted at 85–87° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: NO_2, 24.8. Found: NO_2, 24.3.

4-Dimethylamino-1-phenylheptane (VII).—Twenty-two grams of the heptanone was treated with 10 g. of hydroxylamine hydrochloride in 100 ml. of pyridine. The solution was heated on the steam-bath for 3 hours. The pyridine was removed *in vacuo* and the residue was partitioned between benzene and water. The benzene phase was washed with water and concentrated to leave 23 g. of a red oil which was used directly in the next step.

Twenty grams of lithium aluminum hydride was covered with 750 ml. of dry ether and treated with an ethereal solution of the crude oxime. The mixture was refluxed 6 hours and allowed to stand overnight. The mixture was treated dropwise with 20% rochelle salt solution and after the vigorous reaction had subsided the whole was stirred for several hours. It was filtered and the cake was washed with ether. The ether solution was separated and concentrated to 200 ml. before being extracted repeatedly with dilute hydrochloric acid. The united acid extracts were made alkaline and the oil removed with ether. The dried solution was distilled to give 7.6 g. of the amine, b.p. 93–95° (0.1 mm.). This was used directly in the next step without further purification. Seven grams of the 1-phenyl-4-aminoheptane was dissolved in 14.5 ml. of 98% formic acid and treated with 17 ml. of 37% formalin. After the initial vigorous reaction had subsided the solution was heated on the steam-bath for 5 hours. The solution was concentrated *in vacuo* to leave an oily residue which was dissolved in water and basified with sodium hydroxide solution. The oil was extracted with ether, dried over sodium sulfate and distilled to give 5.0 g. of a colorless liquid, b.p. 100–110° (0.1 mm.). The picrate which was prepared in ethanol melted at 92.5–93° after two recrystallizations from ethanol. A mixture with the picrate described previously melted at 92.5–94°.

RENSSELAER, NEW YORK

(19) By a suitable modification of this technique it was possible to obtain two methiodides. A solution of 6.2 g. of the dihydro base III in excess methyl iodide was allowed to stand at room temperature for about one hour and then was filtered. The insoluble gummy material was washed with cold acetone, whereupon it was transformed to a white crystalline material, m.p. 135–140°, wt. 6.5 g. The filtrate was diluted with more methyl iodide and allowed to stand overnight. Yellow plates had separated; wt. 4.5 g. These crystals dissolved in acetone readily and on standing the solution deposited a white crystalline material, m.p. 172–174°. After recrystallization from acetone the compound melted at 173–174°. *Anal.* Calcd. for $C_{15}H_{29}IN$: I, 36.1. Found: I, 36.0.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reactions of Orthoesters with Aryl Isocyanates

BY CALVERT W. WHITEHEAD AND JOHN TRAVERSO

RECEIVED SEPTEMBER 11, 1957

Phenyl isocyanates were found to react with triethyl orthoformate to yield 1,3-diaryl-5,5-diethoxyhydantoins. 1-Naphthyl isocyanate and triethyl orthoformate gave 1-(α,α,α-triethoxy)-acetyl-1,3-di-1′-naphthylurea. Phenyl isothiocyanate and triethyl orthoacetate yielded 1,3-diphenyl-6-ethoxy-2,4-dithiouracil. This uracil also was prepared from phenyl isothiocyanate and ketene diethylacetal. Phenyl isocyanates reacted spontaneously with ketene diethylacetal to form β,β-diethoxyacrylanilides.

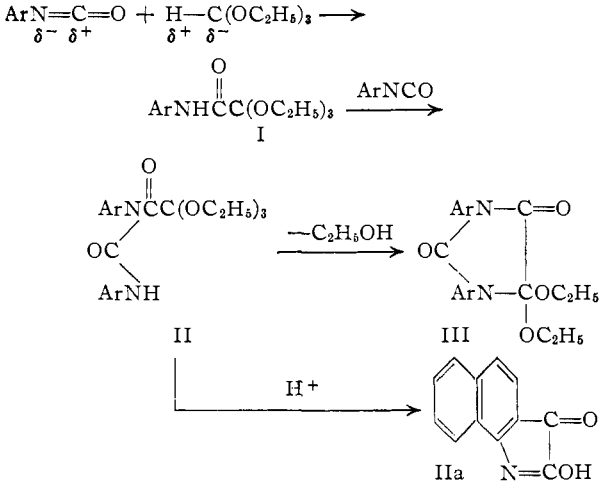
The previously described reactions of orthoesters, including those with Grignard reagents, all occur by replacement of one or more of the alkoxy groups of the orthoester.[1] This indicates that the α-hydrogen of triethyl orthoformate and also the β-hydrogens of triethyl orthoacetate are not easily replaced. This paper is a description of the reactions of aryl isocyanates with triethyl orthoformate and triethyl orthoacetate involving replacement of the α- and β-hydrogens of these orthoesters.

When triethyl orthoformate was allowed to re-

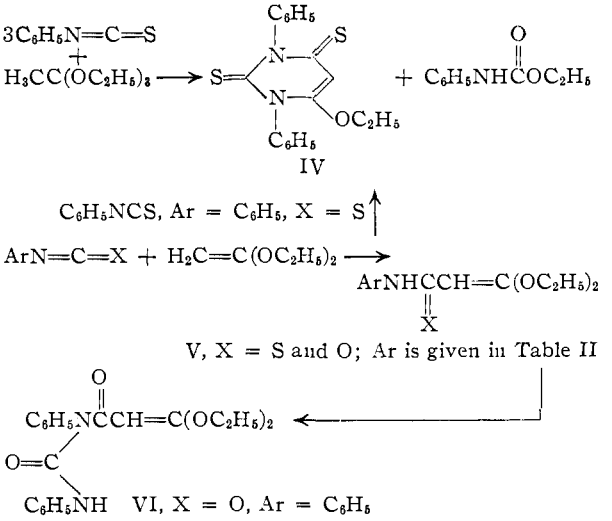
(1) A. E. Tschitschibabin and S. A. Jelgasin, *Ber.*, **47**, 48 (1914).

act with various phenyl isocyanates, the products were 1,3-diphenyl-5,5-diethoxy-hydantoins (III). This structure was confirmed by acid hydrolysis of 1,3-diphenyl-5,5-diethoxyhydantoin to the known 1,3-diphenylparabanic acid. The structure of III is also confirmed by infrared absorption. The two carbonyl groups are shown to be present by bands at 5.55–5.57 and 5.73–5.75 μ.[2] The aryl groups are evident by bands in the 6-μ region.

When 1-naphthyl isocyanate reacted with triethyl orthoformate, the product was not a hydantoin but had the composition of 1-(α,α,α-triethoxyacetyl)-1,3-di-1′-naphthylurea (II, Ar = 1-naphthyl). The infrared spectrum of the product is consistent with this assigned structure. The assigned structure was proved to be correct when II (Ar = 1-naphthyl) was converted by acid to the known α-naphthisatin (IIa). It appears reasonable that II (Ar = 1-naphthyl) is representative of the intermediates formed during the synthesis of III from isocyanates and triethyl orthoformate. Steric effects of the naphthyl groups possibly prevent cyclization of II (Ar = 1-naphthyl) to III. Formation of III from phenyl isocyanates and triethyl orthoformate probably involves three steps. The initial reaction is an addition of the orthoester to the isocyanate yielding an α,α,α-triethoxyacetanilide (I). A second mole of the isocyanate then reacts with the amide nitrogen of I to yield II. The last step is the cyclization of II with the elimination of ethanol.



Phenyl isothiocyanate reacted with triethyl orthoacetate to give 1,3-diphenyl-6-ethoxy-2,4-dithiouracil (IV). The steps in this synthesis of IV are considered to be analogous to those proposed for the formation of the hydantoins. The structure of IV is supported by the following alternate synthesis. Ketene diethylacetal spontaneously reacted with phenyl isothiocyanate to yield β,β-diethoxythioacrylanilide (V, Ar = C_6H_5, X = S). When β,β-diethoxythioacrylanilide was heated with a second mole of phenyl isothiocyanate, the product was identical to the 1,3-diphenyl-6-ethoxy-2,4-dithiouracil obtained from phenyl isothiocyanate and triethyl orthoacetate. Several attempts to prepare pyrimidines of the type IV from substituted phenyl isocyanates failed, and these reactions are under further investigation. Phenyl isocyanates did, however, react spontaneously with ketene diethylacetal to yield β,β-diethoxyacrylanilides (V, X = O). When ketene diethylacetal was heated with phenyl isocyanate, a small yield of a different product, N-(β,β-diethoxyacryl)-carbanilide (VI), was obtained. Due to the small amount of material available an attempt was not made to cyclize VI to the pyrimidine.



Acknowledgment.—The authors thank W. L. Brown, H. L. Hunter, G. Maciak and Miss Gloria Beckmann for the microanalyses; H. Boaz, D. O. Woolfe, L. Howard and Miss Martha Hofmann for the infrared and ultraviolet data and interpretations; and R. G. Jones and E. Van Heyningen for valuable suggestions.

Experimental

1,3-Diaryl-5,5-diethoxyhydantoins, Table I.—One-half mole of the appropriate aryl isocyanate was added to 50–100 ml. (an excess) of triethyl orthoformate and boiled under reflux for 12–24 hr. The excess orthoester was distilled at 9–15 mm. on the steam-bath. Petroleum ether was added to the undistilled residue and the solution cooled. The 1,3-diaryl-5,5-diethoxyhydantoin crystallized and was further purified by recrystallization from a mixture of ethyl acetate and petroleum ether.

The petroleum ether filtrate was evaporated leaving an oil. The oil was distilled through a small Claisen distilling head to give a near quantitative yield of the known N-arylurethan. The latter crystallized and was identified by the melting point.

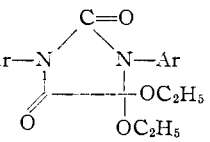
The infrared spectra of the 1,3-diaryl-5,5-diethoxyhydantoins in $CHCl_3$ showed carbonyl bands at 5.55–5.57 and 5.73–5.75 μ. The aryl rings contributed bands at 6.24 and 6.66 μ in the 1,3-diphenyl derivative; at 6.18, 6.22, 6.57 and 6.70 μ in the 1,3-di-biphenyl derivative; at 6.70 μ in the 1,3-di-*p*-bromophenyl derivative and 6.20, 6.29 and 6.72 μ in the 1,3-di-*o*-nitrophenyl derivative. Each 1,3-diaryl-5,5-diethoxyhydantoin had two intense bands at 7.10–7.12 μ and 7.30–7.33 μ and other principal bands at 8.48–8.52, 8.80–8.82, 9.1–9.35, 9.72–9.73, 9.80–9.90, 10.65 and 11.61–11.94 μ. The ultraviolet absorption of the hydantoins each showed one maximum: log $\alpha_{M224\ m\mu}$ = 4.24 for the 1,3-diphenyl derivative; log $\alpha_{M235\ m\mu}$ = 4.24 for the 1,3-di-*p*-bromophenyl derivative and log $\alpha_{M262\ m\mu}$ = 4.69 for the di-biphenyl derivative.

Hydrolysis of 1,3-Diphenyl-5,5-diethoxyhydantoin to 1,3-Diphenylparabanic Acid.—A mixture of 5 g. of 1,3-diphenyl-5,5-diethoxyhydantoin and 50 ml. of 3 *N* hydrochloric acid

(2) Randall, *et al.*, assign the 5.55 μ band of hydantoin to the 4-carbonyl and the 5.73 μ band to the 2-carbonyl; H. M. Randall, N. Fuson, R. G. Fowler and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 173.

TABLE I

1,3-DIARYL-5,5-DIETHOXYHYDANTOINS



Ar	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-BrC_6H_4	$C_{19}H_{18}Br_2N_2O_4$	70	140	45.80	46.05	3.64	3.79	5.62	5.83
o-$NO_2C_6H_4$	$C_{19}H_{18}N_4O_8$	56	188	53.02	53.20	4.21	4.33	13.02	12.81
C_6H_5	$C_{19}H_{20}N_2O_4$	74	111	67.20	67.51	5.93	5.98	8.24	8.12
p-ClC_6H_4	$C_{19}H_{18}Cl_2N_2O_4$	85	134	55.98	55.76	4.44	4.60	6.86	6.81
p-$C_6H_5C_6H_4$	$C_{31}H_{28}N_2O_4$	60	140	75.59	75.60	5.73	5.72	5.69	5.59

TABLE II

β,β-DIETHOXYACRYLANILIDES $RNHCCH{=}C(OC_2H_5)_2$

R	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2,5-$Cl_2C_6H_3$	$C_{13}H_{15}Cl_2NO_3$	79	141	51.33	51.32	4.97	5.01	4.60	4.47
2-$NO_2C_6H_4$	$C_{13}H_{16}N_2O_5$	88	114	55.71	56.08	5.75	5.84	10.00	10.12
2-$CH_3OC_6H_4$	$C_{14}H_{19}NO_4$	40	113	63.58	64.13	7.22	7.32	5.28	5.43
3-ClC_6H_4	$C_{13}H_{16}ClNO_3$	80	102	57.88	57.64	5.98	5.71	Cl, 13.15	Cl, 13.13
2-$CH_3OC_6H_4$	$C_{14}H_{19}NO_4$	50	113					5.28	5.43

was boiled under reflux for two hours. After the mixture was cooled the solid was collected on a filter, dried and recrystallized from ethanol; yield 3 g. (76%), m.p. 204° (lit.[3] 204°). The melting point was not depressed when mixed with an authentic sample of 1,3-diphenylparabanic acid. Also, both samples gave the same X-ray diffraction pattern.

1-(α,α,α-Triethoxyacetyl)-1,3-di-1′-naphthylurea.—A mixture of 100 g. (0.59 mole) of 1-naphthyl isocyanate and 200 ml. of alcohol free triethyl orthoformate was boiled under reflux for 12 hr. The volatile materials were removed by reduced pressure distillation on the steam-bath. The residue was cooled and the crystalline solid was collected. This was recrystallized from ethyl acetate; yield 30 g. (21%), m.p. 184–185°.

Anal. Calcd. for $C_{29}H_{30}N_2O_5$: C, 71.58; H, 6.22; N, 5.76. Found: C, 71.55; H, 6.24; N, 5.61.

The infrared spectrum of 1-(α,α,α-triethoxyacetyl)-1,3-di-1′-naphthylurea in $CHCl_3$ showed bands at 2.90 and 3.11 μ indicating a partially bonded NH group. A broad asymmetric band at 5.77 μ possibly accounts for both carbonyl groups. Broad complex absorption near 9 μ is contributed by the triethoxymethyl group and this absorption is also observed at 9.2 μ in the spectrum of triethyl orthoformate. Other principal bands are present at 6.07, 6.31, 6.55, 7.83, 8.80, 9.31, 9.50, 9.70 and 12.37 μ. The ultraviolet spectrum showed two maxima: log α_{M228} mμ = 4.97 and log $\alpha_{M313\ m\mu}$ = 4.06.

Conversion of 1-(α,α,α-Triethoxyacetyl)-1,3-di-1′-naphthylurea to α-Naphthisatin.—One gram of 1-(α,α,α-triethoxyacetyl)-1,3-di-1′-naphthylurea was dissolved in 20 ml. of 50% ethanol containing 5 drops of 1 *N* NaOH. The solution was boiled for 2–5 minutes and then cooled. The starting material was recovered unchanged in near quantitative yield.

One gram of 1-(α,α,α-triethoxyacetyl)-1,3-di-1′-naphthylurea was dissolved in 30 ml. of 50% ethanol. To this was added one drop of concentrated hydrochloric acid. The solution was boiled for 2–5 minutes during which time it turned red. When the solution was cooled rust-red needles separated which were recrystallized several times from 50% ethanol and from 98% ethanol; yield 0.45 g. (95.7%), m.p. 240–245°. The melting point of α-naphthisatin is reported[4] to be approximately 255°. The phenylhydrazone of α-naphthisatin is, however, reported[4] to have a well defined melting point of 268°.

Two-tenths gram of the product melting at 240–245° was dissolved in 25 ml. of ethanol. To this was added two drops of phenylhydrazine. The solution was concentrated and cooled. A near quantitative yield of the phenylhydrazone of α-naphthisatin (light-red needles) was obtained which melted at 268°.

Anal. Calcd. for $C_{18}H_{13}N_3O$: N, 14.63. Found: N, 14.46.

1,3-Diphenyl-6-ethoxy-2,4-dithiouracil.—A solution of 100 g. (0.74 mole) of phenyl isothiocyanate in 200 ml. (an excess) of triethyl orthoacetate was boiled under reflux for 12 hr. The excess orthoester was distilled at 10 mm. on the steam-bath. The residual oil was extracted with ether and a crystalline solid remained. The solid was recrystallized from a mixture of 90% ethanol and 10% N,N-dimethylformamide; yield 37 g. (29.6%), m.p. 250°.

Anal. Calcd. for $C_{18}H_{16}N_2OS_2$: C, 62.95; H, 4.82; N, 8.38. Found: C, 62.95; H, 4.68; N, 8.22.

β,β-Diethoxythioacrylanilide.—Eleven and six-tenths grams (0.1 mole) of ketene diethylacetal was added to 27 g. (0.2 mole) of phenyl isothiocyanate. The mixture became warm. After 45 minutes yellow crystals had separated and after standing 8 hr. at room temperature the crystals were collected on a filter, washed with ether then recrystallized from ethyl acetate; yield 24 g. (96%), m.p. 108–109°. The infrared spectrum of β,β-diethoxythioacrylanilide in $CHCl_3$ shows an NH band at 3.04 μ, bands for C=S at 7.42 and 8.1 μ, a band for the aromatic ring at 6.70 μ and unassigned principal bands at 6.34, 9.6 and 11.18 μ.

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.14; H, 6.82; N, 5.57; S, 12.75. Found: C, 62.41; H, 6.85; N, 5.68; S, 12.84.

1,3-Diphenyl-6-ethoxy-2,4-dithiouracil from Phenyl Isothiocyanate and Ketene Diethylacetal.—A mixture of 12.5 g. (0.05 mole) of β,β-diethoxythioacrylanilide and 13.5 g. (0.11 mole) of phenyl isothiocyanate was boiled under reflux for 15 min. The cooled solution was diluted with ether and allowed to stand in the refrigerator. The solid was collected and recrystallized from ethyl acetate; yield 3.5 g., m.p. 250°. The melting point was not depressed when mixed with 1,3-diphenyl-6-ethoxy-2,4-dithiouracil prepared from triethyl orthoacetate and phenyl isothiocyanate.

Twenty-seven grams (0.2 mole) of phenyl isothiocyanate and 7.6 g. (0.066 mole) of ketene diethylacetal were mixed and boiled under reflux for 3 hr. The mixture was concentrated under reduced pressure and cooled. A small amount of solid crystallized. This was recrystallized from ethyl acetate; yield 3.0 g. (12.5%), m.p. 250°, not depressed when mixed with 1,3-diphenyl-5-ethoxy-2,4-dithiouracil.

β,β-Diethoxyacrylanilides, Table II.—To a solution of 5.8 g. (0.05 mole) of ketene diethylacetal in 25 ml. of dry ether was added 0.05 mole of the appropriate aryl isocyanate. The solution was allowed to stand at room temperature for

(3) W. Dieckmann and H. Kammerer, *Ber.*, **40**, 3742 (1907).

(4) O. Hinsberg, *ibid.*, **21**, 117 (1888).

24 hr. The crystalline β,β-diethoxyacrylanilide was collected and recrystallized from a mixture of ethyl acetate and ether.

N-(β,β-Diethoxyacryl)-carbanilide.—A mixture of 23.8 g. (0.02 mole) of phenyl isocyanate and 11.6 g. (0.1 mole) of ketene diethylacetal was boiled under reflux for 8 hr. The resulting solution was concentrated under reduced pressure on the steam-bath. The residue was cooled and a small amount of solid crystallized which was recrystallized from ethyl acetate; yield 2 g. (4.5%), m.p. 148–149°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.66; H, 6.16; N, 7.96.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

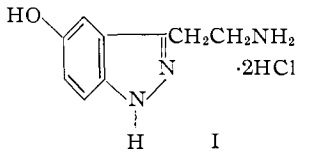
Substituted β-Aminoethylindazoles

BY C. AINSWORTH

RECEIVED SEPTEMBER 27, 1957

The synthesis of derivatives of 3β-aminoethyl-5-hydroxyindazole in which the side chain nitrogen is primary, secondary and tertiary is described, together with the preparation of the two isomeric N-substituted β-aminoethylindazoles. Some preliminary pharmacological findings on these compounds are included.

In a previous publication[1] it was reported that the indazole analog of serotonin, compound I, showed pronounced physiological activity paralleling the actions of serotonin. Included in the

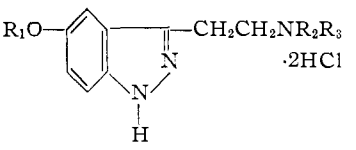


I

present communication is a description of the synthesis of a few selected derivatives of I. Five such compounds together with some preliminary pharmacological observations are listed in Table I.

TABLE I

SUBSTITUTED INDAZOLES,



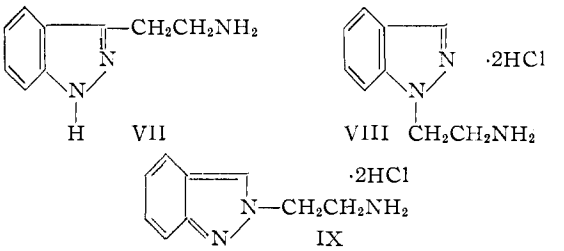
Compound	R_1	R_2	R_3	Pharmacological effects: Smooth muscle[b]		Blood pressure[d]	Ratio[e]
I	H	H	H	0.5γ	S[c]	0.5	1/10
II	H	CH_3	CH_3	2γ	S	0.1	1/2
III	H	H	$CH(CH_3)_2$	5γ	B	1.0	1/20
IV	R[a]	H	H	2γ	B	5.0	1/100
V	R[a]	CH_3	CH_3	2γ	B	1.2	1/25
VI	R[a]	H	$CH(CH_3)_2$	2γ	B	10.0	1/200

[a] R = benzyl. [b] Isolated rat uterus response, S = stimulation, B = block of serotonin stimulation. Values in column are concentration mg./l. Serotonin (5-hydroxytryptamine creatinine sulfate) is active at 0.2–0.4 γ. [c] The stimulating action of I on isolated rat uterus is blocked by a 1:20,000,000 dilution of lysergic acid diethylamide rather than the tenfold value reported in Ref. 1. [d] Concentration mg./kg. i.v. required to cause depressor effect in chloralose anesthetized cat. [e] Ratio of blood pressure effect compared with serotonin.

Compound IV, reported previously,[1] served as the starting material for the preparation of compounds III and VI. Ethyl 5-benzyloxy-3-indazole acetate[1] was converted to the corresponding dimethylamide, and this was reduced with lithium aluminum hydride to give compound V. The amine V was prepared also by reducing the ester to the corresponding alcohol that was converted with thionyl chloride to the β-chloroethyl compound. The latter intermediate upon reaction with dimethylamine gave compound V. Hydrogenolysis of compound V produced II.

5-Hydroxy-3-indazoleacetic acid, which would be an expected metabolite of compound I, was prepared by the hydrogenolysis of 5-benzyloxy-3-indazoleacetic acid.[1]

As an extension of our previous studies[2] on the indazole analog of tryptamine, compound VII, which was found to behave pharmacologically like tryptamine, it seemed of interest to prepare the two isomeric N-substituted β-aminoethylindazoles VIII and IX.



Indazole was alkylated with acrylonitrile at the 1-position as described by Rousseau and Lindwall.[3] The nitrile was hydrolyzed to the acid,[3] and this was converted directly with urea[4] to 1β-carbamylethylindazole. The amide yielded compound VIII when subjected to the Hofmann hypohalite reaction.

Surprisingly, when indazole was alkylated with acrylamide the 2-isomer was the predominant product together with about 15% of the 1-compound. Ultraviolet measurements readily distinguished the 1- and 2-substituted indazoles.[3] Treatment of 2β-carbamylethylindazole with sodium hypochlorite yielded compound IX. Compound IX was prepared also by the following scheme, RH → $RCH_2CO_2C_2H_5$ → RCH_2CONH_2 → RCH_2CN → IX, where the radical R is 2-indazole. The procedure of von Auwers[5] was followed to obtain ethyl 2-indazoleacetate which was con-

(1) C. Ainsworth, THIS JOURNAL, **79**, 5245 (1957).

(2) C. Ainsworth, *ibid.*, **79**, 5242 (1957).

(3) V. Rousseau and H. G. Lindwall, *ibid.*, **72**, 3047 (1950).

(4) E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, **29**, 1438 (1946).

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