

# INDOLE DERIVATIVES

## CVIII.\* ISOCYANATES OF THE INDOLE SERIES

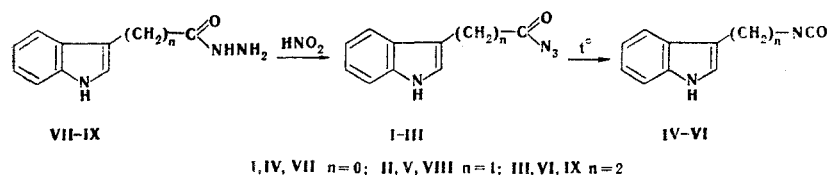
### AND SOME SYNTHESSES BASED ON THEM

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Curtius rearrangement of azides of 3-indolylalkanoic acids gave 3-indolyl isocyanates, which were converted to ureas by the action of ammonia and amines. Urethanes were obtained by alcoholysis of 3-indolyl isocyanate, and 1-(3-indolyl)-2-azetidinone was obtained by reaction with diazomethane. Hydrolysis of 3-indolyl isocyanate and hydrogenolysis of its benzylurethane gave 3-aminoindole hydrochloride, which was characterized by synthesis of the monoacetyl derivative.

3-Indolyl isocyanates (IV-VI) were obtained by Curtius rearrangement of azides of 3-indolylalkanoic acids (I-III).



The rearrangement of azides I-III was previously used only for the preparation of derivatives of isocyanates IV-VI - urethane [2-, N, N-dimethyl-3-indolylacetamide [3], and tryptamines [4, 5]. Isocyanates were not obtained in individual form, apparently because of the difficulty involved in isolation of V and VI from solution.

Manske and Robinson [6], who did not isolate isocyanate VI after heating azide III in benzene, obtained tetrahydrocarboline by bubbling hydrogen chloride into the reaction mixture.

We obtained isocyanates IV-VI in 84-95% yields by heating azides I-III in benzene for 2-5 h, and V and VI were isolated by vacuum evaporation at no higher than 15°C. When the benzene was evaporated at higher temperatures, instead of isocyanates V and VI we obtained substances that did not have individual melting points.

The absorption bands of the  $-\text{N}=\text{C}=\text{O}$  group in the IR spectra of IV-VI lie at 2265-2300  $\text{cm}^{-1}$  [7], and the absorption band of the indole NH bond lies at 3400-3450  $\text{cm}^{-1}$ . The absence in the PMR spectrum [in  $(\text{CD}_3)_2\text{S}=\text{O} + \text{CCl}_4$  (1:2)] of indole 3-H signals at 6.4 ppm [8] and the presence of a 2-H doublet at 7.5 ppm, which is converted to a singlet with the same chemical shift after  $\text{CD}_3\text{OD}$  is added to the solvent, confirms the 3-indolyl-substituted structure of isocyanate IV.

The maximum peak in the mass spectrum of IV is the molecular ion peak ( $\text{M}^+$ ) with  $m/e$  158, the subsequent fragmentation of which is characterized by the following fragment ions: 158, 157, 130, 129,

\*See [1] for communication CVII.

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TABLE 1. Azides I-III and X

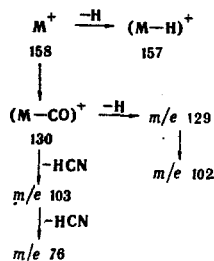
Com- pound	mp, °C	IR spectra, cm <sup>-1</sup>			Yield, %
		C=O	N <sub>3</sub>	NH <sub>indole</sub>	
I	142-144*	1680	2160	3250*	96
II	—	1720 †	2145 †	3490 †	—
III	82-83 ‡	1705	2160	3440	85
X	109-110	1680, 1760	2165	—	96

\*According to [2], this compound has mp 144° and indole NH absorption at 3250 cm<sup>-1</sup>.

†In CCl<sub>4</sub>.

‡According to [6], this compound has mp 83°.

128, 117, 116, 115, 103, 102, 90 and 89.

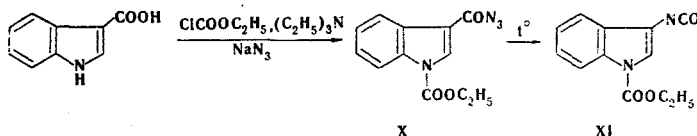


The maximum peak in this mass spectra of V and VI is the peak of a fragment ion with mass 130. The molecular ions of V and VI (with mass 172 and 186, respectively) are the second largest peaks in the spectra. The fragmentation is characterized by the following ion peaks: V 172, 130, 129, 128, 117, 116, 115, 103, 102, 90, and 89, VI 186, 130, 129, 128, 117, 116, 115, 103, 102, 90, and 89.

Azides I-III were obtained from the hydrazides of indole-3-carboxylic acid (VII), 3-indolylacetic acid (VIII), and 3-indolylpropionic acid (IX). Azide I is stable at room temperature. Azide II can be stored without decomposition only in ether or benzene solution at 0°. In the absence of a solvent, azide III undergoes slow decomposition at room temperature.

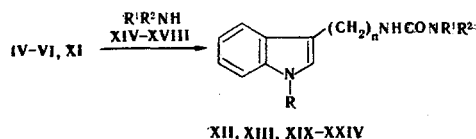
The absorption band of an N<sub>3</sub> group lies at 2145-2160 cm<sup>-1</sup> in the IR spectra of azides I-III.

In order to simplify the synthesis of derivatives of the isocyanates, we obtained the azide of N-carbethoxyindole-3-carboxylic acid (X) directly from indole-3-carboxylic acid through its mixed anhydride with ethyl chlorocarbonate and sodium azide. We were unable to obtain the N-unsubstituted azide by this method.



Like N-unsubstituted azides I-III, azide X is rearranged to isocyanate XI, which readily forms the N-carbethoxyurea (XII) and N-unsubstituted urea XIII by subsequent alkaline hydrolysis of the latter.

Ureas XII, XIII and XIX-XXVI were obtained from isocyanates IV-VI and XI and a number of aliphatic (XIV-XVI) and aromatic (XVII-XVIII) amines.



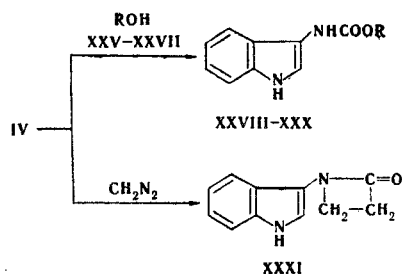
XIV, XII n=0, R=COOC<sub>2</sub>H<sub>5</sub>, R<sup>1</sup>=R<sup>2</sup>=CH<sub>3</sub>; XIV, XIII n=0, R=H, R<sup>1</sup>=R<sub>2</sub>=CH<sub>3</sub>; XV, XIV n=0, R=R<sup>1</sup>=R<sup>2</sup>=H; XVI, XX n=0, R=H, R<sup>1</sup>=R<sup>2</sup>=C<sub>18</sub>H<sub>37</sub>; XVII, XXI n=0, R=R<sup>1</sup>=H, R<sup>2</sup>=C<sub>6</sub>H<sub>5</sub>; XVII, XXII n=1, R=R<sup>1</sup>=H, R<sup>2</sup>=C<sub>6</sub>H<sub>5</sub>; XVII, XXIII n=2, R=R<sup>1</sup>=H, R<sup>2</sup>=C<sub>6</sub>H<sub>5</sub>; XVIII, XXIV n=0, R=R<sup>1</sup>=H, R<sup>2</sup>=3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

Alcoholysis of isocyanate IV with alcohols XXV-XXVII gives urethanes XXVIII-XXX:

TABLE 2. Isocyanates IV-VI and XI

Compound	mp, °C	IR spectra, cm <sup>-1</sup>			Yield, %
		C=O	N=C=O	NH <sub>indole</sub>	
IV	52-53	—	2300	3400	95
V	70-72	—	2265	3420	84*
VI	76-78	—	2280	3450	84
XI	44-45	1750	2270, 2290	—	88

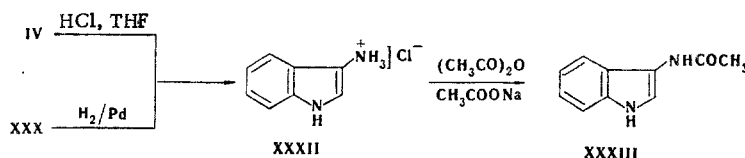
Based on hydrazide VIII.



The absorption band of carbonyl groups lie at 1680-1700 cm<sup>-1</sup> in the IR spectra of urethanes XXVIII-XXX, the NH band is found at 3270-3300 cm<sup>-1</sup>, and the indole NH band lies at 3380-3400 cm<sup>-1</sup>.

As in the case of phenyl isocyanate [9], isocyanate IV is converted to a lactam (XXXI) under the influence of an ether solution of diazomethane, but the yield is lower (~5%). The absorption band of a carbonyl group lies at 1730 cm<sup>-1</sup> in the IR spectrum of lactam XXXI in CHCl<sub>3</sub> and this is in agreement with the literature data for β-lactams [10]. The maximum peak in the mass spectrum of XXXI is the molecular ion peak with mass 186. The PMR spectrum contains signals of two CH<sub>2</sub> groups as triplets at 3.0 and 3.6 ppm.

Hydrolysis of isocyanate IV with hydrochloric acid in tetrahydrofuran (THF) gives 3-aminoindole hydrochloride (XXXII).




In contrast to the other amines of the indole series, the literature does not contain information regarding the preparation of this amine except for a paper by Madelung [11], who obtained the amine by reduction of the sodium salt of isonitrosoindole and identified it as the hydrochloride and acetyl derivative from the results of elementary analysis. The physical constants that we obtained for amide XXXIII are in agreement with those obtained by Madelung.

Hydrochloride XXXII was also obtained by hydrogenolysis of urethane XXX over Pd/C. We were unable to isolate and identify the amine in the form of the free base because of its instability.

The NH<sub>3</sub> deformation vibrations in the IR spectrum of hydrochloride XXXII lie at 1620 cm<sup>-1</sup>, the NH<sub>3</sub> stretching vibrations are found at 2640 cm<sup>-1</sup>, and the indole NH absorption lies at 3350 cm<sup>-1</sup>. The PMR spectrum does not contain an indole 3-H signal at 6.4 ppm but does contain an 2-H signal as a doublet at 7.5 ppm.

Ureas XIII, XX, and XXIV were tested as growth stimulators on a suspension culture of tobacco tissue. According to the results obtained by K. Z. Gamburg (Institute of the Physiology and Biochemistry of Plants, Siberian Branch, Academy of Sciences of the USSR), the tested substances are moderately active in retarding the growth of the tissue and do not display auxinic properties. According to the results obtained by the division of chemotherapy of the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute (under the supervision of Associate Member of the Academy of Medical Sciences of the USSR G. N. Pershin), XIII does not inhibit the growth of tuberculosis bacilli (H-37 RV strain) and does not have antibacterial activity.

TABLE 3. 3-Indolylureas XII, XIII, and XIX-XXIV

Compound	mp, °C	Empirical formula	N, %		IR spectra, cm <sup>-1</sup>			Yield, %
			found	calc.		NH	NH <sub>2</sub> indole	
XII	160-161	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	15.1	15.3	1650, 1740	3350	—	83
XIII	220-221	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O	20.9	20.7	1640	3230	3360	81
XIX	235-236	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> O	24.2	24.0	1640	3370, 3260	3420	85
XX	85-86	C <sub>45</sub> H <sub>81</sub> N <sub>3</sub> O	6.0	6.2	1640	3220	3420	80
XXI	225-226	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O	17.0	16.7	1645	3330	3400	89
XXII	195-196	C <sub>16</sub> H <sub>19</sub> N <sub>3</sub> O	15.8	15.5	1640	3320, 3400	3420	96
XXIII	180-181	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O	15.1	15.0	1650	3320, 3350	3400	88
XXIV	215-216	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> OCl <sub>2</sub>	13.0	13.1	1640	3300	3400	95

\*Compounds XII, XIII, and XIX-XXIV were purified by recrystallization from aqueous alcohol.

Tests showed that XXXII in doses of 0.4 mg/kg does not have radiation-protection activity under conditions of strong  $\delta$  irradiation.

#### EXPERIMENTAL METHOD

The course of the reactions and the purity of the products obtained were monitored by thin-layer chromatography (TLG). The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with JNM-4H-100 and JNM MH-100 spectrometers with tetramethylsilane as the internal standard ( $\delta$  scale). The mass spectra were recorded with an MKh-1303 spectrometer at an ionization chamber temperature of 110° and an ionizing voltage of 50 eV.

The melting points, results of elementary analysis, IR spectra, and yields of reaction products are presented in Tables 1-4.

Indole-3-carboxylic Acid Azide (I, Table 1). A 0.8-g (5.0 mmole) sample of hydrazide VII [12] was dissolved in 40 ml of 50% acetic acid, solution was cooled to 0-5°, and 0.4 g (5.0 mmole) of NaNO<sub>2</sub> in 1 ml of water was added with vigorous stirring. The resulting precipitate was removed rapidly by filtration, washed with water, and vacuum-dried. Compound III (Table 1) was similarly obtained.

3-Indolylacetic Acid Azide (II, Table 1). Benzene (50 ml) and 0.7 g (10 mmole) of NaNO<sub>2</sub> in the minimum amount of water were added to a solution of 1.9 g (10 mmole) of hydrazide VIII [12] in 50 ml of water, after which the mixture was cooled to 5°, and 1 ml of concentrated HCl was added with vigorous stirring. The benzene layer was separated, and the aqueous layer was extracted several times with cold benzene. The combined benzene extracts were washed with water and dried with MgSO<sub>4</sub>. The benzene solution was filtered and used for the preparation of V.

N-Carboethoxyindole-3-carboxylic Acid Azide (X, Table 1). A) A solution of 1.6 g (10 mmole) of indole-3-carboxylic acid in 30 ml of acetone was cooled to -5°, and 2.8 ml (20 mmole) of triethylamine and 1.9 ml (20 mmole) of ethyl chloroformate were added to it successively. The mixture was then stirred at 0° for 30 min, a solution of 0.8 g (12 mmole) of sodium azide in 6 ml of water was added to the resulting mixed anhydride, and the mixture was stirred for another hour. The precipitate was removed by filtration, washed with water, and vacuum-dried.

B) The synthesis was carried out as in method A with equimolar amounts of indole-3-carboxylic acid and ethyl chloroformate to give 0.8 g (34%) of X.

3-Indolyl Isocyanate (IV, Table 2). A solution of 0.6 g (3.2 mmole) of azide I in 30 ml of absolute benzene was heated on a water bath for 5 h, after which the benzene was vacuum-evaporated at 40°. The residual oil began to crystallize on standing. PMR spectrum [in (CD<sub>3</sub>)<sub>2</sub>S = O + CCl<sub>4</sub> (1:2)]: 8.2 ppm (s, \*NH), 6.9-7.7 ppm (m, aromatic protons), and 7.5 ppm (d, 2-H). Compounds V, VI, and XI (Table 2) were similarly obtained, except that the benzene was evaporated at no higher than 15° in the case of V and VI.

Evaporation of the benzene at 40-50° gave a solid with mp 70-100°, and evaporation of the benzene on a boiling-water bath gave a product with mp 150° (dec., in the case of VI).

N,N-Dimethyl-N'-3-indolylurea (XIII, Table 3). Dimethylamine was passed into a solution of 0.3 g (2.0 mmole) of isocyanate IV in 20 ml of absolute benzene for 30 min, after which the precipitate was removed by filtration and washed with ether. Compounds XII and XIX (Table 3) were similarly obtained.

TABLE 4. 3-Indolylcarbamic Acid Esters (XXVIII-XXX)

Com- pound	mp, °C	Empirical formula	Found, %			Calc., %			IR spectra, cm <sup>-1</sup>			Yield, %
			C	H	N	C	H	N	C=O	NH	NH indole	
XXVIII	96-98 Ethanol- petroleum ether	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	64,6	6,1	14,2	64,7	5,9	13,7	1690	3300	3390	91
XXIX	135-136 Benzene-pet- roleum ether	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	66,5	6,8	12,6	66,0	6,5	12,8	1700	3290	3380	80
XXX	163-164* Ethanol-pet- roleum ether	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	—	—	10,5	72,2	5,3	10,5	1680	3270	3400	79.5

\*According to [2], this compound has mp 163-164°

N,N-Dioctadecyl-N'-indolylurea (XX, Table 3). A solution of 0.3 g (2.0 mmole) of isocyanate IV and 1 g (2.0 mmole) of dioctadecylamine in benzene was refluxed for 4 h, after which the solvent was evaporated, and the residue was washed with ether and filtered. Compound XXIV (Table 3) was similarly obtained.

N-Phenyl-N'-3-indolylurea (XXI, Table 3). This compound was obtained by mixing 0.3 g (2.0 mmole) of isocyanate IV and 1 ml of aniline. The precipitate was washed with benzene and filtered. Compounds XXII and XXIII (Table 3) were similarly obtained.

Hydrolysis of N,N-Dimethyl-N'-(N-carbethoxy-3-indolyl)urea (XXII). A total of 5 ml of 10% NaOH solution was added to a solution of 0.3 g (1.0 mmole) of XII in 10 ml of ethanol, and the mixture was allowed to stand overnight. Transparent acicular crystals with mp 209-210° (from ethanol) precipitated from the mixture. No melting point depression was observed for a mixture of this product with urea XIII. The IR spectra of the hydrolysis product and XIII were identical.

Ethyl 3-Indolylcarbamate (XXVIII, Table 4). A 0.3-g (2.0 mmole) sample of isocyanate IV was heated in 20 ml of absolute ethanol on a water bath for 2 h, after which the alcohol was evaporated. The residue was washed with petroleum ether and filtered. Compounds XXIX and XXX (Table 4) were similarly obtained.

1-(3-Indolyl)-2-azetidinone (XXXI). A solution of 30 mmole of diazomethane in ether dried over sodium was added with cooling to 0° to a cooled (from -1 to 0°) solution of 2.4 g (15 mmole) of isocyanate IV in 60 ml of absolute ether, after which the reaction mixture was allowed to stand for 48 h in the dark at -3 to 0°. The resulting yellow precipitate was removed by filtration, and the ether was evaporated. The resulting oil crystallized on trituration with a small amount of cold dry acetone. The precipitated crystals were squeezed on a porcelain plate to give 0.15 g (5.3%) of a product with mp 162-163° (acetone-octane). Found: C 71.0; H 5.4; N 14.9%; M 186 mass spectrometrically). C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O. Calculated: C 71.0; H, 5.4; N 15.1%; M 186. IR spectrum (oil): 1720 (C=O), 3260 cm<sup>-1</sup> (indole NH); (CHCl<sub>3</sub>); 1730 cm<sup>-1</sup> (C=O). PMR spectrum (in C<sub>5</sub>D<sub>5</sub>N): 8.5 ppm (s, NH), 7.1-7.6 ppm (m, aromatic protons), 7.5 ppm (d, 2-H), 3.0 (t, CH<sub>2</sub>), and 3.6 (t, CH<sub>2</sub>).

3-Aminoindole Hydrochloride (XXXII). A) A solution of 0.6 g (4 mmole) of isocyanate IV in 10 ml of THF was heated with 2 ml of HCl (sp. gr. 1.18) for 30 min, after which the solvent was evaporated, and the residue was diluted with water and extracted with ether. The water was vacuum-evaporated and the resulting precipitate was washed with water, dried in vacuo, and purified by reprecipitation (ethanol-methylene chloride) to give 0.6 g (82%) of a product with mp 180° (dec.). Found: C 56.5; H 5.8; N 16.3%. C<sub>8</sub>H<sub>9</sub>N<sub>2</sub>Cl. Calculated: C 57.0; H 5.4; N 16.6%. IR spectrum (oil): 1620 (NH<sub>2</sub>) 2640 (NH) and 3350 cm<sup>-1</sup> (indole NH) PMR spectrum [in (CD<sub>3</sub>)<sub>2</sub>S = O/CCl<sub>4</sub> (3 : 7)]: 7.1-7.7 ppm (m, aromatic protons) and 7.5 ppm (d, 2-H).

B) A 0.1-g (0.4 mmole) sample of urethane XXX was hydrogenated in 40 ml of absolute ethanol at room temperature in the presence of 30 mg of Pd/c. After the calculated amount of hydrogen had been absorbed (10 ml after 2 h) the catalyst was removed by filtration, the alcohol was evaporated, and 0.5 ml of alcohol saturated with HCl was added to give 0.03 g (15%) of XXXII with mp 180° (dec.). The IR spectra of this product and the product obtained by method a were identical.

N-Acetyl-3-aminoindole (XXXIII). A 0.2-ml (2.5 mmole) sample of acetic anhydride was added to a solution of 0.3 g (1.8 mmole) of aminoindole salt XXXII in 6 ml of water, after which a concentrated solution of sodium acetate was added with stirring until the mixture was neutral. The resulting precipitate was removed by filtration and washed with water to give 0.3 g (94%) of a product with mp 162-163° (benzene petroleum ether) (mp 162-163° [11]). IR spectrum (oil): 1630 (C = O), 3120 (NH) and 3300  $\text{cm}^{-1}$  (indole NH). PMR spectrum [in  $(\text{CD}_3)_2\text{S} = \text{O} \cdot \text{CCl}_4$  (3 : 7)]: 10.6 ppm (s, NH) 9.7 ppm (s,  $\text{NHCOCH}_3$ ), and 7.0-7.8 ppm (m, aromatic protons).

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