SYNTHESIS AND PROPERTIES OF SOME LEWIS AND BRÖNSTED ACIDS OF THE INDOLE SERIES

V. S. Belezheva, Yu. V. Erofeev,
N. S. Yares'ko, A. G. Balabushevich,
and N. N. Suvorov

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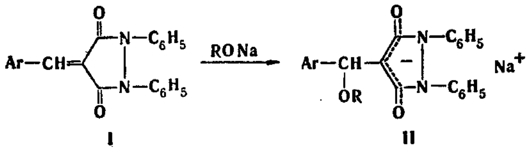
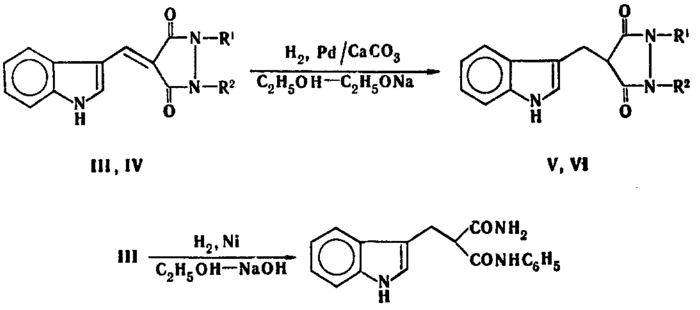
It is shown that the products of condensation of a number of cyclic CH acids and 3-formylindole are Brönsted acids, whereas Lewis acids are obtained in the case of N-substituted 3-formylindole and 2-formylindole. The possibility of the catalytic hydrogenation of Brönsted and Lewis acids in alkaline media was established. The corresponding hydrogenation products are obtained in 80-85 and 36% yields.

According to the data in [1, 2], 4-arylmethylene-1,2-diphenylpyrazolidine-3,5-diones (I) are not hydrogenated in alcoholic alkaline media, since products of addition (II) of the alkoxy group to the exocyclic double bond, which are stable electrically neutral Lewis acids, are formed under these conditions.



However, we have established that the hydrogenation of 4-(3-indolylmethylene)pyrazolidine-3,5-diones (III and IV) in alkaline media in the presence of Raney nickel or Pd/$CaCO_3$ is a convenient method for the preparation of the corresponding saturated V and VI in 80-85% yields.



VII

III, V R^1=H, R^2=C_6H_5; IV, VI R^1=R^2=C_6H_5

Compounds III and IV are not hydrogenated at all in the absence of alkali or ethoxide, evidently because of their extremely low solubilities in most organic solvents used for hydrogenation (alcohols, acetic acid, and Cellosolves).

When III and IV are dissolved in an alcohol solution of ethoxide, their bright-yellow color not only does not vanish but even becomes more intense. However, the bright color of I vanishes when it is dissolved in alcoholic ethoxide.

Additional differences are observed during an examination of the UV and PMR spectra of 4-(3-indolylmethylene)- and arylmethylenepyrazolidine-3,5-diones. A bathochromic shift of the long-wave absorption band with a simultaneous increase in the extinction is observed

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TABLE 1. Long-Wave Absorption Bands in the UV Spectra of Indole-Ring-Containing Brönsted Acids III, IV, and XI-XV (10^{-4} M solutions in ethanol)

	UV spectrum	III[a]	IV[a]	XI	XII	XIII	XIV[a]	XV
Neutral	λ_{max}	416	435	429	448	398[b], 408	400	412
	lg ε	4,520	4,641	4,526	4,727	4,211[b], 4,362	3,380	4,704
1N C_2H_5ONa	λ_{max}	452	445	442	472	454	446	420
	lg ε	4,828	4,830	3,000	4,700	4,641	4,462	4,358

[a] In 0.1% NaOH, λ_{max} (log ε): III 453 (4.590); IV 445 (4.740); XIV 446 (3.430). [b] In heptane.

in the UV spectra of III and IV in alcohol containing an equivalent amount of sodium ethoxide. The same phenomenon is characteristic for the UV spectra of β-diketones in alcohol and alcoholic alkali and is explained by dissociation of the resulting salts.

On the other hand, on passing from solutions in alkali to solutions in alcoholic alkali the long-wave absorption band in the UV spectra of 4-arylmethylenepyrazolidine-3,5-diones I vanishes because of the addition of the base to the double bond [1, 4]. In conformity with this, the PMR spectra of the products of addition of sodium ethoxide to arylmethylene Lewis acids II contain signals of protons of methylidyne and ethoxy groups [4].

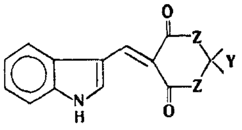
We obtained sodium salts IIIa and IVa by treatment of ethanol solutions of III and IV containing an equimolar amount of sodium ethoxide with absolute ether and established that the UV spectra of IIIa and IVa in alcohol are identical to the spectra of starting III and IV in an alcohol solution of sodium ethoxide. Starting III and IV are re-formed when solutions of salts IIIa and IVa are acidified.

Signals of aliphatic protons are absent in the PMR spectra of salts IIIa and IVa in $(CD_3)_2SO$ and CD_3OD.

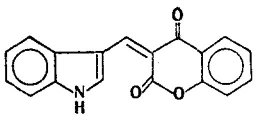
It was found that similar chemical and spectral properties (Table 1) are characteristic for the previously obtained 3-indolylmethylenebarbituric (VIII) and thiobarbituric (IX) acids [5], 3-indolylmethylene-4-hydroxycoumarin (X), -dimedone (XI), -indanedione (XII) [6], and 3-indolylmethylene-5-pyrazolones (XIII and XIV) (regardless of the presence of labile hydrogen atoms in the β-diketone or pyrazolone portion of the molecule).

We established that the product of condensation (XV) of 3-formylindole with 2,2-dimethyl-4,6-dioxo-1,3-dioxane (Meldrum's acid), which has been classified as an electrically neutral Lewis acid by Polansky and co-workers [7, 8],* has the same properties.

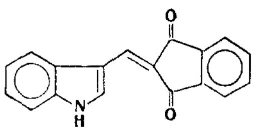
In contrast to III, IV, VIII, and IX-XV, 4-(1-methyl-3-indolylmethylene)-1,2-diphenylpyrazolidine-3,5-dione (XVI) is decolorized when it is dissolved in alcoholic sodium ethox-



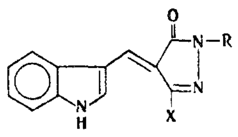
VIII, IX, XI, XV



X



XII



XIII, XIV

VIII Z=NH, Y=O; IX Z=NH, Y=S; XI Z=CH_2, Y=$(CH_3)_2$; XV Z=O, Y=$(CH_3)_2$;
XIII X=CH_3; R=C_6H_5; XIV X=NH_2; R=H

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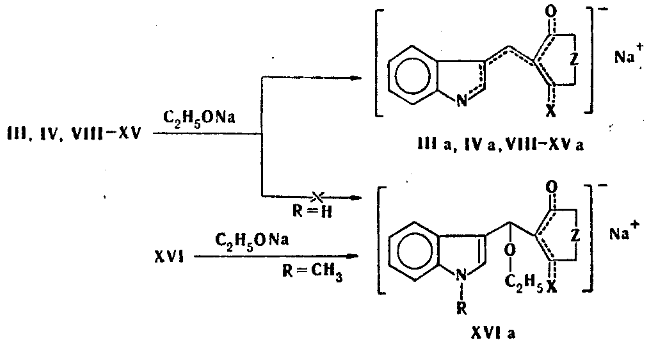
*No spectral or other data that confirm the classification of XV as an electrically neutral Lewis acid are given in [7, 8].

TABLE 2. Data from the PMR Spectra of Indole-Ring-Containing Brönsted Acids (III and IV) and Lewis Acids and Their Salts (IIIa, IVa, and XVIIa)

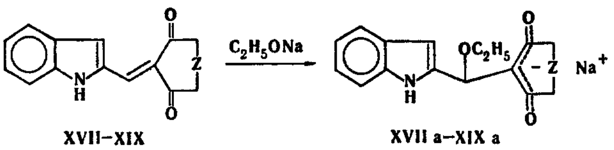
Compound	Solvent	Chemical shifts, δ, ppm (integral intensity, proton units)		
		CH=(–CH<)	NH	$OC_2H_5(OCH_3)$
III	$(CD_3)_2SO$	8,08(1)	9,63 d (2)	—
IIIa	CD_3OD	8,30(1)	9,68 (1)	—
IV	$(CD_3)_2SO$	8,55(1)	9,82 (1)	—
IVa	CD_3OD	8,68(1)	—	—
II ($Ar=C_6H_5$; $R=C_2H_5$)	CD_3OD	5,40(1)	—	1,20 t (3), 3,60 q (2)
XVIIa	CD_3OD	5,60(1)		1,91 (3)

ide. A gradual decrease in the extinction occurs in the UV spectrum of XVI as the NaOH (or sodium ethoxide) concentration is increased, after which the long-wave absorption band vanishes completely; this is characteristic for arylmethylene Lewis acids I [8].

On the basis of these data we assume that cyclic 3-indolylmethylene-β-dicarbonyl compounds III, IV, VIII-XII, and XV, which contain indole rings with an unsubstituted ring nitrogen atom, and 3-indolylmethylene-5-pyrazolones XIII and XIV are Brönsted acids and form anions that are stable because of charge delocalization in ethanol solutions of sodium ethoxide or NaOH.

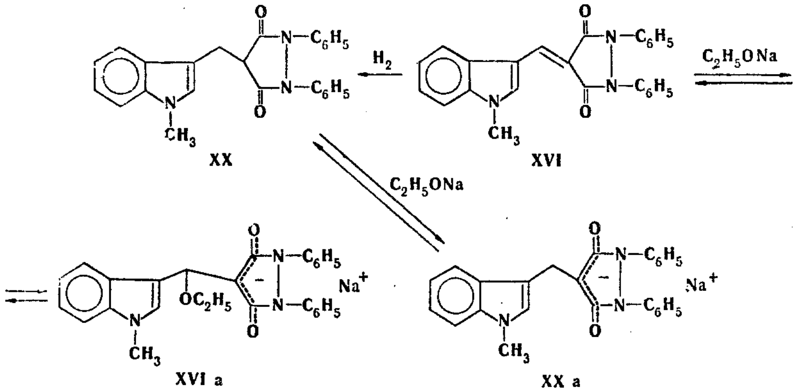


This sort of stabilization of the anion is impossible in the case of salts XVIa and 2-formylindole derivatives — 2-indolylmethylenebarbituric and thiobarbituric acids (XVII and XVIII) and 4-(2-indolylmethylene)-1,2-diphenylpyrazolidine-3,5-dione (XIX). In fact, according to the UV and PMR spectral data (Table 2), XVII-XIX display the properties of arylmethylene Lewis acids I [4].



We have established that, in contrast to arylmethylene Lewis acids I, ionization of III and IV of the type observed for Brönsted acids during hydrogenation in alkaline media does not preceed hydrogenation. Depending on the catalyst used, the hydrogenation of III and IV proceeds either with retention or opening of the pyrazolidine ring. Amide VII is formed in the hydrogenation of III over Raney nickel, whereas 3-indolylmethylpyrazolidine-3,5-dione is formed over Pd/$CaCO_3$. The yields of the products of hydrogenation of III and IV are lowered in the presence of even very small concentrations of water because of Knoevenagel retrocondensation, which competes with hydrogenation.

A C_2H_5ONa/XVI concentration ratio (∿10) at which, on the one hand, the concentration of the product of addition (XVIa) of the ethoxide ion to the exocyclic double bond of XVI is relatively low and, on the other, complete solubility of hydrogenation product XX, which has acid properties, is ensured was selected (from the UV spectral data) for the hydrogenation of XVI (in the form of a suspension). However, the yield of XX did not exceed 36%, evidently because of an increase in the C_2H_5ONa/XVI concentration ratio during the hydrogenation, as a result of which the equilibrium is shifted to favor the formation of addition product XVIa.



EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Specord spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

General Method for the Preparation of III, IV, XIII, XIV, and XVII-XIX. Saturated solutions of 3-formylindole (2-formylindole in the case of XVII-XIX) and the corresponding β-dicarbonyl compound (pyrazolone) in glacial acetic acid containing equimolar amounts of reagents were stirred and heated for 10-30 min. The crystalline precipitate that formed when the reaction mixture was cooled was removed by filtration and washed with acetic acid and ether. Data on III, IV, XIII, XIV and XVII-XIX are presented in Table 3.

In the case of XIV a saturated solution of 3-formylindole in isopropyl alcohol was mixed with a saturated aqueous solution of 3-amino-5-pyrazolone, and the mixture was refluxed with an equimolar amount of triethylamine for 1.5 h (see Table 3).

General Method for the Preparation of Sodium Salts IIIa, IVa, VIIIa-Xa, and XIVa. Compounds II, III, IV, VIII-X, or XIV were addedin small portions to absolute ethanol containing an equimolar amount of sodium ethoxide until the solid dissolved completely (where necessary, with heating to 50-60°C), and the resulting solution was diluted with absolute ether until precipitation ceased. The salt was removed by filtration, washed with absolute ether, and dried in vacuo. The vacuum-dried salt is not hygroscopic and can be stored for a long time under hermetic conditions. Data on IIIa, IVa, VIIa-Xa, and XIVa are presented in Table 4.

General Method for the Catalytic Hydrogenation of III, IV, and XIV on a Palladium Catalyst. A hydrogenation vessel equipped with a thermostatted jacket was charged with 0.1 g of 5% PdO/$CaCO_3$ and 20 ml of absolute ethanol, and the mixture was saturated with hydrogen at 50°C. A solution of sodium ethoxide obtained from 0.18 g of Na and 10 ml of absolute ethanol and 1 mmole of the finely powdered starting compound were added. During hydrogenation at 50°C, the suspension of III, IV, or XVI gradually dissolved, and the solution became colorless. The theoretical amount of hydrogen was absorbed after 2.5 h. The catalyst was removed by filtration, the filtrate was evaporated, and the residue was dissolved in water.

TABLE 3. Products of Condensation of 3- and 2-Formylindoles with Cyclic CH Acids (III, IV, XIII, XIV, and XVI-XIX)

Compound	mp, °C[a]	IR spectrum, cm^{-1}				Found, %			Empirical formula (mol. wt.)	Calc., %			Yield, %
		CH-ar C=C	C=C—C=O	CONH	indole NH	C	H	N		C	H	N	
III	320—321	1585, 1600	1705	1645, 3240	3300	71,6	4,6	13,3	$C_{18}H_{13}N_3O_2$ (303)	71,3	4,3	13,9	73
IV	266—268	1580, 1595	1675	—	3220 br	76,1	4,3	11,2	$C_{24}H_{17}N_3O_2$ (379)	76,0	4,5	11,1	84
XIII	235—237	1600, 1610	1660	—	3260	76,0	4,9	14,1	$C_{19}H_{15}N_3O$ (301)	75,8	5,0	14,0	80
XIV	256—257	1590	1650[b] br		3220—3250 3390[c]	63,7	4,8	24,7	$C_{12}H_{10}N_4O$ (226)	63,7	4,5	24,8	63
XVI	280—282[d]	1580, 1600	1680	—	—	76,3	5,0	10,7	$C_{25}H_{18}N_3O_2$ (393)	76,4	4,8	10,7	79
XVII	350[e]	1670	1750	1690, 3150	3230	61,1	3,5	16,5	$C_{13}H_9N_3O_3$ (255)	61,2	3,6	16,5	91
XVIII	317[e]	1640	1560[g]	1650, 3130	3300	—	—	15,3	$C_{13}H_9N_3O_2S$[f] (271)	—	—	15,5	97
XIX	223—225	1600—1630	1680	1650	3350	76,2	4,7	11,0	$C_{24}H_{17}N_3O_2$ (379)	76,0	4,5	11,1	97

[a] Acetic acid was used as the solvent for recrystallization. [b, c] The assignments of the amide, C=N, and NH bands were not made. [d] From methanol. [e] This compound melts with decomposition. [f] Found: S 11.5. Calculated: S 11.8%. [g] This is the C=S absorption band.

TABLE 4. Properties of Salts of Indole-Ring-Containing Brönsted Acids (IIIa, IVa, VIIIa-Xa, and XIVa)

Compound	Dec. temp. °C	Empirical formula[a]	UV spectrum, λ_{max} (log ε)
IIIa[b]	280	$C_{18}H_{12}N_3O_2Na$	418 (4,402)
IVa[b]	300	$C_{24}H_{16}N_3O_2Na$	442 (4,733)
VIIIa	300	$C_{13}H_8N_3O_3Na \cdot C_2H_5OH$[c]	445 (4,629)
IXa	265	$C_{13}H_8N_3O_2SNa \cdot C_2H_5OH$[c]	448 (4,585)
Xa	290	$C_{18}H_{10}NO_3Na \cdot C_2H_5OH$[c]	456 (4,455)
XIVa[b]	230	$C_{12}H_9N_4Na$	447 (3,416)

[a] Determined by titration. [b] IR spectrum, cm^{-1}: IIIa 1610 (C=C), 1670 (C=C—C=O); IVa 1600 s (C=C) and 1685 w (C=C—C=O); XIVa 1600 s (C=C) and 1690 s (C=C—C=O). The spectra also contain a broad low-intensity band at 3300-3400 cm^{-1}. [c] According to the results of elementary analysis.

TABLE 5. Products of the Catalytic Hydrogenation of 3-Indolylmethylenepyrazoline-3,5-diones (V-VII and XX)

Compound	mp, °C	IR spectrum, cm^{-1}		N found, %	Empirical formula (mol. wt.)	N calc., %	Yield, %
		C=O	NH				
V	323—325[a]	1690, 1750	3100, 3410	13,7	$C_{18}H_{15}N_3O_2$ (305)[b]	13,8	82
VI	236—238	1710, 1730	3340	10,9	$C_{24}H_{19}N_3O_2$ (381)[b]	11,1	80
VII	233—234[c]	1670 br	3200, 3320 3380, 3460	13,2	$C_{18}H_{19}N_3O_3$[d] (325)	12,9	85
XX	169—170[e]	1700, 1730	—	10,5	$C_{25}H_{21}N_3O_2$ (395)[b]	10,6	36

[a] From acetic acid. [b] By mass spectrometry. [c] From aqueous alcohol. [d] Monohydrate (Fischer titration). [e] From methanol.

The aqueous solution was acidified to pH 3 with 5% HCl, and the precipitate was removed by filtration, washed with water until the wash waters were neutral, and crystallized from ethanol. Data on V, VI, and XX are presented in Table 5.

3-Indolylmethylmalonic Acid N-Phenylamide (VII). A 1.5-g sample of Raney nickel was added to a solution of 1.81 g (0.06 mole) of III in 300 ml of 0.05% alcohol solution of NaOH, and the mixture was hydrogenated until it became completely colorless (3.5-4 h). The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The resulting precipitate was removed by filtration, dissolved in the minimum amount of hot ethanol, and reprecipitated by the addition of water.

Data on VII are presented in Table 5.

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INDOLES

L.* m-MONOSUBSTITUTED DIARYLHYDRAZINES IN THE FISCHER INDOLE SYNTHESIS (REACTION MECHANISM)

N. M. Przheval'skii, I. I. Grandberg,
N. A. Klyuev, and A. B. Belikov

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The cyclization of cyclohexanone m-monosubstituted α,α-diphenylhydrazones under the conditions of the Fischer reaction was studied. It is shown that in the case of both donor (R = OCH_3) and acceptor (R = Cl) substituents all three possible isomeric tetrahydrocarbazoles are formed as a result of the reaction. These data constituted an unambiguous confirmation of the concept of the occurrence of the principal step in the Fischer reaction (the step involving the formation of a carbon—carbon bond) via a sigmatropic [3,3]-rearrangement mechanism. The ratios of the tetrahydrocarbazoles in the reaction mixtures under various cyclization conditions were determined independently by PMR, IR, and mass spectrometry and gas—liquid chromatography. The structures of the products were proved by the set of spectral characteristics and by alternative synthesis.

In a previous communication we demonstrated that isomeric tetrahydrocarbazoles are formed in close ratios in the Fischer cyclization of cyclohexanone p-monosubstituted α,α-diphenylhydrazones. These data served as a confirmation of our previously expressed concept of the occurrence of a step involving the formation of a carbon—carbon bond in the Fischer reaction via a [3,3]-sigmatropic rearrangement mechanism [2]. However, one could raise an objection regarding the relatively weak effect of substituents on the relative rates of electrophilic substitution in the meta position.

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*See [1] for communication XLIX.

K. A. Timiryazev Moscow Agricultural Academy, Moscow 125008. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1349-1355, October, 1978. Original article submitted October 24, 1977.

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