of this index for LTC-1. To do so let us consider the whole (square) bond matrix and assume that each of its lines contains four symbols A (higher valences are relatively rare) separated from each other by blank spaces. Let us also consider that one figure is sufficient to write each group of blank spaces (two-place numbers of blank spaces would only be encountered in very large molecules). Thus, writing a whole matrix comprised of such lines would require 8n symbols; writing a triangular matrix would require half that number, i.e., 4n symbols. Consequently, 4 is the maximum value of 1/n for LTC-1.

In order to obtain approval for the LTC-1 code, 120 chemical compounds (as a general rule of different types) were randomly chosen from those on the biological testing list. The average length of the code notation for each sample was 34.9 symbols. Since the average number of nonhydrogen atoms in molecules of the same sample turned out to be equal to 20.7, there must be 1.7 code notation symbols for one such atom on the average.

Thus, a coding system has been developed to describe structural information in IRS with large banks of chemical compounds which occupies a position intermediate between linear and topologic codes. In its compactness the LTC-1 resembles linear coding systems, at the same time retaining the simplicity of topologic codes. The average coding time is about 5 min on the average (when specially prepared matrix blanks are available). Coding instructions are very simple and do not require special knowledge in the field of chemistry.

LITERATURE CITED

1. G. E. Vléduts and E. A. Geivandov, Automated Information Systems for Chemistry [in Russian], Moscow (1974).
2. L. A. Shevyakova, Vopr. Inform. Teor. Prakt., No. 24, 27-60 (1974).

THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF β-(3-INDOLYL)ACRYLIC ACID

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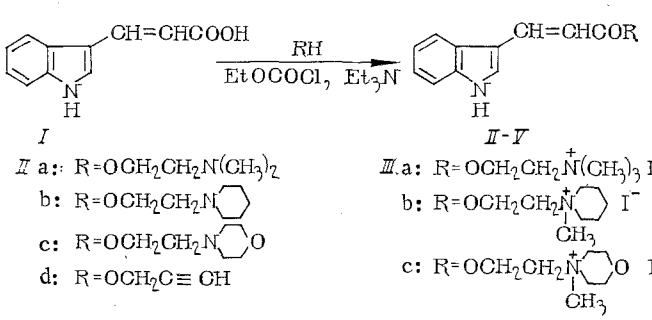
Some of the esters and amides of β-arylacrylic acid show anti-inflammatory [1-3], analgesic [3], anticonvulsive [4], antibacterial [5], and curarelike [6] properties of esters and amides of β-(3-indolyl)acrylic acid have been insufficiently studied, although there are data [8] to indicate the biological activity of β-(3-indoyl)acrylic acid and some of its esters.

In a search for biologically active compounds, we synthesized dialkylaminoesters (IIac), a propargyl ester (IId), quaternary salts of aminoesters (IIIa-c, IVa-c), and amides (Va-e) of trans-β-(3-indolyl)acrylic acid (I) according to the scheme:



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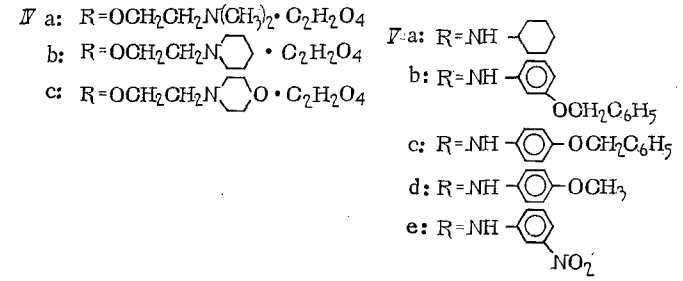

Acid I was obtained in a known fashion [9] by condensation of 1-acetyl-3-indolecarboxaldehyde with malonic acid in a mixture of pyridine and piperidine at 50°C. Modification of the reaction workup and application of activated carbon in one of the synthetic steps allows an increase in the yield of the desired compound from 45-48% to 55-58% without application of the earlier [9] procedure in which two recrystallizations of the technical product from a mixture of ether–petroleum ether and from ethyl acetate were necessary.

Esters IIa-d and amides Va-d were synthesized by the mixed anhydride method, using ethyl chloroformate in the presence of triethylamine, to give yields of 80-90% and 40-70%, respectively (cf. Tables 1 and 2). The interaction of aminoesters IIa-c with methyl iodide in absolute alcohol at room temperature gave the methiodides IIIa-c in 70-90% yield (cf. Table 1). The oxalates IVa-c were obtained in quantitative yield by treating an alcoholic solution of the corresponding aminoester IIa-c with excess saturated solution of anhydrous oxalic acid in anhydrous ether.

The structure of the compounds prepared was supported by IR, PMR, and mass-spectral data. The IR spectra of compounds IIa-d showed the absorption bands of the ester carbonyl group at 1675-1700 cm^{-1} and the C=C bond at 1610-1630 cm^{-1}. The absence of the indole N–H group absorption in aminoesters IIa-c indicates an apparent interaction between the hydrogen on the indole nitrogen and the lateral chain of the dialkylaminoethyl group. The absence of such interaction in the methiodides IIIa-c and oxalates IVa-c is indicated by bands for the indole N-H bond at 3270-3280 cm^{-1} for the methiodides and 3310 cm^{-1} for the oxalates. The IR spectrum of the propargyl ester IId also shows an absorption band for the C≡C bond at 2120 cm^{-1} and for the indole N–H bond at 3350 cm^{-1}. Absorption bands for the carbonyl group at 1645-1650 cm^{-1} (amide I) and 1570-1580 cm^{-1} (amide II) are present in the IR spectrum of amides Va-e, as well as a wide absorption band at 3200-3300 cm^{-1}, attributable to the valence-bond vibrations of the NH bonds of the amide and the indole ring.

The trans-configuration of derivatives II-V was confirmed by the presence of two doublets in the PMR spectra at 6.4 and 7.9 ppm with constant spin–spin coupling for the double bond protons; $J_{\alpha,\beta} = 16$ Hz, which agrees with the literature data [10].

The mass spectra* of compounds IId, Va-e show the molecular ion peak, the mass number of which agrees with the proposed structures [IId, 225 (100%); Va, 268 (73%); Vb, 368 (6%); Vc, 368 (26%); Vd, 292 (29%); Ve, 307 (10%)].

*The relative intensity of the ion peak compared to the maximum is indicated in the parentheses.

TABLE 1. Dialkylaminoethyl Esters of β-(3-indolyl)acrylic Acid and Their Quaternary Salts

Compound	Yield, %	Melting point, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	I		C	H	N	I
IIa	89	139–40	70,09	6,82	11,21	—	$C_{15}H_{18}N_2O_2$	69,74	7,02	10,84	—
IIb	79	102–4	72,54	7,20	9,35	—	$C_{18}H_{22}N_2O_2$	72,45	7,43	9,38	—
IIc	87,5	143–3,5	67,91	6,76	9,58	—	$C_{17}H_{20}N_2O_3$	67,98	6,71	9,32	—
IId	83	131–2	74,96	4,96	6,22	—	$C_{14}H_{11}NO_2$	74,65	4,92	6,22	—
IIIa	95	226–7	48,20	5,19	7,28	31,80	$C_{16}H_{21}IN_2O_2$	48,01	5,29	7,00	31,71
IIIb	81,7	180–1	52,37	5,95	6,62	29,16	$C_{19}H_{25}IN_2O_2$	51,82	5,72	6,36	28,82
IIIc	68	198–201	48,60	5,68	6,43	28,95	$C_{18}H_{23}IN_2O_3$	48,88	5,24	6,33	28,69
IVa	Quantitative	209–10	59,01	5,70	8,13	—	$C_{15}H_{18}N_2O_2 \times C_2H_2O_4$	58,60	5,79	8,04	—
IVb	The same	223–4	61,99	6,36	7,15	—	$C_{18}H_{22}N_2O_2 \times C_2H_2O_4$	61,84	6,23	7,21	—
IVc	» »	222–3	58,44	5,97	7,24	—	$C_{17}H_{20}N_2O_3 \times C_2H_2O_4$	58,45	5,68	7,18	—

TABLE 2. Amides of trans-β-(3-Indolyl)acrylic Acid Va-e

Compound	Yield, %	Melting point, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
Va	38,7	214—5	77,80	7,70	9,26	$C_{17}H_{20}N_2O \cdot {}^1/_2C_6H_6$	78,14	7,54	9,11
Vb	71	186—7	78,24	5,58	7,18	$C_{24}H_{20}N_2O_2$	78,25	5,47	7,60
Vc	46	193—5	78,45	5,81	7,96	$C_{24}H_{20}N_2O_2$	78,25	5,47	7,60
Vd	39,9	224—4,5	73,98	5,99	9,92	$C_{18}H_{16}N_2O_2$	73,95	5,52	9,56
Ve	49	237—9	66,30	4,55	—	$C_{17}H_{13}N_3O_3$	66,44	4,27	13,68

Note: The recrystallization solvent for Va was a mixture of alcohol—benzene (1:1); alcohol was used for the other compounds.

The intensity of the molecular ion peaks of compounds IIa-c was extremely low (less than 2%) as a result of the preponderant amine fragmentation with α- and β-cleavage relative to the nitrogen atom of the dialkylaminoethyl group, with the formation of the fragments m/e 58 (100%), m/e 71 (70%) for IIa; m/e 98 (100%), m/e 111 (60%) for IIb; and m/e 100 (100%), m/e 113 (70%) for IIc.

The general characteristics of the direction of the disintegration of compounds IId, Va-e are determined by the breakage of the ester or amide bond with formation of the fragment Ind—CH=CH—C≡O$^+$ with m/e 170. The peak intensity of the ions obtained establishes the type of ester or amide group. Compounds IId and Va characteristically form the rearrangement fragment Ind—CH=CH_2^-|$\cdot^+$ with m/e 143. The mass spectra of the structural isomers Vb and Vc differ substantially. This difference is shown both in the intensity of the molecular ion peak and the characteristic fragments, and in the mechanism of cleavage: Vb [m/e 368 (61%), 277 (13%), 251 (11%), 199 (19%), 170 (32%), 91 (100%)]; Vc [m/e 368 (26%), 199 (61%), 170 (100%), 108 (47%), 91 (39%)].

The primary course of cleavage of Vb is explained by breakage of the amide bond into the molecular ion with localization of charge on two fragments with m/e 170 and 199. The latter fragment is formed by migration of hydrogen and has the structure of a substituted aniline.

If the aniline fragment contains a p-benzyloxy group (Isomer Vc), the peak with m/e 199 is significantly more intense than for the m isomer Vb. A similar regularity of cleavage is observed for compound Vd, in which a fragment with m/e 123 (100%) is formed. The removal of the benzyl residue in the form of the charged fragment (m/e 91) is more vividly expressed in the m isomer Vb. The fragment Ph—CH_2OH^-|$\cdot^+$ with m/e 108 is observed only from isomer Vc.

The compounds obtained were studied with respect to their analgesic, hypothermal, antispasmodic, and anti-inflammatory activity.

The analgesic activity was studied in experiments on white mice by the "hot plate" method [11]. It was established that compounds IId, IVa, Va-e did not possess analgesic activity.

Hypothermal action was studied in experiments on white mice by rectal thermometry. Substances IVa-c, Vc did not possess hypothermal activity. It was demonstrated that in about 30 min after injection of compounds IId, Va,b,e, all except for IId gave essentially no rectal temperature change. After an additional 60 and 120 min, lower temperatures were noted with all of these compounds compared to a starch paste control.

The hypothermal activity of substances IId, Va,b,e almost approached that of amidopyrine, but in distinction to it, they were devoid of analgesic properties.

A study of compounds IId-Ve did not show antispasmodic activity in the maximal electroshock test.

Anti-inflammatory activity was determined by the use of agar-induced inflammation brought about by sub-plantar injection of 0.15 ml of 1% Difco agar [12] into the back of the paws of white rats. The oncometric increase in volume of the inflamed paws was taken into account

TABLE 3. Influence of Compounds IId-V* on Agar Inflammation

Compound	LD_{50}, mg/kg	Dose, mg/kg	Increase of volume of foot, % of initial value					
			1 h	P	3 h	P	5 h	P
Control			37±2,1		88±4,0		83±5,6	
IId	616	60	40±1,9	>0,05	77±3,1	>0,05	77±6,4	>0,05
IVa	317	30	34±2,0	>0,05	74±6,5	>0,05	93±8,7	>0,05
IVb	238	50	31±2,0	>0,05	63±6,1	<0,01	77±6,5	>0,05
IVc	400	80	18±3,3	<0,05	43±10,1	<0,01	48±7,8	<0,01
Va	1600	100	30±3,1	>0,05	56±2,6	<0,001	60±5,6	<0,001
		200	34±6,6	>0,05	57±9,4	<0,02	59±9,4	<0,02
Vb	1600	50	62±2,1	>0,05	98±3,9	>0,05	92±6,2	>0,05
		100	36±3,2	>0,05	52±3,8	<0,001	54±5,2	<0,001
		200	29±3,6	>0,05	44±4,7	<0,001	45±4,8	<0,001
Vc	1600	160	32±3,2	>0,05	81±9,1	>0,05	92±5,2	>0,05
Vd	1500	150	28±4,2	>0,05	92±4,5	>0,05	91±5,0	>0,05
Ve	1600	100	42±4,5	>0,05	72±4,8	<0,05	66±4,5	<0,05
		200	44±2,9	>0,05	64±5,8	<0,05	68±7,1	<0,05

*Compounds III were not tested because of high toxicity. LD_{50} for IIIa, 50 mg/kg; for IIIb, 34 mg/kg; for IIIc, 34 mg/kg.

in the dynamics (Table 3). About 0.1 LD_{50} of the substance was injected intraperitoneally in a constant volume of 1% starch suspension 1 h after introduction of the agar solution.

Among the studied compounds IVb,c, Va-e, significant anti-inflammatory action equivalent to amidopyrine was given by substances IVc, Va,b,e. They are not of interest as anti-inflammatory agents; however, the anti-inflammatory action is provided by application of a rather large absolute dose (100 and 200 mg/kg) by comparison with Indomethacin (5 mg/kg), which is most comparable in chemical structure to the compounds studied.

It is interesting to note the anti-inflammatory activity of the m-substituted anilides Vb,e whereas the p-isomers Vc, d are inactive.

EXPERIMENTAL

The IR spectra of the compounds were recorded on a Perkin–Elmer-577 spectrometer as suspensions in mineral oil. Mass spectra were measured on MX-1303 and LKB-900 instruments, supplied with a system for the direct introduction of the sample into the source. The ionization potential was 30 and 70 eV, and the temperature of injection of the substances into the source was 30-70°C. PMR spectra were recorded on an IHM-4H-100 instrument in deuterochloroform, with hexamethyldisiloxane as internal standard. The chemical purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates in acetone–chloroform (1:2).

Trans-β-(3-Indolyl)acrylic Acid [1]. A mixture of 30 g of 1-acetyl-3-indole-carboxaldehyde [13], 25.2 g of malonic acid, 150 ml of pyridine, and 3 ml of piperidine was stirred for 3 h at 80-85°C, cooled, poured onto ice, and acidified with a 10% solution of hydrochloric acid. The resulting precipitate was filtered off, washed with water to neutral, and dissolved in stages on the filter in 800 ml of 0.5 N sodium hydroxide. To the filtrate was added 2 g of activated carbon, and the mixture was stirred for 1 h at room temperature, filtered, and to the filtrate was added a little chopped ice, followed by slow acidification with a cold solution of 10% hydrochloric acid. The precipitate was filtered off, washed with cold water, and dried in vacuum to give 19.3 g (64.3%) of I, mp 184-184.5°C. Purification by boiling for 20 min in 100 ml of ether gave 17.2 g (57.4%) of I, mp 191-193°C (literature [9] mp 192-193°C).

β-Dialkylaminoethyl trans-β-(3-Indolyl)acrylates (IIa-c). To a mixture of 0.03 mole of I and 0.03 mole of triethylamine in 50 ml of dry tetrahydrofuran (THF) at −10°C was added dropwise with stirring at −10°C a solution of 0.03 mole of ethyl chloroformate in 10 ml of dry THF. The mixture was stirred for 20 min at −10°C, to which then was added dropwise at −10°C a solution of 0.039 mole of β-dialkylaminoethanol (cooled to −10°C) in 10 ml of dry THF. The reaction mixture was stirred for 2 h at 0°C and kept overnight at room temperature,

and concentrated in vacuum. The residue was triturated with hexane, the precipitate was filtered off, dried in vacuum, and recrystallized from a mixture of benzene–hexane (1:1) to give aminoesters IIa-c (cf. Table 1).

Propargyl trans-β-(3-Indolyl)acrylate (IId). Prepared analogously to esters IIa-c by conducting the reaction in dry methylene chloride (cf. Table 1).

β-Dialkylaminoethyl trans-β-(3-Indolyl)acrylate Methiodide (IIIa-c). To a solution of 0.02 mole of aminoester IIa-c in 20 ml of absolute ethanol was added 0.024 mole of methyl iodide, and the solution was kept at room temperature for 24 h. The reaction solution was diluted threefold with dry ether, the precipitate was crushed up, filtered, and washed with ether, and recrystallized from absolute alcohol to give IIIa-c (cf. Table 1).

β-Dialkylaminoethyl trans-β-(3-Indolyl)acrylate Oxalate (IVa-c). To a solution of 0.02 mole of recrystallized aminoester IIa-c in 20 ml of absolute ethanol was added an ethereal solution of excess anhydrous oxalic acid. The resulting precipitate was crushed up, filtered off, washed with dry ether, and dried in vacuum to give VIa-c in quantitative yield (cf. Table 1).

Trans-β-(3-Indolyl)acrylamides (Va-e). To a mixture of 0.01 mole of I and 0.01 mole of triethylamine in 20 ml of absolute THF at –15°C was added dropwise with stirring 0.01 mole of ethyl chloroformate, and the mixture was stirred at –10°C for 20 min. A mixture of 0.012 mole of amine hydrochloride and 0.012 mole of triethylamine in 10 ml of absolute THF was then added in portions over 10 min. The reaction mixture was stirred at 0°C for 2 h and kept at about 20°C overnight. The reaction mass was diluted with 100 ml of 5% salt solution and extracted 3 times with 50 ml of ethyl acetate. The extract was washed twice with 150 ml of water to pH 7.0, dried, concentrated in vacuum, and the residue was crystallized from ethanol or from a mixture of alcohol–benzene (1:1) to give Va-c (cf. Table 2).

LITERATURE CITED

1. M. Kuchar, B. Brunova, V. Rejholec, et al., Collect. Czech. Chem. Commun., 40, 3545-3556 (1975).
2. M. Kuchar and O. Nemecek, Ref. Zhur. Khim., 11054P (1975).
3. F. S. Alvarez, Ref. Zhur. Khim., 17070P (1977).
4. A. Balsamo, P. L. Barili, P. Grotti, et al., J. Med. Chem., 20, 48-53 (1977).
5. E. J. Nikawitz, Ref. Zhur. Khim., 9059P (1977).
6. D. A. Karkevich, in: Progress in the Creation of New Medicinal Agents [in Russian], Moscow (1973), pp. 140-146.
7. A. Balsamo, P. L. Barili, P. Grotti, et al., J. Med. Chem., 18, 842-846 (1975).
8. L. A. Sabel'eva, "Synthesis and stereochemistry of β-(3-indolyl)acrylic acid," Candidate's Dissertation, Moscow (1970).
9. J. Moffat, J. Chem. Soc., No. 3, 1442-1445 (1957).
10. C. Rappe, Acta Chem. Scand., No. 18, 818-822 (1964).
11. G. Wolfe and A. MacDonald, J. Pharmacol. Exp. Ther., 80, 300-307 (1944).
12. A. S. Zaks and M. L. Suslina, Transactions Perm Med. Inst., 123, 5-7 (1974).
13. G. I. Zhungietu, V. A. Budylin, and A. N. Kost, in: Preparative Chemistry of Indoles [in Russian], Kishinev (1975), pp. 117-118.