gesic activity in 5 of the 12 compounds develops in the course of a similar period of time. All the compounds have an activity similar to that of amidopyrine.

The data obtained show that it is advisable to carry on with a search for antispasmodic and analgesic properties among the 4-quinazolinone derivatives.

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SYNTHESIS AND HYPOCHOLESTEREMIC ACTIVITY OF AMINOACETYLENYL LINOLEATES

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Aminoacetylenyl esters of unsaturated fatty acids have been shown [4] to possess high hypolipidemic activity. It was of interest to examine the hypocholesteremic activity of aminoacetylenyl linoleates. These compounds were obtained as follows:

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOCH_2C{\equiv}CH + CH_2O + HNR_2 \longrightarrow$$
$$\longrightarrow \underset{\text{I}}{CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOCH_2C{\equiv}CCH_2NR_2}$$
$$\text{II—V}$$

II: $NR_2 = N(C_2H_5)_2$; III: $NR_2 = \overline{|NCH_2CH_2CH_2CH_2CH_2|}$; IV: $NR_2 = \overline{|NCH_2CH_2OCH_2CH_2|}$;
V: $NR_2 = N(CH_2C_6H_5)_2$.

Propargyl linoleate (I) was obtained from linoleic acid and propargyl alcohol as described in [3]. The compounds synthesized (II-V) were high-boiling liquids of a dark brown color, soluble in most organic solvents but insoluble in water. The structures of (II-V) were confirmed by their elemental analyses and their IR and PMR spectra.

EXPERIMENTAL (CHEMICAL PART)

IR spectra were obtained on a UR-20 spectrometer (East Germany) in KBr pellets, and PMR spectra on a Hitachi instrument (Japan) (60 MHz, CCl_4 solution, internal standard hexamethyldisiloxane).

4-Diethylamino-2-butynyl Linoleate (II). In a round-bottomed flask, fitted with a reflux condenser with a calcium chloride tube, were heated at 100-105°C for 7 h 0.45 g of paraformaldehyde, 1.2 ml of diethylamine, 3.15 g (0.01 mole) of (I), 0.17 g of copper acetate, and 70 ml of dioxane. When the reaction was complete, 100 ml of water was added to the mixture, which was then acidified with 10% HCl to pH 2.0-3.0, and extracted with diethyl ether. The acidic aqueous layer was basified with ammonia solution to pH 8.0-9.0, then extracted

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TABLE 1. Comparative Hypochloesteremic Activity of Aminoacetylenyl Linoleates

Compound	Total amount of cholesterol in rabbit blood plasma, mg%		Hypocholesteremic effect, %
	before treatment	after treatment	
II	470±4,1	360±4,5	23,4
III	530±5,0	400±3,2	24,5
IV	450±2,4	300±3,7	33,3
V	360±5,6	240±4,1	33,3
Arachidene	263±6,6	218±4,4	17,1

with ether. The ether extracts were dried over anhydrous potassium carbonate, filtered, and the ether evaporated. The residue was distilled in vacuo at 192-193°C (1-2 mm), giving (II), 83% yield, n_D^{20} 1.4645, d_4^{20} 0.9081. Found, %: 77.61; H 11.10; N 3.37. $C_{26}H_{45}O_2N$. Calculated, %: C 77.42; H 11.17; N 3.47. IR spectrum, ν, cm^{-1}: 2250 (—C≡C—), 1625 (—CH=CH—), 2680—2800 (N_{tert}). PMR spectrum, δ, ppm: 0.84 (CH_3—), 1.22 (—CH_2—), 2.24 (—CH_2—CO); 4.60 (—O—CH_2—); 5.35 (—CH=CH—), 2.44 [—$N(CH_2)_2$].

4-Piperidino-2-butynyl Linoleate (III). This was obtained by the method described above from 0.9 g of paraformaldehyde, 2 ml of piperidine, 6.3 g of (I), 0.34 g of copper acetate, and 100 ml of dioxane. Yield 76%, bp 197-199°C (1-2 mm Hg), n_D^{20} 1.4751, d_4^{20} 0.9105. Found, %: C 78.27; H 10.64; N 3.47. $C_{27}H_{45}NO_2$. Calculated, %: C 78.07; H 10.84; N 3.37. IR spectrum, ν, cm^{-1}: 2265 (—C≡C—), 2705—2800 (N_{tert}). PMR spectrum, δ, ppm: 2.50 [—$N(CH_2)_2$], (—CH=CH—), 4.67 (—O—CH_2—).

4-Morpholino-2-butynyl Linoleate (IV). In a flask fitted with a reflux condenser were placed 0.45 g of paraformaldehyde, 1.2 ml of morpholine, and 3.15 g of (I), and the mixture was heated for 8 h at 100-110°C in the presence of 0.17 g of copper acetate and 70 ml of dioxane. After cooling to 20°C, the mixture was acidified with 10% HCl and extracted with ether The ether was then distilled off, and the residue distilled in vacuo to give 80% of (IV), bp 203-205°C (1-2 mm Hg), n_D^{20} 1.4700, d_4^{20} 0.9057. Found, %: N 3.45. $C_{26}H_{43}NO_3$. Calculated, %: C 74.82; H 10.31; N 3.36 . IR spectrum, ν, cm^{-1}: 2720-2800 (N_{tert}), 1735 (—CO). PMR spectrum, δ, ppm: 2.44 [—$N(CH_2)_2$], 3.62 [$O(CH_2)_2$] .

4-Dibenzylamino-2-butynyl Linoleate (V). Obtained as above, from a mixture of 0.9 g of paraformaldehyde, 4.4 g of paraformaldehyde, 4.4 g of dibenzylamine, 6.30 g of (I), 0.3 g of copper acetate, and 100 ml of dioxane. Yield of (V), 84%, bp 210-212°C (1-2 mm), d_4^{20} 0.9165. %: Found, C 82.05; H 9.37; N 2.69. $C_{36}H_{49}O_2N$. Calculated, %: C 81.97; H 9.29; N 2.65 IR spectrum, ν, cm^{-1}: 2260 (—C≡C—), 1635 (—CH=CH—), 1500—1610 (C_6H_5—). PMR spectrum, δ, ppm: 2.55 [$N(CH_2)_2$], 7.35—8.10 (C_6H_5).

EXPERIMENTAL (BIOLOGICAL PART)

The hypocholesteremic activity of (II-V) was studied in rabbits of both sexes weighing 2.5-3 kg. Experimental atherosclerosis was induced by the method of N. N. Anichkov [1], by feeding cholesterol via a probe for three months in a dose of 0.3 mg per kg body weight. The test compounds were given per os as oil solutions for 20 days at a dose of 0.2 ml per kg body weight. The total serum cholesterol was measured colorimetrically by a method based on the Lieberman—Burchardt color reaction [5].

The activities of the test compounds were compared with that of arachidene [2].

The results of the tests showed (Table 1) that these novel aminoacetylenyl linoleates possess high hypocholesteremic activity, some 1.5-2 times greater than that of arachidene. The highest hypocholesteremic activity was shown by (IV) and (V).

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HETEROCYCLIC SEMICARBAZONES AND THIOSEMICARBAZONES. XLIX. ANTIINFLAMMATORY ACTIVITY OF ISATIN THIOSEMICARBAZONES AND THEIR CYCLIZATION PRODUCTS

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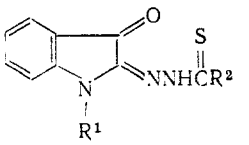
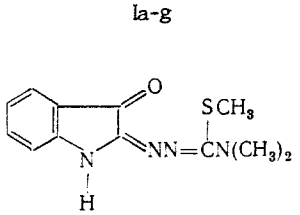
The aim of this investigation was to find active compounds in the isatin series, and to establish relationships between structure and antiinflammatory activity. The isatin thioacyl hydrazones (I-IV) have been obtained, having different radicals attached to the indole nitrogen, and also the number, structures, and positions of the hydrazone groupings at $C_{(2)}$ or $C_{(3)}$. For comparison with these compounds. some of their reaction products have been obtaine in which triazine and thiadiazine rings are formed (V-IX), together with isatin derivatives which do not contain the thiosemicarbazone side chain (X). All these compounds were insoluble in water, with the exception of (IXa, b) and (Xc, d) as their hydrochlorides.

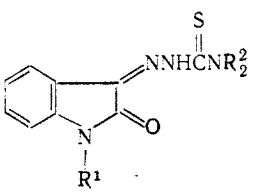


Ia-g

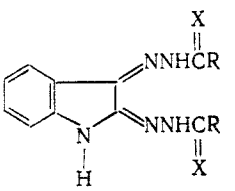
Ia-g: $R^1 = H$ (a-c); CH_3 (d-g); $R^2 = NH_2$ (a), $N(CH_3)_2$ (b,d), SCH_3 (c), NHC_6H_5 (e), $NHC_6H_4OCH_3$-p (f), $NHC_6H_4COOC_2H_5$-p (g)



II

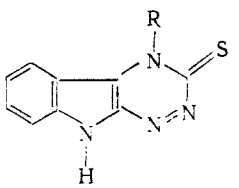


IIIa-c

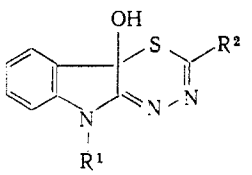


IVa,b

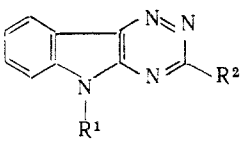
IIIa-c $R^1 = H$ (a), $CH_2COOC_2H_5$ (b), $COCH_3$ (c); $R^2 = H$ (a, b), CH_3 (c) IVa: X = S; $R = NH_2$; IVb X = O; $R = C_2H_5$



Va, b



VIa-h



VIIa-d

Va, b. R = H (a), NH_2 (b); VIa-h, VIIa-d: $R^1 = H$ (VIa,b,f,h; VIIa-d), CH_3 (VIc-e); VIa-h: $R^2 = NH_2$ (a), $N(CH_3)_2$ (b, c), NHC_6H_5 (d), $NHC_6H_4OCH_3$-p (e), C_6H_5 (f), $C_6H_4OCH_3$-p (g), C_6H_4Cl-m (h); VII(a-d) $R^2 = SCH_2CH{=}CH_2$ (a), SH (b), $SCHC_6H_5COC_6H_5$ (c), $NHNH_2$ (d)

Antiinflammatory activity was examined in three models of aseptic pathological inflammation, namely thermal burns, pulmonary adrenalin edema, and cotton wool granulemia. In the thermal burn model, activity was shown by (I), (III-VII), and (X). In the pulmonary adrenalin edema model, activity was observed in a smaller number of compounds, but the structure-activity relationships were substantially the same. In the cotton wool granulemia model, activity was shown by (Ia, b), (IIIc), (Va), (VIIa), (VIII), (IXa, b), and (Xd).

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