Table I.

Compound	Single Dose (mg./kg.)	Anti-leucopenic action (Rate of depression, %)[a]
Batyl alcohol	20(s.c.)	50
	200(p.o.)	50
Cobalt-greenpole[b]	0	60
L-Isoleucine	200[c]	55
DL-Methionine	430	70
Platonin[d]	7.5 γ	70
D. N. A.[e]	10	75
HN_2-O alone	10	70

a) Rate of depression[3] $= \frac{A-A'}{A} \times 100$

A : Initial Leucocyte number.

A' : Leucocyte number at the end of experiment.

b) Commercial product of cobalt-chlorophyllin.

c) Purity, 33% (exclusively contaminated with L-leucine).

d) Commercial product of 4,4′,4″-trimethyl-3,3′,3″-triheptyl-8-(2″-thiazolo)-2,2′-pentamethinethiazolocyanine 3,3″-diiodide.

e) Commercial product of Tokyo Kasei Co. Ltd.

oral administration in preventing the leucopenia of rat induced by HN_2-O. Concerning the other miscellaneous compounds, a slight effect was also observed in the case of L-isoleucine alone, but the rest was proved to be far less or not effective. The activities are not comparable with that of L-cysteine.

It should be noticed however that the leucopenia induced by this experimental method was very acute and serious just as experienced in clinical tumor chemotherapy and, therefore, other means of experiment might be necessary if the anti-leucopenic action of compounds against chronic or mild leucopenia is to be determined.

The author expresses his gratitude to Prof. M. Ishidate and Dr. Y. Sakurai for their constant guidance in the course of this study.

Summary

dl-Octadecyl α-glyceryl ether (batyl alcohol) was synthesized and tested for its inhibiting action on the rat leucopenia induced by administration of N-methyl-bis(2-chloroethyl)amine N-oxide.

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Takahiro Yabuuchi : Studies on Thiophene Derivatives. V.[1] Syntheses of 3-Arylpropenamides.

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Some pharmacologically interesting compounds have been found in the thiophene derivatives and, for example, 3-piperidino-1,1-di(2-thienyl)-1-butene (A) exhibits a potent

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1) This constitutes a part of series entitled "Studies on Thiophene Derivatives" by Ryuichi Kimura. Part IV : This Bulletin, 8, 103(1960).

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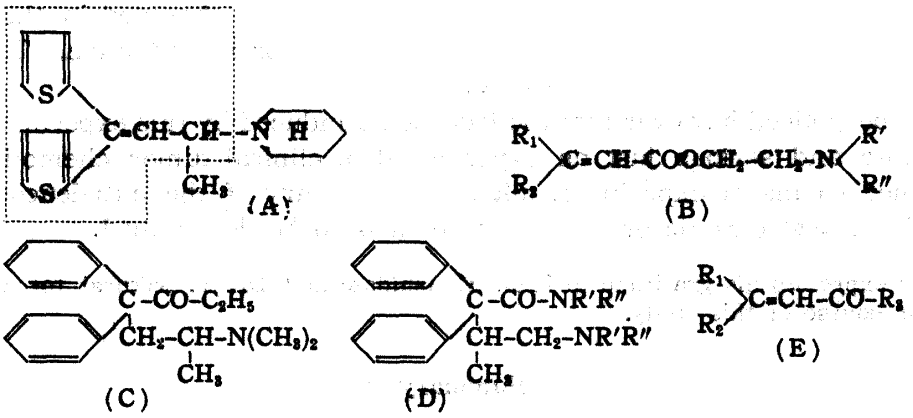
antitussive effect.[2~4] In general, the inhibitors of parasympathetic system and local anesthetics frequently have antitussive action, because the former relaxes the tension of bronchoconstrictor and the latter paralyzes sensory nerves in the vagus which is centripetal way causing a cough. Most of these agents are derivatives of carboxylic acids. Properties of some derivatives of 2-aminoethyl 3,3-diarylpropenoate (B) having a similar structure with compound (A) and a carboxyl were described in the preceding paper.[1]

6-Dimethylamino-4,4-diphenyl-3-heptanone (Methadone) (C) has not only potent analgesic actions as well as several times the antitussive action of codeine, but at the same time, it has untoward side-effects. It has been reported by Janssen[5] that some derivatives of compound (D), in which the ketone group in compound (C) has been replaced by carbonamide group, have stronger analgesic action than that of morphine without too much side-effects. Similar result between diethylaminoethyl diphenylglycolate and the corresponding amide was observed which promoted further study.

In order to observe the relationship between chemical structure and pharmacological activity, an attempt was made to synthesize the derivatives of 3-arylpropenamides (E), in which R_1 represents 2-thienyl group, R_2, 2-thienyl, phenyl, or hydrogen, and R_3, the residual group of amino.



The method of synthesis of these compounds is shown in Chart 1.

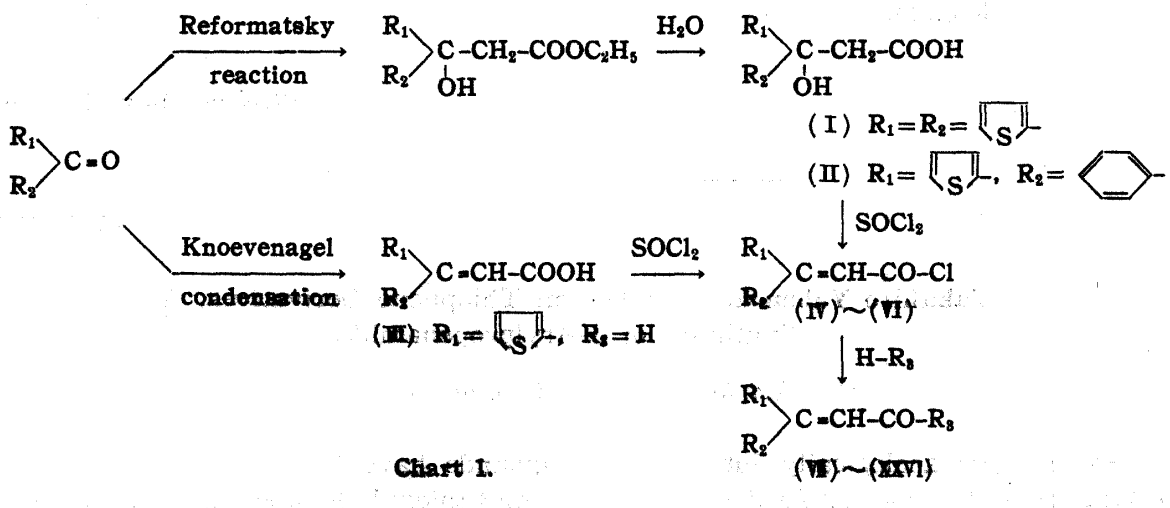


Chart 1.

2) K. Kase, *et al.*: This Bulletin, 3, 394(1955).
3) R. Kimura, T. Yabuuchi: *Ibid.*, 7, 171(1959).
4) *Idem.*: *Ibid.*, 7, 175(1959).
5) A. T. Janssen: J. Am. Chem. Soc., 78, 3862(1956).

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TABLE I. 3-Arylpropenamides $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!C=CH-CO-R_3$

Compd. No.	R_1	R_2	R_3	m.p. (°C)	Crystn. solvent	Appearance	Formula	Analyses (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
(VII)	2-Thienyl	2-Thienyl	-HN-C$_6$H$_5$	135~136	40% EtOH	White prisms	$C_{17}H_{13}ONS_2$	65.58	65.85	4.18	4.20	4.49	4.38
(VIII)	〃	〃	-HN-C$_6$H$_4$-Cl	151~152	90% EtOH	〃	$C_{17}H_{12}ONClS_2$	59.03	59.21	3.49	3.65	4.05	4.23
(IX)	〃	〃	-HN-C$_6$H$_4$-Br	167	〃	〃	$C_{17}H_{12}ONBrS_2$	52.31	52.37	3.07	2.88	3.59	3.33
(X)	〃	〃	-HN-C$_6$H$_4$-OCH_3	123~124	〃	White needles	$C_{18}H_{15}O_2NS_2$	63.32	63.47	4.43	4.67	4.10	4.29
(XI)	〃	〃	-HN-C$_6$H$_4$-OC_2H_5	142	EtOH	〃	$C_{19}H_{17}O_2NS_2$	64.19	64.47	4.82	4.65	3.97	3.87
(XII)	〃	Phenyl	-HN-C$_6$H$_5$	111.5~112.5	90% EtOH	〃	$C_{19}H_{15}ONS$	74.72	74.45	4.95	5.19	4.59	4.64
(XIII)	〃	〃	-HN-C$_6$H$_4$-Cl	178.5~179.5	EtOH	White prisms	$C_{19}H_{14}ONClS$	67.15	67.25	4.15	4.17	4.12	4.24
(XIV)	〃	〃	-HN-C$_6$H$_4$-Br	194~195	〃	〃	$C_{19}H_{14}ONBrS$	59.38	59.37	3.67	3.65	3.65	3.67
(XV)	〃	〃	-HN-C$_6$H$_4$-CH_3	133~134	90% EtOH	White needles	$C_{20}H_{17}ONS$	75.20	75.12	5.37	5.42	4.39	4.57
(XVI)	〃	〃	-HN-C$_6$H$_4$-OCH_3	148.5~149	〃	White prisms	$C_{20}H_{17}O_2NS$	71.62	71.72	5.11	5.21	4.18	4.22
(XVII)	〃	〃	-HN-C$_6$H$_4$-OC_2H_5	167~168	EtOH	White needles	$C_{21}H_{19}O_2NS$	72.18	71.93	5.48	5.39	4.01	4.28
(XVIII)	〃	〃	-HN-C$_5$H$_4$N	151~152	90% EtOH	White prisms	$C_{18}H_{14}ON_2S$	70.56	70.48	4.61	4.75	9.14	9.33
(XIX)	〃	〃	-NH-C$_6$H$_4$	112~113	ligroine+CCl_4 (1:1)	〃	$C_{18}H_{19}ONS$	72.69	72.41	6.44	6.57	4.71	4.61
(XX)	〃	H	-HN-C$_6$H$_4$-Cl	101	60% EtOH	White needles	$C_{13}H_{10}ONClS$	59.20	58.95	3.82	3.79	5.32	5.36
(XXI)	〃	〃	-HN-C$_6$H$_3$Cl$_2$	146	EtOH	〃	$C_{13}H_9ONCl_2S$	52.36	52.27	3.04	3.19	4.69	4.60
(XXII)	〃	〃	-HN-C$_6$H$_4$-Br	190~191	〃	White prisms	$C_{13}H_{10}ONBrS$	50.66	50.69	3.28	3.29	4.55	4.80
(XXIII)	〃	〃	-HN-C$_6$H$_4$-CH_3	143	60% EtOH	〃	$C_{14}H_{13}ONS$	69.11	69.23	5.39	5.48	5.76	5.48
(XXIV)	〃	〃	-HN-C$_6$H$_4$OH	168	90% EtOH	White plates	$C_{13}H_{11}O_2NS$	63.65	63.86	4.52	4.80	5.71	5.54
(XXV)	〃	〃	-HN-C$_6$H$_4$-OC_2H_5	143~144	EtOH	White needles	$C_{15}H_{15}O_2NS$	65.91	66.11	5.53	5.49	5.13	5.43
(XXVI)	〃	〃	-HN-C$_6$H$_4$-$COOC_2H_5$	187~187.5	〃	White prisms	$C_{16}H_{15}O_3NS$	63.77	63.53	5.02	4.98	4.65	4.89

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First, syntheses of 3,3-diarylpropenoyl chlorides (IV～V) were carried out from diaryl ketones as the starting material. Ethyl 3,3-di(2-thienyl)-3-hydroxypropionate and ethyl 3-phenyl-3-(2-thienyl)-3-hydroxypropionate were synthesized by the Reformatsky reaction of ethyl 2-bromoacetate and the corresponding ketones, followed by hydrolysis to 3,3-di(2-thienyl)-3-hydroxypropionic acid (I) and 3-phenyl-3-(2-thienyl)-3-hydroxypropionic acid (II), respectively. These acids (I and II) were chlorinated and dehydrated at the same time by warming with thionyl chloride in a mixture of petroleum ether and chloroform, and were converted to 3,3-di(2-thienyl)propenoyl chloride (IV) and 3-phenyl-3-(2-thienyl)propenoyl chloride (V), respectively. 3-(2-Thienyl)propenoic acid (III) was synthesized by the Knoevenagel condensation of 2-thiophenecarboxaldehyde with malonic acid. This acid (III) was chlorinated with thionyl chloride to obtain 3-(2-thienyl)propenoyl chloride (IV) in the usual way. The crude chlorides (IV～VI) prepared by the above methods were promptly dissolved in dehyd. ether and gradually added to dehyd. ether solution of various amines (except for dehyd. ethanol solution of *m*-aminophenols) and various new derivatives of 3-aryl-2-propenamides (VII～XXVI) were prepared, which are shown in Table I.

Experimental

3-(2-Thienyl)propenoic Acid (III)—A mixture of 22.4 g. (0.2 mole) of 2-thiophenecarboxaldehyde, 50 g. of malonic acid, 100 cc. of pyridine, and 1.7 cc. of piperidine was heated at about 95° in a water bath for 2 hr. and the solution was boiled additionally for 5 min. After cool, the mixture was poured into water and acidified with 20% HCl. The precipitate was collected by suction and recrystallized from EtOH, m.p. 144～145°. Yield, 26.5 g.

3,3-Di(2-thienyl)propenoyl Chloride (IV)—A mixture of 20.7 g. (0.05 mole) of 3,3-di(2-thienyl)-3-hydroxypropionic acid,[1] 80 cc. of petr. ether, 80 cc. of $CHCl_3$, and 100 cc. of $SOCl_2$ was warmed at 55～60° in a water bath for 1 hr., and the solvent and excess $SOCl_2$ were distilled off at 60° under a reduced pressure. The residue obtained was promptly dissolved into ether and used in the next reactions.

3-Phenyl-3-(2-thienyl)propenoyl Chloride (V)—This was prepared from 3-phenyl-3-(2-thienyl)-3-hydroxypropionic acid[1] by warming with $SOCl_2$ in a mixture of petr. ether and $CHCl_3$ at 60～65° for 1 hr., in a similar manner as for (III).

3-(2-Thienyl)propenoyl Chloride (VI)—This was obtained by heating 3-(2-thienyl)propenoic acid with $SOCl_2$ at 65～70° for 1.5 hr., following the same procedure as for (III).

3-Arylpropenamides (VII～XXVI)—A dehyd. ether solution (dehyd. EtOH solution used for *m*-aminophenol) of 2 moles of the amine was added slowly with shaking into a dehyd. ether solution of 1 mole of 3-aryl-2-propenoyl chloride. After allowing the reaction mixture to stand at room temperature for over 5 hr., the crystallized product was collected and washed well with cold water. The crude material was recrystallized from appropriate solvents (see Table I). The yield of pure product was usually 60～75%.

The author is deeply grateful to Prof. Dr. T. Takahashi, Pharmaceutical Institute, University of Kyoto, for his kind encouragement and to Prof. Dr. H. Saikachi, University of Kyushu, for his helpful guidance and advice throughout this work. For microanalyses, the author is indebted to the Analysis Room of the Pharmaceutical Institute, University of Kyoto.

Summary

As some thiophene derivatives have interesting pharmacological actions, some new 3-arylpropenamides having thiophene ring were synthesized. The reactions of amines and 3-arylpropenoyl chloride, which were synthesized from 3,3-di(2-thienyl)-3-hydroxypropionic acid, 3-phenyl-3-(2-thienyl)-3-hydroxypropionic acid, or 3-(2-thienyl)propenoic acid with thionyl chloride, gave the corresponding derivatives of propenamides.

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