erythro- AND *threo*-ISOMERS OF 2,3,4-SUBSTITUTED BUTANOIC ACIDS

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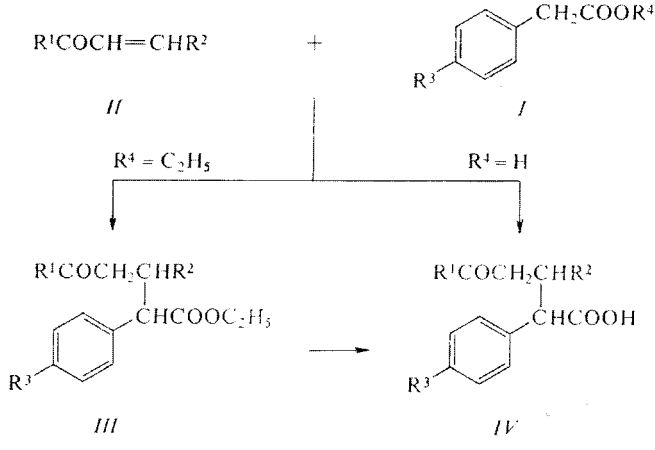
Addition of phenylacetic acid derivatives to the double bond of α,β-unsaturated ketones led to the new 2,3,4-substituted 4-benzoyl and 4-pivaloylbutanoic acids. Their configuration was examined and they were tested for antiinflammatory activity.

The work was stimulated by the findings of biological activity of derivatives of arylacetic and 2-arylpropionic acids (2-(4-isobutylphenyl)acetic acid, ibufenac[1], 2-(3-benzoylphenyl)propionic acid, ketoprofen[2]) and of the favourable effect of the oxo group in the molecules of some 1,2-diphenyl-3,5-dioxopyrazolidines. The useful properties of ketophenylbutazone[3] as compared with phenylbutazone[4] are well known.

The compounds described here (Table I) are substituted 4-benzoyl- and 4-pivaloylbutanoic acids that were prepared by addition of phenylacetic acid derivatives *I* to the double bond of α,β-unsaturated ketones *II*. The starting material was either ethyl phenylacetate or phenylacetic acid. In the first case the reaction was done in ether using sodium ethylate as catalyst (method *A*; see Table II), in the second case it was done in liquid ammonia and sodium amide (method *B*; see Table III). Both methods are described the first for the preparation of esters *III-1*, *III-3* and *III-4* (refs[5,6]), the second for acid *IV-1* (ref.[7,8]). The procedure known from the literature for the preparation of 3-(4-methoxyphenyl)- and 3-(4-chlorophenyl)-2-phenyl-4--benzoylbutanoic acids (*IV-10* and *IV-30*) based on the reaction of sodium lithium phenylacetate with unsaturated ketones[9] was not used here.

Addition of substituted ethyl phenylacetate *I* to α,β-unsaturated ketones *II* in the presence of sodium ethylate (method *A*) was carried out in a modification of an earlier procedure[10] and the esters thus prepared (Table II), with the exception of the pyrrole derivative *IV-29* were hydrolyzed with a mixture of acetic and hydrobromic acids. This hydrolysis was found to be preferable in comparison with that described for acids *IV-1*–*IV-4* (ref.[5,6]). Its drawback lies in the demethylation of the methoxy derivatives and formation of hydrobromides with mostly compounds bearing a 4--methoxy- or a 4-nitrophenyl group at the α-carbon and a 4-dimethylaminophenyl- or 3-pyridyl group at the β-carbon. Hydrolysis of *III-17* and *III-24* led exclusively to hydrobromides of the desired acids. In the case of *IV-20*, the base and the hydrobromide were obtained in practically identical amounts. On the other hand, acid

IV-23, containing a 4-methoxyphenyl group at the α-carbon and a 4-dimethylaminophenyl group at the β-carbon was isolated as base only. No formation of hydrobromide was observed with *IV-5* where the α-carbon is substituted with a phenyl and the β-carbon with a 4-dimethylaminophenyl group. Demethylation was demonstrated with *IV-22* and *IV-24*; in the case of *IV-5* where no hydrobromide was formed, the methoxy group was preserved.



The configuration of the compounds prepared was demonstrated by IR spectra and the degree of purity was checked by the DSC method. The standards used were the *threo*-form of *IV-1*, prepared by a known procedure[8], and the *erythro*-form of *IV-8*. In the region of 1 100 – 1 300 cm^{-1} (deformation bands —CH—) the model *erythro* and *threo* compounds differ markedly both when using the KBr pellet technique and solution of dimethyl sulfoxide. These differences were observed over the entire group of compounds studied and they could be used for defining their configuration.

In agreement with the literature, addition of ethyl phenylacetate and ethyl 4-nitrophenylacetate under catalysis of sodium ethylate to 1,3-diphenylpropen-3-one and 2,2-dimethyl-5-phenyl-4-penten-3-one yielded the *erythro*-forms of the corresponding esters. The *erythro*-form was also the sole or the principal reaction product of most of the new esters prepared in the same way. Only with esters *III-9*, *III-19*, *III-22* and *III-23* was it possible to detect the *threo*-isomer as the prevalent form. Hydrolysis of esters *III-1*, *III-3* and *III-4* led to the corresponding acids in the *erythro*-form, in agreement with the literature. The same result, *i.e.* no change of configuration, was found for the hydrolysis of most of the new derivatives. Only in a few cases was the hydrolysis accompanied by isomerization when *erythro*-esters yielded *threo*-acids or a mixture with prevalent *threo*-form (*IV-7*, *IV-12*, *IV-13*, *IV-24*, *IV-26* and *IV-27*) or *vice versa* (*IV-9* and *IV-19*).

TABLE I
Structure of *III* and *IV*

III *IV*	R^1	R^2	R^3
1	C_6H_5	C_6H_5	H
2	$(CH_3)_3C$	C_6H_5	H
3	C_6H_5	C_6H_5	NO_2
4	$(CH_3)_3C$	C_6H_5	NO_2
5	C_6H_5	4-$(CH_3)_2NC_6H_4$	H
6	C_6H_5	C_6H_5	$(CH_3)_2CHCH_2$
7	C_6H_5	C_6H_5	$(C_2H_5)CH(CH_3)$
8	C_6H_5	4-$(CH_3)_2CHC_6H_4$	H
9	C_6H_5	C_6H_5	$(CH_3)_2CH$
10	C_6H_5	4-ClC_6H_4	H
11	C_6H_5	C_6H_5	Cl
12	$(CH_3)_3C$	C_6H_5	$(C_2H_5)CH(CH_3)$
13	$(CH_3)_3C$	C_6H_5	$(CH_3)_2CHCH_2$
14	$(CH_3)_3C$	4-$(CH_3)_2CHC_6H_4$	H
15	C_6H_5	4-$(CH_3)_2CHC_6H_4$	NO_2
16	C_6H_5	4-$(CH_3)_2CHC_6H_4$	$(C_2H_5)CH(CH_3)$
17	C_6H_5	4-$(CH_3)_2NC_6H_4$	NO_2
18	C_6H_5	4-$(NO_2)C_6H_4$	NO_2
19	C_6H_5	4-$(CH_3)_2NC_6H_4$	$(CH_3)_2CHCH_2$
20	C_6H_5	3-pyridyl	NO_2
21	C_6H_5	3-pyridyl	$(CH_3)_2CHCH_2$
22[a]	C_6H_5	4-$CH_3OC_6H_4$	NO_2
23	C_6H_5	4-$(CH_3)_2NC_6H_4$	CH_3O
24[a]	C_6H_5	3-pyridyl	CH_3O
25	C_6H_5	4-$(CH_3)_2CHC_6H_4$	$(CH_3)_2CH$
26	$(CH_3)_3C$	4-$(CH_3)_2CHC_6H_4$	NO_2
27	$(CH_3)_3C$	4-$(CH_3)_2CHC_6H_4$	$(CH_3)_2CHCH_2$
28	$(CH_3)_3C$	4-$(CH_3)_2CHC_6H_4$	$(CH_3)_2CH$
29	C_6H_5	2-pyrrolyl	H
30	C_6H_5	4-$CH_3OC_6H_4$	H

[a] The hydrolysis of esters *III-22* and *III-24* to the acids was accompanied by a demethylation of the methoxy group; hence for *IV-22* R^2 = = 4-HOC_6H_4, for *IV-24* R^3 = HO.

TABLE II
Ethyl Esters *III-1* and *III-29*

III[a]	Days (yield, %)	M.p., °C (solvent)	Composition of isomers	Formula (mol. wt.)	Calculated/Found		
					% C	% H	% N
III-2	1	129–132	*erythro*	$C_{23}H_{28}O_3$	78·37	8·01	—
	(70)	(ethanol)	up to 5% *threo*	(352·5)	78·45	7·96	
III-5	1	168–170	*erythro*	$C_{27}H_{29}NO_3$	78·04	7·04	3·37
	(66)	(2-propanol)	up to 5% *threo*	(415·5)	77·85	7·26	3·15
III-6	1	144–146	*erythro*	$C_{29}H_{32}O_3$	81·27	7·53	—
	(77)	(2-propanol)	up to 5% *threo*	(428·6)	81·30	7·57	
III-7	1	155–156	*erythro*	$C_{29}H_{32}O_3$	81·27	7·53	—
	(85)	(2-propanol)	up to 5% *threo*	(428 6)	80·95	7·58	—
III-8	6	174–176	*erythro*	$C_{28}H_{30}O_3$	81·12	7·30	—
	(72)	(2-propanol)	up to 5% *threo*	(414·5)	81·30	7·32	
III-9	1	166–167	*threo*	$C_{28}H_{30}O_3$	81·12	7·30	—
	(80)	(nitromethane)	up to 20% *erythro*	(414·5)	81 22	7·68	
III-10[b]	2	161–162	*erythro–threo*	$C_{25}H_{23}ClO_3$	73·81	5·70	—
	(56)	(nitromethane)	1 : 1	(406·9)	74·02	5·68	
III-11[b]	1	161–162	*erythro*	$C_{25}H_{23}ClO_3$	73·81	5·70	—
	(80)	(benzene)	up to 5% *threo*	(406·9)	73·55	5·94	
III-12	1	121–122	*erythro*	$C_{27}H_{36}O_3$	79·37	8·88	—
	(55)	(2-propanol)	up to 5% *threo*	(408·6)	79·15	8·92	
III-13	1	110–112	*erythro*	$C_{27}H_{36}O_3$	79·37	8·88	—
	(70)	(2-propanol)	up to 5% *threo*	(408·6)	79·28	9·00	
III-14	1	137–138	*erythro*	$C_{26}H_{34}O_3$	79·15	8·69	—
	(63)	(nitromethane)	up to 5% *threo*	(394·5)	79·46	8·89	
III-15	1	150–152	*erythro*	$C_{28}H_{29}NO_5$	73·18	6·36	3·05
	(57)	(2-propanol)	up to 5% *threo*	(459·5)	73·26	6·42	3·15
III-16	2	165–166	*erythro*	$C_{32}H_{38}O_3$	81·66	8·14	—
	(85)	(2-propanol)	up to 5% *threo*	(470·6)	81·65	8·07	
III-17	5	166–168	*erythro–threo*	$C_{27}H_{28}N_2O_5$	70·42	6·13	6·08
	(60)	(nitromethane)	1 : 1	(460·5)	70·10	6·19	6·18
III-18	6	185–187	*erythro*	$C_{25}H_{22}N_2O_7$	64·93	4·80	6·07
	(56)	(nitromethane)	up to 5% *threo*	(462·4)	64·89	4·87	6·14
III-19	4	175–176	*threo*	$C_{31}H_{37}NO_3$	78·94	7·91	2·97
	(86)	(ethanol)	5–10% *erythro*	(471·6)	78·73	7·99	2·93
III-20	5	162–163	*erythro*	$C_{24}H_{22}N_2O_5$	68·89	5·30	6·70
	(60)	(ethanol)	up to 5% *threo*	(418·4)	69·00	5·40	6·79

TABLE II
(*Continued*)

III[a]	Days (yield, %)	M.p., °C (solvent)	Composition of isomers	Formula (mol. wt.)	Calculated/Found		
					% C	% H	% N
III-21	3 (36)	124—126 (nitromethane)	*erythro* up to 5% *threo*	$C_{28}H_{31}NO_3$ (429·5)	78·29 78·39	7·27 7·40	3·26 3·50
III-22	2 (61)	143—144 (ethanol)	*threo* up to 5% *erythro*	$C_{26}H_{25}NO_6$ (447·5)	69·78 70·03	5·63 5·82	3·13 3·14
III-23	1 (69)	148—150 (ethanol)	*threo* up to 5% *erythro*	$C_{28}H_{31}NO_4$ (445·5)	75·48 75·74	7·01 7·13	3·14 3·09
III-24	3 (53)	134—136 (2-propanol)	*erythro* up to 5% *threo*	$C_{25}H_{25}NO_4$ (403·5)	74·42 74·73	6·25 6·44	3·47 3·39
III-25	1 (83)	175—176 (nitromethane)	*erythro* up to 5% *threo*	$C_{31}H_{36}O_3$ (456·6)	81·54 81·20	7·95 7·93	—
III-26	7 (53)	133—134 (2-propanol)	*erythro* up to 5% *threo*	$C_{26}H_{33}NO_5$ (439·5)	71·04 70·99	7·57 7·83	3·19 3·11
III-27	5 (54)	106—108 (ethanol–water) 3 : 1	*erythro* 10—15% *threo*	$C_{30}H_{42}O_3$ (450·6)	79·95 80·19	9·39 9·34	—
III-28	1 (65)	132—133 (n-hexane)	*erythro* up to 5% *threo*	$C_{29}H_{40}O_3$ (436·6)	79·77 79·86	9·23 9·66	—
III-29	5 (44)	155—157 (2-propanol)	*erythro* up to 5% *threo*	$C_{23}H_{23}NO_3$ (361·4)	76·43 76·75	6·41 6·68	3·88 3·97

[a] Ethyl esters *III-1*, *III-3* and *III-4* are known. M.p. of *III-1* 152—154°C (154°C in[5]), of *III-3* 187—188°C (188°C in [6]), of *III-4* 153—154°C (153°C in[6]). [b] % Cl: calculated 8·72, found for *III-10* 9·10, for *III-11* 8·74.

On the basis of pharmacological data, compounds *IV-8*, *IV-15* and *IV-26* were selected for a more detailed examination of the effect of configuration on activity. The *threo*-isomers were prepared either by epimerization of the *erythro*-isomers *via* enol-lactones[8], or by the second preparative method, the reaction of phenylacetic acid with unsaturated ketones in liquid ammonia[7,8] (method *B*). Both procedures are described for the preparation of *threo*-2,3-diphenyl-4-benzoylbutanoic acid (*IV-1*). Isomerization attempts (Table IV) with *IV-15* led to a mixture with prevalent *threo*-form while with *IV-8* and *IV-26*, pure *threo*-isomers were obtained. (The starting material in the case of *IV-26* was a practically pure *threo*-form). In attempts to epimerize the known acids *IV-2*, *IV-3* and *IV-4*, the first showed no change in the melting

TABLE III
Acids *IV-1*—*IV-30*

IV[a] (yield, %)	M.p., °C (solvent)	Composition of isomers	Formula (mol. wt.)	Calculated/Found		
				% C	% H	% N
IV-5	261—262	*erythro*	$C_{25}H_{25}NO_3$	77·49	6·50	3·62
(54)	(nitromethane)		(387·5)	77·80	6·66	3·69
IV-6	208—209	*erythro*	$C_{27}H_{28}O_3$	80·96	7·05	—
(80)	(nitromethane)	20—30% *threo*	(400·5)	80·64	7·23	
IV-7	208—210	*threo*	$C_{27}H_{28}O_3$	80·96	7·05	—
(82)	(nitromethane)	up to 5% *erythro*	(400·5)	81·07	7·14	
IV-8	233—234	*erythro*	$C_{26}H_{26}O_3$	80·80	6·78	—
(87)	(nitromethane)	up to 5% *threo*	(386·5)	80·82	6·77	
IV-9	212—213	*erythro*	$C_{26}H_{26}O_3$	80·80	6·78	—
(68)	(nitromethane)	up to 5% *threo*	(386·5)	80·52	6·83	
IV-10[b,c]	252—254	*erythro*	$C_{23}H_{19}ClO_3$	72·91	5·05	—
(67)	(nitromethane)		(378·8)	72·70	5·20	
IV-11	230—231	*erythro*	$C_{23}H_{19}ClO_3$	72·91	5·05	—
(63)	(nitromethane)	up to 5% *threo*	(378·8)	72·71	5·35	
IV-12	202—204	*threo*	$C_{25}H_{32}O_3$	78·91	8·48	—
(83)	(cyclohexane)		(380·5)	78·65	8·63	
IV-13	203—204	*threo*	$C_{25}H_{32}O_3$	78·91	8·48	—
(67)	(cyclohexane)		(380·5)	78·81	8·66	
IV-14	192—193	*erythro*	$C_{24}H_{30}O_3$	78·65	8·25	—
(60)	(nitromethane)	20—40% *threo*	(366·5)	78·34	8·60	
IV-15	208—209	*erythro*	$C_{26}H_{25}NO_5$	72·37	5·84	3·25
(87)	(nitromethane)	up to 5% *threo*	(431·5)	72·08	5·91	3·22
IV-16	220—221	*erythro*	$C_{30}H_{34}O_3$	81·41	7·75	—
(84)	(nitromethane)	5—10% *threo*	(442·6)	81·80	8·00	
IV-17	201—202	*erythro*	$C_{25}H_{24}N_2O_5$	69·43	5·59	6·48
(50)	(nitromethane)	up to 5% *threo*	(432·5)	69·36	5·64	6·61
IV-18	222—223	*erythro*	$C_{23}H_{18}N_2O_7$	63·59	4·18	6·45
(74)	(dioxane)		(432·4)	63·35	4·50	6·10
IV-19	207—208	*erythro*	$C_{29}H_{33}NO_3$	78·52	7·50	3·16
(80)	(nitromethane)	up to 5% *threo*	(413·6)	78·73	7·52	3·38
IV-20	196—197	*erythro*	$C_{22}H_{18}N_2O_5$	67·68	4·65	7·18
(50)	(nitromethane)	up to 10% *threo*	(390·4)	67·30	4·71	6·98
IV-21	205—207	*erythro*	$C_{26}H_{27}NO_3$	77·78	6·78	3·49
(70)	(nitromethane)	up to 5% *threo*	(401·5)	77·90	6·93	3·41

TABLE III
(*Continued*)

IV[a] (yield, %)	M.p., °C (solvent)	Composition of isomers	Formula (mol. wt.)	Calculated/Found		
				% C	% H	% N
IV-22	228—230	*threo*	$C_{23}H_{19}NO_6$	68·14	4·72	3·46
(83)	(nitromethane)		(405·1)	68·15	4·73	3·46
IV-23	256—257	*threo*	$C_{26}H_{27}NO_4$	74·80	6·52	3·36
(68)	(nitromethane)		(417·5)	74·62	6·49	3·44
IV-24	238—140	*threo*	$C_{22}H_{19}NO_4$	73·11	5·30	3·88
(45)	(nitromethane)		(361·4)	72·80	5·20	3·84
IV-25	230—232	*erythro*	$C_{29}H_{32}O_3$	81·27	7·53	—
(72)	(nitromethane)	up to 5% *threo*	(428·6)	81·20	7·76	
IV-26	170—172	*threo*	$C_{24}H_{29}NO_5$	70·05	7·10	3·40
(74)	(ethanol–water) 3 : 1		(411·5)	70·26	7·22	3·40
IV-27	158—159	*threo*	$C_{28}H_{38}O_3$	79·58	9·06	—
(84)	(nitromethane)		(422·6)	79·35	8·97	
IV-28	175—177	*threo*	$C_{27}H_{36}O_3$	79·37	8·88	—
(56)	(cyclohexane)	5—10% *erythro*	(408·6)	79·59	8·98	
IV-29	190—191	*erythro*	$C_{21}H_{19}NO_3$	75·65	5·74	4·20
(65)	(nitromethane)	up to 5% *threo*	(333·4)	75·77	6·00	3·98
IV-30[c]	235—237	*erythro*	$C_{24}H_{22}O_4$	76·98	6·78	—
(20)	(nitromethane)		(374·4)	77·17	6·83	

[a] Compounds *IV-1*—*IV-4* are known, their m.p. are shown in Table IV. [b] % Cl: calculated 9·36, found for *IV-10* 9·33, for *IV-11* 9·35. [c] Compounds *IV-10* and *IV-30* are known, their m.p. 242—243°C and 225·5°C, respectively (ref.[9]).

point or the IR spectrum so that the starting *erythro*-configuration was preserved. In the second case the isomerization was incomplete, yielding an equal amount of both isomers while in the case of *IV-4* a product was obtained with the *threo*-form predominating.

In contrast with reports in the literature[7,8], reaction of phenylacetic acid with 1,3-diphenylpropen-3-one in liquid ammonia (method *B*) did not lead to the expected *threo*-acid *IV-1* but to the lower-melting form of 1,4-dibenzoyl-2,3-diphenylbutane[11]. This was observed whenever one of the reaction components was an α,β-unsaturated ketone in which position 4 of the benzal group was not substituted. Thus in the preparation of isomeric 4-benzoylbutanoic acids substituted with a 4-methoxyphenyl group either at the α- or at the β-carbon, the reaction product in the first case was the

TABLE IV
Results of Isomerization Experiments

IV[a]	Composition before isomerization	M.p., °C m.p., °C (ref.)	Composition after isomerization	M.p., °C[b] (yield, %)
IV-2	*erythro*	234—235 236 (ref.[5])	*erythro*	234—236 (30)
IV-3	*erythro*	220—224 220—225 (ref.[6])	*erythro* : *threo* 1 : 1	211—213 (20)
IV-4	*erythro*	214—218 208—215 (ref.[6])	*threo* up to 10% *erythro*	195—200 (25)
IV-8[c]	*erythro* up to 5% *threo*	233—234	*threo*	202—203 (20)
IV-15	*erythro* up to 5% *threo*	208—209	*erythro*	217—218 (22)
IV-26	*threo*	170—172	*threo*	173—174 (30)

[a] Reproduction of the procedure described for the *threo*-acid *IV-1* had the same results as in ref.[8]. [b] With the exception of *IV-26* which crystallized from aqueous ethanol (3 : 1), all the compounds crystallized from nitromethane. [c] The m.p. of the pure *erythro*-acid *IV-8*, prepared by method *B* is 241—242°C.

above-mentioned diketone, in the second case a pure *erythro*-isomer rather than the expected *threo*-form of acid *IV-30* (ref.[9]). Using the procedure in liquid ammonia, the *erythro*-form of acid *IV-8* was prepared quite pure.

To prepare α,β-unsaturated ketones a procedure common in the chemistry of chalcones was used[12,13]. With the exception of 2,2-dimethyl-5-(4-isopropylphenyl)-4-penten-3-one they are all known from the literature. Similarly, all the phenylacetic acids and their ethyl esters used here are known. The ethyl ester of 4-nitrophenylacetic acid was prepared from 4-nitrobenzyl cyanide, the other esters were obtained from the acids by esterification. With the exception of the nitro derivative, all the phenylacetic acids were prepared from acetophenones by Willgerodt's reaction.

In the series of acids *IV-1*—*IV-30* the highest antiinflammatory activity was found with *IV-21*, containing a 4-isobutylphenyl group at the α-carbon and a 3-pyridyl group at the β-carbon. A high activity was also found with compounds containing a 4-isopropylphenyl group at the β-carbon. Comparison of the two diastereo isomers of the most active compound (*IV-8*) showed the *threo*-form to be about 15% more active than the *erythro*-one.

EXPERIMENTAL

The melting points are not corrected.

2,2-Dimethyl-5-(4-isopropylphenyl)-4-penten-3-one

Procedure described for the preparation of 1,3-diphenylpropen-3-one[13] (reaction period 24 h) and applied here to 18 g 3,3-dimethylbutan-2-one and 30 g 4-isopropylbenzaldehyde yielded 22 g (53%) ketone, b.p. 102–108°C/0·1 Torr. For $C_{16}H_{22}O$ (230·4) calculated: 83·43% C, 9·63% H; found: 83·55% C, 9·65% H.

Addition of Phenylacetates to α,β-Unsaturated Ketones (Method *A*); Compounds *III-1*—*III-29* (Table II)

A solution of 0·033 mol substituted ethyl phenylacetate *I* in 60 ml ether and 0·033 mol α,β-unsaturated ketone *II* in 60 ml ether was added to a solution of 0·01 mol sodium in about 10 ml ethanol from which the ethanol had been removed by distillation at reduced pressure. The mixture was left to stand for 1–7 days at room temperature, the precipitated compound was filtered, washed with water and recrystallized. If no crystals appeared during the reaction period, the solvent was distilled at reduced pressure, the residue was washed with water and recrystallized.

Hydrolysis of Esters *III-1*—*III-28* to Acids *IV-1*—*IV-28* (Table III)

0·03 mol ester *III* was boiled for 2 h with 180 ml acetic acid and 33 ml azeotropic hydrobromic acid, combined with 12 ml hydrobromic acid and heated for another hour. The mixture was cooled to 20°C and the precipitated product was filtered. If no crystals appeared on cooling the product was obtained after diluting the mixture with about 200 ml water. Compounds *IV-17* and *IV-24* were obtained as hydrobromides from which they were liberated with a solution of sodium hydroxide (potentiometric titration). Hydrobromide of *IV-20* was isolated from the mother liquors after crystallization of the reaction product from nitromethane. For the hydrobromide of *IV-17*, melting at 192–194°C (nitromethane) $C_{25}H_{25}BrN_2O_5$ (513·4) calculated: 58·43% C, 4·98% H, 15·56% Br, 5·46% N; found: 58·04% C, 5·06% H, 15·35% Br, 5·78% N. For the hydrobromide of *IV-20*, m.p. 196–197°C (nitromethane) $C_{22}H_{19}BrN_2O_5$ (471·3) calculated: 56·07% C, 4·06% H, 16·95% Br, 5·94% N; found: 56·00% C, 4·20% H, 16·96% Br, 5·73% N. For the hydrobromide of *IV-24*, m.p. 259–260°C (ethanol–ether 1 : 2) $C_{22}H_{20}BrNO_4$ (442·3) calculated: 59·74% C, 4·56% H, 18·07% Br, 3·17% N; found: 59·88% C, 4·62% H, 17·80% Br, 2·89% N.

Hydrolysis of Ester *III-29* to Acid *IV-29* (Table III)

0·03 mol ester was boiled for 2 h with 125 ml 2M-NaOH and 250 ml ethanol. The product was obtained after diluting the mixture with water and acidification with dilute hydrochloric acid.

Addition of Phenylacetic Acid to α,β-Unsaturated Ketones (Method *B*); *erythro*-Acids *IV-8* and *IV-30*

0·033 mol phenylacetic acid and 0·033 mol 1-(4-isopropylphenyl)-3-phenylpropen-3-one in 100 ml liquid ammonia in the presence of 0·066 mol sodium amide yielded (for method see[7]) 23% *erythro*-acid *IV-8*, m.p. 241–242°C (nitromethane). When using a greater amount of ammonia[8], 0·015 mol phenylacetic acid and 0·015 mol 3-phenyl-1-(4-methoxyphenyl)propen-3-one in 120 ml

liquid ammonia in the presence of 0·03 mol sodium amide the *erythro*-isomer of *IV-30* was obtained (Table III).

The method shown for the preparation of *IV-8*, using phenylacetic acid and 1,3-diphenylpropen-3-one, yielded, instead of the expected *threo*-acid *IV-1*, the lower-melting isomer of 1,4-dibenzoyl-2,3-diphenylbutane, m.p. 192—193°C (194°C in ref.[11]).

Epimerization of Acids *IV-2*, *IV-3*, *IV-4*, *IV-8*, *IV-15* and *IV-26* (Table IV)

1 500 ml n-hexane and 500 ml n-heptane were used for 0·024 mol acid (for method see[8]). The crude lactone in the form of the residue obtained by concentration of the solution, was hydrolyzed without further purification by a mixture of acetic and sulfuric acids.

The elementary analyses were carried out in the analytical department of this institute under the direction of Dr J. Körbl.

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